Symptomatic Atherosclerosis

The Tip of the Iceberg

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Symptomatic Atherosclerosis

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Chapter 1

General introduction and outline of the thesis

INTRODUCTION

Vascular surgery patients are at increased risk for developing adverse cardiac events, such as myocardial ischemia or infarction, associated with postoperative morbidity and mortality.[1] Perioperative cardiac complications, therefore, remain an area of clinical interest and concern in patients undergoing vascular surgery. Importantly, it has been demonstrated that the great majority of cardiac events in vascular surgery patients are asymptomatic.[2] The high frequency of perioperative cardiac complications reflects the high prevalence of underlying coronary artery disease.[3] Surgical procedures can be classified to be associated with low-risk (<1%), intermediate-risk (1-5%), or high-risk (>5%) for the development of perioperative cardiac complications. Open lower extremity revascularization and open aortic procedures are considered high-risk surgery. Carotid surgery and endovascular aortic aneurysm repair are considered to have intermediate cardiac risk.[4-5]

Over the years, perioperative risk assessment has evolved significantly in order to detect surgical patients with myocardium at risk due to coronary artery disease. Several risk indices have been developed to identify patients at risk, of which the Revised Cardiac Risk index is currently widely used. Cardiac risk factors imbedded in the Revised Cardiac Risk index are (i) ischemic heart disease, (ii) symptomatic heart failure, (iii) cerebrovascular disease, (iv) insulin dependent diabetes mellitus, (v) renal dysfunction, and (vi) high-risk surgery.[6] However, preoperative risk stratification for adverse cardiac outcome using traditional cardiac risk indices is considered suboptimal, indicating the necessity to improve cardiac evaluation before surgery.[7-8]

OUTLINE OF THE THESIS

Part I: Left ventricular function

These days, the physician needs to inform the patient about his or her perioperative risk. When preoperative risk stratification with, for instance, the use of the Revised Cardiac Risk index identifies the patient to have an increased cardiac risk, additional cardiac testing to diagnose or exclude coronary artery disease is warranted. In **Chapter 2**, tests most frequently used in preoperative cardiac risk stratification are discussed and recommendations provided in most recent perioperative guidelines are summarized.[9-10]

Echocardiography is a well-established imaging technique in the detection and quantification of coronary artery disease. With the use of cardiac echo, regional and global wall motion abnormalities representing ischemic and infarcted regions of the myocardium supplied by a stenotic coronary artery, can be detected. **Chapter 3** describes the role of echocardiography in the detection of coronary artery disease.

Coronary artery disease is the aetiology of heart failure in 60 to 70% of patients, predominantly in the elderly population.[11-12] Whereas the term heart failure describes a clinical syndrome characterized by shortness of breath and exercise intolerance, left ventricular (LV) dysfunction describes the impaired mechanical properties of the left ventricle. Asymptomatic LV dysfunction is considered a precursor of symptomatic heart failure, associated with high mortality.[13] Hypertrophy of the myocardium is associated with abnormal relaxation of the left ventricle causing diastolic LV dysfunction. In addition, dilatation of the left ventricle is associated with systolic LV dysfunction with an impaired LV ejection fraction.[14] The prevalence of asymptomatic systolic LV dysfunction and symptomatic heart failure in vascular surgery patients and pharmacological treatment according to the 'European Society of Cardiology' guidelines for the diagnosis and treatment of acute and chronic heart failure [13] is evaluated in **Chapter 4**. In addition, the prognostic implications of asymptomatic LV dysfunction towards 30-day cardiovascular events and long-term mortality and its relation with chronic obstructive pulmonary disease and high-sensitive C-reactive protein are described in **Chapters 5, 6, and 7**.

Although the pathophysiology of perioperative myocardial ischemia or infarction is not entirely clear, it is well accepted that coronary plaque rupture is an important cause, similar to the nonsurgical setting. The location of the cardiac event is difficult to foresee, because of unpredictable plaque rupture of non-significant, vulnerable coronary artery lesions. In **Chapter 8**, the relation and reproducibility of (i) ischemic LV territories assessed with dobutamine echocardiography before surgery with (ii) new wall motion abnormalities observed with transesophageal echocardiography performed during surgery was examined.

The echo community has put a lot of efforts in guidelines and standardization of LV function assessment. However, echocardiographic assessment of systolic LV function is often performed subjectively, which is increasingly considered suboptimal. In **Chapter 9**, automated assessment of LV volumes and function using three dimensional speckle tracking ultrasound is discussed.

Part II: Asymptomatic atherosclerosis in patients with symptomatic peripheral arterial disease

The heart is an organ with a high metabolic demand and requires a continuous high level of myocardial oxygen-supply. During surgery, high catecholamine production is responsible for vasoconstriction and hemodynamic stress,[15] associated with an increased oxygen-demand of the myocardium. Perioperative myocardial damage may occur when the increased oxygen-demand is not met by an adequate increase of oxygen-supply.[16] **Chapter 10** provides an overview of literature addressing perioperative myocardial damage in vascular surgery patients.

As the population age increases, the prevalence of atherosclerotic disease and its associated adverse outcomes will increase. The process of established atherosclerosis is not limited to a single arterial location. In **Chapter 11**, (i) the prevalence and number of affected

vascular beds and (ii) the prognostic implications of polyvascular disease on short- and long-term outcome is evaluated in vascular surgery patients with symptomatic peripheral arterial disease.

Cardiac risk factors, as summarized in the Revised Cardiac Risk index, have been identified as independent predictors of perioperative cardiovascular events. However, a more direct marker of the underlying atherosclerotic disease may be of predictive value as well, in addition to conventional cardiac risk indices. A correlation between (i) an increased intimamedia thickness of the common carotid artery and (ii) cardiac risk factors and coronary atherosclerosis has been demonstrated,[17] however, limited information is available in vascular surgery patients. In addition, the ankle-brachial index is a simple noninvasive test to screen patients with suspected peripheral arterial disease. A resting low ankle-brachial index (<0.90) has been demonstrated to improve risk prediction for cardiovascular mortality and major nonfatal myocardial infarction (nonsurgical setting), even beyond the risk prediction properties using cardiac risk scores.[18] However, the predictive value of asymptomatic low ankle-brachial index in patients undergoing carotid- or abdominal aortic surgery is less well understood. In **Chapters 12, 13, and 14,** the separate and combined prognostic values of an increased intimamedia thickness of the common carotid artery (>1.25 mm) and low ankle-brachial index (<0.90) towards postoperative outcome of vascular surgery patients is evaluated.

The metabolic syndrome is the concurrence of multiple metabolic abnormalities such as (i) abdominal obesity and abnormal (ii) triglycerides, (iii) high density lipoprotein cholesterol, (iv) blood pressure, and (v) fasting glucose. Metabolic syndrome was primarily developed as a predictor of cardiovascular disease in the healthy population. The prevalence of the metabolic syndrome in patients with occlusive or aneurysmatic peripheral arterial disease and its long-term predictive value is discussed in **Chapter 15**.

N-terminal pro-B-type natriuretic peptide is synthesized in the ventricular myocardium in response to ventricular wall stress, such as in heart failure and coronary artery disease.[19] Although, it has been suggested that measurement of N-terminal pro-B-type natriuretic peptide levels might improve preoperative cardiac risk stratification for surgical patients, several conditions might influence this prognostic value, including anemia. **Chapter 16** evaluates whether anemia confounds the prognostic value of N-terminal pro-B-type natriuretic peptide for predicting 30-day cardiac events in patients undergoing vascular surgery.

Abdominal aortic aneurysms are often asymptomatic and diagnosed at time of (impending) rupture, which leads to a dramatic increase of morbidity and mortality. In **Chapter 17**, the diagnostic accuracy of a new portable ultrasound scanner, developed for automatic abdominal aortic aneurysm detection, is evaluated.

Part III: Prevention and treatment

In order to reduce the incidence of cardiac complications during vascular surgery, two strategies can be considered: (i) pharmacological treatment with i.e. β-blockers and (ii) prophylactic coronary revascularization. An extended and detailed overview of leading observational studies, randomized, controlled trials and guidelines addressing the value of these risk-reducing strategies before vascular surgery is provided in **Chapter 18**.

Early surgery after coronary stent placement is associated with in-stent thrombosis or bleeding complications. This might explain the lack of perioperative benefit derived from preoperative coronary revascularization in order to improve immediate postoperative outcome.[20] Long-term outcome of the randomized, controlled Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography-V trial is analysed in **Chapter 19**, to assess if there is a long-term effect of prophylactic revascularization in high-risk vascular surgery patients.

The prevention of cardiac complications vs. the risk of severe bleeding complications creates a double-edged sword on the timing of surgery and the antiplatelet regimen. Current guidelines from the 'American College of Cardiology/American Heart Association' recommend postponing noncardiac surgery for ≥6 weeks after bare metal stent placement and 1 year after drug-eluting stent placement, however, much debate has ensued about these intervals.[9] In **Chapter 20**, the relation between (i) the interval to noncardiac surgery after percutaneous coronary intervention and (ii) the occurrence of perioperative major adverse cardiovascular events, is addressed.

In the nonsurgical setting, β-blockers are widely used for the prevention and treatment of coronary heart disease and heart failure, both important determinants of perioperative cardiovascular complications. Factors that may relate to the effectiveness of β-blocker therapy are the patients underlying cardiac risk factors and variations in treatment protocols, such as (i) β-blocker type, (ii) β-blocker dose, and (iii) timing of β-blocker initiation before surgery. However, the duration of β-blocker treatment before surgery and its effect on cardiovascular outcome has not been evaluated yet in a cohort of vascular surgery patients. Timing of β-blocker initiation and its influence on preoperative heart rate, preoperative high-sensitive C-reactive protein levels, and postoperative outcome in vascular surgery patients is outlined in **Chapter 21**.

In **Chapter 22**, a brief overview is provided regarding two important randomized, controlled trials evaluating the protective value of β-blockers: (i) the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography-1 trial,[21] and (ii) the multi-centre Perioperative Ischemic Evaluation-trial.[22]

REFERENCES

1. Mangano DT. Perioperative cardiac morbidity. *Anesthesiology.* 1990;72(1):153-184.

2. Biagini E, Schinkel AF, Bax JJ, et al. Long term outcome in patients with silent versus symptomatic ischaemia during dobutamine stress echocardiography. *Heart.* 2005;91(6):737-742.

3. Hertzer NR, Beven EG, Young JR, et al. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Ann Surg.* 1984;199(2):223-233.

4. Schouten O, Dunkelgrun M, Feringa HH, et al. Myocardial damage in high-risk patients undergoing elective endovascular or open infrarenal abdominal aortic aneurysm repair. *Eur J Vasc Endovasc Surg.* 2007;33(5):544-549.

5. Elkouri S, Gloviczki P, McKusick MA, et al. Perioperative complications and early outcome after endovascular and open surgical repair of abdominal aortic aneurysms. *J Vasc Surg.* 2004;39(3):497-505.

6. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation.* 1999;100(10):1043-1049.

7. Utoh J, Goto H, Hirata T, et al. Routine coronary angiography prior to abdominal aortic aneurysm repair: incidence of silent coronary artery disease. *Panminerva Med.* 1998;40(2):107-109.

8. Bayazit M, Gol MK, Battaloglu B, et al. Routine coronary arteriography before abdominal aortic aneurysm repair. *Am J Surg.* 1995;170(3):246-250.

9. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol.* 2007;50(17):e159-241.

10. Poldermans D, Bax JJ, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: the Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur Heart J.* 2009;30(22):2769-2812.

11. Fox KF, Cowie MR, Wood DA, et al. Coronary artery disease as the cause of incident heart failure in the population. *Eur Heart J.* 2001;22(3):228-236.

12. Cleland JG, Swedberg K, Follath F, et al. The EuroHeart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J.* 2003;24(5):442-463.

13. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J.* 2008;29(19):2388-2442.

14. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J Am Coll Cardiol.* 2000;35(3):569-582.

15. Mangano DT. Perioperative medicine: NHLBI working group deliberations and recommendations. *J Cardiothorac Vasc Anesth.* 2004;18(1):1-6.

16. Priebe HJ. Perioperative myocardial infarction--aetiology and prevention. *Br. J. Anaesth.* 2005;95(1):3-19.

17. Lorenz MW, Markus HS, Bots ML, et al. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation.* 2007;115(4):459-467.

18. Fowkes FG, Murray GD, Butcher I, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA.* 2008;300(2):197-208.

19. Yeh HM, Lau HP, Lin JM, et al. Preoperative plasma N-terminal pro-brain natriuretic peptide as a marker of cardiac risk in patients undergoing elective non-cardiac surgery. *Br J Surg.* 2005;92(8):1041-1045.

20. Schouten O, van Domburg RT, Bax JJ, et al. Noncardiac surgery after coronary stenting: early surgery and interruption of antiplatelet therapy are associated with an increase in major adverse cardiac events. *J Am Coll Cardiol.* 2007;49(1):122-124.

21. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med.* 1999;341(24):1789-1794.

22. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet*. 2008;371(9627):1839-1847.

PART I

Left ventricular function

Chapter 2

Preoperative evaluation of patients with possible coronary artery disease

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ABSTRACT

During noncardiac surgery, patients may be at risk for developing cardiac events, related to underlying coronary artery disease. Therefore, perioperative cardiac complications remain an area of clinical interest and concern in patients undergoing noncardiac surgery. Over the years, perioperative risk assessment has evolved significantly to detect surgical patients with myocardium at risk due to the coronary artery disease. In addition, many efforts have been made to reduce the cardiac risk of patients undergoing noncardiac surgery. The present review article will focus on the definition of high cardiac risk surgery and patients related cardiac risk factors will be discussed. In addition, the preoperative cardiac tests available to detect patients with coronary artery disease and strategies to reduce perioperative cardiac risk, as recommended in most recent perioperative guidelines, will be outlined.

INTRODUCTION

Perioperative cardiac complications remain an area of clinical interest and concern in patients undergoing noncardiac surgery. Worldwide, major noncardiac surgery is performed in 230 million patients annually. It is suspected that approximately 1% (2,300,000 patients) suffer perioperative myocardial infarction with a cardiovascular mortality rate around 0.3% (690,000 patients).[1] The high frequency of perioperative cardiac complications reflects the high prevalence of underlying coronary artery disease.[2] The highest incidence of perioperative myocardial infarction is within the first three days after surgery.[3] Over the years, perioperative risk assessment has evolved significantly to detect surgical patients with myocardium at risk due to coronary artery disease. In addition, many efforts have been made to reduce the cardiac risk of patients undergoing noncardiac surgery. This review article will focus on (i) the definition of high cardiac risk surgery, (ii) patients-related cardiac risk factors, (iii) preoperative cardiac tests available to detect patients with coronary artery disease, and (iv) strategies to reduce perioperative cardiac risk.

DEFINING HIGH CARDIAC RISK SURGERY

Patient-related factors are more important than surgery-related factors in the prediction of cardiac risk during noncardiac surgery. However, to cardiac risk stratify patients undergoing elective noncardiac surgery, knowledge of the clinician regarding the cardiac risk related to surgery is inevitable. Cardiac risk imbedded in surgical interventions can differ depending on the magnitude, duration, location, blood loss, and fluid shifts related to the specific procedure.[4] In 2005, Boersma *et al.*[5] developed a model to risk stratify surgical procedures based on the occurrence of 30-day cardiac death and myocardial infarction. Surgical procedures were classified low-risk (<1%), intermediate-risk (1 to 5%), or high-risk (>5%) for the development of 30-day adverse cardiac outcome. An overview of surgical procedures and the cardiac risk estimated is provided in *Table 1*. High-risk surgery is considered to be lower extremity revascularization and open aortic aneurysm or stenosis repair. Endovascular aortic aneurysm repair is considered to have intermediate cardiac risk because it is associated with reduced myocardial stress and the need for lower fluid administration compared with open abdominal aortic aneurysm repair.[6, 7] Interestingly, patients undergoing laparoscopic surgery should be evaluated similar to patients undergoing open surgery, because the cardiac stress evoked during these surgical procedures is similar.[4] Laparoscopic surgery is associated with increased intra-abdominal pressure and reduced venous return due to the pneumoperitoneum used during these procedures, leading to lower cardiac output and increased systemic vascular resistance.[4]

Table 1	Cardiac risk associated with noncardiac surgery	
Low-risk surgery	**Intermediate-risk surgery**	**High-risk surgery**
(<1%)	**(1-5%)**	**(>5%)**
breast	abdominal	open aortic
dental	carotid, PTA and EVAR	peripheral vascular
endocrien	hip and spine	
eye	head and Neck	
gynaecology	neurological	
knee	transplantation	
urologic (minor)	urologic (major)	

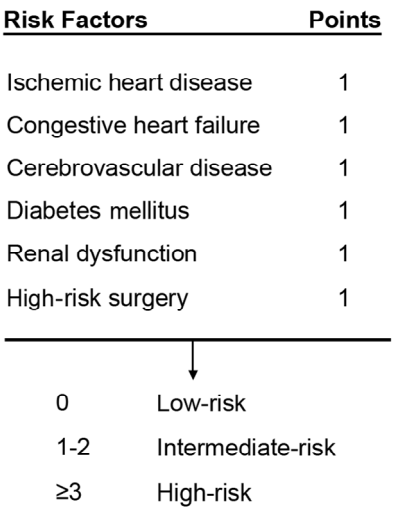
Percutaneous transluminal angioplasty (PTA), endovascular aneurysm repair (EVAR).

PATIENTS RELATED CARDIAC RISK FACTORS

Adequate risk stratification of patients undergoing noncardiac surgery is of utmost importance to identify patients at risk for perioperative cardiac events. Over the years, several cardiac risk indices have been developed to identify those patients at risk. In 1977, Goldman *et al.*[8] developed the first multifactorial risk index specifically for cardiac complications in a large surgical population. The risk index included nine independent risk factors for cardiac complications and was subsequently modified by Detsky *et al.*[9] in 1986. In 1999, Lee *et al.*[10] modified the original Goldman index into the Revised Cardiac Risk (RCR) index, nowadays widely used and considered to be the best available cardiac risk index for patients undergoing noncardiac surgery. Cardiac risk factors imbedded in the RCR index include (i) ischemic heart disease, (ii) congestive heart failure, (iii) cerebrovascular disease, (iv) insulin dependent diabetes mellitus, (v) renal dysfunction, and (vi) high-risk surgery. Based on the presence of none, 1, 2, or ≥3 risk factors, the occurrence of major cardiac complications was estimated in a validation cohort of 1,422 patients. Patients with one to two risk factors were considered to be at intermediate risk (0.9 to 7%) for the development of major cardiac complications and patients with ≥3 risk factors were considered to be at high risk (11%), as demonstrated in *Figure 1*. The inclusion of high-risk surgery in the RCR index underlines the importance of knowledge of the clinician regarding the cardiac risk related to specific surgical procedures.

The predictive value of the RCR index towards cardiovascular mortality has been validated in a cohort study performed by Boersma *et al.*[5] including more than 100,000 patients. In this study, published in 2005, it is demonstrated that the prediction of cardiovascular mortality in noncardiac surgery could be improved by adding the risk factor of age greater than 70 years and a more detailed classification of type of surgical procedure (low-, intermediate-low, intermediate-high and high-risk surgery). C-statistic improved from 0.63 in the RCR index to 0.85 in the Erasmus Cardiac Risk index.[5]

Figure 1: Revised Cardiac Risk index



PREOPERATIVE CARDIAC TESTING

These days, the doctor needs to adequately inform the patient about his or her perioperative risk. When preoperative risk stratification with the use of the RCR index identifies the patients to have an increased cardiac risk, additional cardiac testing is warranted. However, testing is, only recommended if the test results will influence perioperative management.[11] Consequences of testing may include (i) changing the surgical procedure, (ii) initiation of pharmacological treatment to reduce the risk of perioperative complications, (iii) postponing surgery to optimally treat the patient first or, (iv) cancelling surgery. Tools for preoperative cardiac evaluation of patients undergoing noncardiac surgery are (i) rest 12-lead electrocardiography, (ii) resting echocardiography, (iii) noninvasive stress testing, (iv) coronary angiography and, (v) biomarkers.

Commonly used cardiac stress tests are (i) exercise electrocardiography, (ii) exercise or pharmacological-induced stress echocardiography, and (iii) nuclear imaging. Regardless of the technique used, resting images are recorded first and serve as a baseline for comparison with stress images obtained during peak stress or immediately after exercise.[12] The additional value of both rest and stress testing in cardiac risk stratification of patients undergoing noncardiac surgery will be outlined in the following paragraphs, including recommendations provided in most recent 'American College of Cardiology / American Heart Association' (ACC/AHA) and 'European Society of Cardiology' (ESC) perioperative guidelines.

Electrocardiography

Twelve-lead electrocardiography is widely used for cardiac evaluation, both in the surgical and nonsurgical setting. Left ventricular hypertrophy, nonspecific ST-T wave changes, and pathological Q-waves are associated with a reduced long-term prognosis in the general population.[13] Multiple studies have evaluated and confirmed the associations between the presence of rest 12-lead electrocardiogram abnormalities before surgery and adverse postoperative cardiac outcome.[14-16]

Recommendations for preoperative rest 12-lead electrocardiography (ACC/AHA and ESC recommendations) are provided in *Table 2*.[4, 11] In addition to *Table 2*, ACC/AHA guidelines recommend preoperative rest 12-lead electrocardiography in patients with ≥1 RCR factors undergoing high-risk surgery, as well as in patients with (i) known coronary heart disease, (ii) peripheral arterial disease, or (iii) cerebrovascular disease undergoing intermediate-risk surgery. In addition, preoperative rest 12-lead electrocardiography is not indicated in asymptomatic patients undergoing low-risk surgery.[11] In ESC guidelines, standard preoperative evaluation with rest 12-lead electrocardiography is recommended in all patients undergoing intermediate- or high-risk surgery, except for patients with 0 RCR factors undergoing intermediate-risk surgery, in which rest 12-lead electrocardiography may be considered (*Table 2*).[4]

Table 2 **Recommendations on rest electrocardiography before noncardiac surgery**

Revised Cardiac Risk factors	Surgery		
	Low-risk	Intermediate-risk	High-risk
	ACC/AHA GUIDELINES		
0*	not recommended (III B)		is reasonable (IIa B)
1-2**		may be reasonable (IIb B)	recommended (1 B)
≥3***		may be reasonable (IIb B)	recommended (1 B)
	ESC GUIDELINES		
0*	not recommended (III B)	may be considered (IIb B)	recommended (1 B)
1-2**	should be considered (IIa B)	recommended (1 B)	recommended (1 B)
≥3***	should be considered (IIa B)	recommended (1 B)	recommended (1 B)

** low cardiac risk, ** intermediate cardiac risk, *** high cardiac risk. American College of Cardiology / American Heart Accociation (ACC/AHH), European Society of Cardiology (ESC).*

Several exercise stress tests are available for perioperative risk assessment to detect myocardial ischemia and identify coronary artery disease. The most commonly used stress test is treadmill or cycle electrocardiography, which is considered to induce the most physiological form of stress. This test provides an estimate of the functional capacity and hemodynamic response of the patient and detects myocardial ischemia by ST-segment changes. The criterion of exercise-induced ischemia detected with stress electrocardiography is generally accepted as an ST segment depression ≥1 mm.[17] Studies have shown a positive association between electrocardiographic responses and cardiovascular mortality in patients with ≥3 RCR factors without symptoms of coronary artery disease.[18, 19] Compared with other stress tests, such as stress echocardiography or nuclear imaging, exercise electrocardiography has shown reasonable sensitivity and specificity to predict perioperative cardiac complications.[20] Exercise electrocardiography is widely available at relatively low costs and should therefore be considered as a preoperative diagnostic tool in patients with ≥3 RCR factors undergoing noncardiac surgery. The recommendations (ACC/AHA and ECS) towards preoperative stress testing (i.e. exercise electrocardiography, stress echocardiography or nuclear imaging) are provided in *Table 3*.[4, 11] In both AHA/ACC and ESC guidelines, preoperative noninvasive stress testing is recommended in patients with an active cardiac condition before proceeding with noncardiac surgery. In addition, preoperative stress testing should only be performed if the results derived from the test are likely to influence perioperative cardiac management.

Echocardiography

Echocardiography is a well-established imaging technique in the detection and quantification of coronary artery disease. Regional and global wall motion abnormalities represent ischemic and infarcted myocardial regions supplied by a stenotic coronary artery. ACC/AHA guidelines state that it is reasonable to perform preoperative noninvasive evaluation of left ventricular function (i.e. with rest echocardiography) in patients with (i) dyspnea of unknown origin or (ii) current or prior heart failure experiencing worsening of dyspnea (class IIa recommendation, level of evidence C [IIa C]). Reassessment of left ventricular function is not well established in clinically stable patients with previously documented cardiomyopathy [IIIb C].[11] In ESC guidelines it is stated that rest echocardiography should be considered in all patients undergoing high-risk surgery [IIIa C].[4] However, routine rest echocardiography for the assessment of left ventricular function in asymptomatic patients is not recommended in ACC/AHA or ESC perioperative guidelines.[4 11]

Recently, Flu *et al.* evaluated more than 1,000 vascular surgery patients with standard preoperative rest echocardiography, irrespectively of the presence of heart failure symptoms. Diastolic and/or systolic left ventricular dysfunction was present in half of the patients, of which 80% was asymptomatic.[21] In open vascular surgery patients, both asymptomatic systolic and isolated diastolic left ventricular dysfunction were associated with 30-day cardiovascular events and long-term cardiovascular mortality. In addition, almost one third of the patients

Table 3	Recommendations on stress testing before noncardiac surgery		
Revised Cardiac Risk factors	Surgery		
	Low-risk	Intermediate-risk	High-risk
	ACC/AHA GUIDELINES		
0*	not useful (III C)	not useful (III C)	
1-2**	not useful (III C)	may be considered (IIb B)****	may be considered (IIb B)******
≥3***	not useful (III C)	may be considered (IIb B)****	is reasonable IIa B****
	ESC GUIDELINES		
0*	not recommended (III C)	may be considered (IIb C)	may be considered (IIb B)
1-2**	not recommended (III C)	may be considered (IIb C)	may be considered (IIb B)
≥3***	not recommended (III C)	may be considered (IIb C)	recommended (1C)

** low cardiac risk, ** intermediate cardiac risk, *** high cardiac risk, **** poor functional capacity of <4 metabolic equivalents,***** good functional capacity of ≥4 metabolic equivalents. American College of Cardiology / American Heart Accociation (ACC/AHH), European Society of Cardiology (ESC).*

with asymptomatic left ventricular dysfunction did not receive pharmacological treatment as recommended. The authors concluded that routine preoperative evaluation of left ventricular function with rest echocardiography could reveal patients with asymptomatic left ventricular dysfunction eligible for pharmacological treatment.[21] Another recent study performed by Matyal *et al.* studied 313 vascular surgery patients with intraoperative transesophageal echocardiography and found isolated diastolic left ventricular dysfunction to be a predictor of adverse cardiovascular outcome.[22]

Due to physiological stress during surgery, the myocardial oxygen-demand is increased and therefore demand-ischemia may occur in patients with a coronary artery stenosis. Echocardiography during stress, evoked with treadmill/bicycle exercise or pharmacologically induced stress, can (i) detect reversible ischemia, (ii) distinguish reversible ischemia from scarred myocardium, and (iii) identify the myocardial region at risk. When physiological stress induces myocardial ischemia, echocardiography permits wall motion analysis. The images are analyzed using a model with 17-segments assigned to one of the three major coronary arteries. Wall motion and wall thickness are scored in each myocardial segment on a four-point scale. Test results are considered positive when wall motion or wall thickness deteriorates by one grade or more in any segment [23].

In treadmill echocardiography, images must be taken immediately after the exercise is performed. However, wall contraction abnormalities can recover very rapidly and persist only for several minutes. Therefore, treadmill echocardiography can miss resolved wall contraction abnormalities. This may lead to false-negative results affecting the sensitivity of treadmill echocardiography to detect ischemia. The overall sensitivity of exercise echocardiography has

been reported to range from 76 to 89%, and sensitivity is greater with more high-grade coronary disease.[24, 25] Meta-analyses performed by Noguchi *et al.* and Kwok *et al.*[24, 25] demonstrated exercise stress echocardiography to have a specificity of 84 and 89%, respectively.

Another important limitation of exercise echocardiography is the frequently limited exercise capacity of elderly patients undergoing noncardiac surgery, due to the presence of (i) claudication, (ii) arthrosis, or (iii) chronic obstructive pulmonary disease. Therefore, nonphysiological stress tests, such as dobutamine or dipyridamole echocardiography, are used in patients with limited exercise capacity. A recent meta-analysis performed in nonsurgical patients by Picano *et al*, analysed five studies addressing the diagnostic accuracy of dobutamine vs. dipyridamole stress echocardiography. They noted dipyridamole and dobutamine to have similar accuracy, sensitivity, and specificity for the detection coronary artery disease.[26] In patients undergoing vascular surgery, many reports demonstrated that pharmacological stress echocardiography predicts perioperative events.[27-30] The negative predictive value of pharmacological stress echocardiography is high, however, the positive predictive value is lower. Kertai *et al.* reported a weighted sensitivity of 85% (95%-CI: 74 to 97%) and a specificity of 70% (95%-CI: 62 to 79%) for dobutamine stress echocardiography, in 850 patients included in eight studies.[20]

Nuclear imaging

Since their introduction in the early 1970s, positron emission tomography (PET) and single photon emission computed tomography (SPECT) have been widely used as a diagnostic tool in the detection of coronary artery disease. The detection of coronary artery disease is based on a difference in myocardial uptake of radiotracers caused by an altered blood-flow distribution through the left ventricular myocardium. These perfusion abnormalities can be explained by insufficient coronary blood-flow, caused by coronary artery stenosis.[31, 32] Husmann *et al.* evaluated the diagnostic accuracy of PET (13N-ammonia-PET) and SPECT (201-TICI-SPECT and MIBI-SPECT) imaging using coronary angiography as the standard of reference. Positron emission tomography imaging showed a higher sensitivity for locating coronary artery stenosis compared with SPECT (95 and 77%, respectively), however no difference in specificity was found (84% in both groups). In the detection of ischemia, the specificity of PET was 91% compared with 74% for SPECT.[33]

A meta-analysis by Shaw *et al.* identified the results of 10 articles describing the use of dipyridamole-thallium-201 nuclear imaging in vascular surgery patients during a 10-year period. The occurrence of cardiac death and nonfatal myocardial infarction was correlated with reversible defects detected with thallium-201 nuclear imaging. Cardiac event rates were low in patients without a history of coronary artery disease, compared with: (i) patients with coronary artery disease and a normal or fixed defect pattern and (ii) patients with ≥1 thallium-201 redistribution abnormalities (1.0% [N=176], 4,8% [N=83] and 18,6% [N=97], p = 0,0001,

respectively).[34] Boucher *et al.* evaluated 49 patients scheduled for peripheral vascular surgery and performed dipyridamole-thallium imaging preoperatively. Half of the patients with thallium redistribution had cardiac events, whereas no events occurred in patients with a normal scan or with nonreversible defects only.[35]

Studies indicate that nuclear imaging is highly sensitive in predicting cardiac complications, however the positive predictive value remains less satisfactory. A meta-analysis conducted by Kertai *et al.* reported a sensitivity of 83% (95%-CI: 77 to 89%) and a much lower specificity of 47% (95%-CI: 41 to 57%) for thalium-201 nuclear imaging to predict perioperative cardiac events.[20] Although nuclear imaging demonstrated lower diagnostic accuracy compared with dobutamine stress echocardiography, they concluded that nuclear imaging is a valuable test for cardiac risk assessment, especially in patients with contraindications to dobutamine stress echocardiography. Beattie *et al.* concluded that dobutamine stress echocardiography has a superior negative predictive value in preoperative cardiac risk assessment compared with nuclear imaging.[36] Their meta-analysis identified 75 studies addressing preoperative noninvasive testing, including 25 nuclear imaging and 50 dobutamine stress echocardiography studies involving vascular surgery patients over a 20 year period. They demonstrated that the likelihood ratio of a postoperative cardiac event was higher for dobutamine stress echocardiography (likelihood ratio: 4.09, 95%-CI: 3.21 to 6.56, p = 0.001) compared with nuclear imaging (likelihood ratio: 1.83, 95%-CI: 1.59 to 2.1. p = 0.001).[37]

Coronary angiography

Coronary angiography is a well-established invasive diagnostic procedure for cardiac evaluation of nonsurgical patients; however there is lack of information focusing on the efficacy of coronary angiography in patients scheduled for noncardiac surgery. Both ACC/AHA and ESC guidelines suggest that indications for preoperative coronary angiography are similar to angiography indications in the nonsurgical setting. Indications for coronary angiography constitute of active cardiac conditions such as (i) unstable angina, (ii) decompensated heart failure, (iii) significant arrhythmias, and (iv) severe valvular disease.[4, 11] The central question following coronary angiography is whether or not a patient should receive coronary revascularization before noncardiac surgery. This important topic will be discussed in the paragraph addressing the 'clinical implications'.

Biomarkers

In patients scheduled for noncardiac surgery, a biomarker associated with adverse cardiac events, could be useful to indentify patients who might benefit from (i) additional cardiac testing or (ii) therapeutic interventions. Brain natriuretic peptide (BNP) and its inactive precursor N-terminal proBNP (NT-proBNP) are synthesized by cardiomyocytes in response to elevated ventricular wall stress or ischemia.[38, 39] Brain natriuretic peptide and NT-proBNP are therefore associated with cardiac pathologies such as (i) left ventricular dysfunction, (ii) valvular heart disease, and (iii) acute coronary syndromes. N-terminal proBNP can be

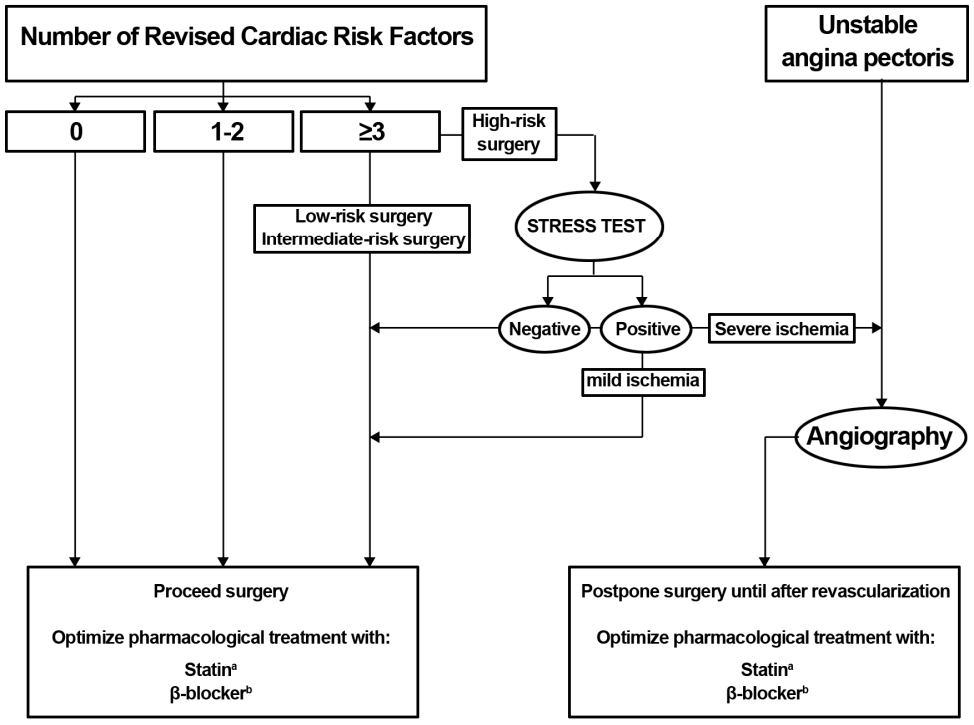
measured in plasma using automated immunoassays and is increasingly used as a screening test to identify patients with heart failure.[40] Recently, two meta-analyses demonstrated that elevated preoperative NT-proBNP measurements have the potential to identify surgical patients at increased risk for adverse postoperative cardiovascular events.[41,42] Routine biomarker sampling is not recommended (III C), however ESC guidelines state that NT-proBNP and BNP measurements should be considered for obtaining prognostic information in patients with ≥3 RCR factors.[4]

It is estimated that of the 230 million patients undergoing major surgery annually, approximately 1% (2,300,000 patients) suffer perioperative myocardial infarction with a cardiovascular mortality rate around 0.3% (690,000 patients).[1] Importantly, the incidence of asymptomatic perioperative myocardial damage is suspected to be as high as 20% in patients undergoing high-risk surgery.[43] In addition, the highest incidence of perioperative myocardial infarction is within the first three days after surgery.[3] Cardiac troponin T and I biomarkers are used to diagnose myocardial infarction and provide prognostic information, complementary to other indicators of cardiac risk, such as (i) electrocardiographic alterations and (ii) left ventricular function. In order to detect asymptomatic myocardial infarction in vascular surgery patients, routine assessment of cardiac troponin release and continuous electrocardiogram monitoring is required during the first postoperative days. Perioperative guidelines do not provide recommendations for standard troponin T measurements. However, the prevalence of asymptomatic myocardial infarction in patients undergoing high-risk surgery could indicate that troponin T measurements could be useful in these subjects.

CLINICAL IMPLICATIONS

In preoperative evaluation of patients with possible coronary artery disease, it is of utmost importance to define high-risk surgery and to address patient-related cardiac risk factors. An algorithm, including patients and surgery related cardiac risk, is demonstrated in *Figure 2,* summarizing the appropriate courses of action to prevent perioperative cardiac events in patients undergoing noncardiac surgery. Noncardiac surgery can proceed without a delay in asymptomatic patients with 0 to 2 RCR factors. In addition, noncardiac surgery should not be delayed in asymptomatic patients with ≥3 RCR factors undergoing low- or intermediate-risk surgery. However, appropriate pharmacological treatment with statins and β-blockers should be initiated as indicated in perioperative guidelines.[4, 11, 44]

Figure 2: Detection nd management of coronary artery disease in patients undergoing noncardiac surgery.



a: *ACC/AHA guidelines recommend statin initiation in:*

1) *patients with 0 RCR factors undergoing high-risk surgery [IIa B]*
2) *patients with 1-2 RCR factors undergoing intermediate- [IIb C] or high-risk surgery [IIa B]*
3) *patients with ≥3 RCR factors undergoing intermediate- [IIb C] or high-risk surgery [IIa B]*

ESC guidelines recommend statin initiation in:

4) *patients with 0 RCR factors undergoing low-, intermediate- [IIa B], or high-risk surgery [I B]*
5) *patients with 1-2 RCR factors undergoing low-, intermediate- [IIa B], or high-risk surgery [I B]*
6) *patients with ≥3 RCR factors undergoing low, intermediate- [IIa B], or high-risk surgery [I B]*

b: *ACC/AHA guidelines recommend β-initiation and titration in:*

1) *patients with 1-2 RCR factors undergoing intermediate- [IIa B] or high-risk surgery [IIa C]*
2) *patients with ≥3 RCR factors undergoing intermediate- [IIa B] or high-risk surgery [IIa C]*

ESC guidelines recommend β-initiation and titration in:

3) *patients with 0 RCR factors undergoing intermediate- [IIb B] or high-risk surgery [I B]*
4) *patients with 1-2 RCR factors undergoing low- [IIb B], intermediate- [IIa B], or high-risk surgery [I B]*
5) *patients with ≥3 RCR factors undergoing low- [IIb B], intermediate- [IIa B], or high-risk surgery [I B]*

American College of Cardiology /American Heart Accociation (ACC/AHH), European Society of Cardiology (ESC, Revised Cardiac Risk (RCR).

Preoperative stress testing is recommended (i) in patients with ≥3 RCR factors undergoing high-risk surgery or (ii) in patients with stable coronary artery disease. In patients with a positive stress test demonstrating mild ischemia, noncardiac surgery should be postponed at least 30 days to initiate and optimize preoperative pharmacological treatment with statins and β-blockers. Patients with (i) a positive stress test demonstrating severe ischemia or (ii) unstable angina pectoris should receive coronary angiography before surgery and, if needed, revascularization should be performed.

Most recent ESC guidelines state that prophylactic revascularization may be considered in patients with ≥3 RCR factors and proven ischemic heart disease [IIb B], however not in patients with 1 to 2 [III B] or none [III C] RCR factors. In patients with unstable angina pectoris, prophylactic revascularization is recommended before elective noncardiac surgery [I A].[4] ACC/AHA guidelines provide a Class I Level of evidence A recommendation for prophylactic revascularization before elective noncardiac surgery in patients with stable angina who have (i) significant left main coronary artery stenosis, (ii) three-vessel disease, (iii) two-vessel disease in combination with significant proximal left anterior descending stenosis + left ventricular ejection fraction <50% or ischemia during noninvasive testing, (iv) unstable angina pectoris or non-ST elevation myocardial infarction and (v) acute ST elevation myocardial infarction.[11] In addition, it is stated that the usefulness of prophylactic revascularization is not well established for high-risk (dobutamine stress echocardiogram with wall motion abnormalities in ≥5 segments) or low-risk ischemic patients (wall motion abnormalities in up to 4 segments).[11]

Both ACC/AHA and ESC guidelines provide the following recommendations for noncardiac surgery after revascularization. In patients with previous coronary stenting, a time window to surgery of at least 6 weeks for bare metal stents and 1 year for drug-eluting stents is recommended. After coronary artery bypass grafting, noncardiac surgery should be postponed at least 1 month. In patients who underwent coronary angiography without stent placement, noncardiac surgery should be postponed at least 2 weeks.[4, 44] Continuing (single or dual)-antiplatelet therapy in the perioperative period should be considered in patients with coronary artery disease, during the time frame that requires antiplatelet therapy. In patients who require temporary interruption of antiplatelet therapy, ESC guidelines recommend that treatment should be stopped at least 5 days before surgery and be resumed 24 hours after surgery, when adequate haemostasis is achieved.[4, 11]

CONCLUSION

Perioperative risk stratification has evolved over the years to detect patients with possible coronary artery disease at risk for perioperative and postoperative adverse cardiac events. Models incorporating patient-related cardiac risk factors and the classification of low-,

intermediate- or high-risk surgery form the basis of preoperative risk stratification and guide the clinician when to initiate medical treatment strategies (statins, β-blocker titration) to reduce the risk for cardiac events. In patients with ≥3 RCR factors, stress testing or coronary angiography is needed to address if surgery should be postponed in order to (i) optimize medical treatment or (ii) perform coronary revascularization. Recently it is demonstrated that high-risk surgery is accompanied with a high prevalence of asymptomatic left ventricular dysfunction, reflecting the need for evaluation of possible coronary artery disease. In preoperative risk stratification, incorporating biomarkers (i.e. BNP) or rest echocardiography could be argued and regarded as an interesting research topic in the years lying ahead.

REFERENCES

1. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet.* 2008;372(9633):139-144.

2. Hertzer NR, Beven EG, Young JR, et al. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Ann Surg.* 1984;199(2):223-233.

3. Abraham N, Lemech L, Sandroussi C, et al. A prospective study of subclinical myocardial damage in endovascular versus open repair of infrarenal abdominal aortic aneurysms. *J Vasc Surg.* 2005;41(3):377-380; discussion 380-371.

4. Poldermans D, Bax JJ, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: the Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur Heart J.* 2009;30(22):2769-2812.

5. Boersma E, Kertai MD, Schouten O, et al. Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index. *Am J Med.* 2005;118(10):1134-1141.

6. Schouten O, Dunkelgrun M, Feringa HH, et al. Myocardial damage in high-risk patients undergoing elective endovascular or open infrarenal abdominal aortic aneurysm repair. *Eur J Vasc Endovasc Surg.* 2007;33(5):544-549.

7. Elkouri S, Gloviczki P, McKusick MA, et al. Perioperative complications and early outcome after endovascular and open surgical repair of abdominal aortic aneurysms. *J Vasc Surg.* 2004;39(3):497-505.

8. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med.* 1977;297(16):845-850.

9. Detsky AS, Abrams HB, Forbath N, et al. Cardiac assessment for patients undergoing noncardiac surgery. A multifactorial clinical risk index. *Arch Intern Med.* 1986;146(11):2131-2134.

10. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation.* 1999;100(10):1043-1049.

11. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *Circulation.* 2007;116(17):1971-1996.

12. Kraunz RF, Kennedy JW. Ultrasonic determination of left ventricular wall motion in normal man. Studies at rest and after exercise. *Am Heart J.* 1970;79(1):36-43.

13. Kannel WB, Gordon T, Castelli WP, et al. Electrocardiographic left ventricular hypertrophy and risk of coronary heart disease. The Framingham study. *Ann Intern Med.* 1970;72(6):813-822.

14. Jeger RV, Probst C, Arsenic R, et al. Long-term prognostic value of the preoperative 12-lead electrocardiogram before major noncardiac surgery in coronary artery disease. *Am Heart J.* 2006;151(2):508-513.

15. Landesberg G, Einav S, Christopherson R, et al. Perioperative ischemia and cardiac complications in major vascular surgery: importance of the preoperative twelve-lead electrocardiogram. *J Vasc Surg.* 1997;26(4):570-578.

16. Noordzij PG, Boersma E, Bax JJ, et al. Prognostic value of routine preoperative electrocardiography in patients undergoing noncardiac surgery. *Am J Cardiol.* 2006;97(7):1103-1106.

17. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *J Am Coll Cardiol.* 2002;40(8):1531-1540.

18. Balady GJ, Larson MG, Vasan RS, et al. Usefulness of exercise testing in the prediction of coronary disease risk among asymptomatic persons as a function of the Framingham risk score. *Circulation.* 2004;110(14):1920-1925.

19. Rywik TM, O'Connor FC, Gittings NS, et al. Role of nondiagnostic exercise-induced ST-segment abnormalities in predicting future coronary events in asymptomatic volunteers. *Circulation.* 2002;106(22):2787-2792.

20. Kertai MD, Boersma E, Bax JJ, et al. A meta-analysis comparing the prognostic accuracy of six diagnostic tests for predicting perioperative cardiac risk in patients undergoing major vascular surgery. *Heart.* 2003;89(11):1327-1334.

21. Flu WJ, van Kuijk JP, Galal W, et al. Prevalence and pharmacological treatment of left ventricular dysfunction in patients undergoing vascular surgery. *Eur J Heart Fail.* 2010;12(3):288-293.

22. Matyal R, Hess PE, Subramaniam B, et al. Perioperative diastolic dysfunction during vascular surgery and its association with postoperative outcome. *J Vasc Surg.* 2009;50(1):70-76.

23. Douglas PS, Khandheria B, Stainback RF, et al. ACCF/ASE/ACEP/AHA/ASNC/SCAI/SCCT/SCMR 2008 appropriateness criteria for stress echocardiography: a report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, American Society of Echocardiography, American College of Emergency Physicians, American Heart Association, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance: endorsed by the Heart Rhythm Society and the Society of Critical Care Medicine. *Circulation.* 2008;117(11):1478-1497.

24. Noguchi Y, Nagata-Kobayashi S, Stahl JE, et al. A meta-analytic comparison of echocardiographic stressors. *Int J Cardiovasc Imaging.* 2005;21(2-3):189-207.

25. Kwok Y, Kim C, Grady D, et al. Meta-analysis of exercise testing to detect coronary artery disease in women. *Am J Cardiol.* 1999;83(5):660-666.

26. Picano E, Molinaro S, Pasanisi E. The diagnostic accuracy of pharmacological stress echocardiography for the assessment of coronary artery disease: a meta-analysis. *Cardiovasc Ultrasound.* 2008;6:30.

27. Poldermans D, Arnese M, Fioretti PM, et al. Improved cardiac risk stratification in major vascular surgery with dobutamine-atropine stress echocardiography. *Journal of the American College of Cardiology.* 1995;26(3):648-653.

28. Sicari R, Ripoli A, Picano E, et al. Perioperative prognostic value of dipyridamole echocardiography in vascular surgery: A large-scale multicenter study in 509 patients. EPIC (Echo Persantine International Cooperative) Study Group. *Circulation.* 1999;100(19 Suppl):II269-274.

29. Eichelberger JP, Schwarz KQ, Black ER, et al. Predictive value of dobutamine echocardiography just before noncardiac vascular surgery. *Am J Cardiol.* 1993;72(7):602-607.

30. Shaw LJ, Eagle KA, Gersh BJ, et al. Meta-analysis of intravenous dipyridamole-thallium-201 imaging (1985 to 1994) and dobutamine echocardiography (1991 to 1994) for risk stratification before vascular surgery. *Journal of the American College of Cardiology.* 1996;27(4):787-798.

31. van der Vaart MG, Meerwaldt R, Slart RH, et al. Application of PET/SPECT imaging in vascular disease. *Eur J Vasc Endovasc Surg.* 2008;35(5):507-513.

32. Vesely MR, Dilsizian V. Nuclear cardiac stress testing in the era of molecular medicine. *J Nucl Med.* 2008;49(3):399-413.

33. Husmann L, Wiegand M, Valenta I, et al. Diagnostic accuracy of myocardial perfusion imaging with single photon emission computed tomography and positron emission tomography: a comparison with coronary angiography. *Int J Cardiovasc Imaging.* 2008;24(5):511-518.

34. Shaw LJ, Eagle KA, Gersh BJ, et al. Meta-analysis of intravenous dipyridamole-thallium-201 imaging (1985 to 1994) and dobutamine echocardiography (1991 to 1994) for risk stratification before vascular surgery. *J Am Coll Cardiol.* 1996;27(4):787-798.

35. Boucher CA, Brewster DC, Darling RC, et al. Determination of cardiac risk by dipyridamole-thallium imaging before peripheral vascular surgery. *N Engl J Med.* 1985;312(7):389-394.

36. Beattie WS, Abdelnaem E, Wijeysundera DN, et al. A meta-analytic comparison of preoperative stress echocardiography and nuclear scintigraphy imaging. *Anesth Analg.* 2006;102(1):8-16.

37. Beller GA, Zaret BL. Contributions of nuclear cardiology to diagnosis and prognosis of patients with coronary artery disease. *Circulation.* 2000;101(12):1465-1478.

38. Alter P, Rupp H, Rominger MB, et al. B-type natriuretic peptide and wall stress in dilated human heart. *Mol Cell Biochem.* 2008;314(1-2):179-191.

39. Weidemann A, Klanke B, Wagner M, et al. Hypoxia, via stabilization of the hypoxia-inducible factor HIF-1alpha, is a direct and sufficient stimulus for brain-type natriuretic peptide induction. *Biochem J.* 2008;409(1):233-242.

40. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. *Heart.* 2006;92(6):843-849.

41. Karthikeyan G, Moncur RA, Levine O, et al. Is a pre-operative brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide measurement an independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery? A systematic review and meta-analysis of observational studies. *J Am Coll Cardiol.* 2009;54(17):1599-1606.

42. Ryding AD, Kumar S, Worthington AM, et al. Prognostic value of brain natriuretic peptide in noncardiac surgery: a meta-analysis. *Anesthesiology.* 2009;111(2):311-319.

43. Feringa HH, Karagiannis S, Vidakovic R, et al. Comparison of the incidences of cardiac arrhythmias, myocardial ischemia, and cardiac events in patients treated with endovascular versus open surgical repair of abdominal aortic aneurysms. *Am J Cardiol.* 2007;100(9):1479-1484.

44. Fleisher LA, Beckman JA, Brown KA, et al. 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. *Circulation.* 2009;120(21):e169-276.

Chapter 3

Echocardiography and the detection of coronary artery disease

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ABSTRACT

Coronary artery stenosis causes an imbalance between myocardial oxygen-supply and demand, leading to myocardial ischemia and infarction. Echocardiography is a well-established imaging technique in the detection and quantification of coronary artery disease. Regional and global wall motion abnormalities represent ischemic and infarcted myocardial regions supplied by a stenotic coronary vessel. With the use of stress echocardiography (exercise, dobutamine or dipyridamole), reversible ischemia can be distinguished from irreversible myocardial infarction. Contrast enhancement exerts beneficial effects in identifying the endocardial border of the left ventricle cavity, allowing a more subtle assessment of myocardial perfusion and contractility. LV dysfunction is a major predictor of mortality after myocardial infarction, may be manifest as LV enlargement and reduced ejection fraction. Echocardiography plays a pivotal role in the detection of CAD complications, including infarct expansion, mitral valve regurgitation, ventricular wall rupture, right ventricle infarction and pericardial effusion. Technical developments such as tissue Doppler, strain rate imaging and speckle tracking will further improve the quantitation of echocardiography.

INTRODUCTION

Coronary artery stenosis causes an imbalance between myocardial oxygen-supply and demand, leading to myocardial ischemia and infarction. Echocardiography is a well-established imaging technique in the detection and quantification of coronary artery disease (CAD). Regional and global wall motion abnormalities represent ischemic and infarcted myocardial regions supplied by a stenotic coronary vessel. With the use of stress echocardiography (exercise, dobutamine, or dipyridamole), reversible ischemia can be distinguished from irreversible myocardial infarction (MI). Contrast enhancement exerts beneficial effects in identifying the endocardial border of the left ventricle (LV) cavity, allowing a more subtle assessment of myocardial perfusion and contractility. Left ventricular dysfunction is a major predictor of mortality after MI and may be manifest as LV enlargement and reduced ejection fraction. Echocardiography plays a pivotal role in the detection of CAD complications, including infarct expansion, mitral valve regurgitation, ventricular wall rupture, right ventricle infarction, and pericardial effusion. Technical developments such as tissue Doppler, strain rate imaging, and speckle tracking will further improve the quantitation of echocardiography.

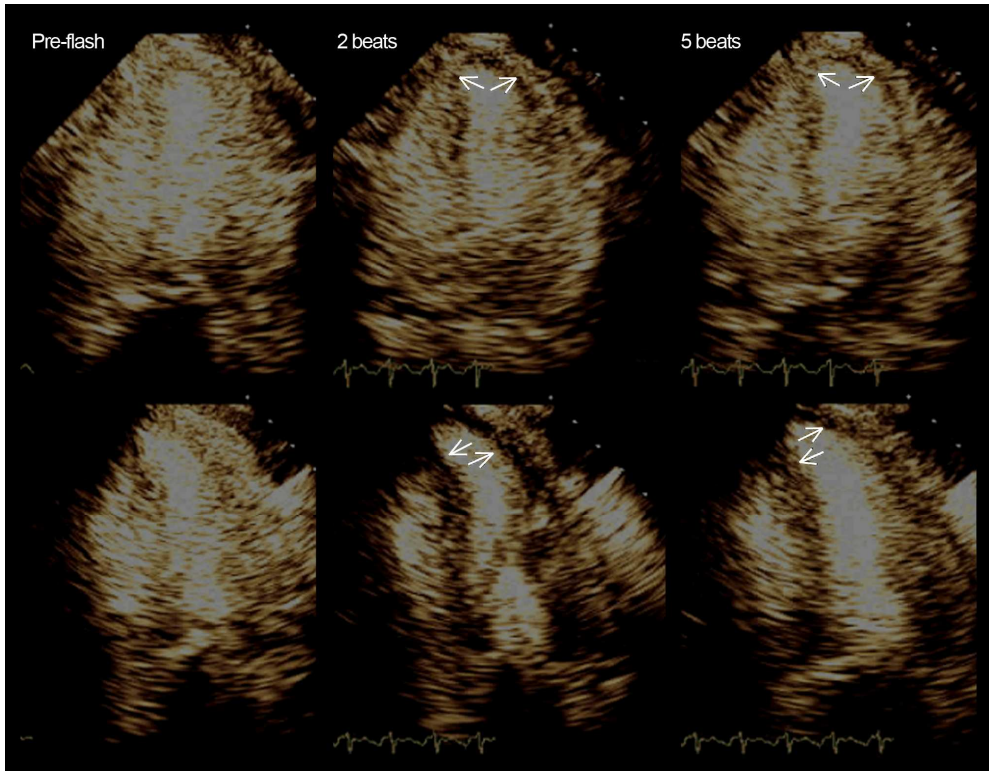
Edler and Hertz introduced echocardiography in 1954 with the publication of their milestone paper 'The use of ultrasonic reflectoscope for continuous recordings of the movements of heart valves'.[1] Echocardiography has developed to be an established noninvasive imaging technique widely available for cardiovascular investigation. With the introduction of M-mode and two-dimensional (2D) ultrasound, pivotal information about the anatomy of the heart could be obtained, including cardiac valves, ventricular wall, tumours and masses. The introduction of Doppler ultrasound made it possible to perform flow-related measurements providing information about cardiac function such as diastolic and systolic ventricular function. Without directly visualizing (most of) the coronary arteries, echocardiography has proven to be an excellent diagnostic tool in the detection and quantification of CAD.

CORONARY ARTERY DISEASE: PATHOPHYSIOLOGY

The heart, an active metabolic organ, requires a high level of oxygen-supply. Due to the high metabolic demand of the heart, the myocardium is susceptible to ischemia and infarction. The progression of coronary atherosclerosis causes a gradual reduction in vascular cross-sectional area, which leads to coronary artery stenosis/occlusion and causes a critical flow reduction to the myocardium. An imbalance between myocardial oxygen-supply and demand will lead to ischemia, followed by (i) metabolic changes, (ii) regional wall contraction alterations, and, at a later stage (iii) ECG changes, (iv) global LV dysfunction and (v) chest pain, described in the "classic ischemic cascade". Thus when the ischemic cascade is triggered, it causes myocardial dysfunction with ischemia present as (i) wall motion abnormalities alone ('super-silent'

ischemia), (ii) wall motion abnormalities with ST segment alterations ('silent' ischemia), and (iii) wall motion abnormalities and symptoms of angina pectoris with or without ECG changes (symptomatic ischemia).[2] Not all patients follow the reassuring paradigm proposed in the 'classic ischemic cascade'. ECG changes in combination with chest pain may occur in patients without wall contraction alterations detectable with echocardiography, a process called the 'alternative ischemic cascade'.[3] Explanations for this apparent paradox could be a reduction in coronary flow reserve, not detectible as regional or global wall contraction alterations, but as local perfusion defects,[4] as well as subendocardial ischemia with preservation of overall segmental function due to the intact subepicardium.

Figure 1: End-systolic freeze-frames showing left anterior descendens territory (apical septum, lateral, inferior and anterior walls) subendocardial perfusion abnormalities, after opacification of the remaining muscle and persisting up to five beats post flash. The accompanying loops show no inducible wall motion abnormalities.



Myocardial ischemia generally occurs at the time of occlusion when decreased blood flow is associated with low adenosine triphosphate (ATP) production and contractile failure secondary to a decreased energy supply. Five myocardial outcomes are possible during or after a coronary occlusion: (i) normal structure and function, (ii) myocardial ischemia, (iii) stunned

myocardium, (iv) myocardial hibernation, and (v) MI. After a coronary occlusion, normal structure and function of the myocardium is maintained when myocardial perfusion is preserved due to the presence of collateral vessels. The subendocardium is the most functionally active myocardial layer with the lowest perfusion reserve and, therefore, the greatest vulnerability to ischemia and infarction.[5, 6] Myocardial ischemia starts in the endocardium and may lead to a non-transmural MI (non-Q-wave MI). Because less severe ischemia does not lead to irreversible damage, myocytes become damaged (but not necrotic) and maintain viability. The myocardium becomes stunned (reduction or absence of normal contractility) after a coronary occlusion has been relieved. Myocardial dysfunction due to stunning (i) can persist in the absence of irreversible damage and despite restoration of a normal coronary flow, (ii) can last weeks to months after normal perfusion has been recovered, and (ii) often lies adjacent to an infarcted necrotic myocardial segment.[7, 8] After prolonged coronary occlusion (4-6 h), myocardial necrosis progresses from endocardium to epicardium in a wave-front. If perfusion is reinstituted, an incomplete (non-transmural) MI results, but if not, a complete (transmural, or 'Q-wave') MI will occur.[9, 10] In necrotic myocardium, the local capillary network becomes thrombosed and occluded, leading to irreversible damage of membrane integrity, glycolytic or mitochondrial function, and absence of contractile potential. Changes in myocardial function and perfusion can be detected by echocardiography as global systolic and diastolic LV dysfunction, regional wall motion and wall thickening abnormalities, and LV perfusion defects.[11] (*Figure 1*).

ECHOCARDIOGRAPHY DETECTING CORONARY ARTERY DISEASE

Regional wall motion assessment

Rest echocardiography

In the early 1970s, M-mode recordings were used to assess wall motion of the LV; however, 2D imaging has replaced M-mode echocardiography for evaluation of global and regional wall motion. With 2D echocardiography, ischemic segmental wall motion abnormalities can be detected in patients with CAD. Visual assessment ('eyeball approach') categorizes wall motion as being normal or abnormal on the basis of degree of endocardial excursion (which is subject to tethering and translational motion), thickening, the timing of motion and the shape of the LV. Timing is particularly important, and accurate wall motion assessment requires frame-by-frame review to overcome the limited temporal resolution of the human eye.[12] Wall motion abnormalities are characterized as hypokinetic, akinetic, or dyskinetic, and changes in LV shape are important and often neglected (*Figure 2*). Normally the endocardium thickens during systole; however ischemic myocardium shows different patterns of wall thickening or even thinning during systole as shown in *Table 1* and *Figure 3A-B*.

Table 1		Regional systolic wall function	
Normal	1	normal inward systolic motion	4-10 mm systolic thickening - double thickness
Mild hypokinesia	2	mildly reduced inward systolic motion	mildly reduced systolic thickening - delayed
Severe hypokinesia	2.5	severely reduced inward systolic motion	severely reduced systolic thickening - delayed
Akinesia	3	absent inward systolic motion	absent systolic thickening
Dyskinesia	4	abnormal outward systolic motion	systolic thinning
Aneurysmal	5	abnormal shape at rest	systolic thinning

Although there is tremendous variability in the coronary artery blood supply to the myocardium, a model with 17-segments assigned to one of the three major coronary arteries is recommended for visual interpretation of regional LV wall motion abnormalities (*Figure 4*). Unfortunately, the true apical cap is rarely visualised by echo, so some investigators continue to use the 16-segment model.[13] Therefore, individual myocardial segments can be assigned to one of the three major coronary arteries with recognition that there is anatomic variability. Wall motion abnormalities at rest may represent scar tissue (caused by transmural MI), hibernation or myocardial stunning (viable myocardium with a reduction or absence of contractility). Ischemic myocardial segments can have a normal or abnormal function at rest with development of wall motion abnormalities during exercise or stress. In general, wall motion and wall thickening abnormalities show the highest specificity in the determination of CAD, representing the 'classic ischemic cascade'. Myocardial perfusion is the most sensitive indicator for CAD, as it includes the 'alternative ischemic cascade'. Two dimensional echocardiography in combination with a contrast agent (further discussed in the section on contrast enhanced echocardiography) provides a means of recognition of subendocardial hypoperfusion with high spatial resolution. The combination of perfusion and wall motion affords a simple method to predict functional recovery of dysfunctional segments after revascularization by evaluating end-diastolic wall thickness and perfusion abnormalities, as shown in *Table 2*.[14]

Table 2	Likelihood of functional recovery after revascularization
End-diastolic wall thickness >11, perfusion +	highest likelihood of recovery
End-diastolic wall thickness >11, perfusion -	high likelihood of recovery
End-diastolic wall thickness <11, perfusion +	intermediate likelihood of recovery
End-diastolic wall thickness <11, perfusion -	low likelihood of recovery

Figure 3A: End-systolic freeze-frames showing left anterior descendens territory infarction without wall thinning (arrows) in two and three dimensional images (below). Accompanying loops show no inducible ischemia.

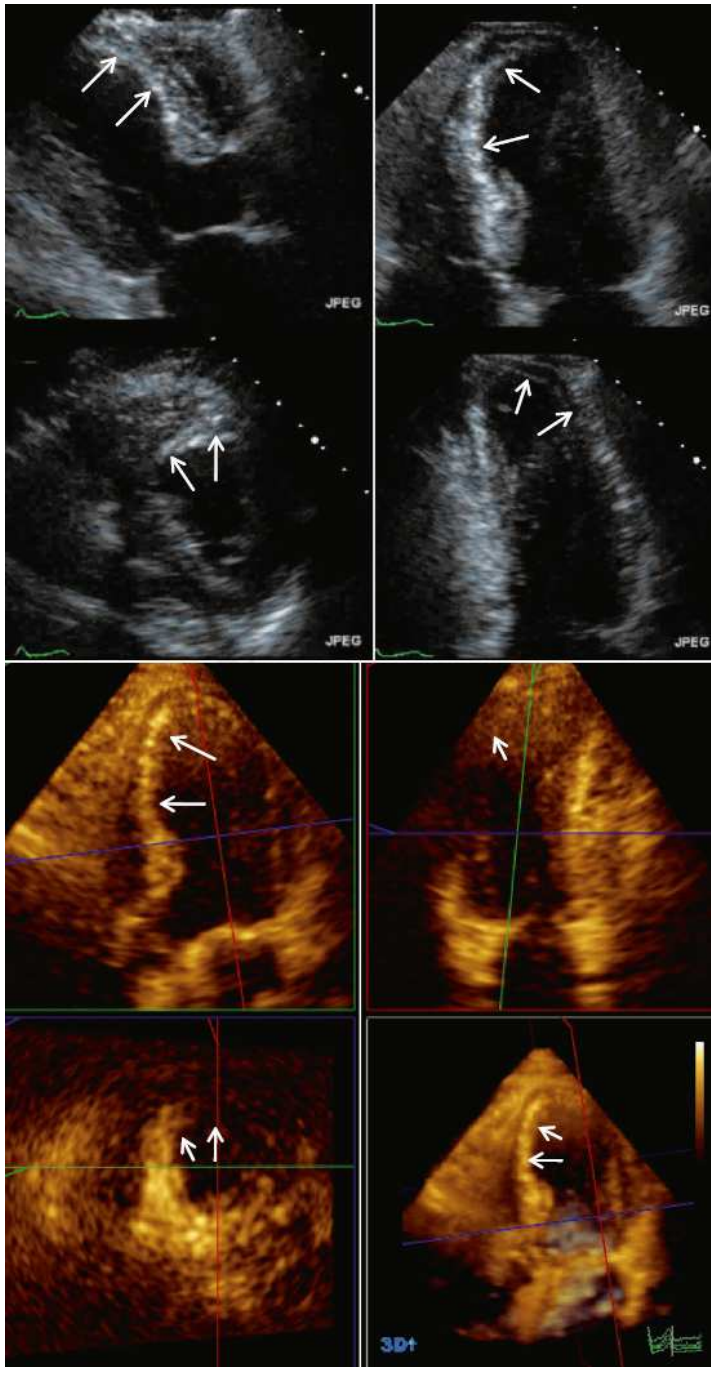
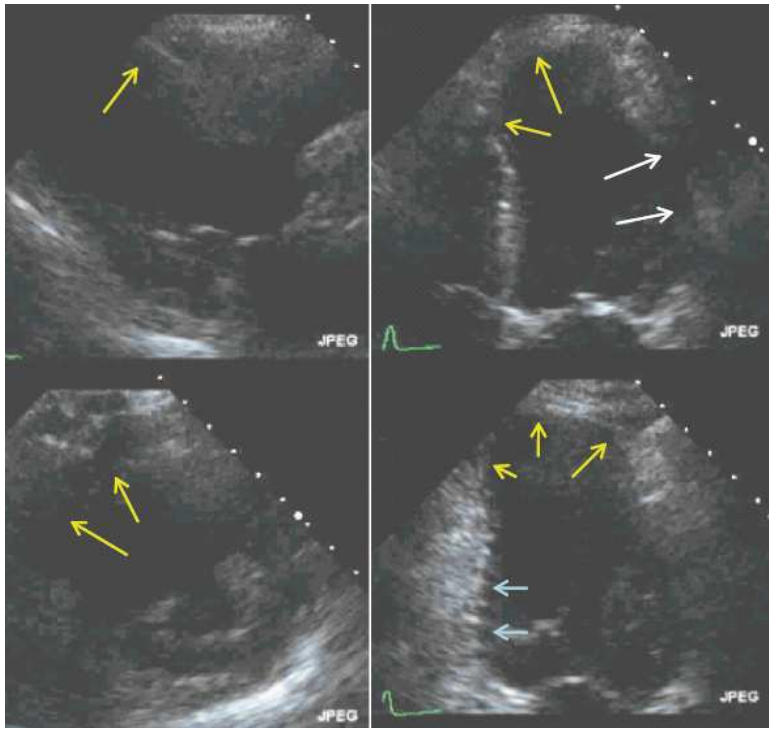


Figure 3B: End-systolic freeze-frames showing infarction in the left anterior descendens territory with wall thinning (yellow arrows), as well as left circumflexus territory (white arrows) and right coronary artery territory akinesis (blue arrows). Accompanying loops show no inducible ischemia.



Stress echocardiography

During exercise or stress, the myocardial oxygen-demand is increased and demand ischemia occurs in patients with a coronary artery stenosis. Stress testing can detect reversible ischemia, distinguish ischemia and viability from scar, and identify regions supplied by a specific coronary vessel. When stress testing induces ischemia, it permits wall motion analysis during stress with the use of treadmill and bicycle exercise or pharmacologically induced stress. Regardless of the technique used, rest images are recorded first and serve as a baseline for comparison [15] with stress images obtained during peak stress or immediately after exercise. The images are analysed using a segmental model. Wall motion and wall thickness is scored in each myocardial segment on a 4-point scale, and test results are considered positive when wall motion or wall thickness deteriorates by one grade or more in any segment.[16] During stress testing, five different ventricular wall motion response patterns can be observed: (i) normokinesis or normal systolic wall motion, (ii) hyperkinesis or increased inward systolic wall movement, (iii) hypokinesis or reduced inward systolic wall movement, (iv) akinesis or no systolic wall movement and, (v) dyskinesis or outward systolic wall movement. Necrotic

myocardium can be akinetic or dyskinetic at rest. Akinetic and dyskinetic myocardium could be viable as well, and assessing the ventricular wall motion response to stress can make a distinction between viable and necrotic tissue. Although hypokinetic myocardium is sometimes labelled as viable, it may not necessarily show improvement after revascularization, for instance, when hypokinesis is caused by subendocardial scar. In the normal response to stress, normokinetic wall segments remain normokinetic during stress or becomes hyperkinetic. During an ischemic response, wall segments become hypokinetic, akinetic, or dyskinetic during stress (*Figure 5A-C*). In a necrotic response, wall segments that are akinetic or dyskinetic at rest will remain akinetic or dyskinetic during stress. A viable response is seen when hypokinetic, akinetic, or dyskinetic segments show improved contractility during stress (*Table 3*). Hibernating myocardium is identified when improved contractility at low stress rate is followed by reduced contractility at high stress rate, i.e., the biphasic response.[17] Stunned myocardium shows sustained improvement of myocardial contraction at both low and high stress rates. Because hibernating myocardium improves after revascularization, separating hibernating from stunning myocardium is of great clinical importance. The three most common stressors used in stress echocardiography are (i) exercise, (ii) dobutamine, and (iii) dipyridamole.

Exercise stress testing

Exercise testing can be subdivided into treadmill and bicycle testing. Scanning during exercise can be performed but it is difficult. Therefore, images must be taken immediately after the exercise is performed, and echocardiographic examination must be completed within 1-2 min. When exercise is terminated, myocardial oxygen-demand gradually declines with recovery of reversible wall motion abnormalities. New or increased wall motion abnormalities can persist up to 30 min postexercise, demonstrating stunned myocardium depending on the severity and extent of the underlying CAD. Stunning is often induced by treadmill testing.[18] However, when wall motion recovers very rapidly and persists only for several minutes, treadmill testing can miss resolved wall motion abnormalities. This may lead to false negative results affecting the sensitivity of the test in detecting ischemia. Bicycle exercise is performed in upright and supine position and permits echocardiographic examination during exercise. With the patient in the supine posture, it is possible to record images from multiple views during graded exercise. In the upright posture, imaging is generally limited to either apical or subcostal views. The overall sensitivity of exercise echocardiography has been reported to range from 76 to 89%, and sensitivity is greater with more high-grade coronary disease.[19, 20] However, although angiographic comparison is respected as a common metric for the assessment of the accuracy of these tests, it should be remembered that the angiogram is imperfect because the severity of diffuse narrowing can be underestimated and because this anatomic test ignores the contribution of vascular function to perfusion, even in the context of normal conduit vessels.

Figure 5A-B: The spectrum of ischemic wall motion responses to stress. Probable angina in a 61-year-old man with multiple risk factors. Normal rest electrocardiogram. Exercise test showed no chest pain, 1 mm ST depression, submaximal heart rate (79%), seven MET ex capacity. Noncontrast and left ventricle opacification images (see loops) show questionable inferoseptal hypokinesis. Use of destruction-replenishment imaging to examine myocardial perfusion shows inferior (A) and apical perfusion defects (B).

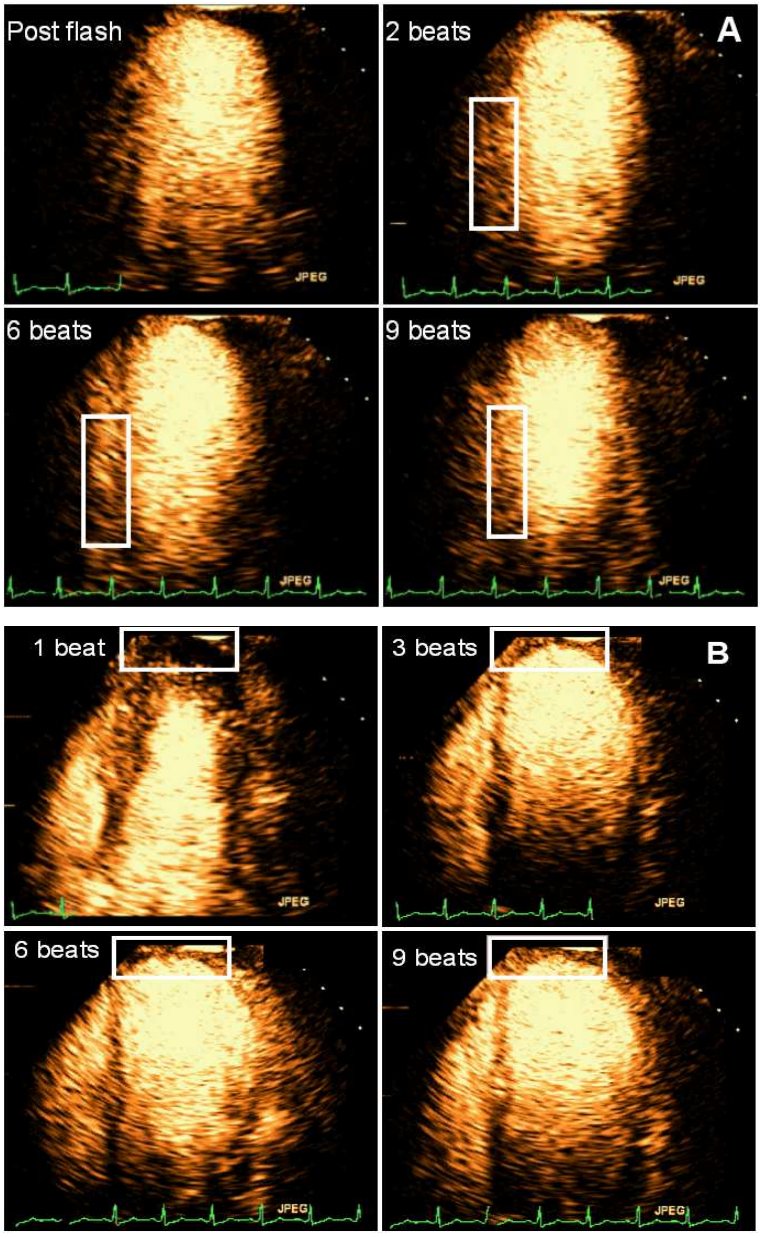


Figure 5C: Coronary angiography showed significant 70% distal right coronary artery and 60% mid left coronary artery.

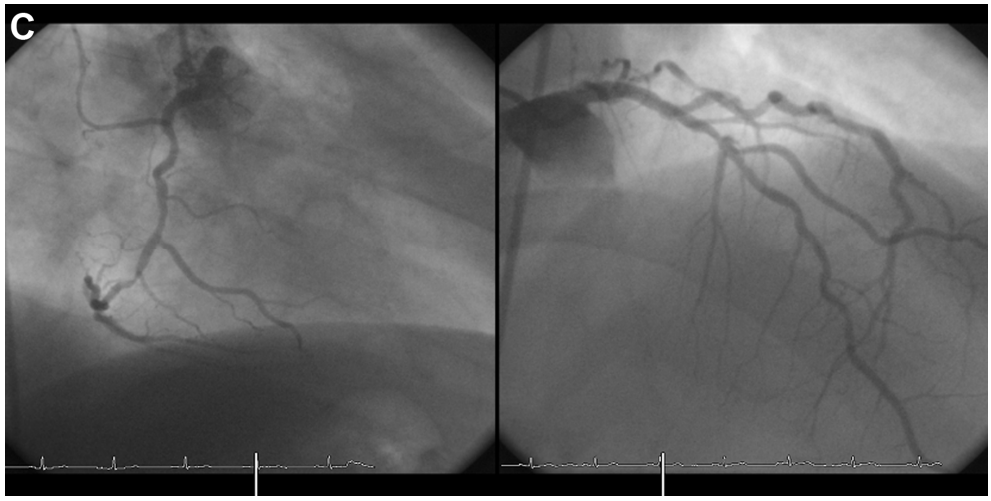


Table 3	Wall motion response to stress	
Rest	**Stress**	**Diagnosis**
Normal hypokinesia	normal	normal
	hyperkinesia	normal
	hypokinesia	nontransmural infarction
Normal hypokinesia	hypokinesia	ischemia
	akninesia	ischemia
	dyskinesia	ischemia
Akinesia	normal	viable
	hypokinesia	viable
Akinesia	akninesia	necrosis
Dyskinesia	dyskinesia	necrosis

Pharmacological stress testing

Although exercise testing is more physiologic than pharmacologic stress, it is not feasible in many situations. Out of five patients referred for stress, one will not exercise and one will exercise submaximally.[21] For instance, patients with peripheral vascular disease are unable to exercise maximally, so with a pharmacologic stress, echocardiography serves as a good alternative in these patients. Pharmacologic stress testing is performed during the infusion of dobutamine or dipyridamole. These two stressors induce ischemia through different hemodynamic mechanisms. Dobutamine stimulates adrenoreceptors, thereby increasing ventricular contractility and myocardial oxygen-demand during stress testing.[22] Dipyridamole exerts vasodilatory properties by stimulating adrenaline receptors – although steal phenomena are commonly cited, experimental evidence suggests that ischaemia is more likely caused by

tachycardia and hypotension in the setting of reduced subendocardial flow reserve.[23] Although dipyridamole is often cited as the stressor of preference in the assessment of myocardial perfusion and dobutamine may be preferred to assess regional wall motion abnormalities, either can be used for each purpose. Dobutamine infusion increases myocardial oxygen-demand through positive chronotropic and inotropic effects and impairs myocardial oxygen-supply by shortening diastole. These effects result in myocardial ischemia and systolic dysfunction in myocardial regions supplied by critically stenotic arteries.

Performing these tests requires careful patient monitoring, access to antidotes to stress agents, and the presence of an experienced physician. A graded dobutamine infusion starting at 5 μg/kg/min and increasing at 5 min stage to 10, 20, 30 and 40 μg/kg/min is the standard for dobutamine stress echocardiography. To assess myocardial viability, a thorough evaluation at rest is important (*Figure 6A*) followed by multiple low-dose stages – in most cases, the study should progress to peak dose dobutamine to check for ischemia (*Figure 6B-C*). The recommended protocol for dipyridamole echocardiography includes continuous echocardiographic monitoring during a two-stage infusion. The first stage consists of 0.56 mg/kg dipyridamole over 4 min. Monitoring continues for 4 min, and if there is no clinical effect, an additional 0.28 mg/kg is infused over 2 min. Aminophylline (240 mg i.v.) should be available for use in case of an adverse events related to dipyridamole. Adenosine can be used in a similar manner and is typically infused at a maximum dose of 140 mg/min during imaging.[24] Patients undergoing pharmacological stress testing often take β-blockers, which may limit heart-rate response and influence the sensitivity of the test to detect CAD. In both dobutamine and dipyridamole echocardiography, atropine can be added after the second stage to increase heart rate and improve sensitivity.[25, 26] Atropine should be used at the minimum effective dose and administered in 0.25 mg increments every 60 s until the desired heart response is seen.

Side effects and contraindications

There are few contraindications (e.g., severe aortic stenosis), and side effects (e.g., MI, death, arrhythmia) associated with physical exercise are uncommon. Pharmacological stress testing with dobutamine and dipyridamole is considered to be a safe test that is generally well tolerated. Major complications such as MI, death, and bronchospasm occur in ~1:1000. Potential side effects of pharmacological stress testing are transient arrhythmias and hemodynamic abnormalities, which resolve rapidly after cessation of the infusion. Dobutamine is contraindicated in patients with current ventricular or atrial arrhythmias and moderate-to-severe hypertension (defined as diastolic blood pressure above 110 mmHg). Stress echocardiography with dipyridamole is contraindicated in patients with high-grade heart block, bronchospasm, unstable carotid disease, and patients receiving theophylline treatment.[24] Minor, self-limiting side effects such as chest pain, nausea and headache can occur infrequently during dipyridamole infusion.

Figure 6A: Rest echocardiogram (end-systolic images) showing left ventricular enlargement and rest wall motion abnormalities with preserved wall thickness in the anteroseptum, septum, and apex. The bull's eye display shows reduced longitudinal shortening in these areas (numbers correspond to regional strain; normal strain is approximately 18%).

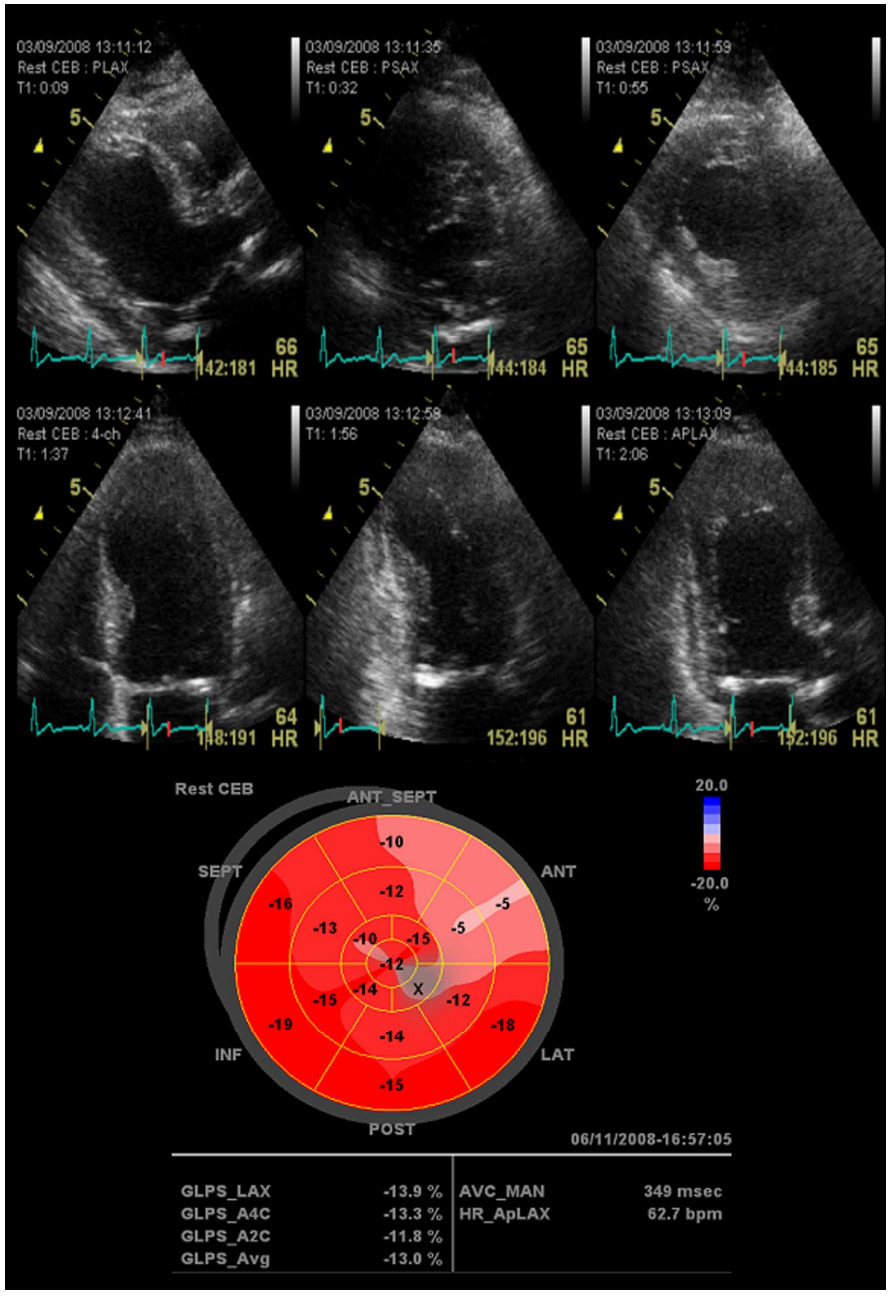
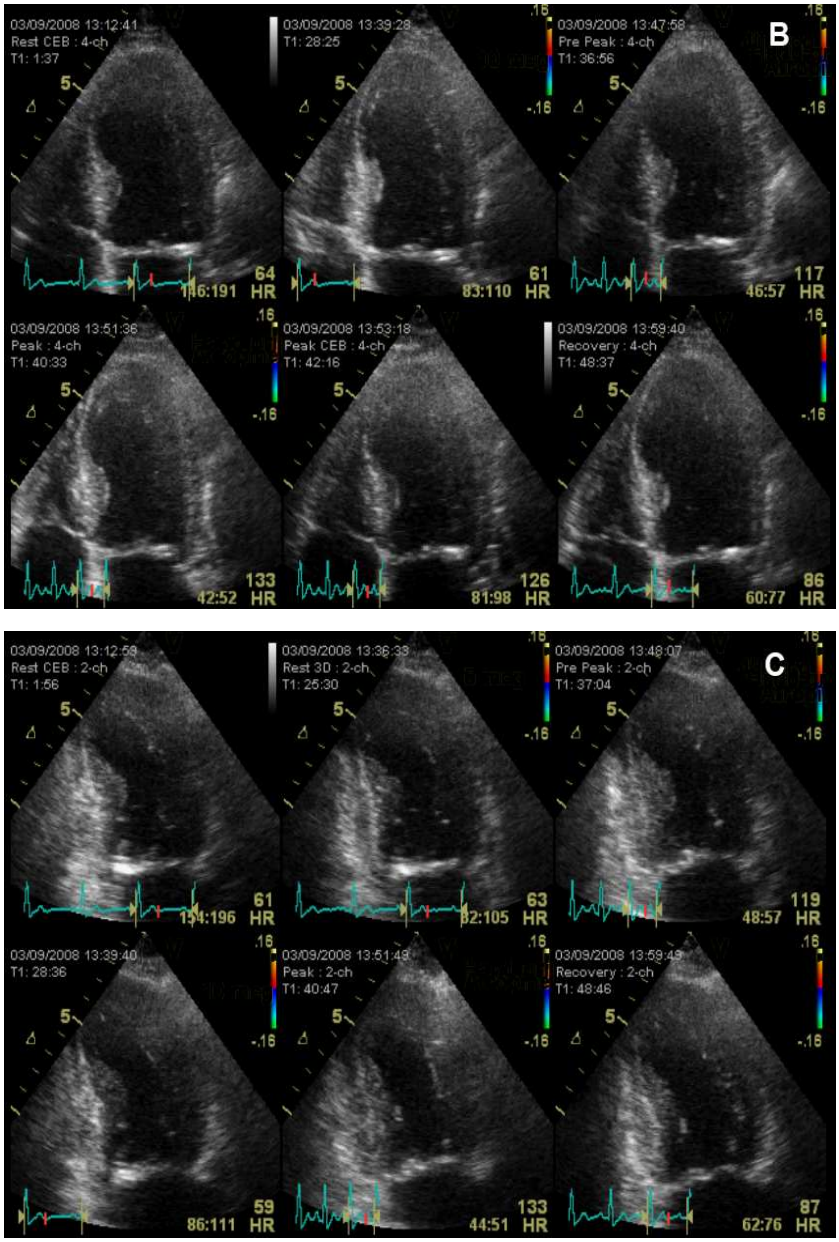


Figure 6B and C: End-systolic images at rest, low, peak dose, and recovery in the apical four-chamber view. The apical and mid-septal akinetic area does not change at low dose and therefore suggests a nonviabile area. The apical lateral wall improves at peak stress, indicating nontransmural infarction (B). End-systolic images at rest, low, peak dose, and recovery in the apical two-chamber view. The apical inferior akinetic area thickens at the 10 mcg dose, but does not deteriorate, denoting a nontransmural infarction. The antero-apical wall deteriorates at peak stress, indicating ischemia (C).



Comparison of diagnostic and prognostic performance of exercise and pharmacological stress testing

The results from multiple meta-analyses comparing exercise, dobutamine and, dipyridamole stress testing are shown in *Table 4*. A recent meta-analysis conducted by Picano *et al,* analysed five studies regarding the diagnostic accuracy of dobutamine vs. dipyridamole stress echocardiography. They noted dipyridamole and dobutamine to have similar accuracy (87%, 95%-CI: 83 to 90%, vs. 84%, 95%-CI: 80 to 88%, $p = 0.48$), sensitivity (85%, 95%-CI: 80 to 89%, vs. 86%, 95%-CI: 78 to 91%, $p = 0.81$), and specificity (89%, 95%-CI: 82 to 94% vs. 86%, 95%-CI: 75 to 89%, $p = 0.15$) for the detection CAD.[27] These conclusions are in line with other meta-analyses, shown in *Table 4*, generally concluding that stress echocardiography shows a higher specificity than sensitivity.[19, 20, 27-29] A higher sensitivity than specificity is seen in a meta-analysis performed by Bax *et al,* in which low-dose dobutamine was administered in the assessment of myocardial viability, as shown in *Table 4*.[30] The prognostic performance of dobutamine stress echocardiography in the prediction of postoperative cardiac events is outlined in *Table 4*.[31]

Table 4 **Accuracy of stress echocardiography**

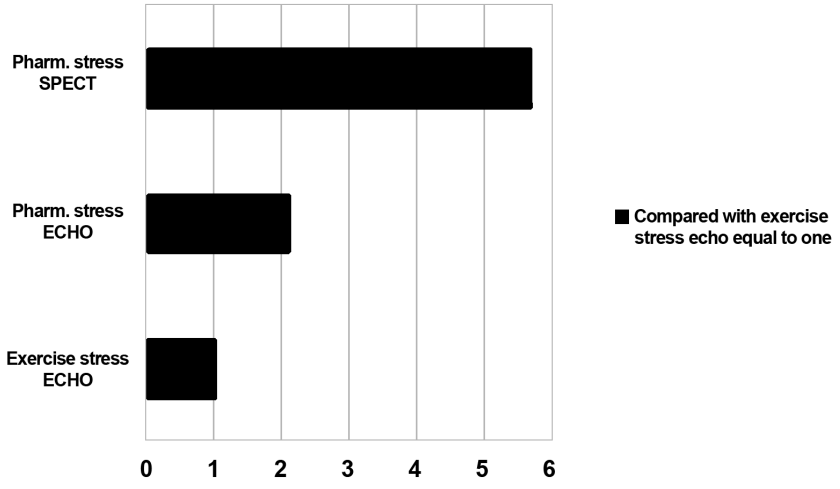
Meta-analyses	Year	Studies	Outcome	Sensitivity (%)			Specificity (%)		
				Exe	Dob	Dip	Exe	Dob	Dip
A. Diagnostic performance of stress echocardiography									
Picano *et al.*	2008	5	CAD	-	85	86	-	92	87
Noguchi *et al.*	2005	164	CAD	83	80	71	84	85	92
Kim *et al.*	2001	60	CAD	-	80	70	-	84	93
Picano *et al.*	2000	12	CAD	-	77	71	-	87	93
Kwok *et al.*[a]	1999	3	CAD	76	-	-	89	-	-
B. Viability assessment of stress echocardiography									
Schinkel *et al.*	2007	41	viability	-	80	-	-	78	-
Bax *et al.*[b]	2001	28	viability	-	82	-	-	79	-
C. Prognostic performance of stress echocardiography									
Kertai *et al.*[c]	2003	12	postoperative CE	-	85	74	-	70	86

Sensitivity and specificity relate to correct identification or exclusion of A. significant coronary stenoses (criteria vary from 50 to 70% in different trials), B. recovery of regional function after revascularization, and C. perioperative cardiac events. [a] Low dose dobutamine, [b] in women and [c] cardiac events. Coronary artery disease (CAD), cardiovascular events (CE), dipyridamole (Dip), dobutamine (Dob), exercise (Exe).

Comparison of stress testing with other noninvasive imaging techniques

Stress echocardiography has the advantage to be a safe, widely available, noninvasive technique, feasible in almost all circumstances at low cost. Furthermore, pharmacological stress echocardiography is a reliable method for diagnosing CAD in patients with a cardiac pacemaker, whereas for instance, exercise myocardial SPECT may show false positive results in pacemaker patients.[32] However, image quality is negatively affected by obstructive lung disease, chest deformation, and obesity. During peak stress, the image quality is negatively affected by an increased heart rate and breathing artifact. Furthermore; mechanical tethering, defined as decreased contractility of noninfarcted regions adjacent to infarcted regions, may lead to an overestimation of the extent of an infarcted region.[33, 34] Finally, the accuracy of stress echocardiography is dependent on operator experience. A meta-analysis conducted by Beattie *et al.* analyzed the predictive value of pharmacological stress testing in predicting perioperative cardiac events, compared with thallium myocardial perfusion scintigraphy. This report included 25 studies (3,373 patients) of mainly dobutamine and several dipyridamole stress echocardiography. The likelihood ratio of a perioperative event with a positive stress echocardiogram was 4.09 (95%-CI: 3.21 to 6.56) compared with 1.83 (95%-CI: 1.59 to 2.10) in patients undergoing thallium myocardial perfusion scintigraphy.[35] *Table 5* shows various meta-analyses comparing sensitivity and specificity of pharmacological stress testing in detecting CAD[28, 31] and functional improvement after revascularization.[30, 36]. The cost differential between noninvasive tests for coronary disease is summarized in *Figure 7*. The following guidelines (*Table 6*) have been described in the 2008 ACC/AHA guidelines concerning the appropriateness criteria for stress echocardiography with or without contrast enhancement.[16] These criteria are also in agreement with ESC guidelines.

Figure 7. Relative costs of stress testing procedures.



Pharmacological (Pharm), single photon emission computed tomography (SPECT).

Table 5	Accuracy of various stress tests			
Meta-analyses	Studies	Outcome	Sens (%)	Spec (%)
Performance in detecting coronary artery disease and predicting cardiac events				
Kim *et al.*				
Dipyridamole stress echo	20	CAD	70	93
MPS, dipyridamole SPECT	21	CAD	89	65
Dobutamine stress echo	40	CAD	80	84
MPS, dobutamine SPECT	14	CAD	82	75
Kertai *et al.*				
Dobutamine stress echo	8	perioperative CE	85	70
Dipyridamole stress echo	4	perioperative CE	74	86
MPS, Tl-201	23	perioperative CE	83	49
Exercise electrocardiography	7	perioperative CE	74	69
Performance in predicting functional improvement after revascularization				
Bax *et al.*				
Dobutamine stress echo [a]	28	functional recovery	82	79
MPS, Tl-201 (rest-redistribution)	22	contractile function	86	59
MPS Tl-201 (reinjection)	11	contractile function	88	50
MPS, Tc-99m labelled (nitrates)	13	functional recovery	79	58
MPS, Tc-99m labelled (no nitrates)	7	functional recovery	81	66
MPS, PET 18-FDG	20	contractile function	93	58
Schinkel *et al.*				
Dobutamine stress echo	41	regional wall function	82	80
MPS, Tl-201 (rest-redistribution)	28	regional wall function	87	56
MPS, Tl-201 (reinjection)	343	regional wall function	87	50
MPS, Tc-99m labelled	25	regional wall function	83	65
MPS, PET 18-FDG	24	regional wall function	92	63
MRI	13	regional wall function	84	63

[a] *Low dose. 18-Fluorodeoxyglucose (18-FDG), coronary artery disease (CAD), cardiovascular events (CE), myocardial perfusion scintigraphy (MPS), magnetic resonance imaging (MRI), positron emission tomography (PET), sensitivity (Sens), specificity (Spec), single photon emission computed tomography (SPECT).*

Table 6	Appropriateness criteria for stress echocardiography
Evaluation of chest pain syndrome or anginal equivalent	
- Low pretest probability of CAD - ECG interpretable and able to exercise	inappropriate
- Low pretest probability of CAD - ECG un-interpretable or unable to exercise	appropriate
- Intermediate pretest probability of CAD - ECG interpretable and able to exercise	appropriate
- Intermediate pretest probability of CAD - ECG un-interpretable or unable to exercise	appropriate
- High pretest probability of CAD - Regardless of ECG interpretability and ability to exercise	appropriate
- Prior stress ECG is un-interpretable or equivocal	appropriate
General patient populations	
- Low CHD risk (Framingham risk criteria) - Moderate CHD risk (Framingham risk criteria)	inappropriate
- High CHD risk (Framingham risk criteria)	indeterminate
Acute chest pain	
- Intermediate pretest probability of CAD - ECG; no dynamic ST changes and serial cardiac enzymes negative	appropriate
- High pretest probability of CAD - ECG; ST elevation	inappropriate
New-onset/diagnosed heart failure with chest pain syndrome or anginal equivalent	
- Intermediate pretest probability of CAD - Normal LV systolic function	appropriate
- LV systolic function	indeterminate
Ischemic cardiomyopathy, assessment of viability/ischemia	
- Known CAD on catheterization - In a patient eligible for revascularization	appropriate

Coronary artery disease (CAD), chronic heart disease (CHD), electrocardiogram (ECG), left ventricular (LV).

Contrast-enhanced echocardiography

Stress echocardiography is widely used for the detection of inducible ischemia and regional wall motion abnormalities. Analyzing regional wall motion abnormalities relies on the identification of the endocardial border of the LV cavity. Image quality can be severely impaired in patients with obstructive lung disease, obesity, and chest wall deformities resulting in suboptimal acoustic windows. Furthermore, an increase in heart rate and breathing artifacts due to hyperventilation causes difficulties in identifying the endocardial border of the LV cavity and interpreting the stress images. Since the first report in 1968, contrast has become an indispensable tool for cardiovascular imaging.[37] The development and usage of ultrasound contrast agents have shown to be beneficial in assessing the endocardial border of the LV cavity, and, therefore, exert a beneficial effect in analyzing myocardial contractility and

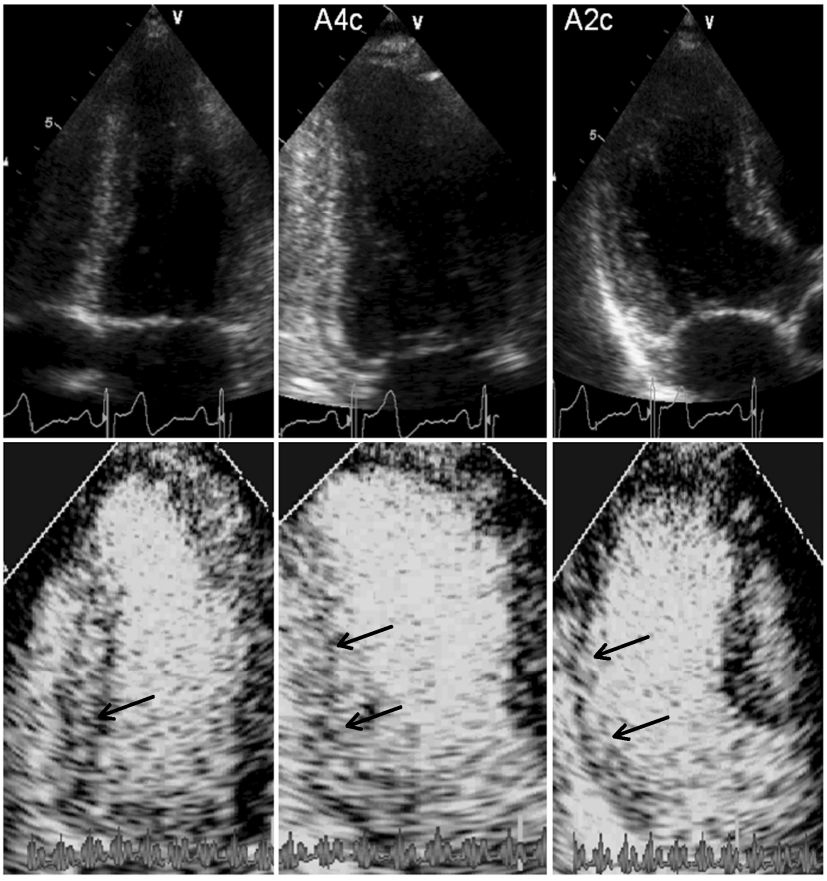
perfusion. Left ventricular opacification has shown to improve (i) image quality, (ii) percentage of wall segments visualized and (iii) confidence of interpretation of wall motion abnormalities both at rest and during peak stress.[38] The contrast agents used are suspensions of microbubbles, which have the same size as red blood cells and are filled with perfluorocarbon gas. Because of the availability of sensitive contrast imaging technologies, only small dosages of contrast (0.1 to 0.3 mL) are needed to obtain enhanced images. The accuracy of end-diastolic wall thickness measurements is improved as well and, can be used, in combination with perfusion abnormalities, to predict recovery of function after revascularization.[14] Contrast-enhanced echocardiography allows visualization of subtle wall motion abnormalities that are difficult to detect with normal echocardiography. Furthermore, the observation of subtle wall motion abnormalities can be confirmed with the identification of perfusion abnormalities. Finally, contrast-enhanced echocardiography can visualize regional perfusion abnormalities before contractile abnormalities evolve, potentially identifying CAD at an earlier stage. Contrast perfusion imaging has proven to be a valuable tool for the detection of myocardial viability. Increased brightness is observed in normally perfused myocardial segments, due to contrast enhancement.[39, 40] Myocardial viability can be expressed as contrast intensity and myocardial replenishment, assessed after 10-15 cardiac cycles after a destructive pulse. Fully replenished myocardium with homogeneous contrast intensity indicates the presence of myocardial viability.[41, 42] (*Figure 8*)

The use of contrast in association with exercise and pharmacologic stress echocardiography improves the visualization of wall motion when this is technically difficult, but is not recommended for all studies. The detection of perfusion abnormalities is an 'off label' use of contrast that is feasible but technically challenging. The development of new contrast agents will be needed in order to move this to mainstream use (*Table 7*).

Table 7 Contrast use

Use of contrast with stress echo	
- Routine use of contrast - All segments visualized on non-contrast images	inappropriate
- Selective use of contrast - Two or more contiguous segments are not seen on noncontrast images	appropriate

Figure 8: Rest and myocardial contrast echocardiography in a 65-year-old man after late presentation myocardial infarction. Despite regional wall motion abnormalities in the inferior wall, perfusion is preserved, (myocardial contrast marked by arrows) suggesting viability.



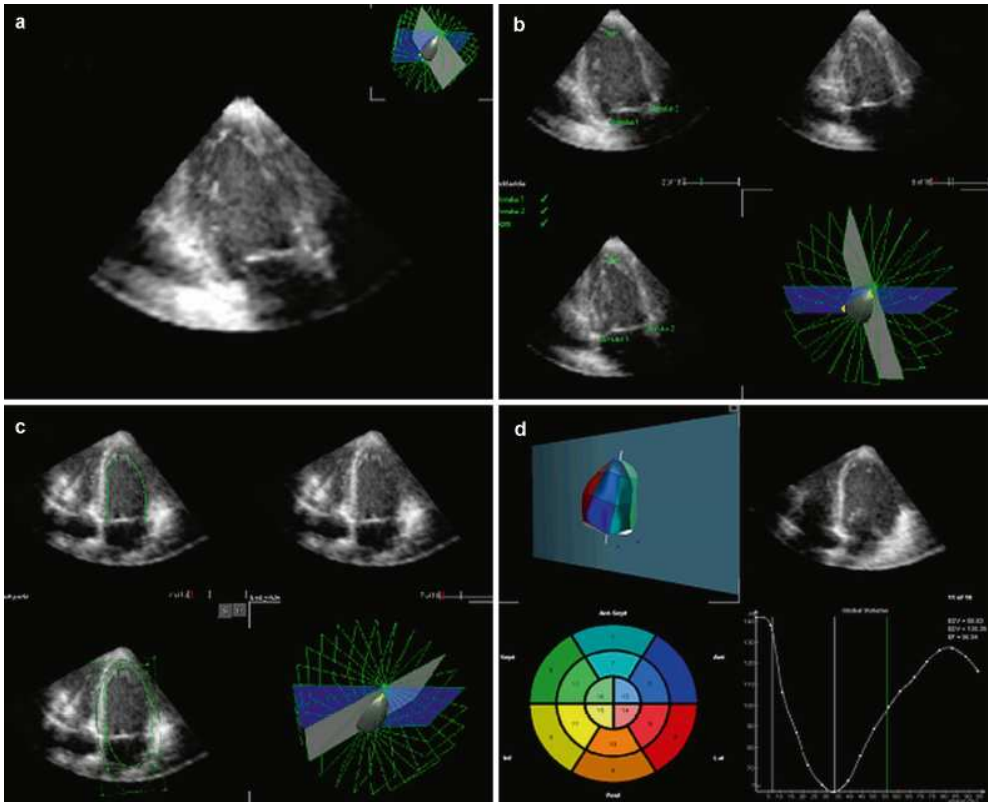
GLOBAL WALL MOTION ASSESSMENT

Heart failure, a clinical syndrome in which the ability of the ventricles to fill with or eject blood is impaired, is a major predictor of mortality after MI. Often, this is transient due to spontaneous recovery in the coronary care unit or after coronary revascularization, but may progress to chronic heart failure.[43] Coronary artery disease is the most common cause of myocardial disease, being the initial cause in 70% of patients with predominantly systolic heart failure.[44, 45]

Rest echocardiography is pivotal in the recognition of systolic heart failure, which is associated with progressive chamber dilation and eccentric remodeling.[46] Left ventricular ejection fraction (the fraction of blood ejected out of the LV during one heartbeat) has a number of limitations, including sensitivity to hemodynamic setting, but has the advantage of being a simple numerical parameter that has been linked to outcome and decision making. In patients with LV dysfunction without heart failure, regional wall motion scoring may be more sensitive than ejection fraction, which may be preserved by compensatory hyperkinesis. Subclinical LV dysfunction describes the situation of apparently normal LV function where sensitive indices such as strain are abnormal, or where LV contractile reserve is reduced. The latter reflects the response to stress, which usually involves a reduction of LV volumes and an increment of LV ejection fraction.

Echocardiographic assessment of global systolic LV function is often performed subjectively, but this is increasingly considered suboptimal. This approach is dependent on the eye of an experienced observer and is misleading in situations of (i) irregular heart rhythm, (ii) very large or small LV size, and (iii) extreme heart rates.[47, 48] The most common method for the quantitation of LV volumes is the modified Simpson's rule, a technique that requires imaging in apical, 4- or 2-chamber views. First the endocardial border has to be outlined in end-diastole and end-systole, and the LV cavity is divided into a series of disks of equal height along its long axis. When the central axis of the LV cavity is defined and the endocardial border is identified, the volume of each disk can be automatically defined. Each disk volume is calculated as disk area x height (height defined as the total length of the LV long axis divided by the number of disks). The surface area of each disk is determined from the diameter of the ventricle at that point. The ventricular volume is calculated by summing the disk volumes, which are equally spaced along the LV long axis. Once the LV volumes have been measured, LV ejection fraction can be calculated as (LV end systolic volume – LV end diastolic volume) x 100/ LV end diastolic volume.[49] In more than 15% of patients examined with ultrasound, poor ultrasonic windows preclude optimal visualization of the endocardial border,[50] despite the use of tissue harmonic imaging. In this situation, the use of LV opacification with contrast-enhanced echocardiography will improve endocardial border definition.[51, 52] Contrast-enhanced echocardiography has also been shown to improve the assessment of LV volumes and LV ejection fraction.[53, 54] The use of contrast may also facilitate 3D assessment, which appears to be the most reproducible and accurate (but not yet the most robust) echocardiographic means of LV volume assessment. The development of real-time 3D imaging has simplified and shortened the process of acquisition and calculation of 3D measurements, to the extent that this is not feasible for routine echocardiography (*Figure 9*).

Figure 9: Four steps for the use of three dimensional echo for left ventricular volume and ejection fraction assessment in the postinfarct heart. (A) Defining landmarks at the base and apex of the left ventricle in end-diastole and end-systole. (B) Selection of imaging planes - we use twelve imaging planes, especially in irregularly shaped hearts. (C) Contours are defined automatically but commonly require revision. (D) Display of the volumes and the ejection fraction using a time volume curve.



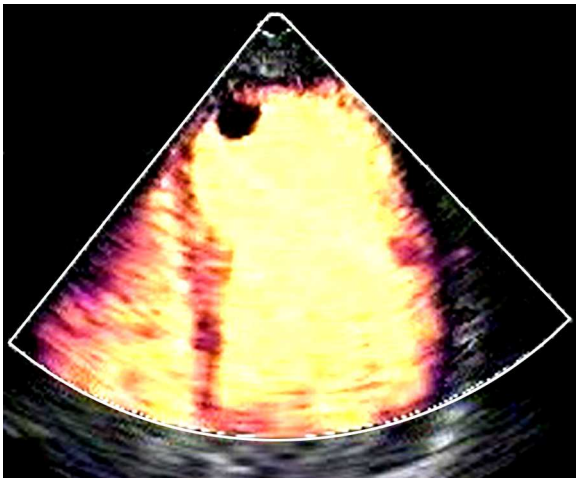
DETECTION OF CORONARY ARTERY DISEASE COMPLICATIONS

In-hospital mortality caused by acute MI is mainly due to circulatory failure resulting from severe LV dysfunction or mechanical complications of MI. These complications of acute MI can be visualized and diagnosed using 2D echocardiography. In the following paragraphs we will discuss mechanical complications caused by acute MI, such as: (i) infarct expansion leading to LV aneurysm and possible thrombus formation (ii) mitral regurgitation, (iii) ventricular wall rupture, (iv) right ventricular infarction, and (v) pericardial effusion. These mechanical complications can occur in the setting of a well-preserved LV function. Accurate diagnostics with the use of echocardiography will guide proper treatment in often life threatening situations.

Infarct expansion

Infarct expansion represents acute thinning of the ventricular wall occurring 24-72 h after the occurrence of a transmural (Q-wave) MI. The expansion area consists of necrotic myocardial tissue with disruption of cells leading to a 50% reduction of wall thickness (i.e., 4-6 mm compared with the normal 10-11 mm) in the affected region.[55] Infarct expansion is an important precursor for the development of LV aneurysm.[56] A true ventricular aneurysm is characterized by disturbance of diastolic shape and thinning of the LV wall, usually due to transmural MI; more than 85% are localized in the apical and antero-septal walls.[57] Alteration of normal LV contraction and filling properties can result in congestive heart failure, and more than 50% of patients with true LV aneurysms develop mural thrombi.[58] In contrast, pseudo-aneurysms form when free wall rupture is contained by overlying adjacent pericardium (see below).[59] Ventricular thrombi are most commonly localized in the antero-apical segments and should be visualized in more than one echocardiographic view, preferably from different transducer positions. Thrombus protrusion and mobility can be identified with 2D echo and are associated with risk of embolization.[60-62] The use of contrast-enhanced echocardiography can improve the diagnostic accuracy of 2D echocardiography in situations of suboptimal acoustic windows leading to poor image quality (*Figure 10).*

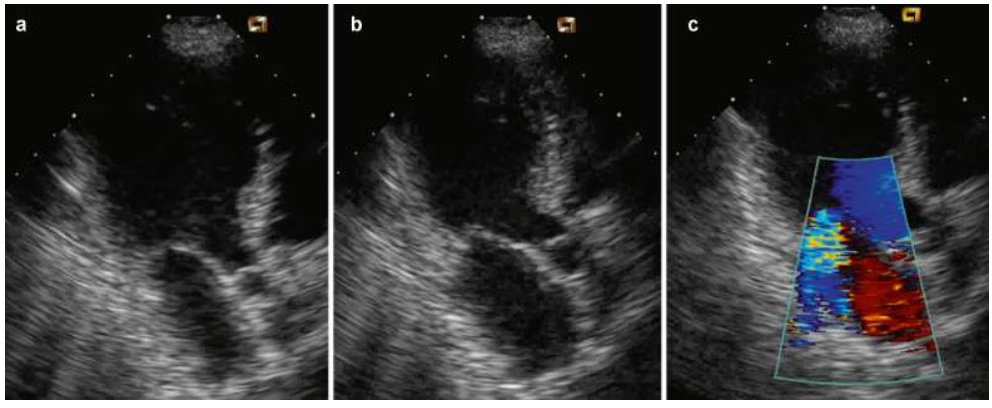
Figure 10: Value of left ventricular opacification in the detection of left ventricular mural thrombus.



Mitral valve regurgitation

Ischemic mitral valve regurgitation (MR) most often occurs in the setting of an inferior MI. The incidence of MR is 38% in patients with inferior MI compared with 10% of patients with an anterior MI.[63] Ischemic MR occurs due to papillary muscle rupture, dysfunction or displacement (*Figure 11*). Functional MR may also arise from LV dilatation, sphericity, annular dilatation, or papillary muscle dyssynchrony. Papillary muscle displacement is mostly caused by chronic ischemic heart disease, whereas papillary muscle rupture is associated with the acute phase of MI. Mild-to-moderate MR is common in the early phase after an acute MI and often decreases or resolves after reverse remodeling. Severe acute MR caused by papillary muscle rupture is a rare but life-threatening situation, which accounts for approximately 5% of acute MI deaths and (unlike other complications) is not necessarily associated with a large infarct. Predominantly, the postero-medial papillary muscle is involved, because its blood supply is primarily derived from the posterior descending coronary artery.[64] Colour flow Doppler echocardiography is the standard diagnostic tool for detecting MR, but a high level of clinical suspicion may be needed, as the usual semiquantitative measure of MR severity (based on jet size in relation to the left atrium) [65] can be misleading. This is because rapid increment in left atrial pressure due to severe MR may cause pressure equalization and limit flow. A marked systolic expansion of the left atrium and flail or incomplete closure of the mitral valve are important correlative findings. Incomplete closure caused by a posterior flail leaflet usually leads to an anterior directed eccentric jet.

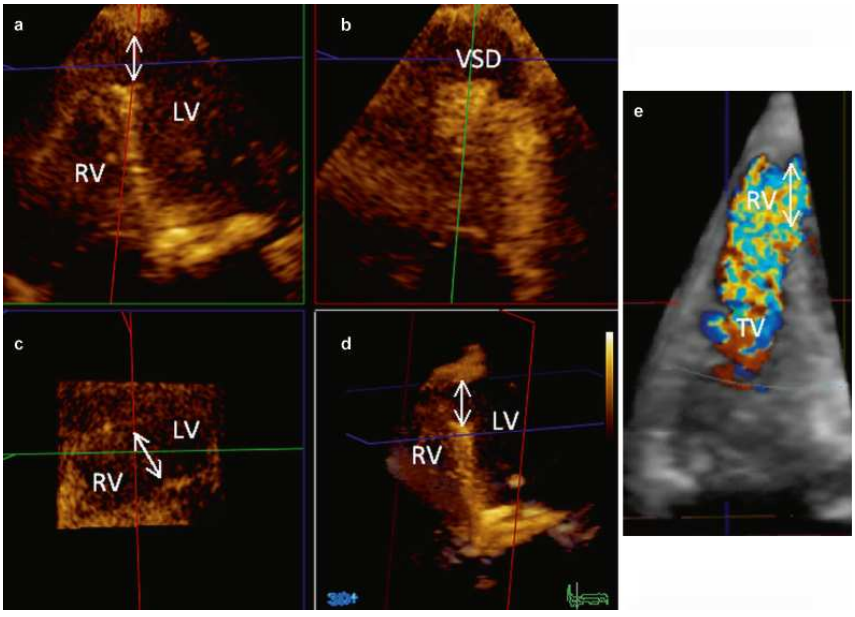
Figure 11: Typical ischemic mitral valve regurgitation due to papillary muscle displacement (note the same location of the posterior wall in end-diastole (A) and end-systole (B). This causes tethering of the posterior mitral leaflet with posteriorly directed mitral valve regurgitation (C).



Ventricular wall rupture

Unlike papillary muscle rupture, ventricular wall rupture is noted in anterior and inferior MI, in the same frequency and generally preceded by infarct expansion. Free wall rupture has been reported to complicate 4 to 24% of acute MI.[66-69] Septal wall rupture is associated with anterior MI and the defect is most commonly found in the apical septum (*Figure 12*) and contrasts with inferior MI where septal rupture occurs at the base of the heart. The characteristic echocardiographic findings are a distinct break in the septal contour and the detection of turbulent flow directed from the LV to the in the differential diagnosis of right ventricular infarction and dysfunction associated right ventricular cavity. Right ventricular dilatation due to shunt should be considered with inferior MI.[70] Contrast echocardiography is useful for the detection of cardiovascular shunts.[71] Risk factors for postinfarction LV free wall rupture include: (i) age > 60 years, (ii) female gender, (iii) preexisting hypertension, (iv) absence of LV hypertrophy, (v) first MI, and (vi) midventricular or lateral wall transmural MIs.[72] The majority of ruptures occur within the first week after MI, and suspicious features on echocardiography include (i) thinning and delineation of the free wall, (ii) pseudo-aneurysm, and (iii) accumulation of pericardial fluid suggestive for pericardial effusion or cardiac tamponade. Although echocardiography is considered the diagnostic tool of choice, in most cases free wall rupture will lead to instant death (*Figure 13*).

Figure 1: Multiplanar reconstruction of an apical VSD showing defect diameter (arrow) in the four chamber view (A), defect circumference in a modified two-chamber view (B) where it is seen "en face", a short-axis cut through the defect (C) and a 3D display (D). The color map (E) shows the left-right shunt.

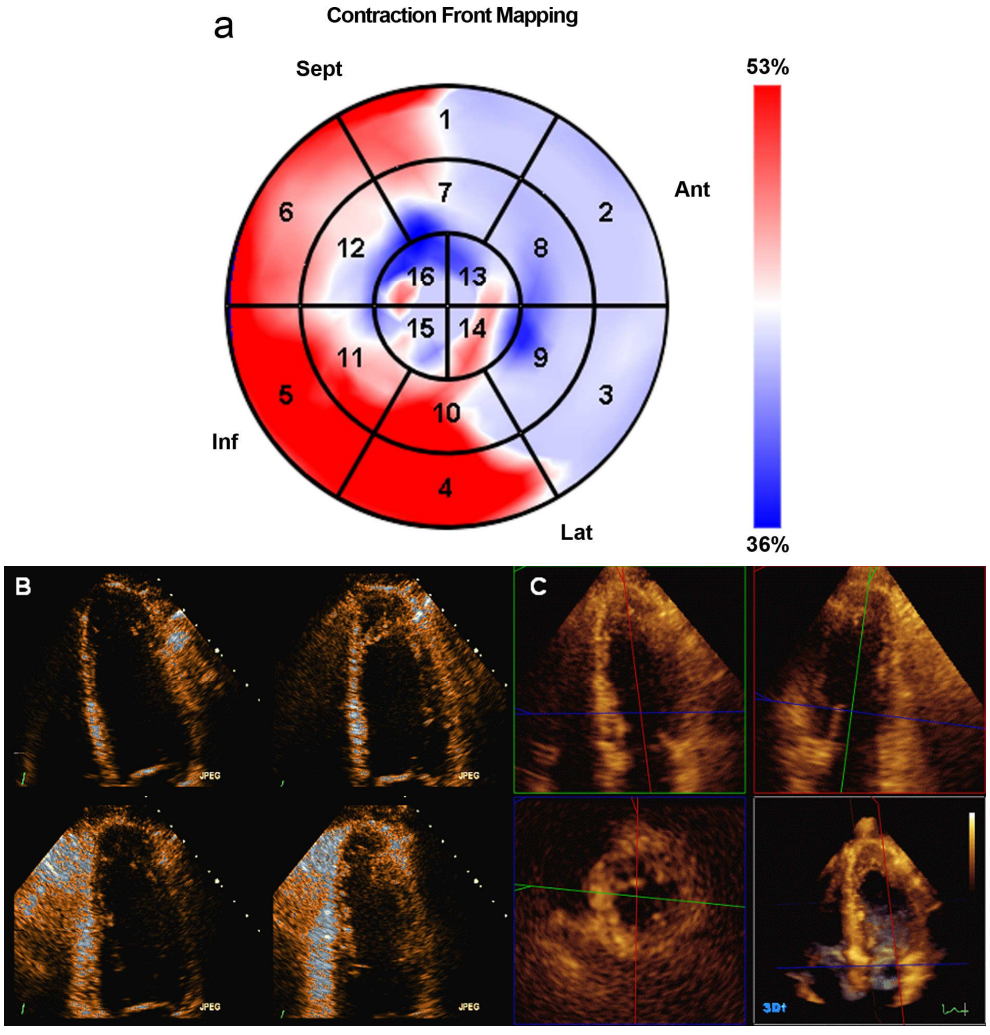


Left ventricle (LV), right-ventricle (RV), ventricular septum defect (VSD).

Right ventricular infarction

Right ventricular MI is strongly associated with inferior MI caused by a proximal occlusion of the right coronary artery. Right ventricular dilation may cause tricuspid annulus dilation resulting in acute tricuspid insufficiency.[72] Wall motion abnormalities can be best visualized in subcostal and parasternal short-axis views.

Figure 13: Contained apical rupture following antero-apical infarction. The contraction front map display derived from the 3D dataset (A) shows akinesis of the anteroseptal, anterior, and anterolateral walls (colored blue). The 2D images (B) show a contained rupture (white arrow) at the apex, confirmed on the 3D images (C).



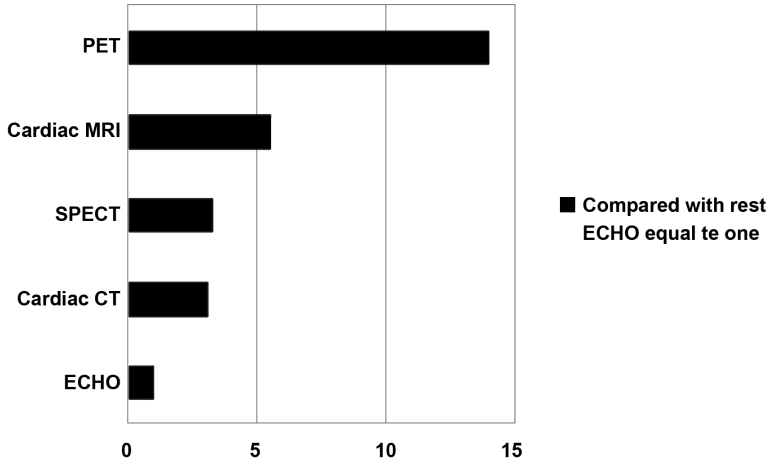
Pericardial effusion

Pericardial effusion can be seen as an echo-free space surrounding the heart, which does not extend posterior to the descending aorta (unlike pleural effusion). Inflammation might be an important cause for post-ischemic pericardial effusion.[73] However, large amount of pericardial fluid with a hemorrhagic appearance is suggestive for myocardial rupture.

ADVANTAGES AND LIMITATIONS OF ECHOCARDIOGRAPHY

In comparison with other noninvasive cardiac imaging procedures, such as nuclear cardiology, cardiac computed tomography (CT), and magnetic resonance imaging (MRI), 2D echocardiography has some limitations and advantages. As already noted, the impairment of image quality in patients with obstructive lung disease, obesity, and chest wall deformities can be minimized by use of echocardiographic contrast agents, albeit at additional cost.[74] Increases in heart rate and hyperventilation may cause difficulties in the analysis of echocardiographic images. Two-dimensional echocardiography has the advantage of being (i) safe (i.e., no radiation or ionizing substances required), (ii) widely available, (iii) noninvasive, and (iv) feasible in almost all circumstances at low cost (*Figure 14*).[75] Cardiac MRI has the ability to provide information about cardiac anatomy, function and perfusion simultaneously and has a superior spatial resolution to 2D echocardiography. However, cardiac MRI has a lower

Figure 14: Costs of cardiac imaging procedures relative to echo.



Computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission computed tomography (SPECT).

temporal resolution (which is a problem for flow measurement, especially diastology), usually requires breath-holding sequences during data acquisition, and is relatively expensive and less available than echocardiography. According to the 2008 Appropriateness Criteria for Stress Echocardiography, the use of stress echocardiography and SPECT nuclear imaging show similar bodies of evidence to support their use for ischemia detection.[16] Nuclear cardiology (e.g., PET and SPECT imaging) has the advantages of (i) higher sensitivity, (ii) higher technical success rate, and (iii) better accuracy when multiple resting left wall abnormalities are present, compared with echocardiography. The following advantages are in favor of echocardiography: (i) higher specificity, (ii) higher versatility, and (iii) greater convenience.[76] The ability to directly visualize the coronary arteries with coronary CT represents a major shift from the functional assessment of CAD to an anatomic evaluation. The ramifications of this on revascularization decisions and cost-effectiveness are unexplored. Apart from the requirements for breath-holding sequences and bradycardia (<65 beats/min), CT is less versatile in the assessment of wall motion abnormalities, ventricular function, valve abnormalities, and pericardial disease.

FUTURE DEVELOPMENTS OF ECHOCARDIOGRAPHY

There are unifying attractions in the application of new echocardiographic technologies to improve the quantitation of echocardiography. Ejection fraction is a widely used parameter in decision making, and the reliability of 2D ejection fraction is tenuous when the implications of this measurement (e.g., implantable defibrillator insertion) are considered. The use of contrast has been shown to improve reliability of these measurements,[53] and 3D ejection fraction may also be attractive. Likewise, although LV volumes are known to be a powerful prognosticator, the reliability of these measurements with 2D echocardiography is limited, and 3D imaging has been shown to produce analogous measures to MRI.[77] The interpretation of regional function (including stress echocardiography) is the most challenging aspect of echocardiography, as well as the most difficult to quantify. Recent developments in tissue Doppler, strain rate imaging and speckle tracking echocardiography may prove useful for this purpose. The contribution of tissue Doppler in ischemic heart disease is limited by its lack of site specificity, which makes its measurements susceptible to translation and tethering problems.[78] In contrast, strain measurements are specific to location, and strain rate in particular has been used to facilitate the identification of viable myocardium.[79] The use of deformation analysis to facilitate the recognition of ischemia is problematic – tissue-velocity based strain may be limited by signal noise, and the tracking process for speckle strain is challenging at high heart rates. Further technical developments will facilitate the clinical adoption of these techniques.

CONCLUSION

Echocardiography is central in the evaluation and management of the patient with ischemic heart disease. Although the imaging choices for the evaluation of ischemic heart disease have expanded over the last few years, echocardiography remains the initial test in most settings. The utility of echo will likely be increased by a number of new developments.

REFERENCES

1. Edler I, Lindstrom K. The history of echocardiography. *Ultrasound Med Biol.* 2004;30(12):1565-1644.

2. Nesto RW, Kowalchuk GJ. The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. *Am J Cardiol.* 1987;59(7):23C-30C.

3. Picano E, Palinkas A, Amyot R. Diagnosis of myocardial ischemia in hypertensive patients. *J Hypertens.* 2001;19(7):1177-1183.

4. Legrand V, Hodgson JM, Bates ER, et al. Abnormal coronary flow reserve and abnormal radionuclide exercise test results in patients with normal coronary angiograms. *J Am Coll Cardiol.* 1985;6(6):1245-1253.

5. Gallagher KP, Matsuzaki M, Koziol JA, et al. Regional myocardial perfusion and wall thickening during ischemia in conscious dogs. *Am J Physiol.* 1984;247(5 Pt 2):H727-738.

6. Grattan MT, Hanley FL, Stevens MB, et al. Transmural coronary flow reserve patterns in dogs. *Am J Physiol.* 1986;250(2 Pt 2):H276-283.

7. Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. *Circulation.* 1982;66(6):1146-1149.

8. Marwick TH. The viable myocardium: epidemiology, detection, and clinical implications. *Lancet.* 1998;351(9105):815-819.

9. Bogaert J, Maes A, Van de Werf F, et al. Functional recovery of subepicardial myocardial tissue in transmural myocardial infarction after successful reperfusion: an important contribution to the improvement of regional and global left ventricular function. *Circulation.* 1999;99(1):36-43.

10. Reimer KA, Lowe JE, Rasmussen MM, et al. The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation.* 1977;56(5):786-794.

11. Hauser AM, Gangadharan V, Ramos RG, et al. Sequence of mechanical, electrocardiographic and clinical effects of repeated coronary artery occlusion in human beings: echocardiographic observations during coronary angioplasty. *J Am Coll Cardiol.* 1985;5(2 Pt 1):193-197.

12. Kvitting JP, Wigstrom L, Strotmann JM, et al. How accurate is visual assessment of synchronicity in myocardial motion? An In vitro study with computer-simulated regional delay in myocardial motion: clinical implications for rest and stress echocardiography studies. *J Am Soc Echocardiogr.* 1999;12(9):698-705.

13. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation.* 2002;105(4):539-542.

14. Biagini E, Galema TW, Schinkel AF, et al. Myocardial wall thickness predicts recovery of contractile function after primary coronary intervention for acute myocardial infarction. *J Am Coll Cardiol.* 2004;43(8):1489-1493.

15. Kraunz RF, Kennedy JW. Ultrasonic determination of left ventricular wall motion in normal man. Studies at rest and after exercise. *Am Heart J.* 1970;79(1):36-43.

16. Douglas PS, Khandheria B, Stainback RF, et al. ACCF/ASE/ACEP/AHA/ASNC/SCAI/SCCT/SCMR 2008 appropriateness criteria for stress echocardiography: a report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, American Society of Echocardiography, American College of Emergency Physicians, American Heart Association, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance: endorsed by the Heart Rhythm Society and the Society of Critical Care Medicine. *Circulation.* 2008;117(11):1478-1497.

17. Cornel JH, Bax JJ, Elhendy A, et al. Biphasic response to dobutamine predicts improvement of global left ventricular function after surgical revascularization in patients with stable coronary artery disease: implications of time course of recovery on diagnostic accuracy. *J Am Coll Cardiol.* 1998;31(5):1002-1010.

18. Kloner RA, Allen J, Cox TA, et al. Stunned left ventricular myocardium after exercise treadmill testing in coronary artery disease. *Am J Cardiol.* 1991;68(4):329-334.

19. Noguchi Y, Nagata-Kobayashi S, Stahl JE, et al. A meta-analytic comparison of echocardiographic stressors. *Int J Cardiovasc Imaging.* 2005;21(2-3):189-207.

20. Kwok Y, Kim C, Grady D, et al. Meta-analysis of exercise testing to detect coronary artery disease in women. *Am J Cardiol.* 1999;83(5):660-666.

21. Sicari R, Nihoyannopoulos P, Evangelista A, et al. Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur J Echocardiogr.* 2008;9(4):415-437.

22. Mazeika P, Nihoyannopoulos P, Joshi J, et al. Evaluation of dipyridamole-Doppler echocardiography for detection of myocardial ischemia and coronary artery disease. *Am J Cardiol.* 1991;68(5):478-484.

23. Bin JP, Le E, Pelberg RA, et al. Mechanism of inducible regional dysfunction during dipyridamole stress. *Circulation.* 2002;106(1):112-117.

24. Armstrong WF, Pellikka PA, Ryan T, et al. Stress echocardiography: recommendations for performance and interpretation of stress echocardiography. Stress Echocardiography Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr.* 1998;11(1):97-104.

25. McNeill AJ, Fioretti PM, el-Said SM, et al. Enhanced sensitivity for detection of coronary artery disease by addition of atropine to dobutamine stress echocardiography. *Am J Cardiol.* 1992;70(1):41-46.

26. Picano E, Pingitore A, Conti U, et al. Enhanced sensitivity for detection of coronary artery disease by addition of atropine to dipyridamole echocardiography. *Eur Heart J.* 1993;14(9):1216-1222.

27. Picano E, Molinaro S, Pasanisi E. The diagnostic accuracy of pharmacological stress echocardiography for the assessment of coronary artery disease: a meta-analysis. *Cardiovasc Ultrasound.* 2008;6:30.

28. Kim C, Kwok YS, Heagerty P, et al. Pharmacologic stress testing for coronary disease diagnosis: A meta-analysis. *Am Heart J.* 2001;142(6):934-944.

29. Picano E, Bedetti G, Varga A, et al. The comparable diagnostic accuracies of dobutamine-stress and dipyridamole-stress echocardiographies: a meta-analysis. *Coron Artery Dis.* 2000;11(2):151-159.

30. Bax JJ, Poldermans D, Elhendy A, et al. Sensitivity, specificity, and predictive accuracies of various noninvasive techniques for detecting hibernating myocardium. *Curr Probl Cardiol.* 2001;26(2):147-186.

31. Kertai MD, Boersma E, Bax JJ, et al. A meta-analysis comparing the prognostic accuracy of six diagnostic tests for predicting perioperative cardiac risk in patients undergoing major vascular surgery. *Heart.* 2003;89(11):1327-1334.

32. Ciaroni S, Bloch A, Albrecht L, et al. Diagnosis of coronary artery disease in patients with permanent cardiac pacemaker by dobutamine stress echocardiography or exercise thallium-201 myocardial tomography. *Echocardiography.* 2000;17(7):675-679.

33. Lieberman AN, Weiss JL, Jugdutt BI, et al. Two-dimensional echocardiography and infarct size: relationship of regional wall motion and thickening to the extent of myocardial infarction in the dog. *Circulation.* 1981;63(4):739-746.

34. Scherrer-Crosbie M, Liel-Cohen N, Otsuji Y, et al. Myocardial perfusion and wall motion in infarction border zone: assessment by myocardial contrast echocardiography. *J Am Soc Echocardiogr.* 2000;13(5):353-357.

35. Beattie WS, Abdelnaem E, Wijeysundera DN, et al. A meta-analytic comparison of preoperative stress echocardiography and nuclear scintigraphy imaging. *Anesth Analg.* 2006;102(1):8-16.

36. Schinkel AF, Bax JJ, Poldermans D, et al. Hibernating myocardium: diagnosis and patient outcomes. *Curr Probl Cardiol.* 2007;32(7):375-410.

37. Gramiak R, Shah PM, Kramer DH. Ultrasound cardiography: contrast studies in anatomy and function. *Radiology.* 1969;92(5):939-948.

38. Garcia-Fernandez MA, Bermejo J, Perez-David E, et al. New techniques for the assessment of regional left ventricular wall motion. *Echocardiography.* 2003;20(7):659-672.

39. Linka AZ, Sklenar J, Wei K, et al. Assessment of transmural distribution of myocardial perfusion with contrast echocardiography. *Circulation.* 1998;98(18):1912-1920.

40. Olszewski R, Timperley J, Szmigielski C, et al. The clinical applications of contrast echocardiography. *Eur J Echocardiogr.* 2007;8(3):S13-23.

41. Hayat SA, Senior R. Contrast echocardiography for the assessment of myocardial viability. *Curr Opin Cardiol.* 2006;21(5):473-478.

42. Janardhanan R, Moon JC, Pennell DJ, et al. Myocardial contrast echocardiography accurately reflects transmurality of myocardial necrosis and predicts contractile reserve after acute myocardial infarction. *Am Heart J.* 2005;149(2):355-362.

43. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart

Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J.* 2008.

44. Murdoch DR, Love MP, Robb SD, et al. Importance of heart failure as a cause of death. Changing contribution to overall mortality and coronary heart disease mortality in Scotland 1979-1992. *Eur Heart J.* 1998;19(12):1829-1835.

45. Fox KF, Cowie MR, Wood DA, et al. Coronary artery disease as the cause of incident heart failure in the population. *Eur Heart J.* 2001;22(3):228-236.

46. Ciampi Q, Villari B. Role of echocardiography in diagnosis and risk stratification in heart failure with left ventricular systolic dysfunction. *Cardiovasc Ultrasound.* 2007;5:34.

47. Foster E, Cahalan MK. The search for intelligent quantitation in echocardiography: "eyeball," "trackball" and beyond. *J Am Coll Cardiol.* 1993;22(3):848-850.

48. Marwick TH. Techniques for comprehensive two dimensional echocardiographic assessment of left ventricular systolic function. *Heart.* 2003;89 Suppl 3:iii2-8.

49. Stamm RB, Carabello BA, Mayers DL, et al. Two-dimensional echocardiographic measurement of left ventricular ejection fraction: prospective analysis of what constitutes an adequate determination. *Am Heart J.* 1982;104(1):136-144.

50. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr.* 1989;2(5):358-367.

51. Cohen JL, Cheirif J, Segar DS, et al. Improved left ventricular endocardial border delineation and opacification with OPTISON (FS069), a new echocardiographic contrast agent. Results of a phase III Multicenter Trial. *J Am Coll Cardiol.* 1998;32(3):746-752.

52. Crouse LJ, Cheirif J, Hanly DE, et al. Opacification and border delineation improvement in patients with suboptimal endocardial border definition in routine echocardiography: results of the Phase III Albunex Multicenter Trial. *J Am Coll Cardiol.* 1993;22(5):1494-1500.

53. Hoffmann R, von Bardeleben S, ten Cate F, et al. Assessment of systolic left ventricular function: a multi-centre comparison of cineventriculography, cardiac magnetic resonance imaging, unenhanced and contrast-enhanced echocardiography. *Eur Heart J.* 2005;26(6):607-616.

54. Malm S, Frigstad S, Sagberg E, et al. Accurate and reproducible measurement of left ventricular volume and ejection fraction by contrast echocardiography: a comparison with magnetic resonance imaging. *J Am Coll Cardiol.* 2004;44(5):1030-1035.

55. Hutchins GM, Bulkley BH. Infarct expansion versus extension: two different complications of acute myocardial infarction. *Am J Cardiol.* 1978;41(7):1127-1132.

56. Meizlish JL, Berger HJ, Plankey M, et al. Functional left ventricular aneurysm formation after acute anterior transmural myocardial infarction. Incidence, natural history, and prognostic implications. *N Engl J Med.* 1984;311(16):1001-1006.

57. Friedman BM, Dunn MI. Postinfarction ventricular aneurysms. *Clin Cardiol.* 1995;18(9):505-511.

58. Antunes MJ, Antunes PE. Left ventricular aneurysms: from disease to repair. *Expert Rev Cardiovasc Ther.* 2005;3(2):285-294.

59. Brown SL, Gropler RJ, Harris KM. Distinguishing left ventricular aneurysm from pseudoaneurysm. A review of the literature. *Chest.* 1997;111(5):1403-1409.

60. Haugland JM, Asinger RW, Mikell FL, et al. Embolic potential of left ventricular thrombi detected by two-dimensional echocardiography. *Circulation.* 1984;70(4):588-598.

61. Keren A, Goldberg S, Gottlieb S, et al. Natural history of left ventricular thrombi: their appearance and resolution in the posthospitalization period of acute myocardial infarction. *J Am Coll Cardiol.* 1990;15(4):790-800.

62. Visser CA, Kan G, Meltzer RS, et al. Embolic potential of left ventricular thrombus after myocardial infarction: a two-dimensional echocardiographic study of 119 patients. *J Am Coll Cardiol.* 1985;5(6):1276-1280.

63. Kumanohoso T, Otsuji Y, Yoshifuku S, et al. Mechanism of higher incidence of ischemic mitral regurgitation in patients with inferior myocardial infarction: quantitative analysis of left ventricular and mitral valve geometry in 103 patients with prior myocardial infarction. *J Thorac Cardiovasc Surg.* 2003;125(1):135-143.

64. Reeder GS. Identification and treatment of complications of myocardial infarction. *Mayo Clin Proc.* 1995;70(9):880-884.

65. Helmcke F, Nanda NC, Hsiung MC, et al. Color Doppler assessment of mitral regurgitation with orthogonal planes. *Circulation.* 1987;75(1):175-183.

66. Pollak H, Nobis H, Mlczoch J. Frequency of left ventricular free wall rupture complicating acute myocardial infarction since the advent of thrombolysis. *Am J Cardiol.* 1994;74(2):184-186.

67. Raitt MH, Kraft CD, Gardner CJ, et al. Subacute ventricular free wall rupture complicating myocardial infarction. *Am Heart J.* 1993;126(4):946-955.
68. Pollak H, Diez W, Spiel R, et al. Early diagnosis of subacute free wall rupture complicating acute myocardial infarction. *Eur Heart J.* 1993;14(5):640-648.
69. Veinot JP, Walley VM, Wolfsohn AL, et al. Postinfarct cardiac free wall rupture: the relationship of rupture site to papillary muscle insertion. *Mod Pathol.* 1995;8(6):609-613.
70. Anderson DR, Adams S, Bhat A, et al. Post-infarction ventricular septal defect: the importance of site of infarction and cardiogenic shock on outcome. *Eur J Cardiothorac Surg.* 1989;3(6):554-557.
71. Soliman OI, Geleijnse ML, Meijboom FJ, et al. The use of contrast echocardiography for the detection of cardiac shunts. *Eur J Echocardiogr.* 2007;8(3):S2-12.
72. Hansing CE, Rowe GG. Tricuspid insufficiency. A study of hemodynamics and pathogenesis. *Circulation.* 1972;45(4):793-799.
73. Abbate A, Bonanno E, Mauriello A, et al. Widespread myocardial inflammation and infarct-related artery patency. *Circulation.* 2004;110(1):46-50.
74. Mulvagh SL, Rakowski H, Vannan MA, et al. American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography. *J Am Soc Echocardiogr.* 2008;21(11):1179-1201; quiz 1281.
75. Pennell DJ, Sechtem UP, Higgins CB, et al. Clinical indications for cardiovascular magnetic resonance (CMR): Consensus Panel report. *Eur Heart J.* 2004;25(21):1940-1965.
76. Picano E. Stress echocardiography. *Expert Rev Cardiovasc Ther.* 2004;2(1):77-88.
77. Jenkins C, Bricknell K, Marwick TH. Use of real-time three-dimensional echocardiography to measure left atrial volume: comparison with other echocardiographic techniques. *J Am Soc Echocardiogr.* 2005;18(9):991-997.
78. Marwick TH. Measurement of strain and strain rate by echocardiography: ready for prime time? *J Am Coll Cardiol.* 2006;47(7):1313-1327.
79. Hanekom L, Jenkins C, Jeffries L, et al. Incremental value of strain rate analysis as an adjunct to wall motion scoring for assessment of myocardial viability by dobutamine echocardiography: a follow-up study after revascularization. *Circulation.* 2005;112(25):3892-3900.

Chapter 4

Prevalence and pharmacological treatment of left ventricular dysfunction in patients undergoing vascular surgery

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ABSTRACT

Aims This study evaluated the prevalence of left ventricular (LV) dysfunction in vascular surgery patients and pharmacological treatment, according guidelinesof the European Society of Cardiology (ESC).

Methods Echocardiography was performed preoperatively in 1,005 consecutive patients. Left ventricular ejection fraction (LVEF) ≤50% defined systolic LV dysfunction. Diastolic LV dysfunction was diagnosed based on E/A-ratio, pulmonary vein flow, and deceleration time. Optimal pharmacological treatment to improve LV function was considered as: (i) angiotensin-blocking agent (ACE-I/ABR) in patients with LVEF ≤40%, (ii) ACE-I/ABR, and β-blocker in patients with LVEF ≤40% + heart failure symptoms or previous myocardial infarction; and (iii) a diuretic in patients with symptomatic heart failure, regardless of LVEF.

Results Left ventricular dysfunction was present in 506 patients (50%), of whom 209 (41%) had asymptomatic diastolic LV dysfunction, 194 (39%) had asymptomatic systolic LV dysfunction, and 103 (20%) had symptomatic heart failure. Treatment with ACE-I/ABR and/or β-blocker could be initiated/improved in 67 (34%) of the 199 patients with (a)symptomatic LVEF ≤40%. A diuretic could be initiated in 32 patients (31%) with symptomatic heart failure (regardless of LVEF).

Conclusion This study demonstrated a high prevalence of LV dysfunction in vascular surgery patients and under-utilization of ESC recommended pharmacological treatment. Standard preoperative evaluation of LV function could be argued based on our results to reduce this observed care gap.

INTRODUCTION

Patients undergoing vascular surgery are known to be at increased risk of perioperative complications due to frequently underlying (a)symptomatic coronary artery disease. Coronary artery disease is the aetiology of heart failure in 60 to 70% of patients, predominantly in the elderly population.[1, 2] Coupled to the growing prevalence of heart failure and the elderly population, is the increase in surgical procedures. In addition, many invasive surgical interventions (such as major vascular surgery) are increasingly performed in elderly patients. Worldwide, about 100 million adults undergo noncardiac surgery annually and by the year 2020 the number of patients eligible for surgery will increase by 25%, with the largest group of patients aged >65 years.[3]

Considerable improvements have been made in the treatment of heart failure. Guidelines of the European Society of Cardiology (ESC) recommend treatment with angiotensin-converting enzyme inhibitors (ACE-I) in patients with systolic left ventricular (LV) dysfunction, defined as LV ejection fraction (LVEF) ≤40%, irrespective of the presence of heart failure symptoms to improve ventricular function.[4] An angiotensin-receptor blocker (ARB) is recommended in case of ACE-I intolerance.[4] Patients with asymptomatic systolic LV dysfunction and a myocardial infarction (MI) in past history are recommended to receive a β-blocker as well. A diuretic is recommended next to these agents in patients with symptomatic heart failure.[4]

The aim of the current study was to evaluate (i) the prevalence and pharmacological treatment for asymptomatic systolic LV dysfunction or symptomatic heart failure, according to the ESC guidelines, in the vascular surgery population and (ii) the impact of treatment on late outcome.

METHODS

Study population and baseline characteristics

The patient population consisted of 1,005 consecutive vascular surgery patients at the Erasmus Medical Center (Rotterdam, the Netherlands) during the period between 2002 and 2008. The study was approved by the hospital's ethics committee and performed with the informed consent of all patients. A detailed history was obtained from every patient and clinical data included: age, gender, ischemic heart disease (history of angina pectoris, coronary revascularization, or myocardial infarction), cerebrovascular disease (history of ischemic or hemorrhagic stroke), renal dysfunction (serum creatinine >2.0 mg/dL), diabetes mellitus (fasting blood glucose ≥7.0 mmol/L or requirement for anti-diabetic medication), hypertension (blood pressure ≥140/90 mmHg in non-diabetics and ≥130/80 mmHg in diabetics or requirement for antihypertensive medication), dyslipoproteinemia (low-density lipoprotein

cholesterol >3,50 mmol/L or requirement of lipid-lowering medication), and chronic obstructive pulmonary disease.

Left ventricular dysfunction

Preoperatively, transthoracic echocardiography was performed in all patients using a handheld Acuson Cypress Ultrasound System (7V3c transducer). Standard images were obtained at rest with the patient in the left lateral decubitus position as recommended.[5] Left ventricular end-systolic and end-diastolic volumes were determined and LVEF was calculated using the biplane Simpson's technique.[6] Systolic (S) and diastolic (D) pulmonary vein flow, deceleration time, and mitral inflow E/A ratios of peak velocities (at early rapid filling E and late filling due to atrial contraction A) were determined in apical 4-chamber view as recommended [7]. An LVEF ≤50% was defined as reduced and an LVEF ≤40% was eligible for pharmacological treatment.[4] Diastolic LV dysfunction was confirmed in patients with E/A-ratio <0.8 or >2.[8] Abnormal pulmonary vein flow (S/D <1) was used to distinguish normal and pseudo-normal diastolic LV function in patients with E/A-ratio between 0.8 and 2.[9] Deceleration time >220 or <140 ms defined diastolic LV dysfunction in patients with atrial fibrillation.[9] Patients with both systolic and diastolic LV dysfunction were classified as systolic LV dysfunction. The presence of LV dysfunction in combination with heart failure symptoms (shortness of breath, fatigue, exercise intolerance, signs of fluid retention)[4] defined symptomatic heart failure. Two experienced investigators performed off-line assessments of the obtained ultrasound images. When there was disagreement between the two assessors, a third investigator viewed the images without knowledge of the previous assessment and a majority decision was reached.

European Society of Cardiology treatment recommendations

During the first preoperative visit to the outpatient clinic, the use of the prescription medications was recorded and included ACE-Is, ARBs, β-blockers, diuretics, statins, aspirin, oral anticoagulants, and nitrates. In the current study, the following ESC treatment recommendations were used: (i) treatment of all patients with an LVEF ≤40% with at least ACE-I/ARB, (ii) treatment of patients with an LVEF ≤40% and a history of myocardial infarction with ACE-I/ARB and a β-blocker, (iii) treatment of heart failure symptoms with a diuretic, regardless of LVEF, and (iv) treatment of LVEF ≤40% in combination with heart failure symptoms with ACE-I/ARB in combination with a β-blocker and diuretic.

Contraindications for ACE-I/ARB were confirmed in patients with known ACE-I/ARB intolerance, history of angio-oedema, bilateral renal artery stenosis, serum potassium concentration >5.0 mmol/L, serum creatinine >2.5 mg/dL, and severe aortic stenosis.[4] Contraindications for β-blocker treatment were confirmed in patients with known β-blocker intolerance, sinus bradycardia <50 beats per minute, second- or third degree heart block, sick sinus syndrome, or asthma.[4] In addition, contraindication for diuretic treatment was confirmed in patients with known diuretic intolerance, renal failure, clinical signs of hypovolemia or

dehydration, serum potassium concentration <3.5 mmol/L, serum magnesium concentration <1.2 mmol/L, or serum sodium concentration <135 mmol/L.[4]

Follow-up

Long-term mortality was assessed by approaching the municipal civil registries. Survival status and medication use was completed by approaching the referring physician. All surviving patients received a mailed questionnaire (80% response rate) addressing medication use. Medication use in patients who died or patients who did not respond the questionnaire, was completed by approaching the referring physician. Mean follow-up was 2.2 ± 1.8 years.

Statistical analysis

Dichotomous data are presented as numbers and percentages and categorical data are compared using the χ^2 test. The continuous variables age, blood pressure, and heart rate are described as means ± standard deviation (SD) and compared using ANOVA. The relation between ACE-I/ARB use in patients with an LVEF ≤40% and long-term mortality was evaluated with Cox regression analyses with propensity score adjustment for treatment with ACE-I/ARB. Multivariate analyses were adjusted for demographics (age and gender), cardiovascular risk factors (ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, and smoking status) and medication use (β-blockers, statins, and aspirin). We report (crude and adjusted) hazard ratios with their 95% confidence interval. For all tests, a *p*-value <0.05 (two-sided) was considered significant. All analyses were performed using SPSS version 15.0 statistical software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics

The baseline study population consisted of 1,005 vascular surgery patients, of which the majority were males (77%) and the mean age was 67 (SD ± 10) years. Patients with LV dysfunction were older and more often male compared with patients with normal LV function. In addition, LV dysfunction was associated with ischemic heart disease, renal dysfunction, hypertension, and chronic obstructive pulmonary disease (*Table 1*).

Prevalence of left ventricular dysfunction

Left–ventricular dysfunction was diagnosed in 506 (50%) patients (*Figure 1*), of which 403 (80%) patients had asymptomatic LV dysfunction and 103 (20%) patients had symptomatic heart failure. Of the patients with asymptomatic LV dysfunction, 209 (52%) had asymptomatic isolated diastolic LV dysfunction and 194 (48%) had asymptomatic systolic LV dysfunction. In total, 130 (67%) patients with asymptomatic systolic LV dysfunction had an LVEF ≤40% (*Figure 2*). In this group, a medical history of myocardial infarction could be appointed as a

cause of LV dysfunction in 63 (49%) patients. In addition, valvular stenosis and/or regurgitation could be appointed in 33 (25%) patients as a possible cause of LV dysfunction.

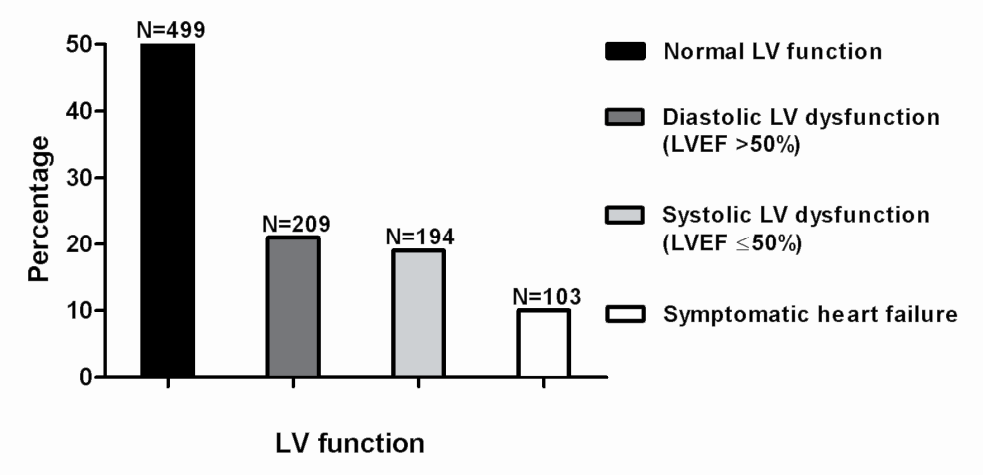
Of the 103 patients with symptomatic heart failure, 72 (70%) patients had NYHA II, 28 (27%) patients had NYHA III, and 3 (3%) patients had NYHA IV. In addition, 69 (67%) patients had an LVEF ≤40%. In this group, a medical history of myocardial infarction could be appointed as a cause of LV dysfunction in 52 (75%) patients. In addition, valvular stenosis and/or regurgitation could be appointed in 10 (15%) patients as a possible cause of LV dysfunction.

Table 1 **Baseline characteristics according to left ventricular function**

	Normal LV function [N=499]	LV dysfunction [N=506]	*p*-value
Demographics			
Age in years (± SD)	65 (11)	70 (10)	<0.01
Male (%)	363 (73)	406 (80)	0.005
Medical history (%)			
Ischemic heart disease	165 (33)	265 (52)	<0.01
Cerebrovascular disease	169 (34)	184 (36)	0.407
Renal dysfunction	61 (12)	114 (23)	<0.01
Diabetes mellitus	98 (20)	117 (23)	0.178
Hypertension	294 (59)	364 (72)	<0.01
Hypercholesterolemia	233 (47)	249 (49)	0.425
Chronic obstructive pulmonary disease	145 (29)	222 (44)	<0.01

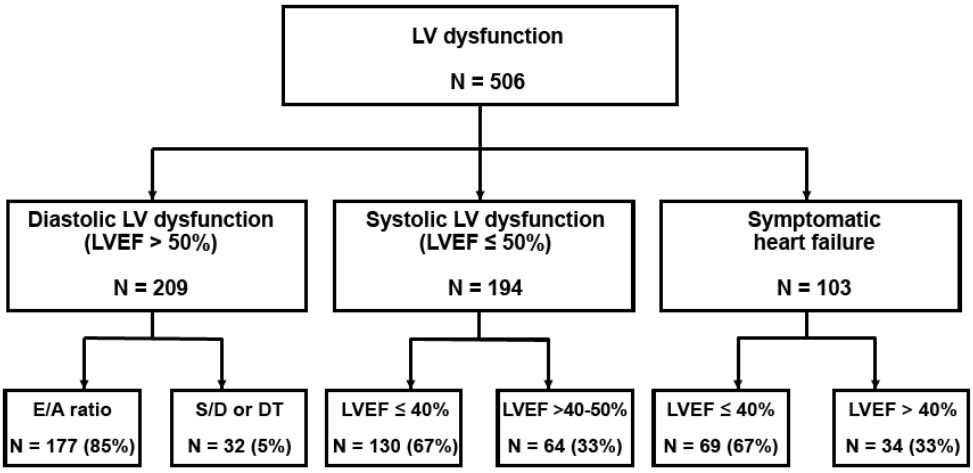
Left-ventriccular (LV), standard deviation (SD).

Figure 1: Prevalence of left ventricular dysfunction in patients undergoing vascular surgery.



Left ventricular (LV), left ventricular ejection fraction (LVEF).

Figure 2: Distribution of the different types of left ventricular dysfunction.



Deceleration time (DT), left ventricular (LV), left ventricular ejection fraction (LVEF).

Pharmacological treatment at first presentation

Medication use was recorded during the first presentation at the outpatient clinic. Most frequently, we observed the use of (i) statins (N=527 or 52%), (ii) aspirin (N=430 or 43%) (iii) β-blockers (N=366 or 36%), (iv) ACE-I (N=310 or 31%), (v) diuretics (N=253 or 25%), (vi) oral anticoagulants (N=164 or 16%), (vii) ARB (N=144 or 14%), and (viii) nitrates (N=101 or 10%). Medication use stratified according to LV function is demonstrated in *Table 2*. The use of ACE-I, ARB, β-blockers, diuretics, oral anticoagulants, and nitrates was associated with LV dysfunction.

Table 2 **Medication use stratified according to left ventricular function at first presentation to the outpatient clinic**

MEDICATION USE (%)	Normal LV function	Diastolic LV dysfunction (LVEF >50%)	Systolic LV dysfunction (LVEF ≥50%)	Symptomatic heart failure	*p* for trend
	[N=499]	[N=209]	[N=194]	[N=103]	
ACE-I	129 (26)	65 (31)	63 (33)	53 (52)	<0.001
ARB	67 (13)	28 (13)	28 (14)	21 (20)	0.005
β-blockers	138 (28)	80 (38)	81 (42)	67 (65)	<0.001
Diuretics	95 (19)	54 (26)	57 (29)	47 (46)	<0.001
Statins	249 (50)	108 (52)	114 (59)	564 (54)	0.433
Aspirin	165 (33)	83 (40)	102 (53)	80 (78)	<0.001
Oral anticoagulants	61 (12)	35 (17)	41 (21)	27 (26)	<0.001
Nitrates	32 (6)	19 (9)	20 (10)	30 (29)	<0.001

Angiotensin-converting enzyme inhibitor (ACE-I), angiotensin-receptor blocker (ARB), left ventricular (LV).

Pharmacological treatment to improve left ventricular function

As demonstrated in *Table 3*, 71 patients with an LVEF ≤40% and NYHA = 1 did not have a myocardial infarction in their past history. Of these patients, 31 (44%) patients received no treatment and 25 (35%) patients received optimal treatment with ACE-I/ARB to improve LV function. In addition, 128 patients with an LVEF ≤40% did have a myocardial infarction in their past history and/or had current NYHA ≥2. Of these patients, 31 (24%) patients received no treatment and 52 (41%) patients received optimal treatment with ACE-I/ARB in combination with a β-blocker to improve LV function. Of the patients who received no or suboptimal treatment to improve LV function, 55 (28%) patients had a contraindication to ACE-I/ARB and/or β-blockers. Therefore, pharmacological treatment to improve LV function could be initiated or improved in 67 (34%) of the patients with an LVEF ≤40%.

Table 3 **Treatment with angiotensin blocking agents and β-blockers to improve left ventricular function in patients with left ventricular ejection fraction ≤40%**

LVEF ≤40%			No previous MI and current NYHA 1 [a]	Previous MI and/or current NYHA ≥2 [b]
			[N=71]	[N=128]
ACE-I/ARB -	β-blocker -	(%)	31 (44)	31 (24)
ACE-I/ARB +	β-blocker -	(%)	17 (24)	24 (19)
ACE-I/ARB -	β-blocker +	(%)	15 (21)	21 (16)
ACE-I/ARB +	β-blocker +	(%)	8 (11)	52 (41)
Optimal treatment		(%)	25 (35)	52 (41)
Suboptimal treatment	contraindication: no	(%)	9 (13)	24 (19)
	contraindication: yes	(%)	6 (9)	20 (16)
No treatment	contraindication: no	(%)	18 (25)	16 (12)
	contraindication: yes	(%)	13 (18)	15 (12)

[a] *Treatment for LV function should at least contain ACE-I/ARB,* [b] *Treatment for left ventricular function should at least contain an ABA in combination with β-blocker. Angiotensin-converting enzyme inhibitor (ACE-I), angiotensin-receptor blocker (ARB), left ventricular ejection fraction (LVEF), myocardial infarction (MI), New York Heart Association (NYHA).*

Pharmacological treatment to reduce heart failure symptoms

In total 103 patients had heart failure symptoms with a severity of NYHA class 2 or more during the first presentation at the outpatient clinic (*Table 4*). Of these, 47 (46%) patients received a diuretic. After adjustment for contraindications, initiation of diuretic treatment was possible in 32 (31%) of the patients. In addition, of the patients with an LVEF ≤40% and heart failure symptoms NYHA ≥2 (N=68), 20 (29%) patients received optimal treatment with ACE-I/ARB in combination with a β-blocker and a diuretic. Of the patients who received no or suboptimal treatment to reduce heart failure symptoms, 29 (43%) patients had a contraindication to ACE-I/ARB, β-blockers or diuretics. Pharmacological treatment to reduce heart failure symptoms could therefore be initiated or improved in 19 (28%) patients with and an LVEF ≤40% and heart failure symptoms NYHA ≥2.

Table 4 **Treatment with diuretics for symptom relief in patients with symptomatic heart failure**

	NYHA ≥2		LVEF ≤40%	LVEF >40%
			[N=68]	[N=35]
Diuretic		(%)	34 (50)	13 (37)
No diuretic	contraindication: no	(%)	18 (26)	14 (40)
	contraindication: yes	(%)	16 (34)	8 (23)

Left ventricular ejection fraction (LVEF), New York Heart Association (NYHA).

Pharmacological treatment at time of discharge

In total, 199 patients with an LVEF ≤40% were recommended to receive at least ACE-I/ARB treatment to improve their LV function. Of these patients, 139 (70%) patients were treated with an ACE-I/ARB, and 187 (94%) patients with a β-blocker at time of discharge. Multivariate analyses demonstrated that ACE-I/ARB treatment was independently associated with a reduced risk of long-term mortality (HR 0.53, 95%-CI: 0.33 to 0.87).

DISCUSSION

We have found that LV dysfunction was present in around half of the patients undergoing vascular surgery and the majority (80%) of LV dysfunction was asymptomatic. Of the patients with asymptomatic LV dysfunction, around half the patients had asymptomatic systolic LV dysfunction. In addition, we found that in approximately one-third of the patients with LV dysfunction (asymptomatic or symptomatic), pharmacological treatment, as recommended in ESC guidelines, could be initiated or improved.

In countries represented by the ESC, the prevalence of LV dysfunction is suspected to be around 4% in the general population. In septo- and octogenarians, the prevalence is between 10 and 20%.[4] In our sub-population, of patients undergoing vascular surgery (mean age 67 years), we found a prevalence of LV dysfunction of around 50%. With respect to adherence of ESC recommendations, the EuroHeart Failure Survey provided information on the state of implementation of the guidelines.[10] The following prescription rates in patients with an LVEF <40% were reported: (i) ACE-I: 80%, (ii) ARB: 6%, (iii) β-blocker: 49%, and (iv) diuretics: 88%.[10] Drechsler *et al.* assessed pharmacological treatment in 747 patients with symptomatic heart failure (LVEF ≤40%) and found that 84% received ACE-I, 72% received ACE-I + β-blocker, and 38% received ACE-I + β-blocker + diuretic.[11]

The above-mentioned studies included patients with symptomatic heart failure and concluded that there is insufficient adherence to the ESC guidelines. All patients included in the present study received routine preoperative echocardiography, which allowed the evaluation of asymptomatic LVEF ≤40% as well. We found that half of the patients with

symptomatic LVEF ≤40% and one-third of patients with symptomatic diastolic LV dysfunction received a diuretic. In addition, less than one-third of the patients with symptomatic LVEF ≤40% received an ACE-I/ARB + β-blocker + a diuretic. Therefore, we found that optimal treatment for symptomatic heart failure was lower in our vascular surgery population, compared with the population described by Drechsler *et al.*[11] Understandably, the under-use of ACE-I/ARB and β-blockers was more pronounced in patients with asymptomatic LVEF ≤40%.

Peripheral arterial disease patients have a three- to six-fold increased risk for cardiovascular mortality, compared with patients without peripheral arterial disease.[12, 13] There is growing awareness of the systemic vascular risk of patients with peripheral arterial disease. However, the Reduction of Atherothrombosis for Continued Health registry demonstrated that peripheral arterial disease patients do not receive adequate risk factor control, compared with individuals with coronary artery or cerebrovascular disease. In addition, it demonstrated that improved risk factor control is associated with a positive impact on 1 year cardiovascular event rates.[14, 15]

In the latest ESC perioperative guidelines, heart failure symptoms are a well-acknowledged risk factor for cardiac events.[16] In addition, preoperative cardiac risk indices identify symptomatic heart failure to be an important risk factor.[17-19] Asymptomatic LV dysfunction is considered a precursor of symptomatic heart failure, which is associated with high mortality.[4] Currently, routine echocardiography is not recommended for preoperative evaluation of LV function. However, echocardiography may be performed in asymptomatic patients undergoing high-risk surgery, such as vascular surgery.[16] We found that one out of four vascular surgery patients were eligible for pharmacological treatment of LV dysfunction,[4] and more than half of these patients appeared to be asymptomatic. With more routine use of preoperative echocardiography in vascular surgery patients, pharmacological treatment of asymptomatic LV dysfunction could be improved.

Based on cost-effectiveness considerations, preoperative echocardiography might not be applicable for all vascular surgery patients. However, these days biochemical markers such as N-terminal pro-B-type natriuretic peptide, are increasingly used to detect or exclude LV dysfunction.[20] Therefore, standard measurements of this biochemical marker may play an important role in detecting asymptomatic LV dysfunction in vascular surgery patients. In patients with increased levels of N-terminal pro-B-type natriuretic peptide, LV dysfunction could be confirmed with echocardiography.

Potential limitations of these data merit consideration. First, although we included 1,005 patients, the sample size eligible for ESC recommended treatment was relatively small. Second, although experienced investigators performed off-line assessments of the ultrasound images, we cannot rule out interobserver variability to have had minor influence on our results.

Third, the evaluation of diastolic LV function was limited, not including E/E' ratio, isovolumetric relaxation time, or Tissue Doppler Imaging. Finally, our population consisted of patients referred to a tertiary referral center and may not fully represent the general vascular surgery population.

In conclusion, the current study demonstrates that one-third of vascular surgery patients with LV dysfunction do not receive optimal pharmacological treatment, as recommended in ESC guidelines. More routine use of echocardiography before vascular surgery could reduce the observed care gap in vascular surgery patients, with subsequent initiation of ESC recommended pharmacological treatment and thereby improve late outcome.

REFERENCES

1. Fox KF, Cowie MR, Wood DA, et al. Coronary artery disease as the cause of incident heart failure in the population. *Eur Heart J*. 2001;22(3):228-236.

2. Cleland JG, Swedberg K, Follath F, et al. The EuroHeart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J*. 2003;24(5):442-463.

3. Mangano DT. Perioperative medicine: NHLBI working group deliberations and recommendations. *J Cardiothorac Vasc Anesth*. 2004;18(1):1-6.

4. Dickstein. ESC Guidelines for the diagnosing and treatment of acute and chronic heart failure 2008. *Eur Heart J*. 2008;10:1093.

5. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. *Eur J Echocardiogr*. 2006;7(2):79-108.

6. Stamm RB, Carabello BA, Mayers DL, et al. Two-dimensional echocardiographic measurement of Left ventricular ejection fraction: prospective analysis of what constitutes an adequate determination. *Am Heart J*. 1982;104(1):136-144.

7. Quinones MA, Otto CM, Stoddard M, et al. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2002;15(2):167-184.

8. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of Left ventricular diastolic function by echocardiography. *Eur J Echocardiogr*. 2009;10(2):165-193.

9. Persson H, Lonn E, Edner M, et al. Diastolic dysfunction in heart failure with preserved systolic function: need for objective evidence:results from the CHARM Echocardiographic Substudy-CHARMES. *J Am Coll Cardiol*. 2007;49(6):687-694.

10. Cleland JG, Swedberg K, Cohen-Solal A, et al. The Euro Heart Failure Survey of the EUROHEART survey programme. A survey on the quality of care among patients with heart failure in Europe. The Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The Medicines Evaluation Group Centre for Health Economics University of York. *Eur J Heart Fail*. 2000;2(2):123-132.

11. Drechsler K, Dietz R, Klein H, et al. Euro heart failure survey. Medical treatment not in line with current guidelines. *Z Kardiol*. 2005;94(8):510-515.

12. Hackam DG, Sultan NM, Criqui MH. Vascular protection in peripheral artery disease: systematic review and modelling study. *Heart*. 2009;95(13):1098-1102.

13. McKenna M, Wolfson S, Kuller L. The ratio of ankle and arm arterial pressure as an independent predictor of mortality. *Atherosclerosis*. 1991;87(2-3):119-128.

14. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *Jama.* 2006;295(2):180-189.

15. Cacoub PP, Abola MT, Baumgartner I, et al. Cardiovascular risk factor control and outcomes in peripheral artery disease patients in the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Atherosclerosis.* 2009;204(2):e86-92.

16. Poldermans D, Bax JJ, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in noncardiacsurgery: The Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur Heart J.* 2009.

17. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med.* 1977;297(16):845-850.

18. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation.* 1999;100(10):1043-1049.

19. Boersma E, Kertai MD, Schouten O, et al. Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index. *Am J Med.* 2005;118(10):1134-1141.

20. Felker GM, Petersen JW, Mark DB. Natriuretic peptides in the diagnosis and management of heart failure. *Cmaj.* 2006;175(6):611-617.

Chapter 5

Prognostic implications of asymptomatic left ventricular dysfunction in patients undergoing vascular surgery

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ABSTRACT

Background The prognostic value of heart failure symptoms on postoperative outcome is well acknowledged in the American College of Cardiology/American Heart Association and European Society of Cardiology perioperative guidelines. However, the prognostic value of asymptomatic left ventricular (LV) dysfunction remains unknown. This study evaluated the prognostic implications of asymptomatic LV dysfunction, assessed with routine preoperative echocardiography, in vascular surgery patients.

Methods Echocardiography was performed preoperatively in 1,005 consecutive vascular surgery patients. Systolic LV dysfunction was defined as LV ejection fraction <50%. Isolated diastolic LV dysfunction was diagnosed based on the ratio of mitral peak velocity of early filling (E) to mitral peak velocity of late filling (A), pulmonary vein flow, and deceleration time. Troponin T measurements and electrocardiograms were performed routinely before and after surgery. Study endpoints were 30-day cardiovascular events and long-term cardiovascular mortality. Multivariate regression analyses evaluated the relation between LV function and cardiovascular outcome.

Results Left ventricular dysfunction was diagnosed in 506 (50%) patients, of which 80% was asymptomatic. In open vascular surgery (N=649), both asymptomatic systolic and isolated diastolic LV dysfunction were associated with 30-day cardiovascular events (OR 2.3, 95%-CI: 1.4 to 3.6 and OR 1.8, 95%-CI: 1.1 to 2.9) and long-term cardiovascular mortality (HR 4.6, 95%-CI: 2.4 to 8.5 and HR 3.0, 95%-CI: 1.5 to 6.0). In endovascular surgery (N=356), only symptomatic heart failure was associated with 30-day cardiovascular events (OR 1.8, 95%-CI: 1.1 to 2.9) and long-term cardiovascular mortality (HR 10.3, 95%-CI: 5.4 to 19.3).

Conclusions This study demonstrated that asymptomatic LV dysfunction is predictive for 30-day and long-term cardiovascular outcome in open vascular surgery patients. These data suggest that preoperative risk stratification should not solely include heart failure symptoms, but that routine preoperative echocardiography might be considered for risk stratification of patients undergoing open vascular surgery.

INTRODUCTION

Worldwide, about 100 million adults undergo noncardiac surgery every year,[1] and by the year 2020 this number will increase by 25%.[2] The risk of adverse perioperative cardiovascular events after vascular surgery is particularly high compared with other noncardiac surgeries.[3] Although ischemic heart disease is acknowledged to be the most important risk factor for cardiovascular events after noncardiac surgery, several studies indicate that symptomatic heart failure is equally important.[4-6] In the general population the prevalence of symptomatic heart failure is estimated to be around 2 to 3% and increases with age, with a prevalence estimated between 10 to 20% in septo- and octogenarians.[7] Whereas the term heart failure describes a clinical syndrome, left ventricular (LV) dysfunction describes the impaired mechanical properties of the left ventricle. Asymptomatic LV dysfunction is considered a precursor of symptomatic heart failure, associated with high mortality.[7] The prevalence of patients with asymptomatic LV dysfunction and symptomatic heart failure is assumed to be similar.[8]

In the most recent American College of Cardiology/American Heart Association (AHA) and European Society of Cardiology (ESC) perioperative guidelines,[3, 9] the prognostic value of symptomatic heart failure on postoperative outcome is well acknowledged. However, the prognostic implications of asymptomatic LV dysfunction remains unknown. Routine perioperative evaluation of LV function is not recommended in ACC/AHA perioperative guidelines (Class III, Level of Evidence: C).[9] Additionally, LV assessment with rest echocardiography is not recommended in ESC perioperative guidelines (Class III, Level of Evidence: C) for asymptomatic patients.[3]

The present study was conducted to evaluate the impact of asymptomatic isolated diastolic and asymptomatic systolic LV dysfunction, objectified with routine preoperative echocardiography, on postoperative outcome of patients undergoing open or endovascular surgery.

MATERIAL AND METHODS

Study population

The study population has previously been described and consisted of 1,005 consecutive vascular surgery patients undergoing elective (open or endovascular) lower extremity artery, carotid artery or abdominal aorta repair.[10] This prospective cohort study was performed at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period between 2002 and 2008. The study was approved by the hospital's ethics committee and performed with informed consent of all patients.

Baseline characteristics

Before surgery, a detailed history was obtained from every patient. Cardiac history was assessed and ischemic heart disease was defined as a history of angina pectoris, coronary revascularization, or myocardial infarction. Additional clinical data included age, gender, blood pressure, heart rate, cerebrovascular disease (history of ischemic or hemorrhagic stroke), renal dysfunction (serum creatinine >2 mg/dL), diabetes mellitus (fasting blood glucose ≥126 mg/dL or requirement of anti-diabetic medication), hypertension (blood pressure ≥140/90 mmHg in non-diabetics and ≥130/80 mmHg in diabetics,[11] or requirement of antihypertensive medication), hypercholesterolemia (low density lipoprotein cholesterol ≥135 mg/dL or requirement of lipid-lowering medication), chronic obstructive pulmonary disease (according to the Global Initiative on Obstructive Lung Diseases classification), and smoking status. Finally, the use of β-blockers, statins, aspirin, oral anticoagulants, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, diuretics, and nitrates was recorded.

Echocardiography

Preoperatively, transthoracic echocardiography was performed in all patients using a portable Acuson Cypress Ultrasound System (Acuson, A Siemens Company, Mountain View, CA) with a 3V2C transducer (3.0/3.5/2.5/2.0 MHz) for adult cardiac evaluation. Standard parasternal and apical two- and four-chamber views were obtained during rest with the patient in the left lateral decubitus position as recommended.[12] Left ventricular end-systolic and end-diastolic volumes were determined and LV ejection fraction was calculated using the biplane Simpson's technique,[13] with an inter- and intraobserver variability of 9 to 12% and 6%, respectively.[14] Systolic (S) and diastolic (D) pulmonary vein flow, deceleration time and ratio of mitral peak velocity of early filling (E) to mitral peak velocity of late filling (A) were determined in apical 4-chamber. Echocardiographic data were used for research purposes and not for clinical management.

Definition of left ventricular dysfunction

Left ventricular ejection fraction <50%, both with and without accompanying diastolic dysfunction, defined systolic LV dysfunction.[7] Diastolic LV dysfunction was confirmed in patients with E/A-ratio <0.8 (impaired relaxation) or >2 (restrictive relaxation).[15] Abnormal pulmonary vein flow (S/D <1) was used to distinguish normal and pseudo-normal diastolic LV function in patients with E/A-ratio between 0.8 and 2.[16] Deceleration time >220 ms (impaired relaxation) or <140 ms (restrictive relaxation) defined diastolic LV dysfunction in patients with atrial fibrillation.[16] Diastolic LV dysfunction, in the presence of an LV ejection fraction ≥50%, defined asymptomatic isolated diastolic dysfunction. The presence of LV dysfunction in combination with heart failure symptoms (shortness of breath, fatigue, exercise intolerance, signs of fluid retention) defined symptomatic heart failure.[7] Two experienced investigators performed off-line assessments of the obtained ultrasound images. When there was disagreement between the two assessors, a third investigator viewed the images without knowledge of the previous assessment and a majority decision was reached.

Study outcomes

Serial electrocardiograms and troponin T measurements were obtained from all patients before surgery, postoperatively on day 1, 3, 7 and before discharge. Study endpoints were 30-day cardiovascular (CV) events (defined as myocardial ischemia, myocardial infarction and CV mortality) and long-term CV mortality. Myocardial ischemia was present in patients with normal preoperative and elevated (>0.03 ng/mL) troponin T levels postoperatively.[17] Elevated troponin T levels in combination with electrocardiographic changes (new onset ST-T changes and pathological Q waves) defined myocardial infarction.[18] Troponin T level was measured using a whole blood rapid test (TropT version 2, Roche Diagnostics, Mannheim, Germany). Patients with elevated troponin T levels before surgery were not included in the study. Patients were subjected to a follow-up visit with one of the study investigators 30 days post surgery and for those patients who did not attend, the referring physician was approached. In patients still admitted or re-admitted at the Erasmus MC, 30-day follow-up was completed using the Erasmus MC medical records.

Long-term mortality was assessed by approaching the municipal civil registries. Cause of death was ascertained by examining death certificates and otherwise by reviewing medical records. Cause of death was classified as either cardiovascular or noncardiovascular death. Cardiovascular death was defined as any death with a cerebro-cardiovascular complication as the primary or secondary cause and included death following myocardial infarction, serious cardiac arrhythmias (defined as the presence of a sustained cardiac rhythm disturbance that required urgent medical intervention), congestive heart failure, stroke (cerebrovascular event or transient ischemic attack), and surgery related bleeding complications (only a postoperative cause of death). Sudden unexpected death was classified as a cardiovascular death. Cause of death was separately assessed by two authors. In the absence of consensus, a third investigator assessed the cause of death and a majority decision was reached. Follow-up was completed in all patients.

Statistical analysis

Continuous variables are described as means ± standard deviation (SD) and dichotomous data as numbers and percentages. Continuous data were compared using ANOVA for trend and categorical data using the linear by linear association. The prognostic value of LV dysfunction towards 30-day and long-term follow-up was evaluated with logistic and Cox regression analyses, respectively. Multivariate analyses were primarily adjusted for covariates (age, sex, ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, and smoking status) prospectively locked into the model based on the clinical knowledge and belief that these factors might (i) contribute to the study outcomes and (ii) confound the association between the primary echo predictors and the study outcomes. Secondary adjustments were done in a step-wise fashion and these analyses were adjusted for medication use (β-blockers, statins, aspirin, oral anticoagulants, angiotensin-converting enzyme inhibitors, angiotensin-

receptor blockers, diuretics, and nitrates) on top of the covariates used in the primary regression model, (crude and adjusted) odds and hazard ratios with their 95% confidence interval (95%-CI) were reported. For all tests, a *p*-value <0.05 (two-sided) was considered significant. Cumulative long-term survival was determined by the Kaplan-Meier method. All analyses were performed using SPSS version 15.0 statistical software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Patients population

A total of 1,005 patients undergoing open vascular (N=649 or 65%) or endovascular (N=356 or 35%) surgery were included in the study. Of the open vascular surgery patients; 148 patients (23%) underwent carotid artery repair, 249 patients (38%) underwent abdominal aorta repair, and 252 patients (39%) underwent lower extremity artery repair. In comparison, of the endovascular patients; 90 patients (25%) underwent carotid artery repair, 162 patients (46%) underwent abdominal aorta repair, and 104 patients (29%) underwent lower extremity artery repair. All patients undergoing open vascular surgery had general anesthesia and 56 (35%) of the patients undergoing endovascular aortic repair had general anesthesia. General anesthesia was not provided for the percutaneous procedures.

The majority of patients were men (77%) and the mean age was 67 ±10 years. Mean follow-up was 2.2 ± 1.8 years (range 3 to 79 months). Left ventricular dysfunction was diagnosed in 506 (50%) patients. Of the patients with LV dysfunction, 403 (80%) patients had asymptomatic LV dysfunction and 103 (20%) had symptomatic heart failure. Of the patients with asymptomatic LV dysfunction, 209 (52%) had asymptomatic isolated diastolic LV dysfunction and 194 (48%) had asymptomatic systolic LV dysfunction. Of the 103 patients with symptomatic heart failure, 72/70% patients had New York Heart Association Class II, 28/27% patients had New York Heart Association Class III (12 patients had signs of fluid retention objectified as peripheral oedema) and 3/3% patients had New York Heart Association Class IV, with signs of pulmonary oedema objectified with physical examination.

Baseline characteristics

Clinical parameters are shown in *Table 1*. Patients with LV dysfunction were older and had higher incidence of ischemic heart disease, renal dysfunction, hypertension, chronic obstructive pulmonary disease and had higher resting heart rate compared with patients with normal LV function. In addition, patients with LV dysfunction more often received β-blockers, oral anticoagulants, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, diuretics and nitrates. Patients with asymptomatic systolic LV dysfunction or symptomatic heart failure were more often male. A higher number of patients with symptomatic heart failure underwent open surgery compared with the other groups.

Table 1 Baseline characteristics according to left ventricular function

	Normal LV function	Asymptomatic isolated diastolic LV dysfunction	Asymptomatic systolic LV dysfunction	Symptomatic heart failure	*p* for trend
	[N=499]	[N=209]	[N=194]	[N=103]	
Demographics (mean ± SD)					
Age	65 (11)	70 (10)	70 (8)	70 (10)	<0.001
Male (%)	363 (73)	154 (74)	168 (87)	84 (82)	0.001
Systolic blood pressure	141 (24)	142 (24)	141 (26)	135 (23)	0.111
Diastolic blood pressure	79 (12)	80 (12)	79 (12)	77 (12)	0.199
Heart rate	70 (13)	73 (13)	73 (15)	72 (15)	0.012
Medical history (%)					
Ischemic heart disease	165 (33)	83 (40)	102 (53)	80 (78)	<0.001
Cerebrovascular disease	169 (34)	83 (40)	76 (39)	25 (24)	0.603
Renal dysfunction	62 (12)	34 (16)	41 (21)	42 (41)	<0.001
Diabetes mellitus	141 (28)	62 (30)	64 (33)	30 (29)	0.698
Hypertension	294 (59)	153 (73)	135 (70)	76 (74)	<0.001
Hypercholesterolemia	303 (65)	131 (65)	114 (60)	61 (63)	0.729
COPD	100 (20)	49 (23)	50 (26)	32 (31)	<0.001
Smoker, current	225 (45)	85 (41)	69 (36)	41 (40)	0.046
Surgery type (%)					
Open	320 (64)	129 (62)	118 (61)	82 (80)	0.102
Lower extremity	131 (26)	42 (21)	43 (22)	36 (35)	0.926
Abdominal aorta	110 (22)	51 (24)	48 (25)	40 (39)	0.100
Carotid artery	79 (16)	36 (17)	27 (14)	6 (6)	0.062
Endovascular	179 (36)	80 (38)	76 (39)	21 (20)	0.102
Lower extremity	61 (12)	22 (10)	16 (8)	5 (5)	0.179
Abdominal aorta	71 (14)	40 (19)	37 (19)	14 (14)	0.065
Carotid artery	47 (10)	18 (9)	23 (12)	2 (1)	0.633
Medication (%)					
β-blockers	368 (74)	161 (77)	162 (84)	87 (84)	0.001
Statins	352 (71)	145 (70)	149 (77)	72 (70)	0.433
Aspirin	303 (61)	110 (53)	114 (60)	61 (59)	0.578
Oral anticoagulants	61 (12)	35 (17)	41 (21)	27 (26)	<0.001
ACE inhibitors	129 (26)	65 (31)	63 (33)	53 (52)	<0.001
ARB	49 (13)	29 (14)	36 (19)	23 (22)	0.011
Diuretics	95 (19)	54 (26)	56 (29)	49 (48)	<0.001
Nitrates	32 (6)	19 (9)	20 (10)	30 (29)	<0.001

Angiotensin-converting enzyme (ACE), angiotensin-receptor blocker (ARB), chronic obstructive pulmonary disease (COPD), left ventricular (LV), standard deviation (SD).

Thirty-day outcome

During 30-day follow-up, 172 (17%) patients had a nonfatal myocardial event of whom 131 (76%) patients had myocardial ischemia and 41 (24%) patients had myocardial infarction. In total, 51 (10%) patients with normal LV function had a 30-day CV event, compared with 38 (18%) patients with asymptomatic isolated diastolic LV dysfunction, 44 (23%) patients with

asymptomatic systolic LV dysfunction and 50 (49%) patients with symptomatic heart failure ($p < 0.001$, *Table 2*). Multivariate analyses, in patients undergoing open surgery, demonstrated that asymptomatic isolated diastolic LV dysfunction, asymptomatic systolic LV dysfunction, and symptomatic heart failure were all associated with 30-day CV events with odds ratios of 1.8 (95%-CI: 1.1 to 2.9), 2.3 (95%-CI: 1.4 to 3.6) and 6.8 (95%-CI: 4.0 to 11.6), respectively (*Table 3*). Other risk factors associated with 30-day CV events were age, ischemic heart disease, renal dysfunction, and chronic obstructive pulmonary disease with odds ratios of 1.8 (95%-CI: 1.0 to 1.1), 1.7 (95%-CI: 1.1 to 2.6), 3.9 (95%-CI: 2.2 to 7.1), and 1.8 (95%-CI: 1.2 to 2.6), respectively. Multivariate analyses, in patients undergoing endovascular surgery, demonstrated that symptomatic heart failure was associated with 30-day CV events with an odds ratio of 9.3 (95%-CI: 2.3 to 37.7) (*Table 4*). For both types of surgical procedures, additional adjustment for medication use (β-blockers, statins, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and diuretics) did not change the prognostic value of LV dysfunction towards 30-day outcome.

Table 2 **Left ventricular function and postoperative outcome**

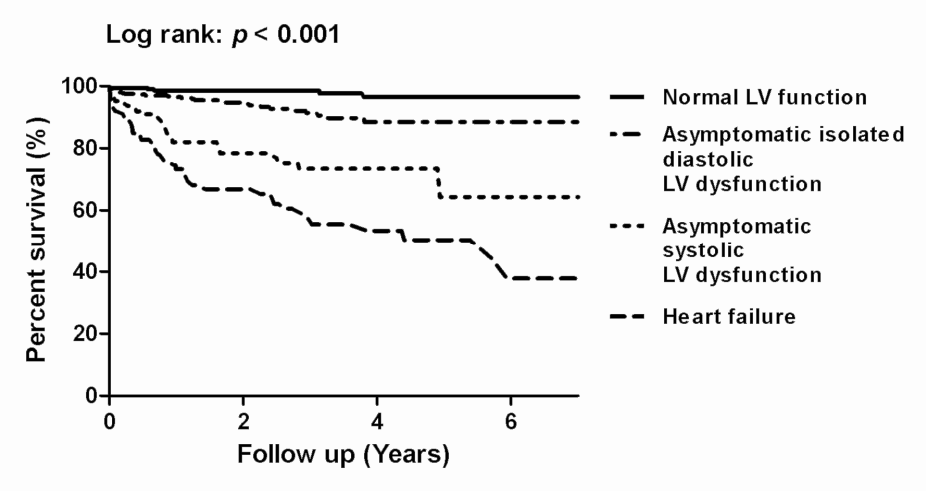
	Normal LV function		Asymptomatic isolated diastolic LV dysfunction		Asymptomatic systolic LV dysfunction		Symptomatic heart failure		*p*-value
	[N=499]		[N=209]		[N=194]		[N=103]		
30-day (%)									
Cardiovascular events	51	(10)	38	(18)	44	(23)	50	(49)	<0.001
Myocardial damage	50	(10)	36	(17)	41	(21)	45	(44)	<0.001
Cardiovascular	2	(0)	4	(2)	7	(4)	11	(11)	<0.001
All-cause mortality	6	(1)	5	(2)	7	(4)	11	(11)	<0.001
Long-term (%)									
Cardiovascular	15	(3)	21	(10)	31	(16)	40	(39)	<0.001
All-cause mortality	54	(11)	31	(15)	38	(20)	41	(40)	<0.001

Left ventricular (LV)

Long-term outcome

During long-term follow-up, 164 (16%) patients died. The study endpoint long-term CV mortality was reached in 107 (11%) patients. In total, 15 (3%) patients with normal LV function died due to CV causes, compared with 21 (10%) patients with asymptomatic isolated diastolic LV dysfunction, 31 (16%) patients with asymptomatic systolic LV dysfunction, and 40 (39%) patients with symptomatic heart failure ($p < 0.001$, *Table 2*).

Figure 1: Left ventricular function and long-term survival after vascular surgery.



Left ventricular (LV).

Table 3 **Association between left ventricular function and postoperative outcome: open vascular surgery**

			Univariate		Multivariate	
30-day CV events	**N**	**(%)**	**OR**	**[95%-CI]**	**OR**	**[95%-CI]**
Normal LV function	44/320	(14)	1.0		1.0	
Isolated diastolic LV dysfunction	30/129	(23)	2.0	1.2-3.1	1.8	1.1-2.9
Systolic LV dysfunction	36/118	(31)	2.6	1.7-4.0	2.3	1.4-3.6
Symptomatic heart failure	44/82	(54)	8.3	5.1-13.4	6.8	4.0-11.6
Long-term CV mortality	**N**	**(%)**	**HR**	**[95%-CI]**	**HR**	**[95%-CI]**
Normal LV function	8/320	(3)	1.0		1.0	
Isolated diastolic LV dysfunction	14/129	(11)	3.5	1.8-6.8	3.0	1.5-6.0
Systolic LV dysfunction	23/118	(20)	5.2	2.8-9.7	4.6	2.4-8.5
Symptomatic heart failure	31/82	(38)	13.6	7.5-24.6	10.3	5.4-19.3
Long-term all-cause mortality	**N**	**(%)**	**HR**	**[95%-CI]**	**HR**	**[95%-CI]**
Normal LV function	37/320	(12)	1.0		1.0	
Isolated diastolic LV dysfunction	20/129	(16)	1.5	0.9-2.3	1.4	0.9-2.1
Systolic LV dysfunction	28/118	(24)	1.8	1.2-2.7	1.7	1.1-2.5
Symptomatic heart failure	32/82	(39)	3.9	2.6-5.8	3.1	2.0-4.8

Multivariate analysis adjusted for: age, gender, ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, and smoking. Cardiovascular (CV), confidence interval (CI), hazard ratio (HR), left ventricular (LV), odds ratio (OR).

Cumulative survival for all patients is shown in *Figure 1* (log rank $p < 0.001$). Of the patients with LV dysfunction who reached the study endpoint long-term CV mortality, 48 patients (52%) demonstrated myocardial ischemia or infarction during 30-day follow-up. Multivariate analyses, in patients undergoing open vascular surgery, demonstrated that asymptomatic

isolated diastolic LV dysfunction, asymptomatic systolic LV dysfunction and symptomatic heart failure were all associated with long-term CV mortality with hazard ratios of 3.0 (95%-CI: 1.5 to 6.0), 4.6 (95%-CI: 2.4 to 8.5) and 10.3 (95%-CI: 5.4 to 19.3), respectively (*Table 3*).

Table 4 **Association between left ventricular function and postoperative outcome: endovascular surgery**

			Univariate		Multivariate	
30-day CV events	**N**	**(%)**	**OR**	**[95%-CI]**	**OR**	**[95%-CI]**
Normal LV function	7/179	(4)	1.0		1.0	
Isolated diastolic LV dysfunction	8/80	(10)	2.7	0.9-7.8	2.2	0.7-6.9
Systolic LV dysfunction	8/76	(11)	2.9	1.0-8.6	2.5	0.8-7.8
Symptomatic heart failure	6/21	(29)	9.8	2.9-33.0	9.3	2.3-37.7
Long-term CV mortality	**N**	**(%)**	**HR**	**[95%-CI]**	**HR**	**[95%-CI]**
Normal LV function	7/179	(4)	1.0		1.0	
Isolated diastolic LV dysfunction	7/80	(9)	2.2	0.8-6.4	1.7	0.5-5.3
Systolic LV dysfunction	8/76	(11)	2.4	0.8-6.5	2.2	0.8-6.6
Symptomatic heart failure	9/21	(43)	14.5	5.4-39.1	11.4	3.7-35.6
Long-term all-cause mortality	**N**	**(%)**	**HR**	**[95%-CI]**	**HR**	**[95%-CI]**
Normal LV function	17/179	(10)	1.0		1.0	
Isolated diastolic LV dysfunction	11/80	(14)	1.5	0.7-3.2	1.2	0.5-2.7
Systolic LV dysfunction	10/76	(13)	1.3	0.6-2.9	1.2	0.5-2.9
Symptomatic heart failure	9/21	(43)	6.1	2.7-13.8	5.1	1.9-13.3

Multivariate analysis adjusted for: age, gender, ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, and smoking. Cardiovascular (CV), confidence interval (CI), hazard ratio (HR), left ventricular (LV), odds ratio (OR).

Other risk factors associated with long-term CV mortality were age, ischemic heart disease, renal dysfunction, and smoking with hazard ratios of 1.1 (95%-CI: 1.1 to 1.2), 1.6 (95%-CI: 1.1 to 2.8), 2.5 (95%-CI: 1.3 to 5.1) and 2.0 (95%-CI: 1.2 to 3.1), respectively. Multivariate analyses, in patients undergoing endovascular surgery, demonstrated that symptomatic heart failure was associated with long-term CV mortality with a hazard ratio of 11.4 (95%-CI: 3.7 to 35.6) (*Table 4*). For both types of surgical procedures, additional adjustment for medication use did not change the prognostic value of LV dysfunction towards long-term outcome.

DISCUSSION

The present study demonstrated that open vascular surgery patients with asymptomatic isolated diastolic- or systolic LV dysfunction, were at increased risk for 30-day CV events and long-term CV mortality. In endovascular surgery patients, only symptomatic heart failure was associated with an increased risk for 30-day CV events and long-term CV mortality. In

ACC/AHA and ESC guidelines, symptoms of heart failure are acknowledged to be an important predictor of postoperative outcome. However, our data suggest that asymptomatic LV dysfunction should be imbedded in preoperative risk stratification of vascular surgery patients, as well.

Left ventricular dysfunction is caused by neuro-hormonal responses activated by cardiac injury or an increased hemodynamic load. These responses are known to induce (i) sympathetic stimulation, (ii) salt and water retention, and (iii) vasoconstriction.[19, 20] Although these responses are initially adaptive, they become maladaptive over time, due to a process called LV remodelling. This process leads to (i) LV hypertrophy (concentric remodelling) associated with diastolic LV dysfunction or (ii) LV dilatation (eccentric remodelling) associated with systolic LV dysfunction.[21] During surgery, high catecholamine production is responsible for vasoconstriction and hemodynamic stress.[2] Surgical stress and perioperative fluid administration increases LV pre- and afterload, making patients with systolic LV dysfunction susceptible for perioperative myocardial damage.[22] During surgery there is an increased oxygen-demand and patients with coronary artery stenosis are at increased risk for perioperative myocardial damage, due to a mismatch between oxygen-supply and demand.[3, 23] Patients with diastolic LV dysfunction have a reduced coronary flow reserve, making them susceptible to perioperative myocardial damage as well.[21] In addition, concentric remodelling causes a reduction of LV compliance, making LV filling dependent upon blood volume contributed by LV preload. Perioperative LV preload reductions can result in tachycardia with concomitant reduction of coronary perfusion, leading to myocardial damage.[24]

Episodes of perioperative myocardial damage are most often silent and therefore patients often remain untreated, which might contribute to an increased risk of long-term CV mortality.[25, 26] We have found that approximately three out of four patients with perioperative damage had LV dysfunction. In line with previous studies, we have found that endovascular surgery was associated with a reduced incidence of perioperative myocardial damage, compared with open surgery, possibly explained by reduced myocardial stress and the need for lower fluid administration during endovascular procedures.[27, 28] In addition, one should keep in mind that carotid surgery is associated with lower cardiac risk compared with abdominal aneurysm repair and lower extremity revascularization.

Myocardial perfusion scintigraphy and pharmacological stress echocardiography are known to accurately stratify patients at risk for perioperative myocardial damage.[29-31] In addition, the presence of wall motion abnormalities at rest has predictive value for the development of perioperative cardiac events as well.[31] Until now, studies addressing the impact of heart failure in surgical patients mainly focused on symptomatic patients with a reduced LV ejection fraction.[5, 23, 32, 33] A retrospective study conducted by Xu-Cai *et al.* evaluated the impact of symptomatic heart failure with a preserved LV ejection fraction, demonstrating an increased risk for long-term mortality. However no increased risk for perioperative mortality was

observed.[34] Recently, Maytal *et al.* studied 313 vascular surgery patients and found diastolic LV dysfunction to be a predictor of adverse CV outcome, however, systolic LV dysfunction was not.[35] Several differences between the study conducted by Maytal *et al.* and the present study that might explain the different outcome regarding the impact of systolic LV dysfunction on CV outcome, such as: (i) subanalysing open vs. endovascular surgery, (ii) troponin T measurements obtained routinely or when clinically indicated, (iii) definition of the LV function groups, and (iv) follow-up duration. To our knowledge, the present study is the first to demonstrate that asymptomatic LV dysfunction (diastolic and systolic) is associated with an increased risk for adverse CV outcome of open vascular surgery patients.

In the most recent ACC/AHA and ESC perioperative guidelines,[3, 9] the prognostic value of symptoms of heart failure on postoperative outcome is well acknowledged and incorporated into the decision process with regard to proceeding directly to surgery. In addition, preoperative cardiac risk indices incorporate symptomatic heart failure as an important risk factor.[4, 6, 36] To define surgical patients at 'high risk' for developing adverse CV events, one point should be assigned to patients with (a medical history of) current symptoms of heart failure, next to other risk factors such as ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus or high-risk surgery. To prevent an underestimation of the 'cardiac risk burden' of vascular surgery patients, our data suggest that asymptomatic LV dysfunction should be imbedded in these risk indices as well.

Our results indicate that asymptomatic LV dysfunction is not associated with increased risk for 30-day CV events and long-term CV mortality in endovascular surgery patients. An explanation could lie in the fact that endovascular surgery is associated with reduced myocardial stress compared with open vascular surgery.[27, 28] The detection of asymptomatic LV dysfunction with routine preoperative echocardiography could, therefore, add valuable information in the decision making between open and endovascular surgery.

Biochemical markers, such as N-terminal pro-B-type natriuretic peptide, are increasingly used in the detection and exclusion of heart failure, [37] and have proven to predict poor outcome after vascular surgery.[38] Standard measurements of this biochemical marker may play an important role to detect asymptomatic LV dysfunction in vascular surgery patients, regardless of the presence of heart failure symptoms. However, the diagnostic value of natriuretic peptides in asymptomatic patients at risk for diastolic or systolic LV dysfunction is controversial. In a recent study conducted by Luers *et al,* plasma levels of natriuretic peptides significantly increased with a decreasing ejection fraction and with a severe degree of diastolic dysfunction.[39] Therefore, the authors suggest that high-risk individuals may be screened most efficiently by using a score system, incorporating clinical data and N-terminal pro-B-type natriuretic peptide. In vascular surgery patients, future studies are needed to evaluate the value of B-type natriuretic peptides vs. echocardiography to detect LV dysfunction in patients with or without heart failure symptoms. In 2003 Grayburn *et al.* proposed to shift the paradigm

from preoperative noninvasive risk stratification to therapy.[40] Routine preoperative evaluation of LV function could reveal patients with asymptomatic LV dysfunction eligible for pharmacological treatment. Before surgery, low-dose β-blockade could be considered, titrated to obtain a heart rate between 60-70 beats per minute.[41] In addition, initiation of angiotensin blockers could be considered after surgery.[42]

Potential limitations of these data merit consideration. First, the study population consisted of patients referred to a tertiary referral center and may not fully represent the general vascular surgery population scheduled. Second, although two experienced investigators performed an off-line assessment of ultrasound images, we cannot rule out interobserver variability to have had a minor influence on our results. Third, the evaluation of diastolic LV function with conventional Doppler, ratio of mitral peak velocity of early filling (E) to mitral peak velocity of late filling (A) and pulmonary vein filling patterns was limited due to preload dependency and not including Valsalva maneuver, ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (E'), isovolumetric relaxation time or Tissue Doppler Imaging.

In conclusion, this study demonstrated that asymptomatic LV dysfunction is a predictor of CV outcome in open vascular surgery patients. These data suggest that preoperative risk stratification should not solely include symptomatic heart failure, already acknowledged in ACC/AHA and ESC perioperative guidelines, however asymptomatic LV dysfunction should be imbedded as well. Standard preoperative evaluation of LV function could be argued based on our results, suggesting a move towards more routine use of cardiac echo in open vascular surgery patients.

REFERENCES

1. Mangano. Peri-operative cardiovascular morbidity: new developments. *Ballieres Clin Anaesthesiol* 1999;13:335-348.

2. Mangano DT. Perioperative medicine: NHLBI working group deliberations and recommendations. *J Cardiothorac Vasc Anesth.* 2004;18(1):1-6.

3. Poldermans D, Bax JJ, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: The Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur Heart J.* 2009.

4. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med.* 1977;297(16):845-850.

5. Hammill BG, Curtis LH, Bennett-Guerrero E, et al. Impact of heart failure on patients undergoing major noncardiac surgery. *Anesthesiology.* 2008;108(4):559-567.

6. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation.* 1999;100(10):1043-1049.

7. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic

Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J.* 2008;29(19):2388-2442.

8. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med.* 2002;347(18):1397-1402.

9. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol.* 2007;50(17):1707-1732.

10. Flu WJ, van Kuijk JP, Galal W, et al. Prevalence and pharmacological treatment of left ventricular dysfunction in patients undergoing vascular surgery. *Eur J Heart Fail.* 2010;12(3):288-293.

11. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003;42(6):1206-1252.

12. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. *Eur J Echocardiogr.* 2006;7(2):79-108.

13. Stamm RB, Carabello BA, Mayers DL, et al. Two-dimensional echocardiographic measurement of left ventricular ejection fraction: prospective analysis of what constitutes an adequate determination. *Am Heart J.* 1982;104(1):136-144.

14. McGowan JH, Cleland JG. Reliability of reporting left ventricular systolic function by echocardiography: a systematic review of 3 methods. *Am Heart J.* 2003;146(3):388-397.

15. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr.* 2009;10(2):165-193.

16. Persson H, Lonn E, Edner M, et al. Diastolic dysfunction in heart failure with preserved systolic function: need for objective evidence:results from the CHARM Echocardiographic Substudy-CHARMES. *J Am Coll Cardiol.* 2007;49(6):687-694.

17. Aviles RJ, Askari AT, Lindahl B, et al. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. *N Engl J Med.* 2002;346(26):2047-2052.

18. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *Eur Heart J.* 2007;28(20):2525-2538.

19. Cohn JN, Levine TB, Francis GS, et al. Neurohumoral control mechanisms in congestive heart failure. *Am Heart J.* 1981;102(3 Pt 2):509-514.

20. Levine TB, Francis GS, Goldsmith SR, et al. Activity of the sympathetic nervous system and renin-angiotensin system assessed by plasma hormone levels and their relation to hemodynamic abnormalities in congestive heart failure. *Am J Cardiol.* 1982;49(7):1659-1666.

21. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J Am Coll Cardiol.* 2000;35(3):569-582.

22. Schrier RW, Ecder T. Gibbs memorial lecture. Unifying hypothesis of body fluid volume regulation: implications for cardiac failure and cirrhosis. *Mt Sinai J Med.* 2001;68(6):350-361.

23. Hernandez AF, Whellan DJ, Stroud S, et al. Outcomes in heart failure patients after major noncardiac surgery. *J Am Coll Cardiol.* 2004;44(7):1446-1453.

24. Frank SM, Beattie C, Christopherson R, et al. Perioperative rate-related silent myocardial ischemia and postoperative death. *J Clin Anesth.* 1990;2(5):326-331.

25. Wallace A, Layug B, Tateo I, et al. Prophylactic atenolol reduces postoperative myocardial ischemia. McSPI Research Group. *Anesthesiology.* 1998;88(1):7-17.

26. Ouyang P, Gerstenblith G, Furman WR, et al. Frequency and significance of early postoperative silent myocardial ischemia in patients having peripheral vascular surgery. *Am J Cardiol.* 1989;64(18):1113-1116.

27. Schouten O, Dunkelgrun M, Feringa HH, et al. Myocardial damage in high-risk patients undergoing elective endovascular or open infrarenal abdominal aortic aneurysm repair. *Eur J Vasc Endovasc Surg.* 2007;33(5):544-549.

28. Elkouri S, Gloviczki P, McKusick MA, et al. Perioperative complications and early outcome after endovascular and open surgical repair of abdominal aortic aneurysms. *J Vasc Surg.* 2004;39(3):497-505.

29. Boucher CA, Brewster DC, Darling RC, et al. Determination of cardiac risk by dipyridamole-thallium imaging before peripheral vascular surgery. *N Engl J Med.* 1985;312(7):389-394.

30. Sicari R, Ripoli A, Picano E, et al. Perioperative prognostic value of dipyridamole echocardiography in vascular surgery: A large-scale multicenter study in 509 patients. EPIC (Echo Persantine International Cooperative) Study Group. *Circulation.* 1999;100(19 Suppl):II269-274.

31. Poldermans D, Arnese M, Fioretti PM, et al. Improved cardiac risk stratification in major vascular surgery with dobutamine-atropine stress echocardiography. *J Am Coll Cardiol.* 1995;26(3):648-653.

32. Ouriel K, Green RM, DeWeese JA, et al. Outpatient echocardiography as a predictor of perioperative cardiac morbidity after peripheral vascular surgical procedures. *J Vasc Surg.* 1995;22(6):671-677; discussion 678-679.

33. McEnroe CS, O'Donnell TF, Jr., Yeager A, et al. Comparison of ejection fraction and Goldman risk factor analysis to dipyridamole-thallium 201 studies in the evaluation of cardiac morbidity after aortic aneurysm surgery. *J Vasc Surg.* 1990;11(4):497-504.

34. Xu-Cai YO, Brotman DJ, Phillips CO, et al. Outcomes of patients with stable heart failure undergoing elective noncardiac surgery. *Mayo Clin Proc.* 2008;83(3):280-288.

35. Matyal R, Hess PE, Subramaniam B, et al. Perioperative diastolic dysfunction during vascular surgery and its association with postoperative outcome. *J Vasc Surg.* 2009;50(1):70-76.

36. Boersma E, Kertai MD, Schouten O, et al. Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index. *Am J Med.* 2005;118(10):1134-1141.

37. Felker GM, Petersen JW, Mark DB. Natriuretic peptides in the diagnosis and management of heart failure. *Cmaj.* 2006;175(6):611-617.

38. Ryding AD, Kumar S, Worthington AM, et al. Prognostic value of brain natriuretic peptide in noncardiac surgery: a meta-analysis. *Anesthesiology.* 2009;111(2):311-319.

39. Luers C, Wachter R, Kleta S, et al. Natriuretic peptides in the detection of preclinical diastolic or systolic dysfunction. *Clin Res Cardiol.*

40. Grayburn PA, Hillis LD. Cardiac events in patients undergoing noncardiac surgery: shifting the paradigm from noninvasive risk stratification to therapy. *Ann Intern Med.* 2003;138(6):506-511.

41. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med.* 1999;341(24):1789-1794.

42. Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol.* 2009;53(15):e1-e90.

Chapter 6

Co-existence of chronic obstructive pulmonary disease and left ventricular dysfunction in vascular surgery patients

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ABSTRACT

Background The co-existence between chronic obstructive pulmonary disease (COPD) and heart failure has been previously described. However, the co-existence between COPD and subclinical left ventricular (LV) dysfunction, without the presence of heart failure symptoms, is less well understood. This study determined the relationship and clinical relevance of COPD and subclinical LV dysfunction in vascular surgery patients.

Methods 1,005 consecutive vascular surgery patients were included in which COPD was determined using spirometry and LV function using echocardiography. Mild COPD was defined as FEV_1 ≥80% of predicted + FEV_1/FVC-ratio <0.70. Moderate/severe COPD was defined as FEV_1 <80% of predicted + FEV_1/FVC-ratio <0.70. Systolic LV dysfunction was defined as LV ejection fraction <50% and diastolic LV dysfunction was diagnosed based on E/A-ratio, pulmonary vein flow and deceleration time. Multivariate regression analyses were used to evaluate the impact of COPD and LV dysfunction on all-cause mortality. The mean follow-up time was 2.2 ± 1.8 years.

Results Both, mild and moderate/severe COPD were associated with increased risk for subclinical LV dysfunction with odds ratios of 1.6 (95%-CI: 1.1 to 2.3) and 1.7 (95%-CI: 1.2 to 2.4), respectively. Mild or moderate/severe COPD in combination with LV dysfunction was associated with an increased risk for all-cause mortality (mild: HR 1.7, 95%-CI: 1.1 to 3.6, moderate/severe: HR 2.5, 95%-CI: 1.5 to 4.7).

Conclusions COPD was associated with an increased risk for subclinical LV dysfunction. COPD + subclinical LV dysfunction was associated with an increased risk for all-cause mortality compared with patients with COPD + normal LV function. Echocardiography may be useful to detect subclinical cardiovascular disease and risk stratify COPD patients undergoing vascular surgery.

INTRODUCTION

Every year, there are 100 million adults who undergo a noncardiac surgical procedure across the world.[1] This number is expected to increase by 25% by the year 2020.[2] The risk of perioperative complications increases in patients with co-morbidities. There is increasing evidence that chronic lung disease, such as chronic obstructive pulmonary disease (COPD), and cardiovascular disease are common co-morbidities in these surgical patients. Interestingly, it appears that these co-morbidities are interrelated and often co-exist in the same patients, independent of age and smoking history.[3, 4] These patients have extremely poor prognosis following surgery. With the increasing preoperative use of echocardiography and spirometry, it may now be possible to identify patients with mild COPD and subclinical left ventricular (LV) dysfunction before surgery, providing an opportunity to determine the clinical significance of mild COPD and subclinical LV dysfunction in patients undergoing noncardiac surgical procedures. In the current study, we determined the relationship of LV dysfunction to COPD and the impact that these co-morbidities have, independently and collectively, on the risk of mortality in these patients. We hypothesized that COPD would be independently associated with LV dysfunction and that the presence of even subclinical LV dysfunction in patients with COPD would significantly increase the risk of mortality.

MATERIAL AND METHODS

Study population

The patient population consisted of 1,005 consecutive patients undergoing lower extremity artery, abdominal aortic aneurysm or abdominal aortic stenosis, or carotid artery repair. Both open and endovascular procedures were included. The study was performed at the department of vascular surgery of the Erasmus Medical Center in Rotterdam, the Netherlands, during the time period between 2002 and 2008. The study was approved by the hospital's ethics committee and performed with informed consent of all patients.

Baseline characteristics

Before surgery, a detailed history was obtained from every patient. Cardiac history was assessed and ischemic heart disease was defined as a history of angina pectoris, coronary revascularization or myocardial infarction. Additional clinical data included: age, gender, cerebrovascular disease (defined as a history of ischemic or hemorrhagic stroke), abdominal aortic disease (defined as abdominal aortic aneurysm or stenosis), renal dysfunction (serum creatinine >2.0 mg/dL), diabetes mellitus (fasting blood glucose ≥7.0 mmol/L or requirement for insulin or oral anti-diabetic medication), hypertension (blood pressure ≥140/90 mmHg in non-diabetic patients and ≥130/80 mmHg in diabetics or the use of antihypertensive medication), hypercholesterolemia (defined as low-density lipoprotein cholesterol >3.5 mmol/L or the requirement of lipid-lowering medication), and smoking status. The use of the

prescription medications was captured and included β-blockers, statins, aspirin, oral anticoagulants, angiotensin-converting enzyme (ACE) inhibitors, diuretics, nitrates, corticosteroids, and bronchodilators.

Chronic obstructive pulmonary disease

The diagnosis of COPD was based on preoperative post-bronchodilator spirometry, which was performed in 95% of the patients according to the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Mild COPD was defined as forced expiratory volume in one second (FEV_1) 80% of predicted or greater in the presence of FEV_1/forced vital capacity (FVC) ratio of <0.70.[5] Moderate/severe COPD was defined as FEV_1/FVC <0.70 and FEV_1 <80% of the predicted. In those patients who did not have spirometry, the diagnosis of COPD was based on symptoms (dyspnea, sputum production, and/or cough) plus the use of a pulmonary medication such as bronchodilators and corticosteroids.

Left ventricular function

Preoperatively, transthoracic echocardiography was performed in all patients using a handheld Acuson Cypress Ultrasound System (7V3c transducer). Standard parasternal and apical two- and four-chamber views were obtained at rest with the patient in the left lateral decubitus position as recommended.[6] Left ventricular end-systolic and end-diastolic volumes were determined and LV ejection fraction was calculated using the biplane Simpson's technique.[7] Systolic (S) and diastolic (D) pulmonary vein flow, deceleration time and mitral inflow E/A ratios of peak velocities (at early rapid filling E and late filling due to atrial contraction A) were determined in apical 4-chamber view as recommended by the American Society of Echocardiography.[8] Systolic LV dysfunction was defined as LV ejection fraction <50%.[9] Diastolic LV dysfunction was confirmed in patients with E/A-ratio <0.8 (impaired relaxation) or >2 (restrictive relaxation).[10] Abnormal pulmonary vein flow (S/D <1) was used to distinguish normal and pseudo-normal diastolic LV function in patients with E/A-ratio between 0.8 and 2.[11] Deceleration time >220 ms (impaired relaxation) or <140 ms (restrictive relaxation) defined diastolic LV dysfunction in patients with atrial fibrillation.[11] Patients with both systolic and diastolic LV dysfunction were classified as systolic LV dysfunction. The presence of LV dysfunction in combination with heart failure symptoms (shortness of breath, fatigue, exercise intolerance, signs of fluid retention)[9] defined symptomatic heart failure, confirmed in patients with New York Heart Association functional class ≥I.

Follow-up and outcome

Survival status was determined using municipal civil registries. The mean follow-up time was 2.2 ± 1.8 years.

Statistical analysis

Dichotomous data are described as numbers and percentages. Continuous variables are described as means ± standard deviation. Continuous data were compared using one-way

ANOVA and categorical data were compared using a χ^2 test. Cumulative long-term survival was determined using the Kaplan-Meier method. Univariate and multivariate Cox regression analyses were performed to evaluate the relationship of COPD and LV dysfunction with all-cause mortality. Multivariate regression analyses were adjusted for age, gender, ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus, hypertension, hypercholesterolemia, and smoking status. A sub-analysis was performed to evaluate the prognostic value of COPD towards postoperative outcome, in addition to the Revised Cardiac Risk (RCR) index.[12] Multivariate regression analyses were adjusted for RCR risk factors (high-risk type of surgery, symptomatic heart failure, ischemic heart disease, cerebrovascular disease, renal dysfunction, and diabetes) next to age, gender hypertension, hypercholesterolemia, and smoking status. We report both the crude and the adjusted hazard ratios (HR) with their 95% confidence interval (95%-CI). For all tests, a *p*-value <0.05 (two-sided) was considered significant. All analyses were performed using SPSS version 15.0 statistical software (SPSS, Inc., Chicago, IL, USA).

RESULTS

The baseline study population consisted of 1,005 patients undergoing lower extremity artery (N=356), abdominal aortic aneurysm or abdominal aortic stenosis (N=411) or carotid artery repair (N=238). Endovascular procedures comprised 36% of the surgical procedures. A majority of the patients were men (77%) and the mean age was 67 ± 10 years.

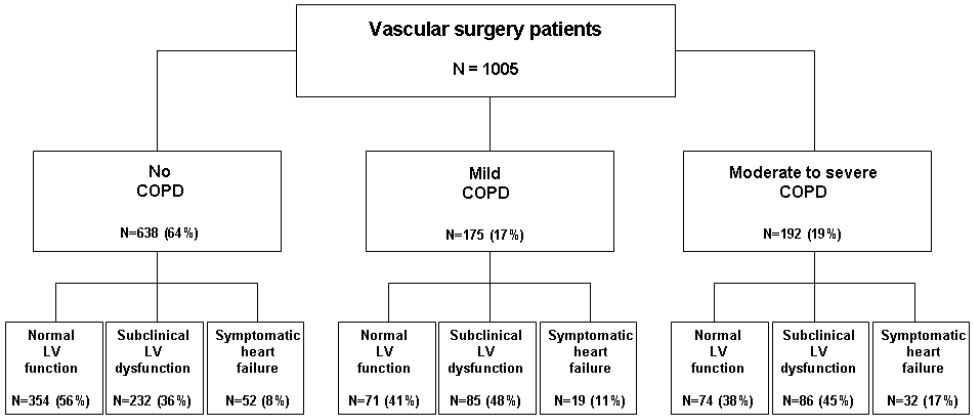
Prevalence of COPD and left ventricular dysfunction

In total, 638 (64%) patients had no COPD and of the 367 (37%) patients with COPD: 175 (17%) patients had mild and 192 (19%) patients had moderate/severe COPD. At baseline, LV dysfunction was present in 506 (50%) patients. Of the 103 patients with symptomatic heart failure, 69 (67%) patients had an LV ejection fraction ≤40 and 34 (33%) patients had an LV ejection fraction >40% + abnormal diastolic parameters. Of the 403 patients with subclinical LV dysfunction, 130 (32%) patients had an LV ejection fraction ≤40%, 64 (16%) patients had an LV ejection fraction >40-50% and 209 (52%) patients had an LV ejection fraction >50% + abnormal diastolic parameters (177 patients with abnormal E/A-ratio and 32 patients with S/D <1 or abnormal deceleration time).

Of the patients with no COPD, 232/638 (36%) had subclinical LV dysfunction and 52/638 (8%) had symptomatic heart failure (*Figure 1*). In addition, subclinical LV dysfunction and symptomatic heart failure were present in 85/175 (48%) and 19/175 (11%) of the patients with mild COPD, respectively. Finally, of the patients with moderate to severe COPD, 86/192 (45%) patients had subclinical LV dysfunction and 32/192 (17%) patients had symptomatic heart failure. Of the 171 patients with COPD and subclinical LV dysfunction, an LV ejection fraction ≤40 was present in 60 (36%) of the patients. In addition, 32/51 (63%) of

the patients with COPD + symptomatic heart failure had an LV ejection fraction ≤40 (p < 0.01).

Figure 1: Prevalence of chronic obstructive pulmonary disease and left ventricular dysfunction in vascular surgery patients.



Chronic obstructive pulmonary disease (COPD), left ventricular (LV).

Baseline characteristics

Clinical parameters are listed in *Table 1*. Patients with (i) COPD, (ii) LV dysfunction or, (iii) COPD + LV dysfunction were older, were likely to be men, had a higher prevalence of ischemic heart disease, abdominal aortic disease and were more likely to be treated with β-blockers or diuretics, compared with patients with normal pulmonary and normal LV function. Patients with COPD or COPD + LV dysfunction were also more often smokers and receiving corticosteroids and bronchodilators, compared with patients with LV dysfunction or patients with normal pulmonary and LV function. In addition, LV dysfunction with or without COPD was associated with an increased risk of renal dysfunction, hypertension and use of oral anticoagulants and ACE inhibitors.

Association between COPD and left ventricular dysfunction

Patients with COPD were less likely to have normal LV function, with an odds ratio (OR) of 0.7 (95%-CI: 0.5 to 0.9) for mild COPD and 0.6 (95%-CI: 0.4 to 0.8) for moderate/severe COPD, compared with patients with normal pulmonary function. Mild and moderate/severe COPD were both associated with subclinical LV dysfunction (mild: OR 1.6, 95%-CI: 1.1 to 2.3, moderate/severe: OR 1.7, 95%-CI: 1.2 to 2.4). Mild COPD was not significantly associated with heart failure (OR 1.2; 95%-CI: 0.6 to 2.4). However, moderate/severe COPD was associated with heart failure with an OR of 2.0 (95%-CI: 1.2 to 3.6). These results are demonstrated in *Figure 2*.

Table 1 **Baseline characteristics**

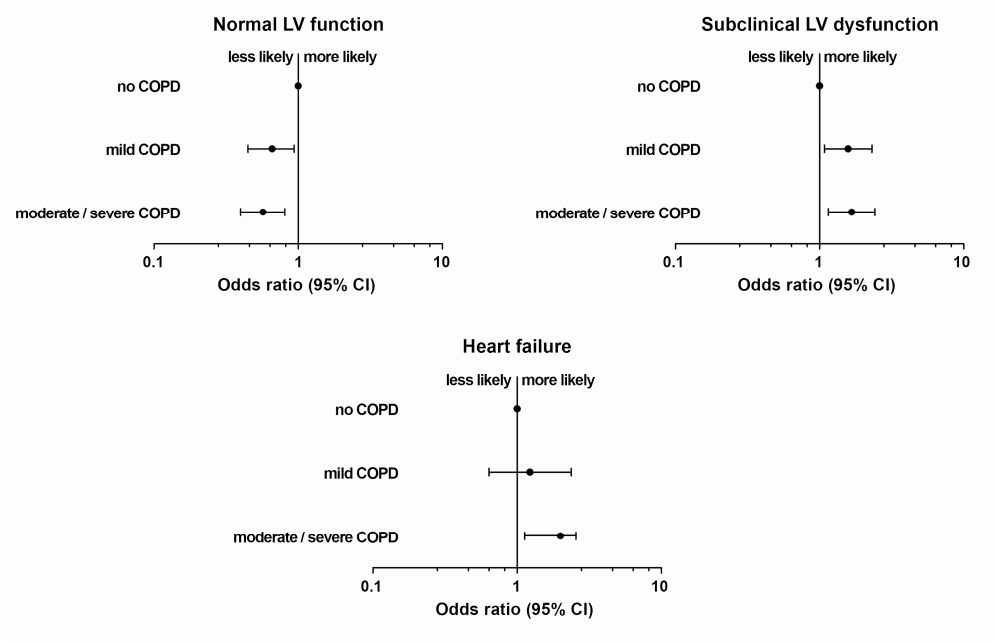
	No COPD, normal LV function	COPD	LV dysfunction	COPD, LV dysfunction	*p*-value
	[N=354]	[N=145]	[N=284]	[N=222]	
Demographics					
Age (± standard deviation)	64 (11)	68 (8)	69 (10)	71 (9)	<0.01
Male (%)	245 (69)	118 (81)	214 (75)	192 (87)	<0.01
Medical history (%)					
Ischemic heart disease	104 (29)	61 (42)	141 (50)	124 (56)	<0.01
Cerebrovascular disease	134 (38)	35 (24)	122 (43)	62 (28)	<0.01
Abdominal aortic disease	112 (32)	71 (49)	116 (41)	134 (60)	<0.01
Renal dysfunction	44 (12)	18 (12)	61 (22)	56 (25)	<0.01
Diabetes mellitus	109 (31)	32 (22)	89 (31)	67 (30)	0.190
Hypertension	207 (59)	87 (60)	209 (74)	155 (70)	<0.01
Hypercholesterolemia	219 (67)	84 (60)	182 (67)	124 (57)	0.056
Smoker, current	145 (41)	80 (55)	99 (35)	96 (43)	0.001
Medication (%)					
β-blockers	246 (70)	122 (84)	220 (78)	190 (86)	<0.01
Statins	253 (72)	99 (68)	209 (74)	157 (71)	0.703
Aspirin	222 (63)	81 (56)	160 (56)	125 (56)	0.263
Oral anticoagulants	45 (13)	16 (10)	64 (23)	39 (18)	0.002
ACE inhibitors	90 (25)	39 (27)	108 (38)	73 (33)	0.004
ARB	42 (12)	25 (17)	51 (18)	29 (13)	0.201
Diuretics	62 (18)	33 (23)	91 (32)	68 (31)	<0.01
Corticosteroids	17 (5)	39 (27)	21 (7)	47 (21)	<0.01
Bronchodilators	14 (4)	44 (30)	17 (6)	69 (31)	<0.01

Angiotensine-converting enzyme (ACE), angiotensin-receptor blocker (ARB), chronic obstructive pulmonary disease (COPD), left ventricular (LV).

Association between COPD, left ventricular dysfunction and long-term follow-up

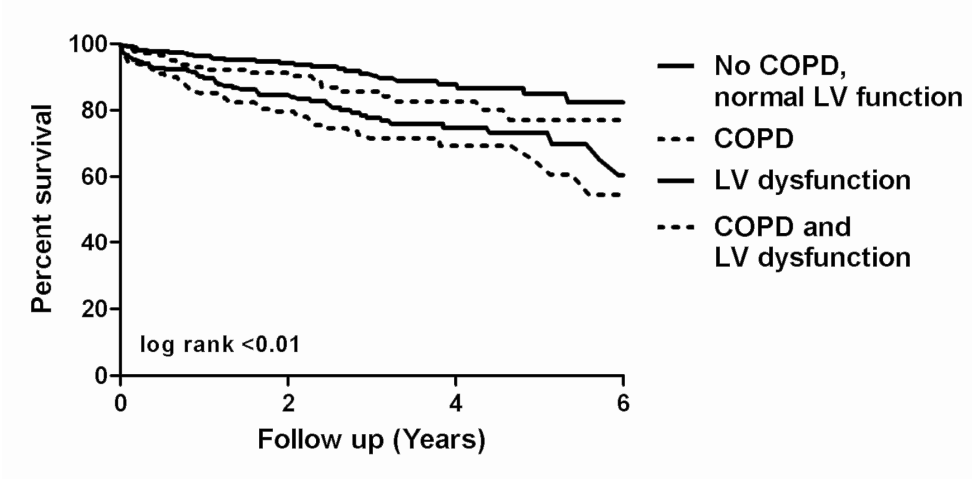
During follow-up, 164 (16%) patients died of whom 77 (47%) patients had COPD. Mortality rate in patients with normal pulmonary + normal LV function was 8%, in those with COPD was 15%, in those with LV dysfunction was 20%, and in patients with COPD + LV dysfunction was 25% ($p < 0.01$). Cumulative 6-year survival rates according to pulmonary and LV function (log rank $p < 0.01$) are shown in *Figure 3*. Of the COPD patients who died during follow-up, 26 (34%) patients had mild COPD and 51 (66%) patients had moderate/severe COPD. A cardiovascular cause of death could be attributed in 54/77 (70%), 19/26 (73%), and 34/51 (67%) patients with no-, mild- or moderate/severe COPD, respectively ($p = 0.351$).

Figure 2: Association between chronic obstructive pulmonary disease and left ventricular function.



Chronic obstructive pulmonary disease (COPD), left ventricular (LV).

Figure 3: Cumulative six-year survival.



Chronic obstructive pulmonary disease (COPD), left ventricular (LV).

Mild COPD

Patients with mild COPD + normal LV function did not have an increased risk for all-cause mortality (HR 1.0, 95%-CI: 0.4 to 2.1), compared with patients with normal pulmonary and LV function. However, patients with mild COPD + subclinical LV dysfunction had an increased risk for all-cause mortality with an HR of 1.7 (95%-CI: 1.1 to 3.6). Patients with mild COPD + overt heart failure had the highest risk for all-cause mortality with an HR of 2.7 (95%-CI: 1.2 to 5.9). These results are shown in *Table 2*.

Moderate/severe COPD

Patients with moderate/severe COPD had an increased risk for all-cause mortality, compared with patients with normal pulmonary function (HR 2.2, 95%-CI: 1.3 to 4.5). Hazard ratio was 2.5 (95%-CI: 1.5 to 4.7) for patients with moderate/severe COPD and subclinical LV dysfunction, and 3.8 (95%-CI: 1.6 to 9.1) for patients with overt heart failure. These results are shown in *Table 2*.

Table 2 **Association between COPD, LV function and long-term all-cause mortality**

				Univariate		Multivariate	
COPD	**LV function**	**N**	**(%)**	**HR**	**95%-CI**	**HR**	**95%-CI**
No	normal	29/354	(8)	reference		reference	
Mild	normal	7/71	(10)	1.2	0.5-2.6	1.0	0.4-2.1
	subclinical dysfunction	13/85	(15)	2.1	1.2-4.1	1.7	1.1-3.6
	heart failure	6/19	(32)	4.5	2.2-9.4	2.7	1.2-5.9
Moderate/severe	normal	15/74	(20)	3.0	1.7-5.4	2.2	1.3-4.5
	subclinical dysfunction	23/86	(27)	3.3	1.8-6.0	2.5	1.5-4.7
	heart failure	13/32	(41)	6.1	2.8-13.4	3.8	1.6-9.1

Multivariate analyses adjusted for: age, gender, ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus, hypertension, hypercholesterolemia, and smoking status. Chronic obstructive pulmonary disease (COPD), hazard ratio (HR), left ventricular (LV).

COPD and Revised Cardiac Risk index

Multivariate analyses demonstrated that mild COPD was not associated with an increased risk for long-term all-cause mortality (HR 1.0, 95%-CI: 0.6 to 1.6), in addition to RCR risk factors. However, moderate/severe COPD was associated with an increased risk for long-term all-cause mortality (HR 1.7, 95%-CI: 1.2 to 2.5), in addition to the RCR risk factors.

DISCUSSION

The present study showed that both mild and moderate/severe COPD are associated with an increased risk of LV dysfunction in vascular surgery patients. Approximately one out of three patients had COPD and in more than half of these patients, LV dysfunction was also present.

In COPD patients with LV dysfunction, thre out of four patients had subclinical LV dysfunction. Both mild and moderate/severe COPD patients, who had subclinical LV dysfunction, were at increased risk for all-cause mortality compared with COPD patients with normal LV function.

Several studies have been performed to evaluate the co-existence between moderate/severe COPD and heart failure. In 2005, Rutten *et al.* evaluated the prevalence of heart failure in COPD patients aged above 65 years during periods of clinical stability. They reported that heart failure was present in 20.5% of these moderate/severe COPD patients,[3] and concluded that the prevalence of heart failure in stable COPD patients may be four times higher than in the general population of individuals over 65 years of age.[3, 13] In another observational study, Macchia *et al.* showed that one out of four patients with heart failure, among a cohort of 1,020 heart failure patients, were also on treatment for COPD. In addition, the presence of COPD reduced the survival of these heart failure patients.[4] The prevalence of LV dysfunction in COPD patients may be increased because both disorders share similar risk factors, such as age, male gender and smoking,[14] or because of systemic inflammation and oxidative stress associated with chronic lung disease.

While preoperative cardiac risk indices, such as the widely used RCR index, are used for more than three decades,[12, 15-17] the development and implementation of preoperative pulmonary risk indices has been complicated by conflicting results from multiple studies addressing this issue.[18-20] However, as stated in a systematic review regarding 'preoperative pulmonary risk stratification for non-cardiothoracic surgery' performed by Smetana *et al,* postoperative pulmonary complications are equally prevalent and contribute similarly to (i) morbidity, (ii) mortality, and (iii) length of hospital stay of surgical patients, in comparison with cardiac complications.[21] Among 15 studies reported in this review article, 13 studies demonstrated that COPD was the most frequently identified risk factor for postoperative pulmonary complications.[21] In preoperative risk stratification of patients undergoing abdominal aortic aneurysm repair, both COPD and heart failure have been adapted as strong risk factors for adverse postoperative events.[22-24] One could therefore ask the question whether it is advisable to use separated cardiac and pulmonary risk indices. Especially, since it is known that COPD and heart failure often co-exist and, as we have shown in the present study that (i) mild COPD and subclinical LV dysfunction often co-exist as well, (ii) the combination of these two is associated with an increased risk for long-term all-cause mortality, and (iii) moderate/severe COPD is independently associated with an increased risk for long-term all-cause mortality, in addition to the RCR index. An important question remains if diagnosing and treatment of pulmonary and LV dysfunction will lead to improved long-term outcome. To address this issue, a randomized, controlled trial including vascular surgery patients undergoing standard preoperative spirometry and echocardiography, could provide us with final answers addressing preoperative risk using an 'integrated cardio-pulmonary risk index'.

Potential limitations of these data merit consideration. First, the study population consisted of patients referred to a tertiary referral center and may not fully represent a general population scheduled for elective vascular surgery. Second, although two experienced investigators performed off-line assessments of the obtained ultrasound images, we cannot rule out interobserver variability to have had minor influence on our results. Third, not all patients did have a preoperative pulmonary function test. In those patients who did not have a pulmonary function test, the diagnosis of COPD was based on symptoms and use of pulmonary medication.

The present study demonstrated that both mild and moderate/severe COPD were associated with an increased risk for subclinical LV dysfunction in patients undergoing vascular surgery. Patients with mild and moderate/severe COPD who had subclinical LV dysfunction were at increased risk for all-cause mortality, compared with COPD patients with normal LV function. These data suggest that preoperative echocardiography may be useful to detect subclinical cardiovascular disease and risk stratify COPD patients undergoing vascular surgery.

REFERENCES

1. Mangano. Peri-operative cardiovascular morbidity: new developments. *Ballieres Clin Anaesthesiol* 1999;13:335-348.

2. Mangano DT. Perioperative medicine: NHLBI working group deliberations and recommendations. *J Cardiothorac Vasc Anesth*. 2004;18(1):1-6.

3. Rutten FH, Cramer MJ, Grobbee DE, et al. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. *Eur Heart J*. 2005;26(18):1887-1894.

4. Macchia A, Monte S, Romero M, et al. The prognostic influence of chronic obstructive pulmonary disease in patients hospitalised for chronic heart failure. *Eur J Heart Fail*. 2007;9(9):942-948.

5. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2007;176(6):532-555.

6. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. *Eur J Echocardiogr*. 2006;7(2):79-108.

7. Stamm RB, Carabello BA, Mayers DL, et al. Two-dimensional echocardiographic measurement of left ventricular ejection fraction: prospective analysis of what constitutes an adequate determination. *Am Heart J*. 1982;104(1):136-144.

8. Quinones MA, Otto CM, Stoddard M, et al. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2002;15(2):167-184.

9. Dickstein. ESC Guidelines for the diagnosing and treatment of acute and chronic heart failure 2008. *Eur Heart J*. 2008;10:1093.

10. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr*. 2009;10(2):165-193.

11. Persson H, Lonn E, Edner M, et al. Diastolic dysfunction in heart failure with preserved systolic function: need for objective evidence:results from the CHARM Echocardiographic Substudy-CHARMES. *J Am Coll Cardiol*. 2007;49(6):687-694.

12. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100(10):1043-1049.

13. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol.* 2004;43(3):317-327.

14. Sin DD, McAlister FA, Man SF, et al. Contemporary management of chronic obstructive pulmonary disease: scientific review. *Jama.* 2003;290(17):2301-2312.

15. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med.* 1977;297(16):845-850.

16. Detsky AS, Abrams HB, Forbath N, et al. Cardiac assessment for patients undergoing noncardiac surgery. A multifactorial clinical risk index. *Arch Intern Med.* 1986;146(11):2131-2134.

17. Boersma E, Kertai MD, Schouten O, et al. Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index. *Am J Med.* 2005;118(10):1134-1141.

18. Fan ST, Lau WY, Yip WC, et al. Prediction of postoperative pulmonary complications in oesophagogastric cancer surgery. *Br J Surg.* 1987;74(5):408-410.

19. Epstein SK, Faling LJ, Daly BD, et al. Predicting complications after pulmonary resection. Preoperative exercise testing vs a multifactorial cardiopulmonary risk index. *Chest.* 1993;104(3):694-700.

20. Melendez JA, Carlon VA. Cardiopulmonary risk index does not predict complications after thoracic surgery. *Chest.* 1998;114(1):69-75.

21. Smetana GW, Lawrence VA, Cornell JE. Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American College of Physicians. *Ann Intern Med.* 2006;144(8):581-595.

22. Steyerberg EW, Kievit J, de Mol Van Otterloo JC, et al. Perioperative mortality of elective abdominal aortic aneurysm surgery. A clinical prediction rule based on literature and individual patient data. *Arch Intern Med.* 1995;155(18):1998-2004.

23. Johnston KW. Multicenter prospective study of nonruptured abdominal aortic aneurysm. Part II. Variables predicting morbidity and mortality. *J Vasc Surg.* 1989;9(3):437-447.

24. Brady AR, Fowkes FG, Greenhalgh RM, et al. Risk factors for postoperative death following elective surgical repair of abdominal aortic aneurysm: results from the UK Small Aneurysm Trial. On behalf of the UK Small Aneurysm Trial participants. *Br J Surg.* 2000;87(6):742-749.

Chapter 7

Prognostic value of left ventricular function and C-reactive protein measured by a high-sensitive method in vascular surgery patients

Submitted

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ABSTRACT

Background Left ventricular (LV) function and high-sensitive C-Reactive Protein (hs-CRP) independently predict cardiac events. The prognostic value of LV dysfunction in patients with normal or elevated hs-CRP is less well understood. The present study evaluated the combined prognostic value of LV function and hs-CRP towards cardiac outcome of vascular surgery patients and the impact of optimal pharmacological treatment.

Methods Echocardiography was performed preoperatively in 1,116 consecutive vascular surgery patients. Using a 17-segment wall motion score index (WMSI), LV function was categorized as normal (WMSI 1 to 1.5), mildly hypokinetic (WMSI >1.52.5) and severely hypokinetic (WMSI >2.5). Hs-CRP was measured in all patients and concentrations >6.5 mg/L were considered elevated, after receiver operating curve analyses. Perioperative troponin T measurements and electrocardiograms were performed routinely. Study endpoints were perioperative cardiac events and long-term mortality. Multivariate regression analyses evaluated the relation between LV function, hs-CRP, standard pharmacological treatment (statins, β-blockers, angiotensin blocking agents) and postoperative outcome.

Results WMSI >1.5 was associated with an increased risk for perioperative cardiac events and long-term mortality, in patients with normal (OR 2.54, 95%-CI: 1.21 to 3.08 and HR 2.10, 95%-CI: 1.08 to 3.12) or elevated hs-CRP (OR 1.84, 95%-CI: 1.29 to 3.73 and HR 2.18, 95%-CI: 1.05 to 2.88). WMSI >1.5 + elevated hs-CRP was associated with the highest risk for perioperative cardiac events or long-term mortality (OR 1.63, 95%-CI: 1.43 to 4.85 and HR 2.37, 95%-CI: 2.81 to 6.11). Standard pharmacological treatment of WMSI >1.5 was associated with improved long-term survival in patients with normal (HR 0.34, 95%-CI: 0.17 to 0.81) or elevated hs-CRP (HR 0.61, 95%-CI: 0.42 to 0.82).

Conclusions The present study demonstrated that LV dysfunction is predictive for postoperative outcome of vascular surgery patients with normal or elevated hs-CRP. Furthermore, increased hs-CRP has additional value to predict postoperative outcome of patients with LV dysfunction. Finally, standard pharmacological treatment of LV dysfunction improved long-term outcome.

INTRODUCTION

Vascular surgery patients are at increased risk for perioperative cardiac events.[1] Over the years, several cardiac risk indices have been developed for preoperative risk stratification.[2, 3] In patients with ≥1 cardiac risk factor, echocardiography should be considered before surgery.[4, 5] In addition, the resting wall motion score index (WMSI), which is widely accepted in evaluating left ventricular (LV) function, has a prognostic value in the prediction of cardiovascular outcome of patients with ischemic heart disease.[6-9]

Biochemical markers, such as high sensitive C-reactive protein (hs-CRP), are increasingly used in cardiac risk stratification. Elevated hs-CRP concentrations reflect an inflammatory state associated with atherosclerosis.[10] In addition, elevated hs-CRP concentrations are associated with an increased risk for cardiac events in patients with and without coronary artery disease.[11-14] Therefore, we hypothesized that WMSI and hs-CRP could have an independent prognostic value in the prediction of future cardiac events. The aim of the present study, performed in vascular surgery patients with normal or elevated hs-CRP, was to evaluate the prognostic value of LV function for postoperative outcome using the WMSI and to address the impact of standard pharmacological treatment for LV dysfunction on long-term survival.

METHODS

Study population

The study population consisted of 1,116 consecutive patients undergoing vascular surgery during the period between 2002 and 2009. The study was performed at the Erasmus Medical Center in Rotterdam, a tertiary hospital in the Netherlands. The study was approved by the hospital's ethics committee and performed with informed consent of all patients.

Baseline characteristics

Before surgery, a detailed history was obtained from every patient. Clinical data included: age, gender, ischemic heart disease (defined as a history myocardial infarction, coronary revascularization or the presence of pathologic Q-waves on preoperative electrocardiogram), cerebrovascular disease (defined as a history of ischemic or hemorrhagic stroke), renal dysfunction (serum creatinine >2.0 mg/dL), diabetes mellitus (fasting blood glucose ≥6.1 mmol/L or requirement of anti-diabetic medication), hypertension (blood pressure ≥140/90 mmHg in non-diabetics and ≥130/80 mmHg in diabetics or requirement of antihypertensive medication), hypercholesterolemia (history of hypercholesterolemia or low density lipoprotein cholesterol >3.5 mmol/L), chronic obstructive pulmonary disease (history of chronic obstructive pulmonary disease or according the Global Initiative on Obstructive Lung Diseases classification),[15] and smoking status. The use of prescription medications was recorded and

included β-blockers, statins, aspirin, oral anticoagulants, angiotensin blocking agents (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), and diuretics.

Biomarkers

Serial troponin T measurements (Roche Diagnostics, Mannheim, Germany) were obtained from all patients before surgery, postoperatively on day 1, 3, 7 and before discharge. Troponin T concentrations >0.03 ng/mL were considered to be elevated.[16] Patients with elevated troponin T concentrations before surgery were not included in the study. Peripheral blood samples for hs-CRP were routinely performed one day before surgery. C-Reactive Protein was measured by a high-sensitive nephelometric assay on a Beckman-Immage analyzer (Beckman-Coulter, Fullerton, California, USA). Optimal specificity and sensitivity of hs-CRP to predict postoperative outcome was calculated using receiver operating curve analyses and a cut off value ≥6.5 mg/L was used in the analyses.

Wall motion score at rest

Preoperatively, transthoracic echocardiography was performed in all patients using a handheld Acuson Cypress Ultrasound System (7V3c transducer). Standard parasternal and apical two- and four-chamber views were obtained during rest with the patient in the left lateral decubitus position as recommended.[17] Wall motion abnormalities were determined using the 17-segment model as recommended by the 'American Society of Echocardiography'.[18] Systolic motion of each segment was graded as follows: 1 = normal, 2 = mild to moderate hypokinesis (reduced wall thickening and excursion), 3 = severe hypokinesis (marked reduced wall thickening and excursion), 4 = akinesis (no wall thickening and excursion), 5 = dyskinesis (paradoxical wall motion away from the center of the left ventricle during systole).[19] If a segment was not visualized because of echo dropout or technical reasons, the score was not given for this segment. Wall motion score index at rest was calculated as the cumulative sum of the scores from each segment divided by the number of segments visualized. Wall motion was categorized normal (WMSI 1 to 1.5 ~ LV ejection fraction >54%), mildly hypokinetic (WMSI >1.5 to 2.5 ~ LV ejection fraction 28 to 53%), severely hypokinetic WMSI >2.5 ~ LV ejection fraction <28%).[20, 21]

Study outcomes

Main study endpoints were perioperative cardiac events (defined as nonfatal myocardial ischemia or infarction up to 30 days after surgery) and long-term mortality. Myocardial ischemia was diagnosed in patients with normal preoperative and elevated troponin T concentrations postoperatively.[16] Elevated troponin T concentrations in combination with electrocardiographic changes (new onset ST-T changes and pathological Q waves) or symptoms of angina pectoris defined myocardial infarction.[22] Long-term mortality was assessed by reviewing the municipal civil registries. Median follow-up was 2 years (interquartile range 1 to 3). Standard pharmacological management of wall motion abnormalities and

cardiovascular risk reduction was considered to be treatment with statins in combination with β-blockers and angiotensin blocking agents.[23, 24]

Statistical analysis

Dichotomous data are described as numbers and percentages. Continuous variables are described as means ± standard deviation (SD) or as median ± interquartile range. Continuous data were compared using ANOVA and categorical data were compared using a χ^2 test. Logistic regression analyses were performed to evaluate the relationship between WMSI and hs-CRP with perioperative myocardial damage. To study the influence of hsCRP on the WMSI groups, interactions terms between hsCRP and WMSI were used. Cox regression analyses were performed to evaluate the relationship between WMSI and hs-CRP with long-term mortality. Cumulative long-term survival was determined using the Kaplan-Meier method. Multivariate regression analyses were adjusted for age, gender, ischemic heart disease, renal dysfunction, diabetes mellitus, hypercholesterolemia, hypertension, smoking, chronic obstructive pulmonary disease and high-risk surgery (Model 1). In Model 2, multivariate regression analyses were adjusted for medication use and the risk factors described in model 1. We report both the crude and the adjusted odds and hazard ratios (OR and HR) with their 95% confidence interval (95%-CI). To evaluate the effect of standard medical treatment (statins + β-blockers or angiotensin blocking agents) on long-term outcome, multivariate Cox regression analyses were performed with propensity score adjustment for optimal medical treatment. Variables used in Model 1 were included in the propensity score model. For all tests, a *p*-value <0.05 (two-sided) was considered significant. All analyses were performed using SPSS version 15.0 statistical software (SPSS, Inc., IL, USA). No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the article, and its final contents.

RESULTS

Study population

A total of 1,116 patients undergoing lower extremity artery (N=387), carotid artery (N=465) and abdominal aorta (N=264) repair were included in the study. Endovascular surgery comprised 35% of the procedures. The majority of patients were men (77%) and the mean age was 67 ± 10 years. A WMSI >1.5 was detected in 474 (42%) patients, of which 268 (57%) patients had a WMSI >1.5 to 2.5 and 206 (43%) patients had a WMSI >2.5. Baseline characteristics stratified to WMSI are provided in *Table 1*. A WMSI >1.5 was associated with increased age and male gender. Ischemic heart disease, renal dysfunction, diabetes mellitus, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, and smoking were associated with WMSI >1.5 as well. In addition, usage of β-blockers, oral anticoagulants, angiotensin blocking agents, and diuretics was higher in patients with a WMSI >1.5. Median

level of hs-CRP was 4.9 (± 6.3) and hs-CRP was elevated (≥6.5 mg/L) in 395 (35%) patients. The distribution of elevated hs-CRP was not significantly different between the WMSI groups.

Table 1 **Baseline characteristics stratified to wall motion score index**

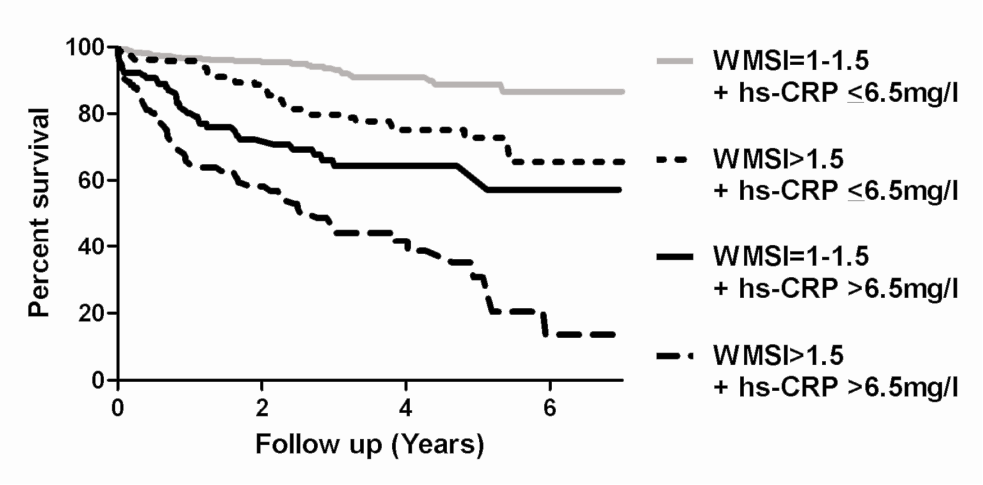
	WMSI 1-1.5	WMSI >1.5	*p*-value
	[N=642]	[N=474]	
Demographics			
Age (± SD)	66 (11)	70 (9)	<0.001
Male (%)	454 (71)	474 (84)	<0.001
Systolic blood pressure (± SD)	142 (24)	139 (24)	0.109
Diastolic blood pressure (± SD)	79 (12)	79 (12)	0.314
Heart rate (± SD)	71 (13)	72 (13)	0.114
Medical history (%)			
Ischemic heart disease	160 (25)	260 (55)	<0.001
Cerebrovascular disease	226 (35)	171 (36)	0.763
Renal dysfunction	89 (14)	104 (22)	<0.001
Diabetes mellitus	120 (19)	118 (25)	0.012
Hypertension	387 (60)	337 (71)	<0.001
Hypercholesterolemia	280 (44)	247 (52)	0.005
Chronic obstructive pulmonary disease	185 (29)	184 (37)	<0.001
Smoker, current	286 (45)	184 (39)	0.035
Surgery type (%)			
Open	401 (63)	316 (67)	0.147
Medication (%)			
β-blockers	475 (74)	370 (78)	0.032
Statins	459 (72)	368 (78)	0.021
Aspirin	374 (58)	293 (62)	0.231
Oral anticoagulants	82 (13)	96 (20)	0.001
Angiotensin receptor blocking agents	219 (38)	204 (49)	0.001
Diuretics	134 (21)	153 (32)	<0.001

High-sensitive C-reactive protein (hs-CRP), standard deviation (SD), wall motion score index (WMSI).

Postoperative outcome

The study endpoint of perioperative cardiac events was reached in 194 (17%) patients and 182 (16%) patients died during follow-up. Cumulative long-term survival stratified to WMSI and hs-CRP is provided in *Figure 1*. Multivariate regression analyses demonstrated that WMSI >1.5 was associated with an increased risk of perioperative myocardial damage (OR 1.84, 95%-CI: 1.10 to 2.89) and long-term mortality (HR 1.72, 95%-CI: 1.09 to 2.77) as depicted in *Table 2*. In addition, elevated hs-CRP was associated with an increased risk of perioperative myocardial damage (OR 2.00, 95%-CI: 1.19 to 3.37) and long-term mortality (HR 2.55, 95%-CI: 1.39 to 3.56). Patient with WMSI >1.5 and elevated hs-CRP had the highest risk for perioperative myocardial damage or long-term mortality (OR 4.16, 95%-CI: 2.54 to 6.81 and HR 4.10, 95%-CI: 2.64 to 6.37, respectively). Interaction terms were used to identify the direct influence of hsCRP on the relation between WMSI and survival rates, and no direct interaction was observed between the different WMSI groups and hsCRP with respect to long-term survival.

Figure 1: Wall motion score index and hs-CRP: cumulative long-term survival.



High-sensitive C-reactive protein (hs-CRP), wall motion score index (WMSI).

Table 2 **Wall motion score index and hs-CRP: postoperative outcome**

				Model 1*		Model 2**	
30-day myocardial damage		**N**	**(%)**	**OR**	**[95%-CI]**	**OR**	**[95%-CI]**
WMSI 1-1.5	hs-CRP ≤6.5 mg/L	38/431	(9)	reference		reference	
WMSI 1-1.5	hs-CRP >6.5 mg/L	37/211	(18)	2.05	1.23-3.43	2.00	1.19-3.37
WMSI >1.5	hs-CRP ≤6.5 mg/L	51/290	(18)	1.83	1.13-3.00	1.84	1.10-2.89
WMSI >1.5	hs-CRP >6.5 mg/L	68/184	(37)	4.45	2.74-7.23	4.16	2.54-6.81
Long-term mortality		**N**	**(%)**	**HR**	**[95%-CI]**	**HR**	**[95%-CI]**
WMSI 1-1.5	hs-CRP ≤6.5 mg/L	33/431	(8)	reference		reference	
WMSI 1-1.5	hs-CRP >6.5 mg/L	42/211	(20)	2.76	1.73-4.39	2.55	1.39-3.56
WMSI >1.5	hs-CRP ≤6.5 mg/L	39/290	(13)	1.80	1.11-2.90	1.72	1.09-2.77
WMSI >1.5	hs-CRP >6.5 mg/L	68/184	(37)	4.19	2.72-6.47	4.10	2.64-6.37

** Model 1: adjusted for age, gender, ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus, hypercholesterolemia, hypertension, smoking, chronic obstructive pulmonary disease and high risk surgery. ** Model 2: adjusted risk factors described in model 1 and the use of β-blocker, statines, aspirin, angiotensin-converting enzyme inhibitors and diuretics. Confidence interval (CI), hazard ratio (HR), high-sensitive C-reactive protein (hs-CRP), odds ratio (OR), wall motion score index (WMSI).*

In patients with normal hs-CRP, WMSI >1.5 was associated with increased risk for perioperative cardiac events and long-term mortality with an OR of 2.54 (95%-CI: 1.21 to 3.08) and a HR of 2.10 (95%-CI: 1.08 to 3.12). A sub-analysis was performed to assess the separate predictive values of a WMSI >1.5 to 2.5 and a WMSI >2.5. This analysis demonstrated that both were associated with an increased risk for perioperative myocardial damage (OR 1.86, 95%-CI: 1.28 to 3.57 and OR 3.31, 95%-CI: 3.01 to 5.13) and long-term

mortality (HR 1.96, 95%-CI: 1.16 to 3.34 and HR 2.38, 95%-CI: 1.31 to 4.03), respectively (*Table 3*).

In patients with elevated hs-CRP; WMSI >1.5 was associated with increased risk for perioperative cardiac events and long-term mortality with an OR of 1.84 (95%-CI: 1.29 to 3.73) and a HR of 2.18 (95%-CI: 1.05 to 2.88). A sub-analysis was performed to assess the predictive value of WMSI >1.5 to 2.5 and WMSI >2.5, which demonstrated that both were associated with an increased risk for perioperative myocardial damage (OR 1.63, 95%-CI: 1.43 to 4.85 and OR 2.37, 95%-CI: 2.81 to 6.11) and long-term mortality (HR 1.61, 95%-CI: 1.19 to 3.06 and HR 2.65, 95%-CI: 2.24 to 4.02), respectively (*Table 3*).

Table 3 **Wall motion score index and postoperative outcome, categorized according to hs-CRP levels ≤6.5 and >6.5 mg/L**

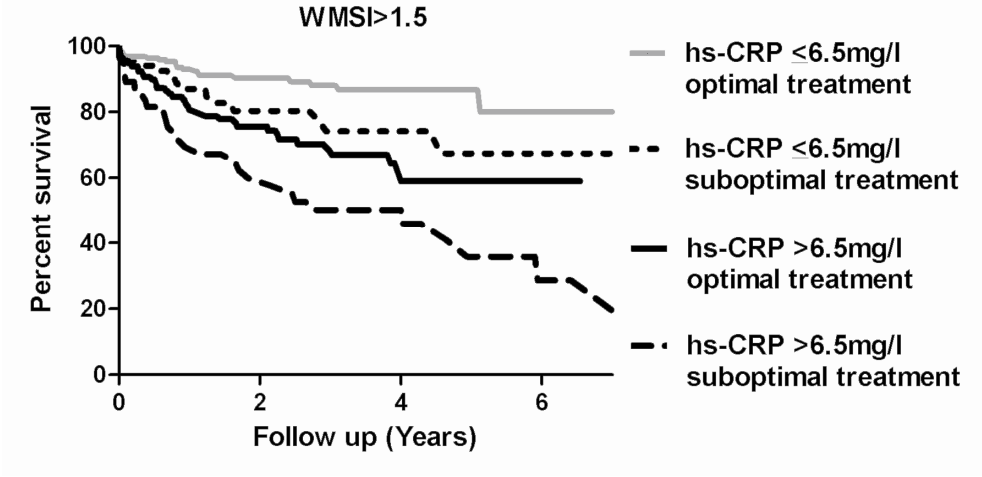
			Model 1*		Model 2**	
30-day myocardial damage	**N**	**(%)**	**OR**	**[95%-CI]**	**OR**	**[95%-CI]**
hs-CRP ≤6.5 mg/L						
WMSI 1-1.5	35/433	(8)	reference		reference	
WMSI >1.5-2.5	24/166	(15)	1.92	1.18-3.50	1.86	1.28-3.57
WMSI >2.5	30/124	(24)	3.24	2.98-4.90	3.31	3.01-5.13
hs-CRP >6.5 mg/L						
WMSI 1-1.5	39/211	(19)	reference		reference	
WMSI >1.5-2.5	32/102	(31)	1.71	1.52-4.97	1.63	1.43-4.85
WMSI >2.5	34/82	(42)	2.48	2.66-5.67	2.37	2.81-6.11
Long-term mortality	**N**	**(%)**	**HR**	**[95%-CI]**	**HR**	**[95%-CI]**
hs-CRP ≤6.5 mg/L						
WMSI 1-1.5	28/433	(6)	reference		reference	
WMSI >1.5-2.5	21/166	(13)	2.20	1.31-3.67	1.96	1.16-3.34
WMSI >2.5	23/124	(19)	3.43	1.48-4.29	3.38	1.31-4.03
hs-CRP >6.5 mg/L						
WMSI 1-1.5	41/211	(19)	reference		reference	
WMSI >1.5-2.5	33/102	(32)	1.67	1.26-3.32	1.61	1.19-3.06
WMSI >2.5	36/82	(44)	2.71	2.13-4.89	2.65	2.24-4.02

** Model 1: adjusted for age, gender, ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus, hypercholesterolemia, hypertension, smoking, chronic obstructive pulmonary disease and high risk surgery. ** Model 2: adjusted risk factors described in model 1 and the use of β-blocker, statines, aspirin, angiotensin-converting enzyme inhibitors and diuretics. Confidence interval (CI), hazard ratio (HR), high-sensitive C-reactive protein (hs-CRP), odds ratio (OR), wall motion score index (WMSI).*

WMSI >1 and standard pharmacological treatment

Of the patients with WMSI >1.5 + normal hs-CRP (N=290), 113 (40%) patients received standard pharmacological treatment (statins + β-blockers + angiotensin blocking agents). In addition, 60/184 (33%) patients with WMSI >1.5 + elevated hs-CRP received standard pharmacological treatment. Cumulative long-term survival of patients with WMSI >1.5 stratified by (i) normal or elevated hs-CRP and (ii) receiving standard or suboptimal pharmacological treatment is demonstrated in *Figure 2*. Standard pharmacological treatment was associated with improved long-term survival in patients with normal (HR 0.34, 95%-CI: 0.17 to 0.81) and elevated hs-CRP (HR 0.61, 95%-CI: 0.42 to 0.82), compared with patients receiving suboptimal pharmacological treatment, as demonstrated in *Table 4*.

Figure 2: Medical treatment in patients with WMSI >1.5: cumulative long-term survival.



High-sensitive C-reactive protein (hs-CRP), wall motion score index (WMSI).

DISCUSSION

Our results indicate that LV dysfunction is predictive for perioperative cardiac events and long-term mortality of vascular surgery patients with normal or elevated hs-CRP. Furthermore, elevated hs-CRP has additional prognostic value of patients with LV dysfunction, to predict postoperative cardiac outcome. Finally, optimal pharmacological treatment of LV dysfunction improved long-term outcome of patients with normal or elevated hs-CRP.

Table 4 **Medical treatment in patients with wall motion score index >1.5: influence on long-term mortality**

			Model 1*		Model 2**	
hs-CRP ≤6.5 mg/L	**N**	**(%)**	**OR**	**[95%-CI]**	**OR**	**[95%-CI]**
Suboptimal medication	18/69	(26)	reference		reference	
Optimal medication	21/221	(10)	0.39	0.18-0.82	0.39	0.18-0.81
hs-CRP >6.5 mg/L	**N**	**(%)**	**OR**	**[95%-CI]**	**OR**	**[95%-CI]**
Suboptimal medication	32/54	(59)	reference		reference	
Optimal medication	36/130	(28)	0.52	0.31-0.88	0.51	0.30-0.86

** Model 1: adjusted for age, gender, ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus, hypercholesterolemia, hypertension, smoking, chronic obstructive pulmonary disease and high risk surgery. ** Model 2: adjusted risk factors described in model 1 and the use of β-blocker, statines, aspirin, angiotensin-converting enzyme inhibitors and diuretics. Confidence interval (CI), hazard ratio (HR), high-sensitive C-reactive protein (hs-CRP), odds ratio (OR), wall motion score index (WMSI).*

Atherosclerosis is a systemic inflammatory disease of the vasculature, known to affect multiple sections of the arterial tree, such as the lower extremity-, abdominal aortic-, carotid- and coronary arteries, simultaneously.[25] Coronary atherosclerosis causes gradual reduction of the vascular cross-sectional area resulting in coronary artery stenosis. Coronary artery stenosis is an important cause of postoperative morbidity and mortality in the vascular surgery population.[26] During vascular surgery there is an increased myocardial oxygen-demand due to high catecholamine production.[1] Intra-operative increases of myocardial oxygen-demand can therefore lead to an oxygen-supply and demand imbalance, in patients with coronary artery stenosis, and subsequent reduced myocardial blood supply. This imbalance will lead to ischemia characterized by metabolic changes, regional systolic wall motion abnormalities and global systolic left ventricular dysfunction at a later stage.[27] Preoperative risk assessment of vascular surgery patients provides information on the likelihood of the occurrence of postoperative cardiac events. Potential tools for preoperative risk assessment are cardiac risk indices,[2, 3] (stress) echocardiography,[28, 29] and biomarkers.[30]

Previous studies have shown that a WMSI at rest has prognostic value to predict adverse outcome, in patients with ischemic heart disease or heart failure.[6-9] Carluccio *et al.* demonstrated that a WMSI >1.5 at rest was a powerful predictor of adverse cardiac events after a first acute myocardial infarction.[6] In addition, Madsen *et al.* demonstrated that resting WMSI >1.3 provided independent prognostic information on survival of patients with congestive heart failure.[8] In line with these studies we found that a WMSI >1.5 at rest was associated with an increased risk for perioperative myocardial damage and long-term mortality.

C-Reactive Protein is an inflammatory marker of atherosclerosis and is found within atherosclerotic plaques of both coronary and peripheral arterial vessels. The median level of hs-CRP has been found to be significantly higher in patients who later develop cardiac events

compared with patients with normal hs-CRP.[13, 30] A patient's individual risk for future cardiovascular disease can therefore be stratified according to their hs-CRP concentrations [31]. We found that hs-CRP >6.5 mg/L was associated with an increased risk for perioperative cardiac events and long-term mortality. In addition, the current study is the first to evaluate the prognostic implications of a WMSI at rest in vascular surgery patients, with a focus on patients with normal or elevated hs-CRP, separately. We found that a WMSI >1.5 at rest was associated with perioperative myocardial damage and long-term mortality in both hs-CRP groups. Importantly, increased hs-CRP has additional value to predict postoperative outcome in patients with LV dysfunction. As a marker of inflammatory state, it indicates for ongoing processes which can influence the general condition, especially in patients with LV dysfunction.

Comprehensive prognostic risk stratification provides an overall framework for physicians to identify risk factors and to help make predictions based on these risk factors. Prognostic information help the clinician in the decision for targeted treatment interventions. Appropriate patient management, therefore, should not only include the assessment of the perioperative cardiac risk, it should however include therapeutic strategies to decrease the risk even more. Our results provide an indication that postoperative survival of patients with a WMSI >1.5 is improved in patients receiving pharmacological treatment with statins in combination with (i) β-blockers or (ii) angiotensin blocking agents, both in patients with normal hs-CRP as in patients with increased hs-CRP. Although patients with a WMSI >1.5 in combination with increased hs-CRP have worst survival, optimal medical treatment might improve the outcome of these patients.

Our results suggest that preoperative risk stratification should not solely include cardiac risk indices. The assessment of the WMSI and hs-CRP could provide the clinician with a guide regarding the presence or absence of coronary artery disease and severity of the atherosclerotic process, both associated with increased risk of perioperative myocardial damage and long-term mortality.

Potential limitations of these data merit consideration. First, the study population consisted of patients referred to a tertiary referral center and may not fully represent a general population scheduled for elective vascular surgery. Second, although two experienced investigators performed an off-line assessment of the ultrasound images, we cannot rule out interobserver variability to have had a minor influence on our results. Third, the current study was not designed as a randomized, controlled trial to evaluate the impact of pharmacological treatment of a WMSI >1.5.

The present study demonstrated that LV dysfunction is predictive for postoperative outcome of vascular surgery patients with normal or elevated hs-CRP. Furthermore, elevated hs-CRP has additional value to predict postoperative outcome of patients with LV

dysfunction. Finally, optimal pharmacological treatment of LV dysfunction improved long-term outcome of patients with normal or elevated hs-CRP. Our data suggest that routine use of cardiac echo and hs-CRP measurements might improve (i) risk stratification and (ii) long-term survival of vascular surgery patients.

REFERENCES

1. Mangano DT. Perioperative cardiac morbidity. *Anesthesiology.* 1990;72(1):153-184.

2. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med.* 1977;297(16):845-850.

3. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation.* 1999;100(10):1043-1049.

4. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol.* 2007;50(17):e159-241.

5. Poldermans D, Bax JJ, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: The Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur Heart J.* 2009.

6. Carluccio E, Tommasi S, Bentivoglio M, et al. Usefulness of the severity and extent of wall motion abnormalities as prognostic markers of an adverse outcome after a first myocardial infarction treated with thrombolytic therapy. *Am J Cardiol.* 2000;85(4):411-415.

7. Fleischmann KE, Lee TH, Come PC, et al. Echocardiographic prediction of complications in patients with chest pain. *Am J Cardiol.* 1997;79(3):292-298.

8. Madsen BK, Videbaek R, Stokholm H, et al. Prognostic value of echocardiography in 190 patients with chronic congestive heart failure. A comparison with New York Heart Association functional classes and radionuclide ventriculography. *Cardiology.* 1996;87(3):250-256.

9. Stein JH, Neumann A, Preston LM, et al. Improved risk stratification in unstable angina: identification of patients at low risk for in-hospital cardiac events by admission echocardiography. *Clin Cardiol.* 1998;21(10):725-730.

10. Tsimikas S, Willerson JT, Ridker PM. C-reactive protein and other emerging blood biomarkers to optimize risk stratification of vulnerable patients. *J Am Coll Cardiol.* 2006;47(8 Suppl):C19-31.

11. Morrow DA, Rifai N, Antman EM, et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. Thrombolysis in Myocardial Infarction. *J Am Coll Cardiol.* 1998;31(7):1460-1465.

12. Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med.* 1997;336(14):973-979.

13. McDermott MM, Lloyd-Jones DM. The role of biomarkers and genetics in peripheral arterial disease. *J Am Coll Cardiol.* 2009;54(14):1228-1237.

14. Ridker PM, Danielson E, Fonseca FA, et al. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. *Lancet.* 2009;373(9670):1175-1182.

15. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med.* 2007;176(6):532-555.

16. Aviles RJ, Askari AT, Lindahl B, et al. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. *N Engl J Med.* 2002;346(26):2047-2052.

17. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr.* 2005;18(12):1440-1463.

18. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr.* 1989;2(5):358-367.

19. Chaudhry FA, Tauke JT, Alessandrini RS, et al. Prognostic implications of myocardial contractile reserve in patients with coronary artery disease and left ventricular dysfunction. *J Am Coll Cardiol.* 1999;34(3):730-738.

20. Feigenbaum H, Armstrong WF, Ryan T. *Feigenbaum's Echocardiography.* 6 ed; 2004.

21. Lebeau R, Di Lorenzo M, Amyot R, et al. A new tool for estimating left ventricular ejection fraction derived from wall motion score index. *Can J Cardiol.* 2003;19(4):397-404.

22. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *Eur Heart J.* 2007;28(20):2525-2538.

23. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *J Am Coll Cardiol.* 2006;47(6):1239-1312.

24. Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol.* 2009;53(15):e1-e90.

25. Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. *Circulation.* 2004;109(21 Suppl 1):II2-10.

26. Mangano DT, Goldman L. Preoperative assessment of patients with known or suspected coronary disease. *N Engl J Med.* 1995;333(26):1750-1756.

27. Nesto RW, Kowalchuk GJ. The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. *Am J Cardiol.* 1987;59(7):23C-30C.

28. Poldermans D, Arnese M, Fioretti PM, et al. Improved cardiac risk stratification in major vascular surgery with dobutamine-atropine stress echocardiography. *J Am Coll Cardiol.* 1995;26(3):648-653.

29. Sicari R, Ripoli A, Picano E, et al. Perioperative prognostic value of dipyridamole echocardiography in vascular surgery: A large-scale multicenter study in 509 patients. EPIC (Echo Persantine International Cooperative) Study Group. *Circulation.* 1999;100(19 Suppl):II269-274.

30. Howard-Alpe GM, Sear JW, Foex P. Methods of detecting atherosclerosis in non-cardiac surgical patients; the role of biochemical markers. *Br J Anaesth.* 2006;97(6):758-769.

31. Koenig W, Sund M, Frohlich M, et al. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA

(Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation*. 1999;99(2):237-242.

Chapter 8

The relation between preoperative and intraoperative new wall motion abnormalities in vascular surgery patients: a transesophageal echocardiographic study

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ABSTRACT

Background Coronary revascularization of the suspected culprit coronary lesion assessed by preoperative stress testing is not associated with improved outcome of vascular surgery patients.

Methods Fifty-four major vascular surgical patients underwent preoperative dobutamine echocardiography and intraoperative transesophageal echocardiography. The locations of left ventricular rest wall motion abnormalities and new wall motion abnormalities (NWMAs) were scored using a seven-wall model. During 30-day follow-up, postoperative cardiac troponin release, myocardial infarction, and cardiac death were noted.

Results Rest wall motion abnormalities were noted by dobutamine echocardiography in 17 patients (31%), and by transesophageal echocardiography in 16 patients (30%). NWMAs were induced during dobutamine stress echocardiography in 17 patients (31%), whereas NWMAs were observed by transesophageal echocardiography in 23 patients (43%), κ-value = 0.65. Although preoperative and intraoperative rest wall motion abnormalities showed an excellent agreement for the location (κ-value = 0.92), the agreement for preoperative and intraoperative NWMAs in different locations was poor (κ-value = 0.26 to 0.44). The composite cardiac endpoint occurred in 14 patients (26%).

Conclusions There was a poor correlation between the locations of preoperatively assessed stress-induced NWMAs by dobutamine echocardiography and those observed intraoperatively using transesophageal echocardiography. However, the composite endpoint of outcome was met more frequently in relation with intraoperative NWMAs.

INTRODUCTION

Vascular surgical patients represent a population at increased risk for developing postoperative adverse cardiac outcome.[1, 2] Cardiac stress testing before surgery is widely used to identify patients at increased risk for postoperative cardiac events. Recently, prophylactic coronary revascularization was studied in vascular surgery patients.[3] However, revascularization of the suspected intraoperative culprit coronary lesion, assessed by preoperative testing, was not associated with improved outcome.

Although the pathophysiology of perioperative myocardial infarction (MI) is not entirely clear, it is now well accepted that coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion, is an important cause. This is similar to the nonsurgical setting. The surgical stress response includes a catecholamine surge with associated hemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation, and consequent hypercoagulability.[4] In patients with significant coronary artery disease (CAD), MI may also be caused by a sustained myocardial supply or demand mismatch due to tachycardia and increased myocardial contractility. The association of postoperative MI with myocardial ischemia and nontransmural or circumferential subendocardial infarction supports this mechanism. Although transmural ischemia is considered to be relatively uncommon, half of all fatalities have direct evidence of plaque disruption defined as fissure or rupture of plaque and hemorrhage into the plaque cavity.[5-7]

The use of intraoperative transesophageal echocardiography (TEE) recognized a high prevalence of transient myocardial ischemic episodes causing regional wall motion abnormalities (WMAs) in patients undergoing major noncardiac surgery and requiring vigilant monitoring for serious cardiac outcome.[8-10] Those transient events reflect the balancing effects of coronary reserve and myocardial viability vs. a multifactorial perioperative ischemic load (burden). Different detection modalities, such as persantine-thallium scintigraphy and electrocardiography were compared with intraoperative TEE in detecting ischemia with inconclusive results.[11, 12] However, the location of ischemic events has never been a primary goal in all previous investigations.

Our hypothesis is that, although dobutamine echocardiography (DE) can identify patients at risk, the location of the cardiac event is difficult to foresee because of the unpredictable plaque rupture of non-significant, vulnerable, coronary artery lesions. In this study, we matched preoperative assessed ischemic left ventricular (LV) territories using DE and intraoperatively observed new wall motion abnormalities (NWMAs) using TEE to examine the chance of reproducibility of a NWMA at the same location pre- and intraoperatively. This matching correlation would be more emphasizing if perioperative NWMAs were predictive of postoperative cardiac outcomes.

MATERIAL AND METHODS

Study participants

In this prospective cohort study, patients older than 40 years scheduled for noncardiac vascular surgery at Erasmus University Medical Center, Rotterdam, the Netherlands, between June 2005 and September 2008 were candidates for inclusion. Patients had to be scheduled for abdominal aortic aneurysm repair, abdominal aortic stenosis surgery, or lower limb arterial reconstruction. We used the Lee's Revised Cardiac Risk index, which included a history of ischemic heart disease, heart failure, cerebrovascular accidents, insulin therapy for diabetes mellitus, and renal disease with serum creatinine >2.0 mg/dL, to abbreviate the cardiac risk factors and to identify patients at risk.[13] All patients underwent DE before surgery. Exclusion criteria for the study were the inability to retrieve adequate echocardiographic views pre- or intraoperatively. After approval from the medical ethics committee board and after obtaining informed consent from the patients, we included 54 consecutive adult patients.

Dobutamine echocardiography

All patients underwent DE to evaluate LV wall motion using dobutamine (± atropine) as a stressor. Two-dimensional echocardiography was performed at rest using Hewlett-Packard Sonos 1000 echo apparatus (*Hewlett-Packard*, Andover, MA) with 2.5- and 3.5-MHz transducers. The technique yielded standard parasternal and apical echocardiographic views under basal conditions and throughout graded dobutamine infusion. A stepwise incremental dose of dobutamine was administered, beginning at 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and increased by 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ every 3 min until a definite endpoint was attained.[14-16] During the dobutamine infusion, heart rate, blood pressure, and electrocardiography were monitored. When the target heart rate (85% of maximum age- and gender-predicted heart rate) was not obtained at the maximum dobutamine dose (40 $\mu g \cdot kg^{-1} \cdot min^{-1}$), atropine (0.25 to 1.0 mg) was administered.[15, 17] Test endpoints were achievement of (i) target heart rate, (ii) maximal dose of dobutamine and atropine, (iii) extensive NWMAs, (iv) more than 2 mV downsloping ST-segment depression measured 80 ms after the J-point compared with the baseline, (v) hypertension (blood pressure >240/120 mmHg), (vi) a decrease in systolic blood pressure of more than 40 mmHg compared with at rest, (vii) significant arrhythmias, or (viii) any intolerable adverse effects considered to be the result of dobutamine or atropine. An intravenous β-blocker (metoprolol 1 to 5 mg) was available to reverse the adverse effects of dobutamine/atropine. The test was completed only after all ischemic regions had returned to baseline.

Transesophageal echocardiography

After induction of anesthesia and endotracheal intubation, the TEE probe was inserted. We based our TEE examination on the recommendations of the 'American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists' guidelines for performing a comprehensive intraoperative multiplane TEE examination.[18] The LV wall motion was monitored in six views, namely, three

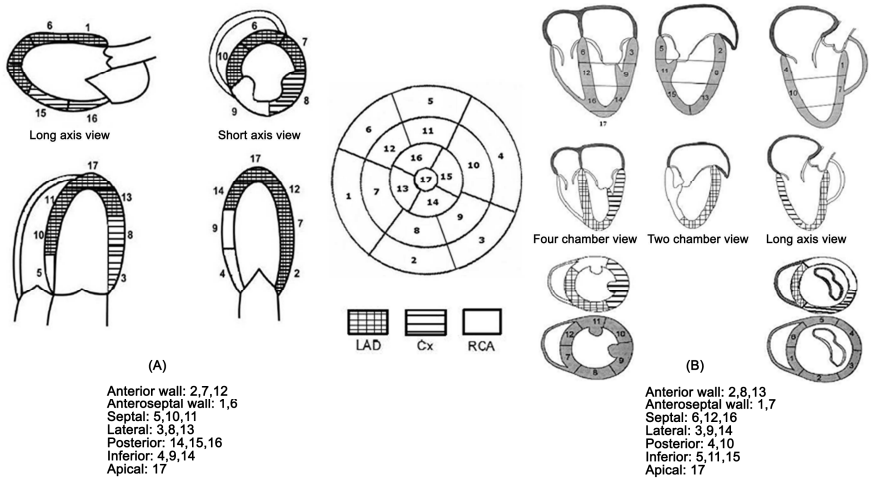
midesophageal views (the four-chamber midesophageal view, the midesophageal two-chamber view, and the midesophageal long-axis view) and three transgastric views (basal, midpapillary, and apical transgastric views). Baseline images of the LV in short- and long-axis were acquired and tape-recorded for offline analysis. The TEE probe depth and imaging planes of the basal views were noted to reproduce equivalent views intraoperatively. To improve the detection of intraoperative NWMAs, we adopted a semicontinuous method, keeping the TEE probe in the transgastric position with the midpapillary LV short-axis view continuously displayed and repeating the whole set of the examination views every 10 minutes and whenever there was echocardiographic suspicion of (i) NWMAs, (ii) hemodynamic change, or (iii) surgical maneuver requiring special attention. For safety reasons, echocardiographic monitoring was freezed whenever the probe temperature exceeded 37.5°C, which allowed the probe to cool down shortly.

Transesophageal echocardiography images were obtained using a standard adult 5-MHz multiplane transesophageal probe (GE LOGIQ 500 Probe, model H4552TB; General Electric, Stockton, CA) and the VingMed® System 5 Echocardiographic Imaging System (General Electric-VingMed Ultrasound, Horton, Norway). The main investigator was responsible for intraoperative image acquisition and passed a comprehensive training in transesophageal echocardiography in the study institute and performed 150 comprehensive TEE examinations as recommended by the 'American society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists'.[18] The occurrences of LV NWMAs, as well as the segmental location of each abnormality, were recorded for each patient. The training physicians (anesthesiologists and surgeons) were blinded to intraoperative echocardiographic findings except if significant NWMAs (involving more than four segments) necessitating immediate management were apparent on the screen.

Interpretation of echocardiographic views

Dobutamine echocardiography test results and intraoperative TEE recordings were scored for rest WMAs and NWMAs using a 17-segment model as proposed by the 'American Society of Echocardiography' and interpreted accordingly into a seven-wall LV model.[19-21] Transcription of LV segments to their LV wall involvement was performed as shown in *Figure 1,* redrawn based on the illustrations of LV wall in the transthoracic echocardiography reports recommended by our institute and in the recommendation of the 'American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists' for the comprehensive TEE examination.[18]

Figure 1: Left ventricular (LV) myocardial segmentation for echocardiographic wall motion analysis with corresponding disitribution of coronary arterial blood supply, showing segmental distribution of the seven LV walls in dobutamine echocardiography (A) and in transesophageal echocardiography (B).



Circumflex artery (Cx), left anterior descending coronary artery (LAD), right coronary artery (RCA).

A five-point scale was used for wall motion analysis: 1 = normal, 2 = mild-moderate hypokinesis, 3 = severely hypokinetic, 4 = akinesis, 5 = dyskinetic, as used earlier.[14-17] Recorded echocardiographic loops were displayed simultaneously with rest images in a cine-loop format for interpretation. All images were analyzed at one time by two experienced readers blinded to clinical, electrocardiography, or other perioperative patient data. A NWMA was interpreted whenever a new or worsening regional LV motion was observed. Normal wall motion or an unchanged rest WMA was not considered for myocardial ischemia. Disagreements in interpretation were resolved by consensus.

Definition of endpoints

All patients were monitored postoperatively for the development of adverse cardiac events. Standard electrocardiography and cardiac troponin T (cTnT) were serially measured after surgery on days 1, 3, 7, and 30, or at discharge. Tests were repeated when patients had symptoms and/or signs of clinical myocardial ischemia. Troponin T level was measured by an electrochemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostics, Mannheim, Germany). The recommended lower limit of 0.03 ng/mL was used to define positive troponin T levels because lower levels do not meet the imprecision criteria of less than 10%.

The study endpoint was the combination of elevated cTnT, MI, and cardiac death. Criteria for MI diagnosis included at least two of the following: cTnT ≥0.1 ng/mL, typical electrocardiographic changes (new Q waves >1 mm or >30 ms in electrocardiogram), and typical chest pain complaints. Cardiac death was defined as fatal MI (postmortem evidence of acute MI or definite criteria for MI within the 24 h before death) and sudden cardiac death. Sudden cardiac death was defined as unexpected natural death due to cardiac causes, within 1 h of the onset of acute symptoms.

Statistical analysis

Categoric variables are expressed as percentages and were compared using the Pearson's χ^2 test. Continuous variables are presented as mean (± SD) and were compared using the unpaired Student t-test. Correlation between DE and intraoperative TEE results in different LV locations was tested by means of kappa statistic ($\varkappa$), to verify whether a paired rest WMA or NWMA locality, estimated by both techniques, might differ from agreement that could occur by chance alone. The $\varkappa$ measure of agreement between two observations ranges between 0 and 1 (0 = chance agreement, less than 0.4 = poor agreement, 0.4 to 0.75 = fair to good agreement, and more than 0.75 = excellent agreement). The measured $\varkappa$ value is presented in table or text. For all tests, a *p*-value <0.05 (two-sided) was considered significant. All analyses were performed using the syntax commands of SPSS® v15.0 statistical package for Windows® (SPSS Inc., Chicago, IL).

RESULTS

Fifty-four consecutive patients were enrolled in the study. Preoperative baseline clinical characteristics, including baseline echocardiographic variables, are shown in *Table 1*. None of the examined patients had pacing devices. Operative characteristics are shown in *Table 2*. We excluded six eligible patients from our study: two because of inability to insert the TEE probe that encountered resistance and four cases because of improper visualization of standard echo views mentioned in the methods.

Dobutamine echocardiography and TEE showed rest WMAs in 17 (31%) and 16 (30%) patients, respectively: $\varkappa$ value on patient base = 0.92. The agreement for location of rest WMAs was excellent: $\varkappa$ range = 0.77 to 1.0. Stress-induced NWMAs during DE occurred in 17 patients (31%), whereas intraoperative NWMAs were observed by TEE in 23 patients (43%): $\varkappa$ value on patient base = 0.65. However, the agreement for location of NWMAs, using a seven-wall model was poor: $\varkappa$ range = 0.26 to 0.44. Echocardiographic locations of NWMAs are presented in *Figure 2* and *Table 3*. $\varkappa$ value for interobserver variability for the different LV walls ranged between 0.91 and 0.98. A random sample of 10 patients was selected and rescored for LV wall motion by each scoring investigator. Intraobserver $\varkappa$ value for the different LV walls ranged between 0.97 and 1.00.

Table 1 **Baseline and perioperative patient characteristics in all and sub-populations, based on the acquisition of a perioperative NWMA**

	Preoperative dobutamine echocardiography			Intraoperative transesophageal echocardiogeraphy		
	NWMA absent	NWMA present	*p*-value	NWMA absent	NWMA present	*p*-value
	[N=17]	[N=37]		[N=23]	[N=31]	
Demographics (mean ± SD)						
Age	70 (12	64 (12)	NS	71 (12)	61 (11)	< 0.05
Male (%)	15 (88)	33 (89)	NS	20 (87)	28 (90)	NS
Medical history (%)						
Angina pectoris	6 (46)	7 (54)	NS	10 (44)	3 (10)	NS
Myocardial infarction	10 (59)	14 (38)	NS	14 (61)	10 (32)	< 0.05
Coronary revascularization [a]	6 (43)	7 (57)	NS	7 (30)	7 (23)	NS
Stroke	5 (29)	6 (16)	NS	7 (30)	4 (13)	NS
Diabetes mellitus [b]	8 (47)	4 (11)	< 0.05	6 (26)	6 (19)	NS
Renal dysfunction [c]	5 (29)	3 (8)	< 0.05	6 (26)	2 (7)	< 0.05
Hypertension [d]	11 (65)	23 (62)	NS	15 (65)	19 (61)	NS
Hypercholesterolemia	13 (77)	16 (43)	< 0.05	15 (65)	14 (45)	NS
COPD	8 (47)	14 (38)	NS	13 (57)	9 (29)	< 0.05
Congestive heart failure	0 (0)	3 (8)	NS	3 (13)	0 (0)	< 0.05
Echocardiography (mean ± SD)						
LV hypertrophy (%)	9 (53)	14 (38)	NS	14 (61)	9 (29)	NS
Ejection fraction	45 (10)	48 (7)	NS	45 (6)	45 (5)	NS
Fractional area change	44 (8)	43 (8)	NS	45 (9)	43 (8)	NS
Fraction shortening	25 (5)	28 (5)	NS	26 (4)	27 (6)	NS
ASA physical status classification (%)						
ASA class I	0 (0)	3 (8)	NS	0 (0)	3 (10)	NS
ASA class II	4 (24)	9 (24)	NS	5 (22)	8 (26)	NS
ASA class III	8 (47)	21 (57)	NS	12 (52)	17 (55)	NS
ASA class IV	5 (29)	4 (11)	NS	6 (26)	3 (10)	NS
Revised Cardiac Risk factors (%)						
I	0 (0)	17 (46)	0.001	2 (9)	15 (48)	< 0.05
II	3 (18)	11 (30)	NS	6 (26)	8 (26)	NS
≥ III	14 (61)	9 (39)	< 0.001	15 (65)	8 (26)	< 0.01
Medication (%)						
β-blockers	17 (100)	37 (100)	NS	23 (100)	31 (100)	NS
Statins	14 (82)	15 (41)	< 0.05	16 (70)	13 (42)	< 0.05
ACE inhibitors	7 (41)	6 (16)	< 0.05	9 (39)	4 (13)	< 0.05
Calcium-channel blockers	6 (35)	3 (8)	< 0.05	6 (26)	3 (10)	NS
Aspirin	11 (65)	24 (65)	NS	14 (61)	21 (68)	NS
Nitrates	1 (6)	1 (3)	NS	2 (9)	0 (0)	NS
Diuretics	5 (29)	7 (19)	NS	8 (35)	4 (13)	NS

[a] Coronary artery bypass graft surgery and/or percutaneous coronary intervention procedures. [b] Fasting blood sugar ≥7 mmol/L or use of hypoglycemic agents. [c] Serum creatinine level ≥2.0 mg/dL [177 mmol/L] or requirement of dialysis. [d] Arterial blood pressure ≥140/90 mmHg or use of antihypertensive drugs. Continuous variables are shown as mean (±SD), while dichotomous variables are shown as number (% of column totals). American Society of Anesthesiologists (ASA), chronic obstructive pulmonary disease (COPD), left ventricular (LV), new wall motion abnormality (NWMA), non significant (NS), standard deviation (SD).

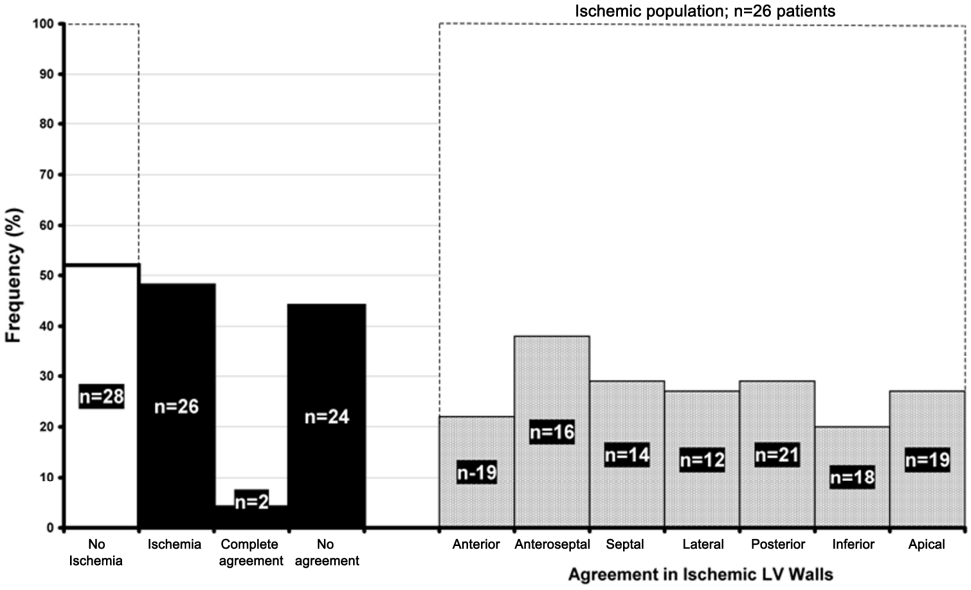
Table 2 **Population operative characteristics with respect to the distribution of hemodynamic covariates on the acquisition of a perioperative NWMA**

		All patients	Intraoperative transesophageal echocardiogeraphy		
			NWMA absent	NWMA present	*p*-value
		[N=54]	[N=23]	[N=31]	
Anesthetic technique					
General anesthesia	(%)	31 (57)	10 (44)	21 (68)	NS
Combined anesthesia	(%)	23 (43)	13 (57)	10 (32)	NS
Surgical procedure					
Open aortic prosthetic repair	(%)	34 (63)	17 (74)	17 (55)	NS
Clamping duration (minute)	(mean ± SD)	49.4 (54.6)	52.4 (45.1)	47.9 (55.7)	NS
Lower extremity revascularization	(%)	20 (38)	6 (26)	14 (45)	NS
Procedure duration (minute)	(mean ± SD)	267 (72)	275 (45)	265 (64)	NS
Operative blood loss (liter)	(median ± IQR)	0.5 (.6-1.9)	0.6 (.2-1.9)	0.5 (.4-1.8)	NS
Intraoperative fluid administration					
Crystalloids (liter)	(mean ± SD)	4.0 (.2)	4.6 (2.9)	3.8 (1.9)	NS
Colloids (liter)	(mean ± SD)	1.5 (.8)	1.6 (.8)	1.4 (.7)	NS
Packed cells (units)	(mean ± SD)	4.3 (1.5)	3.8 (1.8)	4.5 (1.2)	NS
Plasma in (units)	(mean ± SD)	3.0 (1.0)	2.5 (1.1)	3.1 (.8)	NS
Cell-saver blood (units)	(median ± IQR)	0.4 (.3-1.2)	0.4 (.2-1.0)	0.6 (.3-1.4)	NS
Hemodynamic variables					
Heart rate (bpm)	(mean ± SD)	67.1 (11.9)	69.6 (11.5)	66.5 (7.7)	NS
Mean arterial pressure (mmHG)	(mean ± SD)	77.7 (13.4)	80.5 (11.5)	73.2 (15.4)	NS
Intraoperative urine output (liter)	(median ± IQR)	0.5 (.4-.7)	0.7 (.5-.8)	0.6 (.4-.7)	NS

Interquartile range (IQR), new wall motion abnormality (NWMA), non significant (NS), standard deviation (SD).

During 30-day follow-up, the composite endpoint occurred in 15 patients (28%); cTnT release in 14 (26%), MI in 6 (11%), and cardiac death in 3 (6%) (*Table 4*). Of these 15 patients, 10 (67%) experienced both pre- and intraoperative NWMAs, whereas in 4 (27%), only intraoperative NWMAs were observed. Troponin release was observed in only one patient (7%) without pre- and intraoperative NWMAs. This patient did not experience ischemic symptoms or electrocardiographic abnormalities. The relation of pre- and intraoperative NWMAs and postoperative outcome is presented in *Table 4*. In all six patients who experienced a postoperative MI, the location of electrocardiographic changes matched with the intraoperatively observed NWMAs by TEE, whereas in 2 patients (33%), there was an agreement with the preoperatively induced ischemia during DE.

Figure 2: Agreement for location in ischemic left ventricular (LV) walls between pre- and intraoperative echocardiography.



During 30-day follow-up the composite endpoint occurred in 15 (28%) patients; cTnT release in 14 (26%), MI in 6 (11%), and cardiac death in 3 (6%), (*Table 4*). In these 15 patients, 10 (67%) experienced both pre and intraoperative NWMAs, while in 4 patients (27%) only intraoperative NWMAs were observed. In only one patient (7%) without pre- and intraoperative NWMAs, troponin release was observed. This patient did not experience ischemic symptoms or electrocardiographic abnormalities. The relation of preoperative and intraoperative NWMAs and postoperative outcome is presented in *Table 4*. In all 6 patients who experienced a postoperative MI, the location of electrocardiographic changes matched with the intraoperatively observed NWMAs by TEE, while in 2 (33%) there was an agreement with the preoperative induced ischemia during DE.

Figure 3 represents the subdivision of the total population according to pre- and intraoperative development of NWMAs and postoperative cardiac outcome. The presence of multivessel CAD as detected by DE and intraoperatively by TEE was in favor of a composite outcome ($p < 0.05$ for DE and $p = 0.001$ for intraoperative TEE) but not a single-vessel disease (p = NS). In *Table 5*, we present the calculated diagnostic indices of both preoperative DE and intraoperative TEE for the study outcomes.

Table 3 **Agreement for the association and locality distribution of (i) rest and (ii) ischemic LV walls presenting with WMAs during preoperative DE and intraoperative TEE**

	Preoperative dobutamine echocardiography	Intraoperative transesophageal echocardiography	*K*
	N (%)	N (%)	
Patiens with rest WMA	17 (31)	16 (30)	0.917
Location			
Anterior wall	7 (41)	9 (56)	0.821
Antero-septal wall	10 (59)	12 (75)	0.843
Septal wall	11 (65)	11 (69)	1.0
Lateral wall	7 (41)	9 (56)	0.821
Posterior wall	7 (41)	7 (44)	1.0
Inferior wall	9 (53)	9 (56)	1.0
Apical wall	13 (76)	10 (63)	0.769
Patients with NWMA	17 (31)	23 (89)	0.653
Location			
Anterior wall	5 (29)	6 (26)	0.292
Antero-septal wall	8 (47)	14 (61)	0.440
Septal wall	9 (53)	13 (57)	0.321
Lateral wall	5 (29)	9 (39)	0.351
Posterior wall	4 (24)	5 (22)	0.260
Inferior wall	4 (24)	8 (35)	0.395
Apical wall	9 (53)	4 (17)	0.351
Single vessel reversible ischemia	7 (41)	8 (35)	0.233
Multivessel reversible ischemia	10 (69)	15 (65)	0.336

Dobutamine echocardiography (DE), Kappa measurement value (K), left ventricular (LV), new wall motion abnormalities (NWMA), transesophageal echocardiography (TEE), wall motion abnormalities (WMA).

Table 4 **Postoperative patient outcomes according to ischemia wall agreement between pre- and intraoperative NWMAs**

	All patients	Preoperative dobutamine echocardiography			Intraoperative transesophageal echocardiogeraphy		
		NWMA absent	NWMA present	*p*-value	NWMA absent	NWMA present	*p*-value
	[N=54]	[N=17]	[N=37]		[N=23]	[N=31]	
Postoperative outcomes							
p.o. cTnT release	14 (26)	9 (53)	5 (14)	< 0.05	13 (57)	1 (3)	< 0.001
p.o. MI	6 (11)	6 (35)	0 (0)	< 0.001	6 (26)	0 (0)	< 0.05
Cardiac death	3 (6)	2 (12)	1 (3)	NS	3 (13)	0 (0)	< 0.05
Composite outcome	15 (28)	10 (59)	5 (14)	0.001	14 (61)	1 (3)	< 0.001

New wall motion abnormalities (NWMAs), postoperative cardiac troponin T (p.o. cTnT), postoperative myocardial infarction (p.o. MI).

Figure 3: Composite cardiac outcome according to perioperative new wall motion abormalities (NMWAs).

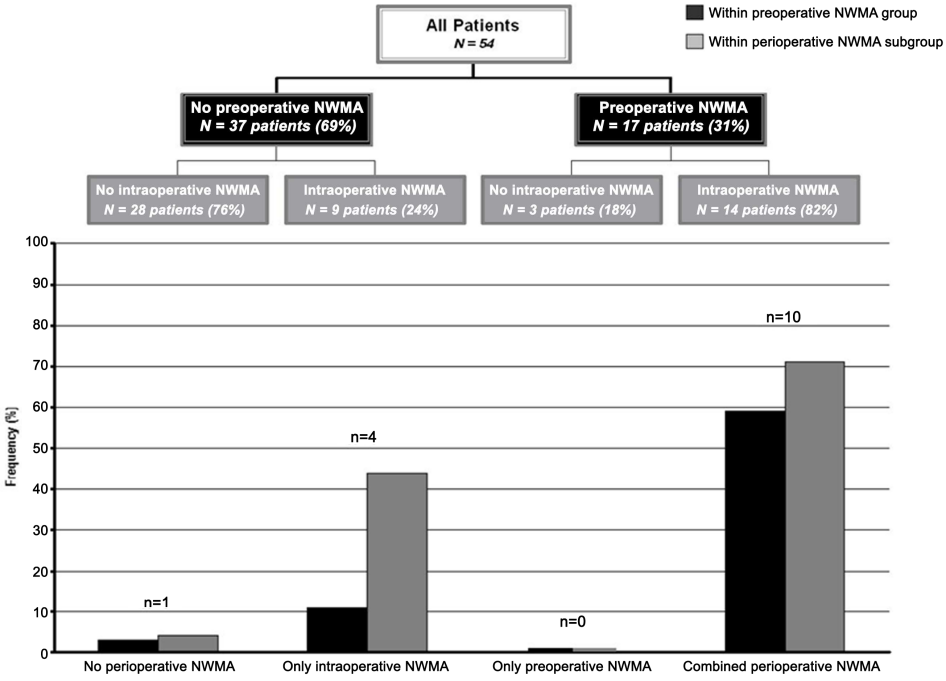


Table 5 **Sensitivity, specificity, positive, and negative predictive value of preoperative DE and intraoperative TEE for the study outcomes**

Echocardiographic technique	Intraoperative NWMA	p.o. cTnT	p.o. MI	Cardiac death	Composite endpoint
		Sensitivity			
DE	61%	64%	100%	67%	67%
TEE	-	93%	100%	100%	93%
		Specificity			
DE	90%	80%	77%	71%	82%
TEE	-	75%	65%	61%	77%
		Positive predictive value			
DE	82%	53%	35%	12%	59%
TEE	-	57%	26%	13%	61%
		Negative predictive value			
DE	76%	87%	100%	97%	87%
TEE	-	97%	100%	100%	97%

Dobutamine echocardiography (DE), postoperative cardiac troponin T (p.o. cTnT), postoperative myocardial infarction (p.o. MI), transesophageal echocardiography (TEE).

DISCUSSION

In this study, we used echocardiography to observe the location of NWMAs induced preoperatively during DE and those developed intraoperatively by TEE monitoring in 54 high-risk vascular surgery patients. By using the $\varkappa$ coefficient, we observed an excellent correlation between pre- and intraoperative rest WMAs ($\varkappa$ range 0.8 to 1.0), indicating concordance between pre- and intraoperative echocardiographic recordings. However, poor agreement correlations were found between pre- and intraoperative locations of NWMAs ($\varkappa$ range $\leq$0.4).

Although patients with severe and unstable CAD are warranted to undergo preoperative stress testing to direct towards the optimal prophylactic strategy, those who have stable CAD do not show much benefit from stress testing over clinical stratification. Dobutamine echocardiography, among other stress tests, accurately determines reversible ischemic regions. However, those tests have stronger negative than positive predictive power, particularly in the stable CAD population. Perioperative β-blockade has proven to be a sufficient prophylactic regime in such patients. In the current investigation, approximately 45% of our population presented with established CAD, 14% presented with two risk factors, and 43% presented with three or more risk factors among the Lee's Revised Cardiac Risk index, with fair LV function in average estimated by mean ejection fraction. This stratification puts this population in the gray zone of where optimized medical therapy is weighed against coronary revascularization. The purpose of this study was to determine which of the two prophylactic measures is optimal in order to provide better postoperative cardiac outcome.[22, 23]

Autopsy studies have shown the pathologic similarity of perioperative MI to that occurring in the nonoperative setting, however, they were unsuccessful in predicting the site of vulnerable plaque rupture in most instances of perioperative MI based on the severity of coronary stenosis.[6, 7] This means that selective targeting of isolated culprit plaques by means of a focused revascularization technique as a prophylactic measure cannot be used with adequate results.

Because of the high propensity of CAD in the peripheral arterial disease population requiring elective surgical intervention, preoperative cardiac evaluation might suggest an indication for coronary revascularization in those presenting with severe coronary artery stenosis.[5, 24, 25] Pooled data from previous studies were not favor of preoperative coronary revascularization before major noncardiac surgery. In the Coronay Artery Revascularization Prophylaxis (CARP)-trial, coronary arterial revascularization in 258 symptomatically stable patients with severe CAD, did not confer beneficial perioperative or long-term outcome compared with the control group (252 patients) before major vascular operations.[3] Similar findings were shown in the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE-V) randomized pilot study, in which 101 high-risk vascular surgery patients were randomized either to no intervention (N=52) or coronary

revascularization before vascular surgery (N=49).[26] The Coronary Artery Surgery Study (CASS)-trial investigators suggested similar conclusions when equivocal long-term outcomes were observed between coronary artery bypass graft surgery and intensive medical treatment patient groups.[27] These findings remained unchanged after 10 year of follow-up. Comparable results were shown by medical treatment, surgical treatment, or percutaneous coronary intervention.[28] Finally, reports of unwanted outcomes have been addressed for percutaneous coronary intervention before noncardiac surgery in the population at risk for CAD.[29, 30] Indeed, the reason that coronary artery bypass grafting was found superior to percutaneous coronary intervention before vascular surgery in one study, was the more extensive revascularization in the coronary artery bypass graft group.[31]

We reported postoperative cardiac outcomes as 26, 11 and 6% for postoperative cTnT release, MI, and cardiac death, respectively. These events were predictable by the induction of NWMAs by a DE stress test and even better predicted by the occurrence of intraoperative NWMAs. In our population, NWMAs induced during DE or detected intraoperatively by TEE presented more with multivessel CAD form, which was also correlated with the combined cardiac outcome ($p = 0.003$ for multivessel reversible ischemia by preoperative DE and $p = 0.001$ for multivessel reversible ischemia by intraoperative TEE) but not a single coronary vessel-related NWMAs (p = NS). This indicated the more extensive nature of CAD they had.

We found perfect matching of intraoperative NWMA location with postoperative electrocardiographic locality of MI, indicating the accumulation of most perioperative stressors on the vulnerable myocardium of the vascular surgery patient in the intraoperative phase exhausting the moribund coronary reserve around the end of surgery, which would hence yield most fatal MIs in the immediate postoperative phase up to 12 hours. This coincides with the well-established knowledge that more than 50% of perioperative MIs do occur in the immediate postoperative period and lead to recommending twice daily electrocardiography in the first postoperative day. In addition, we reported postoperative cTnT release in 14 patients (26%). In 8 (57%) of them, troponin release was not associated with MI. LeManach *et al.* found earlier postoperative abnormal troponin in a larger cohort of vascular surgical patients (14% of 1,136 patient population). Increased cardiac troponins were related to postoperative MI (in 35% of the patients with increased troponin levels) in two distinct fashions (early and late), indicating two different sets of myocardial stressors nearer and later from the end of surgery.[32] The prevalence of increased postoperative troponin in our study is similar to or even reduced to that reported in other research in similar populations.[25, 33, 34] Silent myocardial ischemic events would result from the effects of perioperative stressors in a myocardial demand or supply mismatch insufficient to progress to evident myocardial damage. This is supported by the finding that perioperative cTnT is related to poor long-term cardiac outcomes. This would explain the higher rates of subclinical ischemic events (increased cTnT or transient NWMAs) over harder cardiac events in our and other populations.[23, 25, 35]

Intraoperative TEE showed an additional incremental value on the prediction of postoperative cardiac events. Both preoperative NWMAs during DE and intraoperative NWMAs detected by TEE had a significant association with the composite cardiac outcome ($p < 0.001$). No events of cardiac death or postoperative MI occurred in patients without intraoperative NWMAs.

We had several limitations in this study. Some patients were excluded for either technical difficulty in image acquisition at any stage or inappropriate views to judge LV wall motion. We could not continue to enroll more patients because of time factors, limiting the level of power of our significant results, especially those related to the regression analysis. Some NWMAs were probably missed, particularly before probe insertion after the start of anesthesia induction. Coronary angiography was not clinically indicated preoperatively in the studied patients, and hence, we could not relate our findings to the more pathognomonic angiographic data. Some reversible segmental LV WMAs could have been missed in some views while obtaining others for offline analysis. Nevertheless, concomitant mechanical effects such as tethering by a coexisting myocardial scarring or ballooning effect during aortic cross-clamping would have influenced our judgment for a NWMA. Finally, $\varkappa$ measurement is a useful statistic to look for the chance of agreement between two sets of readings. However, it has few flaws, particularly its vulnerability towards difference in prevalence regardless a fixed specificity and sensitivity between the two readings, particularly when sophisticated variables and heterogenous examination groups are used.[36, 37]

In patients undergoing major vascular surgery, preoperative DE and intraoperative TEE monitoring of wall motion changes had good correlation with postoperative cardiac cTnT release and MI. However, TEE had a stronger association with all postoperative cardiac events. Reproducibility of WMAs in the same myocardial wall locations at different perioperative times was not achievable. This suggests the superiority of optimized medical therapies over the invasive interventions focused on particular culprit lesions for the prophylaxis against perioperative myocardial ischemia. In our population, receiving β-blocking medication, the higher predictive power of intraoperative TEE over preoperative DE for postoperative outcomes further emphasizes the importance of optimized medical treatment over preoperative cardiac testing in fairly stable populations with CAD.

REFERENCES

1. Mackey WC, Fleisher LA, Haider S, et al. Perioperative myocardial ischemic injury in high-risk vascular surgery patients: Incidence and clinical significance in a prospective clinical trial. *J Vasc Surg.* 2006;43:533-538.

2. Newman AB, Shemanski L, Manolio TA, et al. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. The Cardiovascular Health Study Group. *Arterioscler Thromb Vasc Biol.* 1999;19:538-545.

3. McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med.* 2004;351:2795-2804.

4. Sautter RD, Myers WO, Ray JF 3rd, et al: Relationship of fibrinolytic system to postoperative thrombotic phenomena. *Arch Surg.* 1973;107:292-296.

5. Ellis SG, Hertzer NR, Young JR,et al. Angiographic correlates of cardiac death and myocardial infarction complicating major nonthoracic vascular surgery. *Am J Cardiol.* 1996;77:1126-1128.

6. Dawood MM, Gutpa DK, Southern J, et al. Pathology of fatal perioperative myocardial infarction: Implications regarding pathophysiology and prevention. *Int J Cardiol.* 1996;57:37-44.

7. Cohen MC, Aretz TH. Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. *Cardiovasc Pathol.* 1999;8:133-139.

8. Gewertz BL, Kremser PC, Zarins CK, et al. Transesophageal echocardiographic monitoring of myocardial ischemia during vascular surgery. *J Vasc Surg.* 1987;5:607-713.

9. London MJ, Tubau JF, Wong MG, et al. The "natural history" of segmental wall motion abnormalities in patients undergoing noncardiac surgery. S.P.I. Research Group. *Anesthesiology.* 1990;73:644-655.

10. Koolen JJ, Visser CA, Reichert SL, et al. Improved monitoring of myocardial ischaemia during major vascular surgery using transoesophageal echocardiography. *Eur Heart J.* 1992;13:1028-1033.

11. Mangano DT, London MJ, Tubau JF, et al. Dipyridamole thallium-201 scintigraphy as a preoperative screening test. A reexamination of its predictive potential. Study of Perioperative Ischemia Research Group. *Circulation.* 1991;84:493-502.

12. Watters TA, Botvinick EH, Dae MW, et al. Comparison of the findings on preoperative dipyridamole perfusion scintigraphy and intraoperative transesophageal echocardiography: Implications regarding the identification of myocardium at ischemic risk. *J Am Coll Cardiol.* 1991;18:93-100.

13. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation.* 1999;100:1043-1049.

14. Thatipelli MR, Pellikka PA, McBane RD, el al. Prognostic value of ankle-brachial index and dobutamine stress echocardiography for cardiovascular morbidity and all-cause mortality in patients with peripheral arterial disease. *J Vasc Surg.* 2007;46:62-70.

15. Poldermans D, Fioretti PM, Forster T, et al. Dobutamine-atropine stress echocardiography for assessment of perioperative and late cardiac risk in patients undergoing major vascular surgery. *Eur J Vasc Surg.* 1994 ;8: 286-293.

16. Bax JJ, Poldermans D, Elhendy A, et al. Improvement of left ventricular ejection fraction, heart failure symptoms and prognosis after revascularization in patients with chronic coronary artery disease and viable myocardium detected by dobutamine stress echocardiography. *J Am Coll Cardiol.* 1999;34:163-169.

17. Poldermans D, Arnese M, Fioretti PM, et al. Improved cardiac risk stratification in major vascular surgery with dobutamine-atropine stress echocardiography. *J Am Coll Cardiol.* 1995;26:648-653.

18. Shanewise JS, Cheung AT, Aronson S, et al. ASE/SCA guidelines for performing a comprehensive intraoperative multiplane transesophageal echocardiography examination: Recommendations of the American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography. *Anesth Analg.* 1999;89:870-884.

19. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr.* 1989;2:358-367.

20. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. *J Am Soc Echocardiogr.* 2005;18:1440-1463.

21. Bayés de Luna A, Wagner G, Birnbaum Y, et al. International Society for Holter and Noninvasive Electrocardiography: A new terminology for left ventricular walls and location of myocardial infarcts that present Q wave based on the standard of cardiac magnetic resonance imaging: A statement for healthcare professionals from a committee appointed by the International Society for Holter and Noninvasive Electrocardiography. *Circulation.* 2006;114:1755-1760.

22. Fleisher LA, Beckman JA, Brown KA, et al. American College of Cardiology; American Heart Association Task Force on Practice Guidelines; Writing Committee to Update the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery; American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Rhythm Society; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology. ACC/AHA 2006 guideline update on perioperative cardiovascular evaluation for noncardiac surgery: Focused update on perioperative beta-blocker therapy--a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Anesth Analg.* 2007;104:15-26.

23. Parent MC, Rinfret S. The unresolved issues with risk stratification and management of patients with coronary artery disease undergoing major vascular surgery. *Can J Anaesth.* 2008;55:542-556.

24. Hertzer NR, Beven EG, Young JR, et al. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Ann Surg.* 1984;199:223-233.

25. Feringa HH, Karagiannis SE, Vidakovic R, et al. The prevalence and prognosis of unrecognized myocardial infarction and silent myocardial ischemia in patients undergoing major vascular surgery. *Coron Artery Dis.* 2007;18:571-576.

26. Poldermans D, Schouten O, Vidakovic R, et al. DECREASE Study Group: A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: The DECREASE-V Pilot Study. *J Am Coll Cardiol.* 2007;49:1763-1769.

27. Coronary artery surgery study (CASS): A randomized trial of coronary artery bypass surgery. Survival data. *Circulation.* 1983;68:939-50.

28. Espinola-Klein C, Rupprecht HJ, Erbel R, et al. Ten-year outcome after coronary angioplasty in patients with single-vessel coronary artery disease and comparison with the results of the Coronary Artery Surgery Study (CASS). *Am J Cardiol.* 2000;85:321-326.

29. Kałuza GL, Joseph J, Lee JR, et al. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. *J Am Coll Cardiol.* 2000;35:1288-1294.

30. Posner KL, Van Norman GA, Chan V. Adverse cardiac outcomes after noncardiac surgery in patients with prior percutaneous transluminal coronary angioplasty. *Anesth Analg.* 1999;89:553-560.

31. Ward HB, Kelly RF, Thottapurathu L, et al. Coronary artery bypass grafting is superior to percutaneous coronary intervention in prevention of perioperative myocardial infarctions during subsequent vascular surgery. *Ann Thorac Surg.* 2006;82:795-800.

32. Le Manach Y, Perel A, Coriat P, et al. Early and delayed myocardial infarction after abdominal aortic surgery. *Anesthesiology.* 2005;102:885-891.

33. Feringa HH, Karagiannis S, Vidakovic R, et al. Comparison of the incidences of cardiac arrhythmias, myocardial ischemia, and cardiac events in patients treated with endovascular versus open surgical repair of abdominal aortic aneurysms. *Am J Cardiol.* 2007;100:1479-1484.

34. Bottiger BW, Snyder-Ramos SA, Lapp W, et al. The investigators of the Multicenter Study of Perioperative Ischemia (MCSPI) Research Group, Inc. and the Ischemia Research and Education Foundation: Association between early postoperative coagulation activation and peri-operative myocardial ischaemia in patients undergoing vascular surgery. *Anaesthesia.* 2005;60:1162-1167.

35. Smith JS, Cahalan MK, Benefiel DJ, et al. Intraoperative detection of myocardial ischemia in high-risk patients: Electrocardiography versus two-dimensional transesophageal echocardiography. *Circulation.* 1985;72:1015-1021.

36. Maclure M, Willett WC. Misinterpretation and misuse of the kappa statistic. *Am J Epidemiol.* 1987;126:161-169.

37. Tooth LR, Ottenbacher KJ. The kappa statistic in rehabilitation research: An examination. *Arch Phys Med Rehabil.* 2004;85:1371-1376.

Chapter 9

Three dimensional speckle tracking echocardiography: a novel approach in the assessment of left ventricular function?

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LEFT VENTRICULAR VOLUME AND FUNCTION

Over the last decades, echocardiography has developed to be an established noninvasive imaging technique, widely available for cardiovascular investigation. Determination of myocardial function is vital for the clinical evaluation of cardiovascular diseases. Altered cardiac function can be detected with echocardiography as regional myocardial wall motion abnormalities, changes in left ventricular volumes, and global left ventricular dysfunction.[1]

Regional wall motion abnormalities can identify and quantify areas of previous myocardial infarction. Visual assessment categorises wall motion on the basis of the (i) degree of endocardial excursion, (ii) degree of endocardial thickening during systole, (iii) timing of motion, and (iv) shape of the left ventricle. Timing is particularly important and accurate wall motion assessment requires a frame-by-frame review to overcome the limited temporal resolution of the human eye.[2]

Although there is tremendous variability in the coronary artery blood supply to the myocardium, a model with 16-segments assigned to one of the three major coronary arteries is recommended for visual interpretation of regional wall motion.[3] Therefore, individual myocardial segments can be assigned to one major coronary artery with recognition of anatomic variability. Normally, the endocardium thickens during systole; however, ischemic myocardium shows different patterns of wall thickening or even thinning during systole. Wall motion abnormalities at rest represent scar tissue (irreversible myocardial damage) or viable myocardium (reversible myocardial damage).

Echocardiographic assessment of left ventricular volumes plays an important role in the evaluation of pathologic remodelling, a process leading to left ventricular dilatation (eccentric remodelling) which is associated with systolic left ventricular dysfunction.[4] Progressive ventricular dilatation can result in (i) distortion of the cavity shape and (ii) disruption of the mitral annulus and sub-valvular apparatus, which is an important cause of mitral regurgitation.[5] Evaluating left ventricular volumes is, therefore, essential for optimal timing of surgical mitral valve replacement. Left ventricular dilatation is associated with global systolic left ventricular dysfunction, characterized by a reduced left ventricular ejection fraction.[4] The left ventricular ejection fraction is widely used to diagnose systolic heart failure and in decision making of pacemaker or internal automatic defibrillator implantation.

The biplane Simpson's method is considered to be the preferred method to calculate left ventricular volumes and ejection fraction and requires imaging in apical, four- or two-chamber views. First, the endocardial border has to be outlined in end-diastole and end-systole, and the left ventricular cavity is divided into a series of disks of equal height, along its long-axis. When the central-axis of the left ventricular cavity is defined and the endocardial border is identified, the volume of each disk can be automatically calculated. In addition, the ventricular

volume is calculated by summing the disk volumes, which are equally spaced along the left ventricular long-axis. Once the left ventricular volumes have been measured, left ventricular ejection fraction can be calculated.[6] However, in more than 15% of patients examined with ultrasound, poor ultrasonic windows preclude optimal visualisation of the endocardial border.[7]

Analysing left ventricular volumes and function relies on the identification of the endocardial border of the left ventricular cavity and is often performed subjectively with the use of visual interpretation ('eye-balling'). This approach is dependent on the eye of an experienced observer and can be misleading in situations of (i) irregular heart rhythm, (ii) very large or small left ventricle size, and (iii) extreme heart rates.[8, 9] The biplane Simpson's method is considered to be semi-objective because it requires manual tracing of the endocardial border.[8]

Two-dimensional echocardiography, currently the most frequently used technique for the structural analysis of the heart, has limitations regarding the observation of the cardiac anatomy. Two-dimensional estimation of left ventricular volumes and ejection fraction are flawed due to foreshortening errors and reliance upon geometric models. The development of three-dimensional echocardiography has improved the reproducibility and accuracy to determine left ventricular volumes and ejection fraction, compared with two-dimensional echocardiography.[10] In addition, measurements of changes in left ventricular volumes and ejection fraction with three-dimensional echocardiography have shown to be similar to those obtained with cardiac magnetic resonance.[9]

STRAIN RATE IMAGING IN ECHOCARDIOGRAPHY

The main application of new technologies is to improve the quantification of echocardiography. The interpretation of regional myocardial function is the most challenging aspect of echocardiography, as well as the most difficult to quantify. Recent developments in tissue-Doppler, strain rate imaging, and speckle tracking echocardiography may prove useful for this purpose.

Tissue-Doppler imaging is a technique which measures high amplitude signals of myocardial tissue motion. Echocardiographic techniques utilizing tissue-Doppler imaging are more sensitive than conventional echocardiography in the detection of subtle (regional) changes in left ventricular contractile function.[11] However, because tissue-Doppler imaging is a Doppler-based technique, its angle dependency remains a serious limitation.[12] The assessment of apical myocardial segments, for instance, is known to be suboptimal with tissue-Doppler imaging.[13] Furthermore, due to its Doppler-based properties, tissue-Doppler imaging velocity is unable to discriminate active deformation of the left ventricle (as a result of myocardial fibre shortening and lengthening) from passive deformation.

Strain and strain rate imaging have demonstrated to be a more reliable method to quantify myocardial function. Essentially, myocardial strain represents the rate of myocardial deformation or stretch reflected by (i) longitudinal and circumferential strain (shortening of the myocardium) and (ii) radial strain (lengthening of the myocardium).[12] Myocardial strain measured with tissue-Doppler imaging is dependent on the angle of incidence between the ultrasound beam and myocardial motion. At angles greater than 20º, Doppler-derived strain and strain rate are significantly underestimated.[14] Recently, myocardial stain and strain rate can be measured using speckle tracking derived parameters.

SPECKLE TRACKING ECHOCARDIOGRAPHY

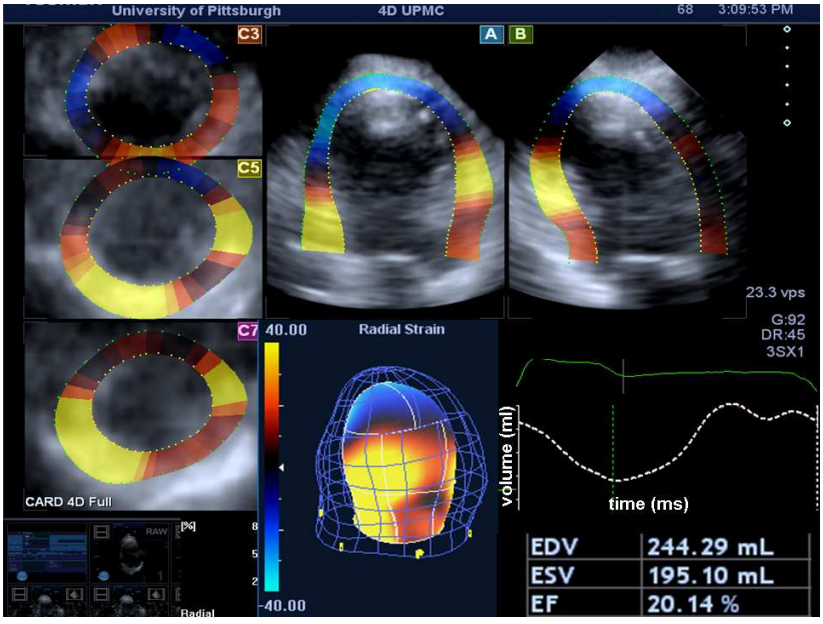
In 1991, speckle tracking echocardiography was introduced, an imaging modality for the quantification of left ventricular volumes and function, which is angle-independent.[15] Speckle tracking is a technique that tracks the movement of natural acoustic markers, or 'speckles', which are present on standard grey scale ultrasound tissue images.[16] These speckles appear as a result of scattering, reflection, and interference of the ultrasound beam in myocardial tissue. With the use of wall motion tracking software, speckle movement (and therefore myocardial tissue movement) can be visualized from frame-to-frame during the cardiac cycle.[17] Speckle tracking echocardiography has the advantage to assess myocardial strain or active thickening, independent of Doppler angle of incidence used in tissue-Doppler strain methods. Therefore, it has been introduced for clinical applications, such as dyssynchrony analysis.[18]

However, speckle tracking applied to two-dimensional images is limited because regions of the myocardium represented by speckle patterns in reality move through three-dimensional space, rather than being limited by the two-dimensional sector, resulting in reliance on geometric modelling.[10, 19] Regardless of its limitations, a study conducted by Nishikage *et al.*[20] demonstrated a significant correlation between two-dimensional speckle tracking echocardiography and cardiac magnetic resonance for measuring left ventricular volumes. A good correlation for left ventricular ejection fraction was found, although a significant underestimation was observed in two-dimensional speckle tracking echocardiography compared with cardiac magnetic resonance. The results demonstrated by Nishikage *et al.* are promising, however, one could ask the question whether three-dimensional speckle tracking echocardiography provides better results.

This question has recently been answered in a manuscript conducted by Nesser *et al.*[21] In this manuscript, the accuracy of three- vs. two-dimensional speckle tracking echocardiography for measuring end-systolic and end-diastolic left ventricular volumes was compared. Cardiac magnetic resonance was used as the reference technique for both two- and three-dimensional echocardiography. The main finding of this study was that the inter- and intraobserver variability was lower and less spread in measurements obtained from three-

dimensional speckle tracking echocardiography compared with two dimensional speckle tracking echocardiography. This might imply that three-dimensional speckle tracking echocardiography could be an attractive new method, not only for the assessment of left ventricular volumes, however for the assessment of left ventricular function as well (*Figure 1*).

Figure 1: An example of a three-dimensional speckle tracking echocardiogram from a heart failure patient with ischemic cardiomyopathy demonstrating the representative long-axis and short-axis tomographic planes, the three-dimensional wire-mesh display, and the time-volume curve.



End-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF).

SPECKLE TRACKING ECHOCARDIOGRAPHY AND CARDIAC MAGNETIC RESONANCE

In comparison with other noninvasive cardiac imaging procedures, such as nuclear cardiology, cardiac computed tomography, and cardiac magnetic resonance, echocardiography has both limitations and advantages. In patients with obstructive lung disease, obesity, chest wall deformities, increases in heart rate, and hyperventilation image quality impairment may cause difficulties in analysis of echocardiographic images. However, echocardiography has the advantage of being (i) safe (i.e. no radiation or ionizing substances required), (ii) widely available, (iii) noninvasive, (iv) feasible in almost all circumstances including interventional settings such as catheterization laboratories or operating rooms, (v) at relatively low cost.[22]

Cardiac magnetic resonance has the ability to provide information about cardiac anatomy, function, and perfusion simultaneously and has a superior spatial resolution compared with echocardiography. However, cardiac magnetic resonance has a lower temporal resolution, usually requires breath-holding sequences during data acquisition, is relatively expensive and less available compared with echocardiography, and may be limited in patients with implanted metallic prosthetics. Nesser *et al.* have compared three-dimensional speckle tracking echocardiography with cardiac magnetic resonance and found that three-dimensional speckle tracking echocardiography measurements were in close agreement with the cardiac magnetic resonance reference values, in the presence of an adequate trans-thoracic two-dimensional acoustic window. However, both inter- and intraobserver variability were lower and less spread in measurements obtained with cardiac magnetic resonance, compared with measurements obtained with three-dimensional speckle tracking echocardiography.[21] These finding are probably related to superior spatial and contrast resolution of cardiac magnetic resonance.

FUTURE PERSPECTIVE

The echo community has put lot of efforts in guidelines and standardization in left ventricular function assessment, being aware of the limitations of non-quantitative measurements as such eye-balling evaluation of ejection fraction and regional myocardial function. Objective quantification of left ventricular volumes and function with three-dimensional speckle tracking echocardiography could be an attractive new method to complete standardization of left ventricular function assessment. In addition, three-dimensional speckle tracking echocardiography might prove its value over cardiac magnetic resonance in interventional settings such as catheterization laboratories and operating rooms. During catheterization or surgery, the use of cardiac magnetic resonance is limited, due to practical reasons. However, an immediate visual and quantitative feedback of left ventricular function, without the need for off-line analysis, is of utmost important in these clinical settings.[23]

To achieve automated assessment of left ventricular volumes and function with three-dimensional speckle tracking ultrasound, shortcomings have to be overcome such as (i) low temporal resolution and (ii) random noise affecting the ability to track speckles during the cardiac cycle.[21] The positive results of Nesser *et al,* however, have provided an insight on how global and regional left ventricular function could be evaluated in the decades lying ahead.

REFERENCES

1. Hauser AM, Gangadharan V, Ramos RG, et al. Sequence of mechanical, electrocardiographic and clinical effects of repeated coronary artery occlusion in human beings: echocardiographic observations during coronary angioplasty. *J Am Coll Cardiol.* 1985;5(2 Pt 1):193-197.

2. Kvitting JP, Wigstrom L, Strotmann JM, et al. How accurate is visual assessment of synchronicity in myocardial motion? An In vitro study with computer-simulated regional delay in myocardial motion: clinical implications for rest and stress echocardiography studies. *J Am Soc Echocardiogr.* 1999;12(9):698-705.

3. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation.* 2002;105(4):539-542.

4. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J Am Coll Cardiol.* 2000;35(3):569-582.

5. Mann DL. Mechanisms and models in heart failure: A combinatorial approach. *Circulation.* 1999;100(9):999-1008.

6. Stamm RB, Carabello BA, Mayers DL, et al. Two-dimensional echocardiographic measurement of left ventricular ejection fraction: prospective analysis of what constitutes an adequate determination. *Am Heart J.* 1982;104(1):136-144.

7. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr.* 1989;2(5):358-367.

8. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr.* 2005;18(12):1440-1463.

9. Jenkins C, Bricknell K, Hanekom L, et al. Reproducibility and accuracy of echocardiographic measurements of left ventricular parameters using real-time three-dimensional echocardiography. *J Am Coll Cardiol.* 2004;44(4):878-886.

10. Jacobs LD, Salgo IS, Goonewardena S, et al. Rapid online quantification of left ventricular volume from real-time three-dimensional echocardiographic data. *Eur Heart J.* 2006;27(4):460-468.

11. Gorcsan J, 3rd, Deswal A, Mankad S, et al. Quantification of the myocardial response to low-dose dobutamine using tissue Doppler echocardiographic measures of velocity and velocity gradient. *Am J Cardiol.* 1998;81(5):615-623.

12. Urheim S, Edvardsen T, Torp H, et al. Myocardial strain by Doppler echocardiography. Validation of a new method to quantify regional myocardial function. *Circulation.* 2000;102(10):1158-1164.

13. Edvardsen T, Skulstad H, Aakhus S, et al. Regional myocardial systolic function during acute myocardial ischemia assessed by strain Doppler echocardiography. *J Am Coll Cardiol.* 2001;37(3):726-730.

14. Nesbitt GC, Mankad S, Oh JK. Strain imaging in echocardiography: methods and clinical applications. *Int J Cardiovasc Imaging.* 2009;25 Suppl 1:9-22.

15. Bohs LN, Trahey GE. A novel method for angle independent ultrasonic imaging of blood flow and tissue motion. *IEEE Trans Biomed Eng.* 1991;38(3):280-286.

16. Leitman M, Lysyansky P, Sidenko S, et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr.* 2004;17(10):1021-1029.

17. Yeung F, Levinson SF, Parker KJ. Multilevel and motion model-based ultrasonic speckle tracking algorithms. *Ultrasound Med Biol.* 1998;24(3):427-441.

18. Suffoletto MS, Dohi K, Cannesson M, et al. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. *Circulation.* 2006;113(7):960-968.

19. Meunier J. Tissue motion assessment from 3D echographic speckle tracking. *Phys Med Biol.* 1998;43(5):1241-1254.

20. Nishikage T, Nakai H, Mor-Avi V, et al. Quantitative assessment of left ventricular volume and ejection fraction using two-dimensional speckle tracking echocardiography. *Eur J Echocardiogr.* 2009;10(1):82-88.

21. Nesser HJ, Mor-Avi V, Gorissen W, et al. Quantification of Left Ventricular Volumes using Three-Dimensional Echocardiographic Speckle Tracking; Comparison with MRI. *Eur Heart J.* 2009.

22. Pennell DJ, Sechtem UP, Higgins CB, et al. Clinical indications for cardiovascular magnetic resonance (CMR): Consensus Panel report. *Eur Heart J.* 2004;25(21):1940-1965.

23. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. *Eur J Echocardiogr.* 2006;7(2):79-108.

PART II

Asymptomatic atherosclerosis in patients with symptomatic peripheral arterial disease

Chapter 10

Perioperative cardiac damage in vascular surgery patients

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ABSTRACT

Background Patients undergoing vascular surgery are at increased risk for developing cardiac complications. Majority of patients with perioperative myocardial damage are asymptomatic. Our objective is to review the available literature addressing the prevalence and prognostic implications of perioperative myocardial damage in vascular surgery patients.

Methods An Internet-based literature search was performed using MEDLINE to identify all published reports on perioperative myocardial damage in vascular surgery patients. Only those studies published from 2000 to 2010 evaluating myocardial damage using troponin I or T, with or without symptoms of angina pectoris were included.

Results Thirteen studies evaluating the prevalence of perioperative myocardial ischemia or infarction were included in the study. The incidence of perioperative myocardial ischemia ranged from 14 to 47% and the incidence of perioperative myocardial infarction ranged from 1 to 26%. In addition, 10 studies evaluating the prognostic value of perioperative myocardial ischemia towards postoperative mortality or the occurrence of major adverse cardiac events were included. In the retrieved studies, hazard ratios varied from 1.9 to 9.0.

Conclusion The high prevalence and asymptomatic nature of perioperative myocardial damage, combined with a substantial influence on postoperative mortality of vascular surgery patients, underline the importance of early detection and adequate management of perioperative myocardial damage.

INTRODUCTION

This article provides an extended overview regarding the prevalence and prognostic value of perioperative myocardial ischemia and infarction in vascular surgery patients. In addition, treatment options in order to reduce the risk of perioperative myocardial damage are provided based on the current available literature.

Perioperative myocardial ischemia and infarction

The heart is an organ with a high metabolic demand and requires a continuous high level of myocardial oxygen-supply. The amount of oxygen supplied to the myocardium is determined by the blood flow in the coronary arteries and the oxygen carrying capacity of the blood. Therefore, an increase of myocardial oxygen-demand must be met by an increase in coronary blood flow. In addition, an imbalance between oxygen-supply and oxygen-demand results in myocardial damage, characterized by myocardial ischemia and myocardial infarction (MI).[1]

In general, myocardial damage can be subdivided according to two pathological processes.[2] Type 1 MI is defined as an acute coronary syndrome that occurs when a vulnerable coronary plaque ruptures, leading to acute coronary thrombosis, ischemia, and infarction. Myocardial damage may also be caused by a prolonged imbalance between myocardial oxygen-supply and demand in the presence of stable coronary artery disease, called type 2 MI. In this case, myocardial damage is caused by an increased myocardial oxygen-demand in response to stress, which is not met by a sufficient increase of coronary blood flow.[3]

During surgery, high catecholamine production is responsible for vasoconstriction and hemodynamic stress,[4] associated with an increased oxygen-demand of the myocardium. Perioperative myocardial damage may occur when the increased oxygen-demand is not met by an adequate increase of oxygen-supply.[5] This is similar to MIs occurring in the nonsurgical setting, however, surgery itself is a significant stress factor leading to an increased risk of plaque rupture. Two retrospective studies investigated the coronary pathology of fatal perioperative MI. As demonstrated in the autopsy study by Dawood *et al,* 55% of the fatal perioperative MIs have direct evidence of plaque disruption defined as fissure or rupture of plaque and haemorrhages into the plaque cavity.[6] Similar autopsy results were found in the study of Cohen and Aretz, who observed that plaque rupture was present in 46% of patients with postoperative MI.[7]

Next to surgical stress, hemodynamic fluctuations during surgery are an important cause of perioperative myocardial damage as well. Perioperative fluid administration increases the pre- and afterload in the left ventricle, making patients susceptible for perioperative myocardial damage.[8] On the other hand, perioperative preload reductions in the left ventricle can result in tachycardia with a concomitant reduction of coronary perfusion, leading to perioperative myocardial damage.[9]

It is estimated that of the 230 million patients undergoing major surgery annually, approximately 1% (2,300,000 patients) suffer perioperative MI with a cardiovascular mortality rate around 0.3% (690,000 patients).[10] However, cardiac risk imbedded in surgical interventions can differ depending on the magnitude, duration, location, blood loss, and fluid shifts related to the specific procedure. In 2005, Boersma *et al.* developed a model to risk stratify surgical procedures, based on the occurrence of 30-day cardiac death and MI.[11] Surgical procedures were classified low cardiac risk (<1%), intermediate cardiac risk (1-5%), or high cardiac risk (>5%) for the development of 30-day adverse cardiac outcome. High cardiac risk surgery is considered to be open lower extremity revascularization and open abdominal aortic surgery. In addition, percutaneous transluminal angioplasty, endovascular aortic aneurysm repair, and carotid surgery are considered to have intermediate cardiac risk because they are associated with reduced myocardial stress and the need for lower fluid administration compared with open lower extremity revascularization and open abdominal aortic surgery.[12]

METHODS

A systematic Medline search was undertaken to identify studies addressing perioperative cardiac damage, assessed with troponin I or T, in patients undergoing elective peripheral vascular surgery published during the period between 2000 and 2010. The keywords used were 'cardiac troponin, vascular surgery', 'perioperative ischemia, vascular surgery', 'cardiac ischemia, vascular surgery' in combination with 'prevalence', 'incidence', 'prognostic value', 'long-term outcome', 'long-term mortality', and 'major adverse cardiac events'. The retrieved articles were also searched for any relevant references. The current manuscript included solely studies addressing the prognostic value of increased troponin T or I levels when using regression analyses or contingency table analyses.

RESULTS

Prevalence of perioperative myocardial damage

Vascular surgery patients are at increased risk for developing perioperative cardiac complications, especially patients undergoing open lower extremity revascularization and open abdominal aortic surgery. In 1981, Brown *et al.* described that around 40% of the patients undergoing elective abdominal aortic aneurysm resection had a history of either MI of angina pectoris.[13] In addition, Hertzer *et al.* performed routine coronary angiography in more than 1000 patients in order to detect uncorrected coronary artery disease in patients with advanced peripheral vascular disease.[14] They found coronary artery disease to be highly present in these patients with a prevalence of severe three-vessel disease in 18% of the patients and left main disease in 4% of patients.[14] In 1989, Oeyang *et al.* observed that episodes of perioperative myocardial damage in patients having peripheral vascular surgery are most often silent.[15] Utoh

et al. performed routine coronary angiography in patients undergoing abdominal aneurysm repair and demonstrated that the incidence of silent ischemia was 20%. In addition, the authors concluded that the number of coronary risk factors and resting electrocardiograms were not worthwhile for predicting silent coronary artery disease.[16]

Perioperative myocardial damage is difficult to diagnose due to its silent nature. In 1994, Adams 3rd *et al.* demonstrated that the measurement of cardiac troponin I is a sensitive and specific method for the diagnosis of perioperative MI in vascular surgery patients.[17] Hereafter, several studies have correlated serial cardiac troponin measurements with continuous 12-lead ST-segment analyses after major vascular surgery.[18] Troponin elevations occurred after prolonged, transient, postoperative ST-segment depression and peak troponin elevations correlated with the duration of ST depression.[19] Landesberg *et al.* demonstrated that 85% of postoperative cardiac complications were preceded by prolonged ST-segment depression [20]. In addition, Fleisher *et al.* found that 78% of patients with cardiac complications had at least one episode of prolonged myocardial ischemia (i.e., >30 minutes) either before or during the cardiac event.[21] The hypothesis that ST-depression can lead to perioperative MI is further supported by increased troponin T levels during or shortly after prolonged ST-depression ischemia.[22] Episodes of perioperative ST-depression, indicating endocardial (non-transmural) myocardial ischemia, has been described in up to 41% of vascular surgery patients and mostly occurs within the first two days after surgery.[23] ST-elevation-type ischemia is considered relative uncommon, confirmed by the incidence of intraoperative ST-elevation (12%) in a study performed by London *et al.*[24] Recent studies using highly sensitive troponin essays demonstrated that low-level (>0.03 ng/mL) troponin elevations postoperatively are common in high cardiac risk patients, even with little or no evidence of ischemia during electrocardiogram monitoring.[25]

In the current study we performed a systematic Medline search to evaluate the prevalence of myocardial ischemia or infarction in vascular surgery patients detected with troponin I or T measurement, whether or not in combination with electrocardiogram changes or symptoms of angina pectoris. As demonstrated in *Table 1,* the incidence of perioperative myocardial ischemia ranged from 14 to 47% and the incidence of perioperative MI ranged from 1 to 26%. The wide range of incidence might be related to (i) different cut off values of troponin I or T used in the study, (ii) a variety of vascular procedures included in the studies, and (iii) that patients specific cardiac risk factors differed between the studies. For example, in the study performed by Ali *et al.* the highest incidence of perioperative myocardial damage (both ischemia and infarction) was found, probable related to the fact that this study only included patients undergoing open abdominal aortic repair. In addition, Schouten *et al.* included only included patients with ≥3 cardiac risk factors (age >70 years, angina pectoris, MI, congestive heart failure, stroke, renal dysfunction, and diabetes mellitus). In the study performed by Abraham *et al*, around 75% of the patients underwent endovascular abdominal

Table 1	Prevalence of perioperative myocardial ischemia or MI in vascular surgery patients					
Study	**Surgical procedure**	**N**	**Myocardial ischemia**		**MI**	
Bollinger *et al.*[26] (2009)	AAA lower extremity	133	cTnI >2.0	14%	-	
Flu *et al.*[27] (2009)	AAA carotid	627	cTnT >0.03	17%	cTnT >0.2 + AP or ECG changes	5%
Ali *et al.* [28] * (2008)	AAA	43	cTnI >0.54	47%	cTnI >0.54 + AP or ECG changes	26%
McFalls *et al.*[29] (2008)	AAA lower extremity	377	cTnI >0.1	27%	cTnI >0.1 + AP or ECG changes	10%
Schouten *et al.*[30] ** (2007)	AAA	77	cTnT >0.03	30%	cTnT >0.2 + AP or ECG changes	7%
Barbagallo *et al.*[31] (2006)	AAA lower extremity	75	cTnI >0.5	33%	cTnT >0.05 + AP or ECG changes	12%
Abraham *et al.*[32] *** (2005)	AAA	149	cTnT >0.02	11%	↑ cTnT + ECG changes	1%
Manach *et al.*[33] (2005)	AAA	1136	cTnI >0.2	14%	cTnI >1.5	5%
Landesberg *et al.*[19] (2003)	AAA lower extremity carotid	503	cTnI >0.6 or cTnT >0.03	23%	↑ cTnI or ↑ cTnT + symptoms	11%
Kim *et al.*[34] * (2002)	AAA lower extremity	229	cTnI >0.4	43%	↑ cTnI + ECG changes	3%
Haggart *et al.*[36] (2001)	AAA lower extremity	35	cTnI >0.5	29%	cTnI >0.5 + AP or ECG changes	14%
Andrews *et al.*[36] (2001)	AAA lower extremity carotid	100	cTnI >0.8	18%	↑ CKMB + AP or ECG changes	12%
Godet *et al.*[38] (2000)	AAA	316	cTnI >0.5	16%	cTnI >1.5	8%

Abdominal aortic aneurysm (AAA), agina pectoris (AP), cardiac troponin I (cTnI), cardiac troponin T (cTnT), electrocardiogram (ECG), myocardial infarction (MI).

aortic aneurysm repair and patients with increased cardiac troponin T in combination with a significant postoperative increase in serum creatinine (>50%) were excluded from the study. Importantly, Abraham *et al.* report the highest incidence of perioperative myocardial damage within the first three days after surgery.[32]

Prognosis after perioperative myocardial damage

In order to put the significance of perioperative myocardial damage into perspective, it is pivotal to address the influence of perioperative myocardial damage on long-term postoperative outcome. Multiple studies have been performed over the years to evaluate this issue. In 1982, Jamieson *et al.* were one of the first to describe the influence of ischemic heart disease on early and late mortality after surgery for peripheral occlusive vascular disease. The authors concluded that coronary artery disease is a major determinant of both early and late mortality after arterial reconstruction and that selective myocardial revascularization may improve survival of these patients.[38] Because perioperative myocardial damage is most often silent, the great majority of patients with perioperative myocardial damage (95%) remain untreated. This might contribute to an increased risk of long-term cardiovascular mortality as well.[15,39,40]

In multiple studies performed between the period between 2000 and 2010, perioperative myocardial damage defined as postoperative troponin elevations whether or not in combination with ST-segment alterations has been related to adverse short-, mid- and long-term cardiac morbidity and mortality, as outlined in *Table 2*.[19,26,28,29,31,33,34,36,41,42] In the current study, hazard ratios describing the prognostic value of troponin T or I towards postoperative mortality or the occurrence of major adverse cardiac events varied from 1.9 to 9.0.

In patients undergoing vascular surgery, asymptomatic elevated troponin T levels were associated with an increased risk, of more than four- to six-fold, for cardiac events during a six month follow-up period, as demonstrated by Kim *et al.*[34] Landesberg *et al.* and Kertai *et al.* studied the prognostic value of low- and intermediate-to-high cut off levels of troponin T elevations on long-term mortality after vascular surgery. These studies demonstrated that postoperative troponin T elevations even at low cut off levels were independent and complementary predictors of long-term mortality.[19,41] In addition, early mortality after perioperative MI ranges between 3.5 to 25% and is higher in patients with an intermediate-to-high level troponin elevation, compared with patients with a low level troponin elevation.[19,29,33].

Endovascular surgery is associated with a reduced incidence of perioperative myocardial damage, compared with open vascular surgery, possibly explained by reduced myocardial stress during endovascular procedures.[12] However, Winkel *et al.* recently demonstrated that asymptomatic perioperative myocardial damage, defined as cardiac troponin T elevations in the absence of ischemic symptoms or electrocardiogram abnormalities, was associated with an increased mortality risk of patients undergoing endovascular abdominal

aortic aneurysm repair.[42] During a 2.9 year follow-up of 220 patients, they found that patients with asymptomatic myocardial damage had a mortality rate of 49%, compared with 15% for patients without perioperative myocardial damage ($p < 0.001$).

Table 2 **Prognostic value of increased perioperative troponin T or I levels for cardiac outcome of vascular surgery patients**

Study	Surgical procedure	N	Troponin I or T	Cardiac outome	
Bollinger *et al.*[26] (2009)	AAA lower extremity	133	cTnI >2.0	MACE, mortality, 1-year	HR 9.0 (3.6-23.2) HR 8.5 (2.9-24.9)
Winkel et al[42] (2009)	AAA	220	cTnT >0.01	mortality, long-term	HR 2.3 (1.1-5.1)
Ali *et al.* [28] * (2008)	AAA	43	cTnI >0.54	MACE, long-term	OR 5.4 (1.2-24)
McFalls *et al.*[29] *(2008)*	AAA lower extremity	377	cTnI >0.1	mortality , 1-year	$p < 0.01$*
Barbagallo *et al.*[31] (2006)	AAA lower extremity	75	cTnI >0.5	MACE, 1-month	$p < 0..003$*
Manach *et al.*[33] (2005)	AAA	1136	cTnI >0.2	mortality, in hospital	$p < 0.05$*
Kertai *et al.*[41] (2004)	AAA lower extremity	393	cTnT >0.1	mortality, long-term	HR 1.9 (1.1-3.1)
Landesberg *et al.*[19] (2003)	AAA lower extremity carotid	447	cTnI >0.6 or cTnT >0.03	mortality, long-term	OR 2.2 (1.48-3.42)
Kim *et al.*[34] * (2002)	AAA lower extremity	229	cTnI >0.4	mortality, 6-month	OR 4.9 (1.3-19)
Andrews *et al.*[36] (2001)	AAA lower extremity carotid	100	cTnI >0.8	MACE, in hostpital	$p < 0.001$*

** Contingency table analyses evaluating increased risk for adverse cardiac outcome associated with perioperative increases of troponin T. Abdominal aortic aneurysm (AAA), cardiac troponin I (cTnI), cardiac troponin T (cTnT), major adverre cardiac event (MACE).*

DISCUSSION

Prevention of perioperative myocardial damage

In general, the management of perioperative myocardial damage is focussed on (i) coronary plaque stabilization to reduce acute coronary syndromes, with subsequent supply-ischemia

(type I MI), that occurs when a coronary plaque ruptures and (ii) limiting surgical stress which is the cause of sustained myocardial oxygen-supply-demand imbalance (type 2 MI). The high incidence of perioperative myocardial damage reflects the high prevalence of underlying ischemic heart disease in the vascular surgery population.[43] Therefore, adequate preoperative evaluation is inevitable to: identify patients at increased cardiac risk, initiate risk reduction therapy, and select optimal surgical and anaesthesia techniques. In conventional preoperative cardiac risk indices, such as the Adapted Lee index; age, heart failure, ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus, and high-risk surgery such as vascular surgery, have been identified as independent predictors of perioperative cardiovascular events.[11]

Pharmacological treatment

The unpredictable progression of an instable coronary plaque during surgical stress is the most important target for systemic pharmacological therapy to reduce the incidence of perioperative myocardial damage.

β-blockers

In the nonsurgical setting β-blockers are widely used for the prevention and treatment of ischemic heart disease and heart failure, all major determinants of adverse postoperative outcome. Proposed mechanisms by which β-blockers exert intraoperative cardioprotective effects include heart rate control, reduction of systolic pressure and ventricular contractile force, and its anti-arrhythmic properties. Long-term; β-blockers reduce mechanical stress imposed to coronary plaques and thereby prevent plaque rupture.[44] In addition, the anti-inflammatory properties of β-blockers exert a beneficial effect towards coronary plaque stabilization as well.[45] In addition, β-blockers are known to reduce the process of adverse cardiac remodelling in patients with impaired left ventricular function, which is highly prevalent in the vascular surgery population, by inhibiting the sympathetic nervous system and hormone activation (A-type and B-type natriuretic peptides and norepinephrine).[46]

In the most recent 'European Society of Cardiology' (ESC) guidelines, β-blockers are recommended (class I, level of evidence B) in patients scheduled for high-risk surgery. In addition, β-blockers should be considered (class IIa, level of evidence B) in patients undergoing intermediate-risk surgery, such as percutaneous transluminal angioplasty, endovascular aortic aneurysm repair, and carotid surgery.[47] Factors which influence the effectiveness of perioperative β-blockers treatment are the patients underlying cardiac risk factors and variations in treatment protocols, such as β-blocker type, β-blocker dose, and timing of β-blocker initiation before surgery. As recommended in ESC guidelines, β-blocker treatment should be initiated optimally between 30 days and at least 1 week before surgery with a target heart rate between 60 to 70 beats per minute and systolic blood pressure >100 mmHG.

Statins

Statins are widely used to decrease low-density lipoprotein cholesterol in patients with hypercholesterolemia. Additionally, statins seem to stabilize atherosclerotic plaques during surgery through pleiotropic effects and therefore have a beneficial influence on cardiovascular outcome.[48] Multiple studies have not only shown beneficial effects of statins in patients with coronary artery disease, but in patients undergoing vascular surgery as well.[49] In the most recent ESC guidelines, initiation of statins is recommended in patients undergoing high-risk surgery, optimally between 30 days and at least 1 week before surgery (class I, level of evidence B).[47\]

Antiplatelet agents

The perioperative surgical stress results in a hypercoagulable state which, in combination with atherosclerotic plaques, serves as the perfect substrate for the development of perioperative cardiac damage. Antiplatelet drugs are established agents in the prevention of cardiovascular and cerebrovascular ischemic events. Treatment with aspirin or clopidogrel is recommended in patients with stable coronary artery disease to prevent cardiovascular events.[50] Aspirin irreversibly blocks platelet cyclo-oxygenase-1 known to decrease the tromboxane-A2 synthesis. Thereby aspirin reduces platelet activation and vasoconstriction.[51] Aspirin reduces the risk of nonfatal MI by 34% and in the setting of secondary prevention reduces cardiovascular events by 27% and cardiovascular deaths by 18%.[52] Most recent ESC guidelines addressing perioperative care state that continuation of aspirin should be considered in the perioperative period of patients previously treated with aspirin (class IIa, level of evidence B).[47] The thienopyridine derivate clopidogrel is an antiplatelet agent that inhibits the adenosine diphosphate mediated platelet aggregation.[53] Randomized, controlled studies are needed to investigate the role of clopidogrel as a preventive treatment in patients with asymptomatic cardiac damage.

Prophylactic revascularization

Preoperative cardiac risk evaluation by means of risk factor assessment and noninvasive testing may identify vascular surgery patients with asymptomatic coronary artery disease. Two randomized, controlled trials have evaluated the potential benefit which may be expected from preoperative revascularization in these patients. The Coronary Artery Revascularization Prophylaxis (CARP) trial randomized 510 patients with significant coronary artery stenosis to either receive revascularization or no revascularization before vascular surgery.[54] The main finding of the CARP trial was that there was no difference in the primary outcome of long-term mortality (median follow-up 2.7 years) of patients who underwent preoperative coronary revascularization compared with patients who received optimized medical therapy (22 vs. 23%, relative risk: 0.98, 95%-CI: 0.70 to 1.37). In the prospectively randomized Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE)-V trial,[55] mainly including patients with three-vessel coronary artery disease, comparable results to the CARP trial were obtained. Although the study population in the DECREASE-V trial

reflected vascular surgery patients at highest cardiac risk, revascularization did not improve cardiovascular outcomes. The incidence of the composite endpoint of 30-day cardiovascular mortality and MI was 43 vs. 33% (OR 1.4, 95%-CI: 0.7 to 2.8). In addition, no benefit was observed during one-year follow-up after coronary revascularization, 49 vs. 44% (OR 1.2, 95%-CI: 0.7 to 2.3; $p = 0.48$). The results from these trials indicate that prophylactic coronary revascularization of cardiac stable patients provides no benefit for postoperative outcome, with an exception for patients with left main coronary artery stenosis. The reasoning behind this apparent lack of benefit could be related to the fact that perioperative myocardial damage is not only caused by a significant blood flow limiting coronary artery stenosis (Type 1 MI). The perioperative stress response (evoking type 2 MI) may cause non-flow limiting coronary plaques to rupture during surgery and to become flow limiting after al. This may explain why surgical or percutaneous treatment of flow-limiting coronary plaques apparently provides insufficient extra protection on top of pharmacological treatment. In the most recent ESC guidelines' addressing perioperative care, it is only recommended to consider prophylactic revascularization in patients undergoing high-risk surgery, such as lower extremity revascularization or open abdominal aortic surgery, with proven ischemic heart disease (class IIb, level of evidence B).[47]

Future perspective: is there a role for remote ischemic preconditioning?

Because prophylactic coronary revascularization had not proven to be successful, there remains a need for alternative strategies to protect the myocardium during vascular surgery. Research performed by Przyklenk *et al.* in a canine heart model demonstrated that brief occlusions of a coronary artery may protect the myocardial bed supplied by that coronary artery from prolonged ischemia.[56] In addition, Gho *et al.* demonstrated that brief ischemia in "remote" organs (i.e. after occlusion of the anterior mesenteric artery or left renal artery) protects the myocardium against infarction as effectively as myocardial preconditioning, described by Przyklenk *et al.*[57] Therefore, brief ischemia followed by reperfusion in one organ may provide systemic protection from prolonged ischemia in another organ. In patients undergoing abdominal aneurysm repair, remote ischemic preconditioning has been evaluated as well. Ali *et al.* included 82 patients which were randomized to conventional abdominal aortic aneurysm repair (control) and abdominal aortic aneurysm repair with remote ischemic preconditioning.[58] Two cycles of intermittent cross clamping of the common iliac artery with 10 minutes ischemia followed by 10 minutes reperfusion served as the remote ischemic preconditioning stimulus. The authors found that remote ischemic preconditioning reduced the incidence of postoperative myocardial injury, MI, and renal impairment. In addition, in a small pilot study, Walsh *et al.* demonstrated that remote ischemic preconditioning reduced urinary biomarkers of renal injury in patients undergoing elective endovascular abdominal aneurysm repair.[59] However, the authors point out that future large scale trials are needed to determine the effect of remote ischemic preconditioning on the occurrence of major adverse cardiac events.

CONCLUSION

The high prevalence and asymptomatic nature of perioperative myocardial damage, combined with a substantial influence on postoperative mortality of vascular surgery patients, underlines the importance of early detection and adequate management of perioperative myocardial damage. With the use of preoperative cardiac risk indices, high cardiac risk patients at risk for developing perioperative myocardial damage during vascular surgery can be unveiled. Routine assessment of perioperative cardiac troponin levels and/or continuous electrocardiogram monitoring can detect perioperative myocardial damage in patients at risk. In order to reduce the risk of developing perioperative myocardial damage, pharmacological treatment with β-blockers, statins, and aspirin has demonstrated to exert beneficial effects. In addition, prophylactic coronary revascularization does not seem to provide sufficient extra protection on top of pharmacological treatment. Future randomized, controlled trials are needed to evaluate if remote ischemic preconditioning or treatment with clopidogrel may serve as novel preventive treatment strategies to reduce asymptomatic myocardial damage during vascular surgery.

REFERENCES

1. Ardehali A, Ports TA. Myocardial oxygen supply and demand. *Chest.* 1990;98(3):699-705.

2. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *J Am Coll Cardiol.* 2007;50(22):2173-2195.

3. Mangano DT. Perioperative cardiac morbidity. *Anesthesiology.* 1990;72(1):153-184.

4. Mangano DT. Perioperative medicine: NHLBI working group deliberations and recommendations. *J Cardiothorac Vasc Anesth.* 2004;18(1):1-6.

5. Priebe HJ. Perioperative myocardial infarction--aetiology and prevention. *Br. J. Anaesth.* 2005;95(1):3-19.

6. Dawood MM, Gutpa DK, Southern J, et al. Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. *International Journal of Cardiology.* 1996;57(1):37-44.

7. Cohen MC, Aretz TH. Histological Analysis of Coronary Artery Lesions in Fatal Postoperative Myocardial Infarction. *Cardiovascular Pathology.* 1999;8(3):133-139.

8. Schrier RW, Ecder T. Gibbs memorial lecture. Unifying hypothesis of body fluid volume regulation: implications for cardiac failure and cirrhosis. *Mt Sinai J Med.* 2001;68(6):350-361.

9. Doesch AO, Celik S, Ehlermann P, et al. Heart rate reduction after heart transplantation with beta-blocker versus the selective If channel antagonist ivabradine. *Transplantation.* 2007;84(8):988-996.

10. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet.* 2008;372(9633):139-144.

11. Boersma E, Kertai MD, Schouten O, et al. Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index. *Am J Med.* 2005;118(10):1134-1141.

12. Elkouri S, Gloviczki P, McKusick MA, et al. Perioperative complications and early outcome after endovascular and open surgical repair of abdominal aortic aneurysms. *J Vasc Surg.* 2004;39(3):497-505.

13. Brown OW, Hollier LH, Pairolero PC, et al. Abdominal aortic aneurysm and coronary artery disease. *Arch Surg.* 1981;116(11):1484-1488.

14. Hertzer NR, Beven EG, Young JR, et al. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Ann Surg.* 1984;199(2):223-233.

15. Ouyang P, Gerstenblith G, Furman WR, et al. Frequency and significance of early postoperative silent myocardial ischemia in patients having peripheral vascular surgery. *Am J Cardiol.* 1989;64(18):1113-1116.

16. Utoh J, Goto H, Hirata T, et al. Routine coronary angiography prior to abdominal aortic aneurysm repair: incidence of silent coronary artery disease. *Panminerva Med.* 1998;40(2):107-109.

17. Adams JE, 3rd, Sicard GA, Allen BT, et al. Diagnosis of perioperative myocardial infarction with measurement of cardiac troponin I. *N Engl J Med.* 1994;330(10):670-674.

18. Landesberg G, Mosseri M, Zahger D, et al. Myocardial infarction after vascular surgery: the role of prolonged stress-induced, ST depression-type ischemia. *J Am Coll Cardiol.* 2001;37(7):1839-1845.

19. Landesberg G, Shatz V, Akopnik I, et al. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. *J Am Coll Cardiol.* 2003;42(9):1547-1554.

20. Landesberg G, Luria MH, Cotev S, et al. Importance of long-duration postoperative ST-segment depression in cardiac morbidity after vascular surgery. *Lancet.* 1993;341(8847):715-719.

21. Fleisher LA, Nelson AH, Rosenbaum SH. Postoperative myocardial ischemia: etiology of cardiac morbidity or manifestation of underlying disease? *J Clin Anesth.* 1995;7(2):97-102.

22. Landesberg G, Mosseri M, Shatz V, et al. Cardiac troponin after major vascular surgery: the role of perioperative ischemia, preoperative thallium scanning, and coronary revascularization. *J Am Coll Cardiol.* 2004;44(3):569-575.

23. Mangano DT, Browner WS, Hollenberg M, et al. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. *N Engl J Med.* 1990;323(26):1781-1788.

24. London MJ, Hollenberg M, Wong MG, et al. Intraoperative myocardial ischemia: localization by continuous 12-lead electrocardiography. *Anesthesiology.* 1988;69(2):232-241.

25. Bursi F, Babuin L, Barbieri A, et al. Vascular surgery patients: perioperative and long-term risk according to the ACC/AHA guidelines, the additive role of post-operative troponin elevation. *Eur Heart J.* 2005;26(22):2448-2456.

26. Bolliger D, Seeberger MD, Lurati Buse GA, et al. A preliminary report on the prognostic significance of preoperative brain natriuretic peptide and postoperative cardiac troponin in patients undergoing major vascular surgery. *Anesth Analg.* 2009;108(4):1069-1075.

27. Flu WJ, van Kuijk JP, Voute MT, et al. Asymptomatic low ankle-brachial index in vascular surgery patients: a predictor of perioperative myocardial damage. *Eur J Vasc Endovasc Surg.*39(1):62-69.

28. Ali ZA, Callaghan CJ, Ali AA, et al. Perioperative myocardial injury after elective open abdominal aortic aneurysm repair predicts outcome. *Eur J Vasc Endovasc Surg.* 2008;35(4):413-419.

29. McFalls EO, Ward HB, Moritz TE, et al. Predictors and outcomes of a perioperative myocardial infarction following elective vascular surgery in patients with documented coronary artery disease: results of the CARP trial. *Eur Heart J.* 2008;29(3):394-401.

30. Schouten O, Dunkelgrun M, Feringa HH, et al. Myocardial damage in high-risk patients undergoing elective endovascular or open infrarenal abdominal aortic aneurysm repair. *Eur J Vasc Endovasc Surg.* 2007;33(5):544-549.

31. Barbagallo M, Casati A, Spadini E, et al. Early increases in cardiac troponin levels after major vascular surgery is associated with an increased frequency of delayed cardiac complications. *J Clin Anesth.* 2006;18(4):280-285.

32. Abraham N, Lemech L, Sandroussi C, et al. A prospective study of subclinical myocardial damage in endovascular versus open repair of infrarenal abdominal aortic aneurysms. *J Vasc Surg.* 2005;41(3):377-380; discussion 380-371.

33. Le Manach Y, Perel A, Coriat P, et al. Early and delayed myocardial infarction after abdominal aortic surgery. *Anesthesiology.* 2005;102(5):885-891.

34. Kim LJ, Martinez EA, Faraday N, et al. Cardiac troponin I predicts short-term mortality in vascular surgery patients. *Circulation.* 2002;106(18):2366-2371.

35. Haggart PC, Adam DJ, Ludman PF, et al. Comparison of cardiac troponin I and creatine kinase ratios in the detection of myocardial injury after aortic surgery. *Br J Surg.* 2001;88(9):1196-1200.

36. Andrews N, Jenkins J, Andrews G, et al. Using postoperative cardiac Troponin-I (cTi) levels to detect myocardial ischaemia in patients undergoing vascular surgery. *Cardiovasc Surg.* 2001;9(3):254-265.

37. Godet G, Dumerat M, Baillard C, et al. Cardiac troponin I is reliable with immediate but not medium-term cardiac complications after abdominal aortic repair. *Acta Anaesthesiol Scand.* 2000;44(5):592-597.

38. Jamieson WR, Janusz MT, Miyagishima RT, et al. Influence of ischemic heart disease on early and late mortality after surgery for peripheral occlusive vascular disease. *Circulation.* 1982;66(2 Pt 2):I92-97.

39. Raby KE, Goldman L, Cook EF, et al. Long-term prognosis of myocardial ischemia detected by Holter monitoring in peripheral vascular disease. *Am J Cardiol.* 1990;66(19):1309-1313.

40. Pasternack PF, Grossi EA, Baumann FG, et al. Beta blockade to decrease silent myocardial ischemia during peripheral vascular surgery. *Am J Surg.* 1989;158(2):113-116.

41. Kertai MD, Boersma E, Klein J, et al. Long-term prognostic value of asymptomatic cardiac troponin T elevations in patients after major vascular surgery. *Eur J Vasc Endovasc Surg.* 2004;28(1):59-66.

42. Winkel TA, Schouten O, van Kuijk JP, et al. Perioperative asymptomatic cardiac damage after endovascular abdominal aneurysm repair is associated with poor long-term outcome. *J Vasc Surg.* 2009.

43. Kannel WB, Abbott RD. Incidence and prognosis of unrecognized myocardial infarction. An update on the Framingham study. *N Engl J Med.* 1984;311(18):1144-1147.

44. Lopez-Sendon J, Swedberg K, McMurray J, et al. Expert consensus document on beta-adrenergic receptor blockers. *Eur Heart J.* 2004;25(15):1341-1362.

45. Warltier DC, Pagel PS, Kersten JR. Approaches to the prevention of perioperative myocardial ischemia. *Anesthesiology.* 2000;92(1):253-259.

46. Kukin ML. Beta-blockers in chronic heart failure: considerations for selecting an agent. *Mayo Clin Proc.* 2002;77(11):1199-1206.

47. Poldermans D, Bax JJ, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: the Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur Heart J.* 2009;30(22):2769-2812.

48. Liao JK. Clinical implications for statin pleiotropy. *Curr Opin Lipidol.* 2005;16(6):624-629.

49. Kapoor AS, Kanji H, Buckingham J, et al. Strength of evidence for perioperative use of statins to reduce cardiovascular risk: systematic review of controlled studies. *Bmj.* 2006;333(7579):1149.

50. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart.* 2005;91 Suppl 5:v1-52.

51. Patrono C. Aspirin as an antiplatelet drug. *N Engl J Med.* 1994;330(18):1287-1294.

52. Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. *Bmj.* 1994;308(6921):81-106.

53. Coukell AJ, Markham A. Clopidogrel. *Drugs.* 1997;54(5):745-750; discussion 751.

54. McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med.* 2004;351(27):2795-2804.

55. Poldermans D, Schouten O, Vidakovic R, et al. A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: the DECREASE-V Pilot Study. *J Am Coll Cardiol.* 2007;49(17):1763-1769.

56. Przyklenk K, Bauer B, Ovize M, et al. Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation.* 1993;87(3):893-899.

57. Gho BC, Schoemaker RG, van den Doel MA, et al. Myocardial protection by brief ischemia in noncardiac tissue. *Circulation.* 1996;94(9):2193-2200.

58. Ali ZA, Callaghan CJ, Lim E, et al. Remote ischemic preconditioning reduces myocardial and renal injury after elective abdominal aortic aneurysm repair: a randomized controlled trial. *Circulation.* 2007;116(11 Suppl):I98-105.

59. Walsh SR, Boyle JR, Tang TY, et al. Remote ischemic preconditioning for renal and cardiac protection during endovascular aneurysm repair: a randomized controlled trial. *J Endovasc Ther.* 2009;16(6):680-689.

Chapter 11

Long-term prognosis of patients with peripheral arterial disease with or without polyvascular atherosclerotic disease

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ABSTRACT

Aims Patients with peripheral atherosclerotic disease often have multiple affected vascular beds (AVB), however, data on long-term follow-up and medical therapy are scarce. We assessed the prevalence and prognostic implications of polyvascular disease on long-term outcome in symptomatic peripheral arterial disease (PAD) patients.

Methods Two thousand nine hundred and thirty-three consecutive patients were screened before surgery for concomitant documented cerebrovascular disease and coronary artery disease. The number of AVB was determined. Cardiovascular medication as recommended by guidelines was noted at discharge.

Results Single, two and three AVB were detected in 1,369 (46%), 1,249 (43%) and 315 (11%) patients, respectively. During a median follow-up of 6 years, 1.398 (48%) patients died, of which 54% secondary to cardiovascular cause. After adjustment for baseline cardiac risk factors and discharge-medication, the presence of 2-AVB or 3-AVB was associated with all-cause mortality (HR 1.3, 95%-CI: 1.2 to 1.5; HR 1.8, 95%-CI: 1.5 to 2.2) and cardiovascular mortality (HR 1.5, 95%-CI: 1.2 to 1.7; HR 2.0, 95%-CI: 1.6 to 2.5) during long-term follow-up, respectively. Patients with 2- and 3-AVB received extended medical treatment compared with 1-AVB at time of discharge.

Conclusions Polyvascular atherosclerotic disease in PAD patients is independently associated with an increased risk for all-cause and cardiovascular mortality during long-term follow-up.

INTRODUCTION

Peripheral arterial disease (PAD) is a multifactorial syndrome that most commonly affects people over 60 years of age.[1] As population age increases, the prevalence of atherosclerotic disease and its associated adverse outcomes will increase. Cardiovascular risk profiles have been established in several large studies, showing an equal risk factor distribution among all populations and across age groups and gender.[2, 3] It has to be noted that the process of established atherothrombosis is not limited to a single arterial location. The Reduction of Atherothrombosis for Continued Health (REACH) registry showed that one out of 6 patients with PAD, cerebrovascular disease (CVD) or coronary artery disease (CAD) had involvement of 1 or 2 other arterial beds.[1, 4] The REACH registry also demonstrated a substantial gap between recommended clinical guidelines and actual clinical practices in the care of patients with or at risk for atherothrombosis. A pattern of underutilization of established medical therapies and lifestyle interventions was shown throughout all geographic regions studies and vascular disease subtypes.[1] Consequently, patients with PAD have a three to six-fold increased risk for the occurrence of cardiovascular mortality compared with patients without PAD.[5, 6] Therefore, the importance of risk factor reduction in patients with PAD has resulted in universally recommended atherothrombotic risk factor reduction, with the objective of decreasing the high incidence of heart disease and cerebrovascular disease associated with PAD.[7, 8]

However, although these large studies have identified the risk factor profiles and treatment protocols of atherosclerotic patients, most data are based on the screening of polyvascular disease, especially in the primary care setting. Therefore, the aim of the current study was to assess (i) the prevalence and number of affected vascular beds, and (ii) the prognostic implications of polyvascular disease on short- and long-term mortality in high-risk vascular surgery patients with symptomatic PAD.

METHODS

Study design and population

This retrospective single-centre study comprised a population of 2,933 consecutive patients with PAD, referred for elective major vascular surgery. All patients underwent a major vascular surgery procedure during the time period 1990 to 2008, and included lower extremity revascularization, abdominal aortic surgery (dilatating or stenotic) or carotid surgery. From 1990 until 2001, standard preoperative screening included a detailed cardiac history, physical examination, electrocardiogram (ECG), standard laboratory measurements and additional (stress)-testing if indicated. After 2002, standard preoperative echocardiography was added to the screening program. The study complies the Declaration of Helsinki. Patient enrolment was

performed after approval of the hospital's ethics committee and after informed consent of all patients (or their guardians) at time of inclusion.

Patient data

At baseline all medical records were reviewed to determine the presence of documented CAD and CVD. Patients undergoing lower extremity revascularization or abdominal aortic surgery were screened for the concomitant presence of documented CAD and CVD. Patients undergoing carotid surgery were screened for CAD and PAD. Coronary artery disease was defined as a documented history of ischemic heart disease [composite of angina pectoris, myocardial infarction (MI), percutaneous coronary intervention or coronary artery bypass grafting], using myocardial stress-testing (ergometry, stress-echocardiography, or CT-scan) or coronary angiogram. Patients with stable or unstable angina pectoris were classified as having documented CAD according the ESC guidelines.[9] The presence of coronary ischemia was established by one of the following techniques: exercise ECG [horizontal or down-sloping ST-segment depression or elevation (≥1 mm (0.1 mV) for ≥60-80 ms after the end of the QRS complex)], or exercise testing with echocardiography, CT-scan (≥50% stenosis in one or more of the coronary arteries).[10] The presence of documented CVD was defined as a history of cerebrovascular accident or transient ischemic attack (TIA). Cerebrovascular accidents had to be confirmed by a CT-scanning report. The diagnosis of TIA had to be confirmed by a neurologist report. Lower extremity arterial disease was defined as current intermittent claudication with ankle-brachial-index <0.9, or a history of intermittent claudication with a previous intervention, such as angioplasty, stenting, atherectomy, peripheral arterial bypass graft, or other vascular intervention including amputation. Polyvascular disease was defined as the presence of 2 or 3-AVB. One-AVB included: PAD, 2-AVB: PAD and CAD or CVD, 3-AVB: PAD and CAD and CVD.

Finally, the use of the following medication was recorded at discharge: aspirin, statins, ß-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, oral anticoagulants, and ticlopidines. Treatment goals were defined according the current guidelines and included low-dose aspirin (75-325 mg daily) and statins (low-intermediate risk patients: target LDL level <100 mg/dL, high-risk patients <70 mg/dL) for patients with PAD, and if necessary combined with antihypertensive drugs to receive a target blood pressure below 140/90 mmHg.[7] Additionally, PAD patients with diabetes should receive ACE-inhibitors to a target blood pressure less than 130/80 mmHg.[7] Patients with CAD should be treated with aspirin, statins (target LDL <100 mg/dL) and ß-blockers, and additionally with ACE-inhibitors or Angiontensin receptor blockers in case of diabetes mellitus and/or heart failure.[11]

Risk factors

All cardiac risk factors were determined at baseline, including age, gender, body mass index, smoking status, hypertension (defined as systolic blood pressure ≥140 mmHg, diastolic blood

pressure ≥90 mmHg in non-diabetics, systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥80 mmHg in diabetics or the use of antihypertensive medication), diabetes mellitus (fasting blood glucose ≥7.0 mmol/L or requirement for insulin and/or oral anti-diabetic medication), hypercholesterolemia (low density lipoprotein cholesterol >135 mg/dL and/or the requirement of lipid-lowering medication), chronic obstructive pulmonary disease (according to the Global Initiative on Obstructive Lung Disease-classification)[12] and chronic renal insufficiency (serum creatinine >2.0 mg/dL). The cardiac risk score was calculated according the adapted Lee cardiac index which assigns 1 point for each of the following characteristics: high-risk surgery, ischemic heart disease, heart failure, cerebrovascular disease, chronic renal insufficiency, and diabetes mellitus.[13]

Follow-up and endpoints

The median follow-up of all patients was 6 years (interquartile range 2 to 9). Primary study endpoint was the occurrence of all-cause mortality. Survival status was assessed by reviewing the municipal civil registries. Cause of death was ascertained by examining death certificates, and otherwise by reviewing medical records. Cause of death was further classified as either cardiovascular or noncardiovascular death. Cardiovascular death was defined as any death with a cerebro-cardiovascular complication as the primary or secondary cause and includes death following MI, serious cardiac arrhythmias (defined as the presence of a sustained cardiac rhythm disturbance that required urgent medical intervention), congestive heart failure, stroke (cerebrovascular event or transient ischemic attack), and surgery related bleeding complications (only a postoperative cause of death). Sudden unexpected death was classified as a cardiovascular death.

Statistics

Continuous data were compared using analysis of variance, and are expressed as mean ± SD. Categorical data are presented as percentage frequencies and compared using χ^2 tests. Analyses for trends in all baseline characteristics (including age) between the number AVB were performed with linear-by-linear association. Logistic regression analysis was used to determine the association between polyvascular disease (2 and 3-AVB compared with 1-AVB) and short-term mortality (30 days). Cumulative survival of patients with 1, 2, or 3-AVB was determined by the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate Cox regression models were used to investigate the association between AVB (patients with 1-AVB as reference group) and mortality during long-term follow-up. All multivariate analyses were primarily adjusted for demographics (age and gender) and cardiovascular risk factors (smoking, hypertension, diabetes mellitus, hypercholesterolemia, renal dysfunction, heart failure and COPD). Secondary adjustments were made for medications usage recommended by the ESC/ACC guidelines in patients with PAD, including aspirin, statins, ß-blockers in case of prior myocardial infarction and angiotensin-converting enzyme (ACE) inhibitors in case of heart failure.[7] Finally, adjustment was made for preoperative hemoglobin levels. To evaluate

the effect of medication use (aspirin, statins, ß-blockers and ACE-inhibitors) on long-term outcome, multivariate Cox regression analyses were performed with propensity score adjustment for each medication. Separate propensity scores were developed with logistic regression analyses for each type of medication. Variables included in the propensity score model were demographics (age and gender), cardiovascular risk factors (smoking, hypertension, diabetes mellitus, hypercholesterolemia, renal dysfunction, heart failure and COPD), medication use and hemoglobin. Statistical analyses were performed using SPSS software (SPSS version 15.0; SPSS, Inc., Chicago, Illinois). Hazard ratios (HR) were calculated from these models along with their 95% confidence intervals (95%-CI). A *p*-value <0.05 (two-sided) was considered statistically significant.

RESULTS

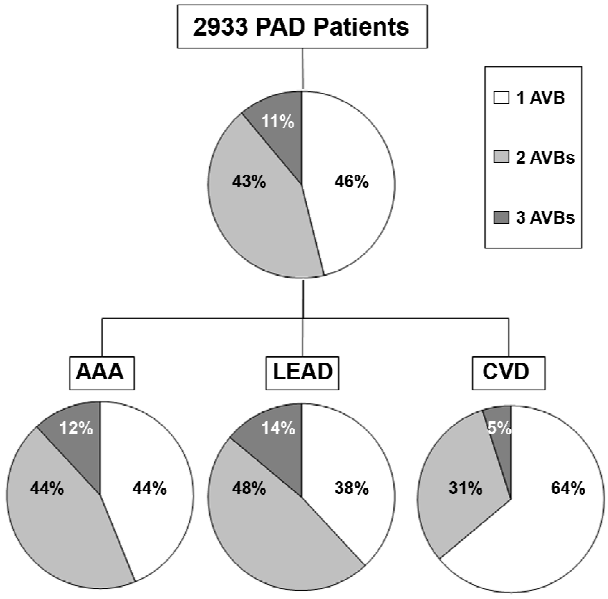
Description of the study population

The study population consisted of 2,933 consecutive patients with PAD referred for elective major vascular surgery. Lower extremity revascularization was performed in 1,031 (35%) patients, abdominal aortic surgery in 1,170 (40%) patients, and carotid surgery in 732 (25%) patients, respectively. Coronary artery and cerebrovascular disease were detected in 1,248 (43%) and 1,037 (35%) patients, respectively. In patients referred for lower extremity revascularization, 454 (44%) and 144 (14%) patients had concomitant documented CAD and CVD, respectively. Coronary artery disease and CVD were present in 575 (49%) and 166 (14%) of the patients referred for abdominal aortic surgery. Patients referred for carotid surgery, 219 (30%) and 79 (11%) patients had concomitant CAD and PAD. The number of affected vascular beds was determined at baseline, and one-vessel disease (1-AVB), two-vessel disease (2-AVB) and three-vessel disease (3-AVB) was detected in 1,369 (46%), 1,249 (43%) and 315 (11%) patients, respectively (*Figure 1*).

Lee cardiac index and number of affected vessels

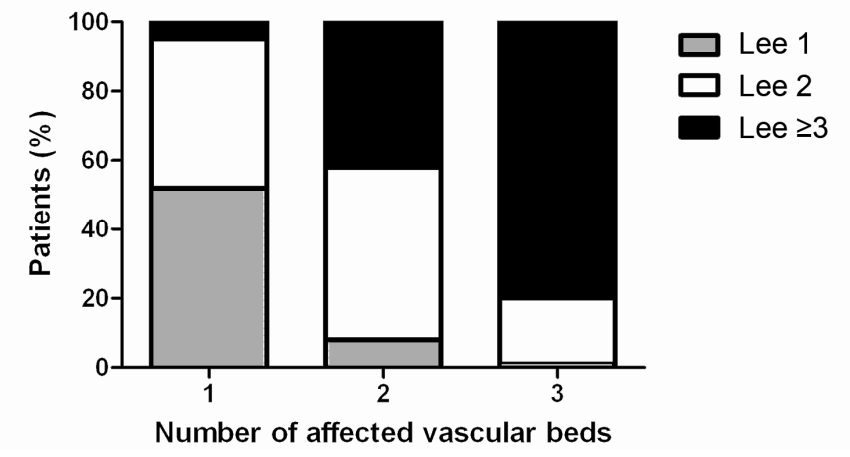
Baseline characteristics of the study population were compared between the groups with different number of affected vascular beds and included demographic parameters and cardiovascular risk factors. A significant trend for an increased number of cardiovascular risk factors was present in patients with 2- or 3-AVB, compared with 1-AVB. Additionally, risk factor patterns were calculated following the Lee cardiac index and showed a relationship with the number of affected vessels. A Lee risk score of ≥3 was only present in 5% of patients with 1-AVB while 252 (80%) patients had a Lee risk score of ≥3 in patients with 3-AVB ($p < 0.001$, *Figure 2*).

Figure 1: Number of affected vascular beds in the total study population and subdivided for type of surgery.



Peripheral arterial disease (PAD), abdominal aortic aneurysm (AAA), lower extremity arterial disease (LEAD), cerebrovascular disease (CVD), affected vascular beds (AVB).

Figure 2: Distribution of the Lee cardiac index according to the number of affected vascular beds.



Medication use and number of affected vessels

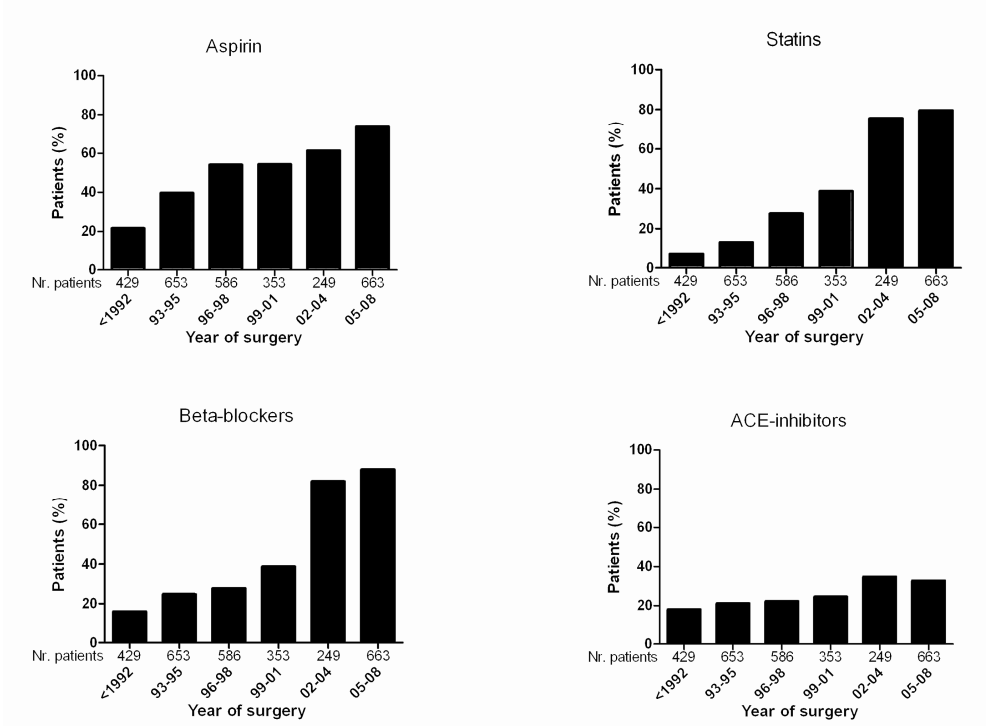
Medication use at time of hospital discharge was registered and compared between the different patient groups (*Table 1*). Aspirin, statins, ß-blockers and ACE-inhibitors were used by 1,502 (51%), 1,131 (39%), 1,293 (44%) and 740 (25%) patients, respectively. There was a clear relationship between the year of surgery and medical treatment intensity after surgery (*Figure 3*). Importantly, aspirin was used in ≥50% of the patients from 1996, whereas statins and ß-blockers were prescribed in ≥50% of the patients from 2002. The number of AVB (1- vs. 2- vs. 3-AVB) showed a relationship with the use of statins (34 vs. 41 vs. 51%, $p < 0.001$), ß-blockers (37 vs. 48 vs. 60%, $p < 0.001$) and ACE-inhibitors (19 vs. 28 vs. 40%, $p < 0.001$). In contrast, there was no significant relationship between the number of AVB and aspirin use (53 vs. 49 vs. 53%, $p = 0.25$).

Table 1 **Baseline characteristics of the study population**

	Total [N=2,933]	1-AVB [N=1,369]	2-AVB [N=1,249]	3-AVB [N=315]	*p*-value
Demographics					
Age (year), mean ± SD	66 (11)	66 (12)	67 (11)	68 (10)	<0.001
Male (%)	2.189 (75)	958 (70)	984 (78)	257 (82)	<0.001
Year of surgery (%)					0.001
< 1992	429 (15)	187 (14)	205 (16)	37 (12)	
1993-1995	653 (22)	323 (24)	270 (22)	60 (19)	
1996-1998	586 (20)	303 (22)	228 (18)	55 (18)	
1999-2001	353 (12)	177 (13)	150 (12)	26 (8)	
2002-2004	249 (9)	96 (7)	112 (9)	41 (13)	
2005-2008	663 (23)	283 (21)	285 (23)	314 (11)	
Cardiovascular risk factors (%)					
Smoking					<0.001
no	1.139 (39)	585 (43)	456 (37)	98 (31)	
current	1.092 (37)	490 (36)	471 (38)	131 (42)	
history	702 (24)	294 (22)	322 (26)	86 (27)	
Hypertension	1.514 (52)	594 (43)	706 (57)	214 (68)	<0.001
Hypercholesterolaemia	798 (27)	289 (21)	392 (31)	117 (37)	<0.001
Renal dysfunction	297 (10)	95 (7)	146 (10)	56 (18)	<0.001
Chronic heart failure	206 (7)	24 (2)	126 (10)	56 (18)	<0.001
COPD	557 (19)	201 (15)	271 (22)	85 (27)	<0.001
Medication at discharge (%)					
Aspirin	1.502 (51)	726 (53)	610 (49)	166 (53)	0.25
Statin	1.131 (39)	463 (34)	506 (41)	162 (51)	<0.001
β-blocking agents	1.293 (44)	506 (37)	599 (48)	188 (60)	<0.001
Diuretics	696 (24)	244 (18)	340 (27)	112 (36)	<0.001
ACE inhibitors	740 (25)	260 (19)	335 (28)	125 (40)	<0.001
Calcium antagonists	711 (24)	265 (19)	360 (29)	86 (27)	<0.001
AT-II antagonists	157 (5)	61 (5)	71 (6)	25 (8)	0.01
Oral anticoagulants	1.108 (38)	463 (34)	505 (40)	140 (44)	<0.001
Ticlopidines	132 (5)	45 (3)	60 (5)	27 (9)	<0.001

Affected vascular beds (AVB), angiotensin converting enzyme (ACE), angiotensin-II (AT-II), chronic obstructive pulmonary disease (COPD).

Figure 3: Postoperative prescription of aspirin, statins, ß-blockers, and ACE-inhibitors stratified according to the year of surgery.



Angiotensin converting enzyme (ACE).

Table 2 **30-day survival**

	Events	Univariate		Multivariate (1)		Multivariate (2)	
	N (%)	OR	[95%-CI]	OR	[95%-CI]	OR	[95%-CI]
All-cause mortality							
1-AVB (N=1,369)	36 (3)	reference		reference		reference	
2-AVB (N=1,249)	57 (5)	1.87	1.22-2.88	1.59	1.01-2.50	1.65	1.03-2.63
3-AVB (N=315)	19 (6)	2.53	1.42-4.50	1.76	0.95-3.27	2.46	1.29-4.71
Cardiovascular mortality							
1-AVB (N=1,369)	29 (3)	reference		reference		reference	
2-AVB (N=1,249)	47 (5)	1.87	1.16-3.00	1.52	0.93-2.50	1.56	0.94-2.60
3-AVB (N=315)	14 (7)	2.23	1.16-4.30	1.44	0.72-2.89	1.94	0.94-4.02

Multivariate (1): adjustment for age, gender, smoking, hypertension, diabetes mellitus, hypercholesterolaemia, renal dysfunction, heart failure, chronic obstructive pulmonary disease, and haemoglobin. Multivariate (2): adjustment for age, gender, smoking, hypertension, diabetes mellitus, hypercholesterolaemia, renal dysfunction, heart failure, chronic obstructive pulmonary disease, haemoglobin + medication use, including: aspirin, statins, ß-blockers, and ACE-inhibitors. Affected vascular beds (AVB), angiotensin converting enzyme (ACE), confidence incidence (CI), odds ratio (OR).

Short-term outcome

During the first 30 postoperative days, 112 (3.8%) patients died, of which 90 (80%) patients died secondary to a cardiovascular cause. Using univariate analysis, patients with 2- or 3-AVB had a significant increased mortality risk compared with patients with 1-AVB (2-AVB: OR 1.9, 95%-CI: 1.22 to 2.88, 3-AVB: OR 2.5, 95%-CI: 1.42 to 4.50), respectively (*Table 2*). This increased risk was present for the occurrence of cardiovascular death as well (2-AVB: OR 1.9, 95%-CI: 1.16 to 3.00, 3-AVB: OR 2.2, 95%-CI: 1.16 to 4.30). In multivariate analysis 2- and 3-AVB were independently associated with all-cause mortality (2-AVB: OR 1.7, 95%-CI: 1.03 to 2.63, 3-AVB: OR 2.5, 95%-CI: 1.29 to 4.71). However, cardiovascular mortality was not longer significantly associated with polyvascular disease during short-term follow-up.

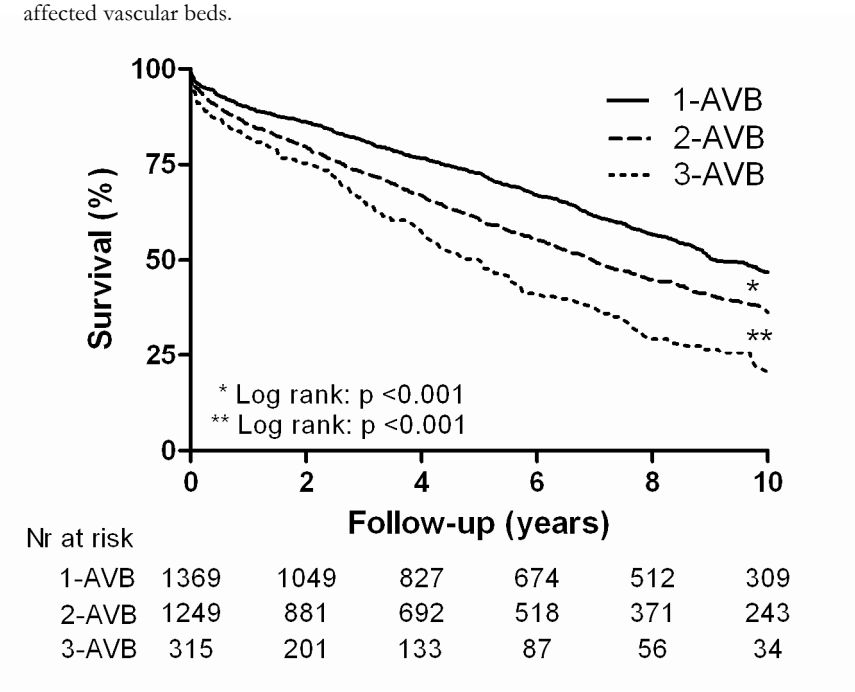
Long-term outcome

After one-year follow-up, 308 (11%) patients died, of which 227 (74%) and 71 (26%) secondary to a cardiovascular or non-cardiovascular cause, respectively. Patients with 2- or 3-AVB had an increased risk for the occurrence of 1-year all-cause mortality (2-AVB: HR 1.3, 95%-CI: 1.03 to 1.7; 3-AVB: HR 1.6, 95%-CI: 1.1 to 2.3) and cardiovascular mortality (2-AVB: HR 1.7, 95%-CI: 1.2 to 2.2; 3-AVB: HR 1.7, 95%-CI: 1.1 to 2.6), compared with patients with 1-AVB, respectively. During long-term follow-up, 1,389 (47%) patients reached the primary endpoint of all-cause mortality. A cardiovascular or non-cardiovascular cause of death was detected in 849 (61%) and 434 (31%) patients, respectively.

In the remaining 106 (3.6%) patients, no specific cause of death could be determined. The occurrence of all-cause mortality showed a significant relationship with the number of affected vascular beds (1-AVB 43%, 2-AVB 50%, 3-AVB 54%, $p < 0.001$). Kaplan-Meier estimates for long-term mortality stratified according the number of AVB showed that patients with 2- or 3-AVB had lower survival compared with patients with 1-AVB (*Figure 4*).

At 1-year follow-up, survival rates in patients with 1-, 2-, and 3-AVB were 91.4, 87.9 and 83.6%, respectively. Furthermore, at 10-year follow-up, survival rates in 1-, 2- and 3-AVB were 48.0, 40.6, 29.2,% respectively. Log rank rest compared cumulative survival between 1- and 2-AVB and 2- and 3-AVB and showed a significant difference in survival between both comparisons ($p < 0.001$). After multivariate regression analysis, adjusted for baseline demographic and risk factors, a strong relationship between the number of AVB and the risk of all-cause and cardiovascular mortality was detected at both 1 and 10 years of follow-up (*Table 3*). During long-term follow-up, patients with 2 or 3-AVB had an increased risk for the occurrence of all-cause mortality (2-AVB: HR 1.3, 95%-CI: 1.15 to 1.45; 3-AVB: HR 1.8, 95%-CI: 1.50 to 2.15), and also for the occurrence of cardiovascular mortality (2-AVB: HR 1.5, 95%-CI: 1.24 to 1.68; 3-AVB: HR 2.0, 95%-CI: 1.60 to 2.51), compared with patients with 1-AVB, respectively.

Figure 4: Kaplan-Meier estimates for long-term all-cause mortality, stratified according to the number of affected vascular beds.



Affected vascular beds (AVB).

Table 3 **Long-term survival**

	Events	Univariate		Multivariate (1)		Multivariate (2)	
	N (%)	HR	[95%-CI]	HR	[95%-CI]	HR	[95%-CI]
All-cause mortality							
1-AVB (N=1,369)	558 (43)	reference		reference		reference	
2-AVB (N=1,249)	630 (50)	1.32	1.18-1.48	1.27	1.13-1.43	1.29	1.15-1.45
3-AVB (N=315)	171 (54)	1.87	1.57-2.22	1.62	1.36-1.94	1.79	1.50-2.15
Cardiovascular mortality							
1-AVB (N=1,369)	334 (24)	reference		reference		reference	
2-AVB (N=1,249)	401 (32)	1.50	1.29-1.73	1.42	1.22-1.65	1.45	1.24-1.68
3-AVB (N=315)	114 (36)	2.14	1.73-2.65	1.81	1.45-2.27	2.00	1.60-2.51

Multivariate (1): adjustment for age, gender, smoking, hypertension, diabetes mellitus, hypercholesterolaemia, renal dysfunction, heart failure, chronic obstructive pulmonary disease, and haemoglobin. Multivariate (2): adjustment for age, gender, smoking, hypertension, diabetes mellitus, hypercholesterolaemia, renal dysfunction, heart failure, chronic obstructive pulmonary disease, haemoglobin + medication use, including: aspirin, statins, ß-blockers, and ACE-inhibitors. Affected vascular beds (AVB), confidence interval (CI), hazard ratio (HR).

Optimal medical therapy according the ESC/ACC guidelines was 57% in the patient group that underwent surgery between 2002 and 2008. During this period, aspirin (HR 0.52, 95%-CI: 0.37 to 0.72), statins (HR 0.38, 95%-CI: 0.27 to 0.53) and ACE-inhibitors (HR 0.32, 95%-CI: 0.11 to 0.94) were significantly associated with lower mortality rates in propensity adjusted analysis. Of note, over 90% of the patients who underwent surgery after 2002 were on perioperative ß-blocker therapy.

DISCUSSION

To our knowledge, the current study is the first to show a strong relationship between the number of affected vessel beds and long-term prognosis in patients with known symptomatic PAD. Compared with 1-AVB, patients with 2- or 3-AVB had significantly higher rates of all-cause and cardiovascular mortality during long-term follow-up after major vascular surgery. The process of atherosclerotic vascular disease is a diffuse progressive condition that usually affects multiple vascular territories concomitantly. All manifestations of arterial diseases are preceded by atherosclerotic plaques formation in the arterial wall. The presence of risk factors like hypertension, diabetes mellitus, smoking and hypercholesterolemia make patients prone for the development of atherosclerotic plaques. Therefore, lifestyle modification and medical treatment are strongly recommended for patients with atherosclerotic disease.[7, 8]

Until now, most data regarding the prevalence and long-term prognosis of patients with polyvascular disease included determination of polyvascular disease in the primary care setting, while follow-up was generally limited to 1-year.[4, 14] In most studies and registries, data on the prevalence of polyvascular disease were mainly on the presence of risk factors, symptoms and medical treatment. Hirsch *et al.* found a prevalence of polyvascular disease (PAD and CVD) of 16% in the primary care setting, which was observed by the REACH registry as well.[1, 15] Recent data from the CRUSCADE investigators in patients presenting with non-ST-segment elevation acute coronary syndrome, reported a prevalence of 12% established PAD, 10% documented CVD, and 43% prior CAD.[16] Objective determination of polyvascular disease by screening and/or additional testing was performed primary by Hertzer *et al.* who observed a prevalence of CAD in 44, 30 and 33% of the PAD patients, respectively.[17] Analysis of the REACH registry showed that 2- or 3-AVB is present in 48 or 14% of PAD patients, respectively.[4] We demonstrated in the current study of patients with known PAD, a documented prevalence of 2- and 3-AVB of 43 and 11%, respectively. The slightly higher prevalence of polyvascular disease in the PAD subset of REACH patients is likely due to the inclusion of patients with ≥3 atherothrombotic risk factors without symptomatic vascular disease, in the REACH registry.

The current study showed a significant association between the presence of multiple risk factors and the presence of polyvascular disease, which was in line with previous studies that focused on the prevalence of risk factors in several atherosclerotic populations.[14, 15, 18] Atherothrombotic risk factor reduction is universally recommended for patients with PAD to reduce their high incidence of heart disease and stroke.[7, 8, 19-21] Although we found that patients with 2- or 3-AVB received better medical treatment compared with patients with lone PAD, there was still a underutilization of medication. In this study, aspirin use was observed in more than 50% of the patients included after 1996 and was associated with increased survival rates, which is in line with a recent meta-analyses.[22] The underutilization of optimal medical therapy is strongly related to the implementation of the guidelines on PAD after 2003, as before the implementation of guidelines only a minority of patients received a combination of aspirin, statins, ACE-inhibitors and in cases of ischemic heart disease additional ß-blockers was used.[7] Thereafter, the use of statins and ß-blockers has strongly increased, and 57% of the patients included in this cohort received optimal medical therapy. As reported by others, aspirin, statins and ACE-inhibitor use were all significantly associated with increased survival rates.[22] The gap between guideline recommendations and clinical practice in PAD patients remains a concerning and significant problem. Potential reasons for this undertreatment could be related to (i) low perception of the risk associated with PAD compared with CAD and CVD, and (ii) the absence of healthcare campaigns directed at providing information to individuals with PAD, especially during the previous decade.

Data regarding the perioperative outcome in the polyvascular patient population are scarce, as most studies are directed at one-year mortality rates. Our study showed that patients with 2- or 3-AVB had higher perioperative mortality rates compared with patients with 1-AVB (5% and 6% vs. 3% $p < 0.001$, respectively). Cardiovascular mortality was present in 75% of the patients that died within the first 30 days after major vascular surgery. In multivariate analyses polyvascular disease was significantly associated with increased all-cause mortality rates. Our data are in keeping with others reporting 30-day mortality rates up to 6%, of which 76% are due to cardiovascular cause in major vascular surgery patients.[18] Bhatt *et al.* reported a 30-day all-cause mortality rate of 7.3% in patients presenting with non-ST-elevation acute coronary syndrome and concomitant 3-AVB. In this study, only 3-AVB was significantly associated with increased all-cause mortality (OR 1.25, 95%-CI: 1.02 to 1.54) in multivariate analysis.[16]

After one-year follow-up, 11% of the patients died of which 74% secondary to a cardiovascular cause. A significant association between the number of AVB and the occurrence of all-cause and cardiovascular mortality was observed. Mortality rates increased from 8% in 1-AVB to 16% in 3-AVB. These findings are in keeping with others, as in the REACH registry one-year all-cause and cardiovascular mortality rates were approximately doubled in patients with polyvascular disease, compared with single arterial disease.[14] Furthermore, the Polyvascular Atherothrombosis Observational Survey (PATHOS) found that

patients with acute myocardial infarction or stroke and concomitant PAD had an increased mortality risk (OR 2.05, 95%-CI: 1.31 to 3.22) compared with patients without PAD.[23] These findings support the need for increased awareness of the cross-risk that is related to the overlap between the various arterial locations of atherothrombosis.

No prior large studies investigated the long-term prognosis of patients with polyvascular atherosclerotic disease up to 10 years. The current study found that after a follow-up period of 5 years, 50% of the patients with 3-AVB had already died, pointing at the grave prognosis of polyvascular disease. Criqui *et al.* performed the first long-term outcome study in 565 patients with large-vessel PAD and detected an increased relative risk for cardiovascular mortality (RR 5.9, 95%-CI: 3.0 to 11.4) after 10-years follow-up, compared with patients without PAD.[5] Eagle *et al.* and Sutton *et al.* observed that during 10-year follow-up, CAD patients with concomitant PAD had a 25% greater likelihood of mortality compared with CAD patients without PAD at any point in time.[24, 25] Recently, Welten *et al.* performed a propensity-matched study in PAD and CAD patients, showing that during a mean follow-up of 6 ± 4 years, patients with PAD had a significantly worse long-term prognosis compared with patients with CAD (unadjusted HR 2.4, 95%-CI: 2.18 to 2.65).[18] Hence, patients with combined PAD, CAD and/or CVD have the worst prognosis. Therefore, early objective detection and treatment of asymptomatic concomitant cardiovascular risk factors in patients with PAD is recommended and strongly emphasized by the current guidelines.[7, 8]

Limitations

Potential limitations of the current study merit consideration. First, this study has the disadvantage of a retrospective design. Second, the standardized protocol for preoperative screening did not include echocardiography before 2002; therefore there could be an underestimation of subclinical atherosclerosis in patients undergoing surgery before this date. In addition, diagnostic methods and accuracy have changed over time, which could have influenced the criteria for the presence of documented CAD or CVD. Third, a specific cause of death could not be established in 3.6% of the patients that died during the follow-up period. One year after the last patient had been included, mortality rates were verified according the civil registries, however, reviewing the death certificates or contacting the treating general practioner could not establish cause of death. Therefore, we performed two additional analyses in which patients for whom cause of death was unknown were regarded either as cardiovascular or noncardiovascular deaths. These analyses found similar results with no influence on the significance of the outcome parameters. Finally, although this study detected significant associations between medical treatment and increased survival rates, these results need to be interpreted with some caution as this study only included medical treatment at discharge and no evaluation of treatment adherence during follow-up was available.

Conclusion

Polyvascular atherosclerotic disease in PAD patients scheduled for elective major vascular surgery is independently associated with an increased risk for all-cause and cardiovascular mortality during long-term follow-up. Peripheral arterial disease patients with polyvascular disease have more atherosclerotic risk factors and receive extended medical treatment, mainly as a result of the implementation of guidelines. However, as PAD patients with polyvascular disease still receive sub-optimal cardioprotective medication, more attention should be given to optimization of life style modification and treatment.

REFERENCES

1. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *Jama.* 2006;295(2):180-189.

2. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet.* 2004;364(9438):937-952.

3. Wilson PW. Framingham and European risk algorithms: implications for African Americans. *Rev Cardiovasc Med.* 2004;5 Suppl 3:S34-41.

4. Cacoub PP, Abola MT, Baumgartner I, et al. Cardiovascular risk factor control and outcomes in peripheral artery disease patients in the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Atherosclerosis.* 2008.

5. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med.* 1992;326(6):381-386.

6. McKenna M, Wolfson S, Kuller L. The ratio of ankle and arm arterial pressure as an independent predictor of mortality. *Atherosclerosis.* 1991;87(2-3):119-128.

7. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation.* 2006;113(11):e463-654.

8. Smith SC, Jr., Blair SN, Bonow RO, et al. AHA/ACC Scientific Statement: AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update: A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation.* 2001;104(13):1577-1579.

9. Fox K, Garcia MA, Ardissino D, et al. [Guidelines on the management of stable angina pectoris; the experts of the European Society of Cardiology on the management of stable angina pectoris]. *Kardiol Pol.* 2006;64(8):823-880.

10. O'Rourke RA, Brundage BH, Froelicher VF, et al. American College of Cardiology/American Heart Association Expert Consensus Document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. *J Am Coll Cardiol.* 2000;36(1):326-340.

11. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina--summary article: a report of the American College of

Cardiology/American Heart Association Task Force on practice guidelines (Committee on the Management of Patients With Chronic Stable Angina). *J Am Coll Cardiol.* 2003;41(1):159-168.

12. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med.* 2007;176(6):532-555.

13. Boersma E, Kertai MD, Schouten O, et al. Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index. *Am J Med.* 2005;118(10):1134-1141.

14. Steg PG, Bhatt DL, Wilson PW, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. *Jama.* 2007;297(11):1197-1206.

15. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *Jama.* 2001;286(11):1317-1324.

16. Bhatt DL, Peterson ED, Harrington RA, et al. Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes. *Eur Heart J.* 2009;30(10):1195-1202.

17. Hertzer NR, Beven EG, Young JR, et al. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Ann Surg.* 1984;199(2):223-233.

18. Welten GM, Schouten O, Hoeks SE, et al. Long-term prognosis of patients with peripheral arterial disease: a comparison in patients with coronary artery disease. *J Am Coll Cardiol.* 2008;51(16):1588-1596.

19. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet.* 1996;348(9038):1329-1339.

20. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002;360(9326):7-22.

21. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med.* 2000;342(3):145-153.

22. Hackam DG, Sultan NM, Criqui MH. Vascular protection in peripheral artery disease: systematic review and modelling study. *Heart.* 2009;95(13):1098-1102.

23. Agnelli G, Cimminiello C, Meneghetti G, et al. Low ankle-brachial index predicts an adverse 1-year outcome after acute coronary and cerebrovascular events. *J Thromb Haemost.* 2006;4(12):2599-2606.

24. Eagle KA, Rihal CS, Foster ED, et al. Long-term survival in patients with coronary artery disease: importance of peripheral vascular disease. The Coronary Artery Surgery Study (CASS) Investigators. *J Am Coll Cardiol.* 1994;23(5):1091-1095.

25. Sutton-Tyrrell K, Rihal C, Sellers MA, et al. Long-term prognostic value of clinically evident noncoronary vascular disease in patients undergoing coronary revascularization in the Bypass Angioplasty Revascularization Investigation (BARI). *Am J Cardiol.* 1998;81(4):375-381.

Chapter 12

Intimamedia thickness of the common carotid artery in vascular surgery patients: a predictor of postoperative cardiovascular events

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ABSTRACT

Background Cardiovascular (CV) complications are the leading cause of morbidity and mortality in vascular surgery patients. The Revised Cardiac Risk (RCR) index, identifying cardiac risk factors, is commonly used for preoperative risk stratification. However, a more direct marker of the underlying atherosclerotic disease, such as the common carotid artery intimamedia thickness (CCA-IMT) may be of predictive value as well. The current study evaluated the prognostic value of the CCA-IMT for postoperative CV outcome.

Methods In 508 vascular surgery patients, the CCA-IMT was measured using high-resolution B-mode ultrasonography. We recorded the RCR factors: ischemic heart disease, heart failure, cerebrovascular disease, diabetes mellitus and renal dysfunction. Repeated troponin T measurements and electrocardiograms were performed postoperatively. The study endpoint was the composite of 30-day CV events and long-term CV mortality. Multivariate regression analyses were used to assess the additional value of CCA-IMT for the prediction of cardiac events.

Results In total, 30-day events and long-term CV mortality were noted in 122 (24%) and 81 (16%) patients, respectively. The optimal predictive value of CCA-IMT, using receiver-operating characteristic curve analysis, for the prediction of CV events was calculated to be 1.25 mm (sensitivity 70%, specificity 80%). An increased CCA-IMT was independently associated with 30-day CV events (OR 2.20, 95%-CI: 1.38 to 3.52) and long-term CV mortality (HR 6.88, 95%-CI: 4.11 to 11.50), respectively.

Conclusions This study shows that an increased CCA-IMT has prognostic value in vascular surgery patients to predict 30-day CV events and long-term CV mortality, incremental to the RCR index.

INTRODUCTION

Cardiovascular (CV) complications are the leading cause of morbidity and mortality in vascular surgery patients.[1] Adequate preoperative evaluation is inevitable to (i) identify patients at increased risk, (ii) initiate risk reduction therapy, and (iii) select optimal surgical and anaesthesia techniques. Heart failure, ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus, and high-risk surgery, as summarised in the Revised Cardiac Risk (RCR) index, have been identified as independent predictors of perioperative CV events.[2, 3] However, a more direct marker of the underlying atherosclerotic disease, such as the common carotid artery intimamedia thickness (CCA-IMT),[4] may be of predictive value as well. Although an increased CCA-IMT is associated with an increased risk for myocardial infarction and stroke,[5, 6] limited information is available concerning the predictive value of an increased CCA-IMT for postoperative CV events in vascular surgery patients. This study evaluated the predictive value of the CCA-IMT for CV events in vascular surgery patients, incremental to the predictive value of the RCR index.

METHODS

Study population

The study population was derived from a cohort of 1,005 consecutive vascular surgery patients undergoing lower extremity artery, abdominal aortic aneurysm, abdominal aortic stenosis, or carotid artery repair during the period between 2002 and 2008. During the period between 2004 and 2008, standard CCA-IMT measurements were performed and 508 consecutive patients with CCA-IMT measurements were included during this time period, with exclusion of patients undergoing carotid artery repair. Both open and endovascular procedures were included. The study was approved by the hospital's ethics committee and performed with informed consent of all patients.

Baseline characteristics

Before surgery, a detailed history was obtained from every patient. Risk factors according to the RCR index were recorded such as: heart failure (defined as the presence of heart failure symptoms according the New York Heart Association classification or previous hospital admission for decompensated heart failure), ischemic heart disease (defined as history of angina pectoris, coronary revascularization, or myocardial infarction), cerebrovascular disease (defined as a history of ischemic or hemorrhagic stroke), renal dysfunction (defined as serum creatinin >2 mg/dL), and diabetes mellitus (defined as fasting blood glucose ≥7.0 mmol/L or requirement for insulin and/or anti-diabetic medication). Cardiac risk score was determined for each patient according the RCR index with one point assigned to each characteristic. Furthermore; age, sex, body mass index, hypertension (blood pressure was measured during preoperative evaluation at the outpatient clinic and hypertension was defined as systolic blood

pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg in nondiabetic patients, systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥80 mmHg in diabetics, or the use of antihypertensive medication), hypercholesterolemia (low-density lipoprotein cholesterol >3.50 mmol/L), chronic obstructive pulmonary disease (according to the Global Initiative on Obstructive Lung Diseases classification), and smoking status were recorded. Finally, use of the following medication was recorded: β-blockers, statins, aspirin, oral anticoagulants, angiotensin-converting enzyme inhibitors, calcium antagonists, and diuretics. Medication use was ascertained if medication was documented at least one month before surgery.

Measurement of the intimamedia thickness

The CCA-IMT was measured according to the 'Mannheim Carotid Intima-Media Thickness Consensus' scanning and reading protocol recommendations.[7-9] Measurements were taken at 10 mm proximal to the carotid bifurcation in the near and far wall of the left and right common carotid artery. Repeated measurements were performed along a minimum of 10 mm length. Four measurements were taken from both the left and right common carotid artery, two of which in the near and two in the far wall. The maximal measurement, of these eight measurements, was used. Plaques (defined as a focal structure encroaching into the arterial lumen of at least 0.5 mm)[7] when present, were not used in the CCA-IMT measurements. Measurements were electrocardiogram-gated at the peak of the QRS complex to control for changes in CCA-IMT during the cardiac cycle. Two sonographers, unaware of the clinical information for each patient, performed the measurements with an interobserver correlation of the 96.2%.

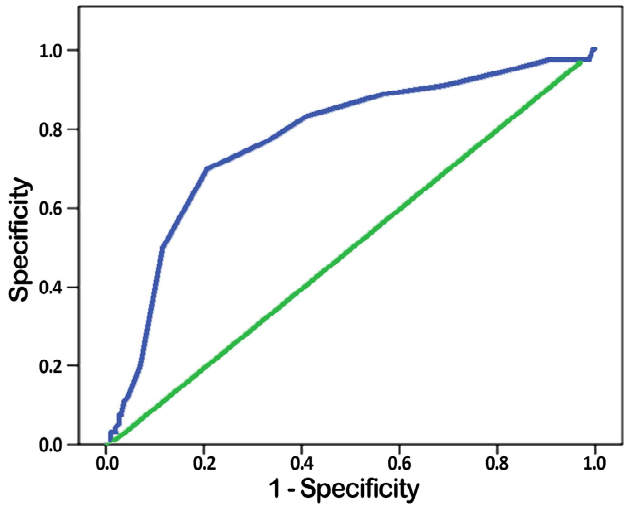
Clinical cardiac outcome and follow-up

Serial electrocardiograms and troponin T measurements were obtained from all patients before surgery, postoperatively on day 1, 3, 7, and before discharge. Main study endpoints were (i) 30-day CV events defined as myocardial infarction, myocardial ischemia, and CV mortality, and (ii) long-term CV mortality. Myocardial ischemia was present when cardiac enzyme levels were elevated >0.03 ng/mL.[10] Myocardial infarction was present when cardiac enzyme levels were elevated >0.03 ng/mL in combination with electrocardiographic changes such as new-onset ST-T changes, new-onset left bundle branch block or development of pathological Q waves.[11] Thirty-day follow-up was completed during regular follow-up visits at the outpatient clinic and, if needed, by reviewing hospital records or the electronic patient file. Long-term mortality was assessed by approaching the municipal civil registries. All surviving patients received a mailed questionnaire and, if needed, survival status was completed by approaching the referring physician. Mortality was considered CV unless explicit proof of a noncardiac cause could be delivered. Mean follow-up was 1.8 ± 1.1 years.

Statistical analysis

Dichotomous data are described as numbers and percentages. The continuous variables age and body mass index are described as means ± SD. Differences in baseline characteristics between CCA-IMT groups were evaluated using χ^2 tests for categorical data. Continuous data were compared using one-way ANOVA. Receiver operating characteristic curve analysis was used to assess the optimal cut off value of CCA-IMT for predicting 30-day CV events and long-term CV mortality. The optimal value of CCA-IMT for predicting 30-day CV events and long-term CV mortality was defined as the concentration with the largest sum of sensitivity plus specificity. Uni- and multivariate logistic regression analysis were performed to evaluate the prognostic value of an increased CCA-IMT towards 30-day CV events and Cox regression analysis towards long-term CV mortality. Multivariate regression analyses were adjusted for age, sex, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, current smoking, β-blocker use, statin use, and aspirin use. We report crude and adjusted odds and hazard ratios (OR and HR) with their 95%-CI. For all tests, a $p < 0.05$ (two-sided) was considered significant. Cumulative long-term survival was determined by the Kaplan-Meier method. All analyses were performed using SPSS version 15.0 statistical software (SPSS, Chicago, IL). No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the article, and its final contents.

Figure 1: Receiver operating characteristics curve analysis of the common carotid artery intimamedia thickness to predict postoperative cardiovascular events. Sensitivity and specificity are plotted for various levels.



RESULTS

A total of 508 patients undergoing lower extremity artery repair (N=245) and abdominal aortic aneurysm or abdominal aortic stenosis repair (N=263) were included in the study. Endovascular procedures comprised 38% of the studied surgical procedures. Mean age was 68 ± 11 years and 78% were men. Mean CCA-IMT (i.e. mean of the maximum CCA-IMT measurements) was 1.07 ± 0.35. In total, 30-day CV events were observed in 122 patients (24%) and long-term CV mortality in 81 patients (16%). The optimal predictive value of CCA-IMT for the prediction of 30-day CV events and long-term CV mortality was calculated to be 1.25 mm (sensitivity 70%, specificity 80%) (*Figure 1*).

Table 1 **Baseline characteristics according to CCA-IMT groups**

	All	CCA-IMT <1.25	CCA-IMT ≥1.25	*p*-value
	[N=508]	[N=363]	[N=145]	
Demographics				
Age (± SD)	68 (11)	67 (11)	71 (10)	0.01
Male (%)	394 (78)	271 (75)	123 (85)	0.01
Body mass index (± SD)	26 (4)	26 (4)	26 (3)	0.70
Medical history (%)				
Heart failure	56 (11)	32 (9)	24 (17)	0.01
Ischemic heart disease	221 (44)	157 (43)	64 (44)	0.86
Cerebrovascular disease	83 (16)	45 (12)	38 (26)	<0.01
Renal dysfunction	103 (20)	63 (17)	40 (28)	0.01
Diabetes mellitus	124 (24)	83 (23)	41 ()28	0.20
Hypertension	340 (67)	235 (65)	105 (72)	0.10
Hypercholesterolemia	249 (49)	174 (48)	75 (52)	0.44
Chronic obstructive pulmonary disease	126 (25)	81 (22)	45 (31)	0.04
Smoker, current	221 (44)	156 (43)	65 (45)	0.70
RCR index (%)				
0-1 risk factors	250 (49)	196 (54)	54 (37)	<0.01
2 risk factors	145 (29)	101 (28)	44 (30)	<0.01
≥3 risk factors	111 (22)	64 (18)	47 (32)	<0.01
Surgery type (%)				
Open	314 (62)	220 (61)	94 (65)	0.376
Medication (%)				
β-blocker	397 (78)	274 (76)	123 (85)	0.02
Statin	343 (68)	241 (66)	102 (70)	0.39
Aspirin	287 (57)	211 (58)	76 (52)	0.24
Oral anticoagulant	87 (17)	57 (16)	30 (21)	0.18
Angiotensin-converting enzyme inhibitor	153 (30)	111 (31)	42 (29)	0.72
Calcium-antagonist	92 (18)	56 (15)	36 (25)	0.01
Diuretic	121 (24)	77 (21)	44 (30)	0.03

Common carotid artery intimamedia thickness (CCA-IMT), revised cardiac risk (RCR), standard deviation (SD).

In total, 145 patients (29%) had an increased CCA-IMT defined as a CCA-IMT ≥1.25 mm. Patients with an increased CCA-IMT were older (71 vs. 67 years, $p = 0.01$) and more likely to be male (85% vs. 75%, $p = 0.013$) compared with patients with a CCA-IMT <1.25 mm. Other factors associated with an increased CCA-IMT were a history of heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, β-blocker use, calcium-antagonist use and diuretic use. Baseline characteristics according the CCA-IMT groups are listed in *Table 1*.

30-day outcome

The study endpoint 30-day CV events was reached in 122 (24%) patients, of which 66 (18%) occurred in patients with a CCA-IMT <1.25 and 56 (39%) in patients with an increased CCA-IMT ($p < 0.01$) as shown in *Table 2*. During 30-day follow-up, 117 (23%) had a nonfatal myocardial event, of which 30 patients (26%) had a myocardial infarction and 87 patients (74%) had myocardial ischemia. In total, 61 (17%) patients with a CCA-IMT <1.25 and 56 (39%) patients with an increased CCA-IMT had a nonfatal myocardial event ($p < 0.01$).

Table 2 **CCA-IMT and postoperative outcome**

		CCA-IMT <1.25	CCA-IMT ≥1.25	Univariate	
		[N=363]	[N=145]		
30-day (%)				**OR**	**[95%-CI]**
Cardiovascular events	[N=122]	66 (18)	56 (39)	2.93	1.85-4.34
All-cause mortality	[N=25]	10 (3)	15 (10)	4.07	1.79-9.30
Long-term (%)				**HR**	**[95%-CI]**
Cardiovascular mortality	[N=81]	24 (7)	57 (39)	6.90	4.23-11.13
All-cause mortality	[N=113]	53 (15)	60 (41)	3.28	2.26-4.77

Confidence interval (CI), common carotid artery intimamedia thickness (CCA-IMT), hazard ratio (HR), odds ratio (OR).

The study endpoint CV mortality was reached in 21 (4%) patients, of which 6 (2%) occurred in patients with a CCA-IMT <1.25 and 15 (10%) in patients with an increased CCA-IMT ($p < 0.01$). Multivariate analysis showed that the RCR index was predictive for 30-day CV events (2 risk factors: OR 1.96, 95%-CI: 1.12 to 3.43; ≥3 risk factors: OR 6.43, 95%-CI: 3.66 to 11.28), as shown in *Table 3 (Model 1)*. When adding CCA-IMT to this model, an increased CCA-IMT was independently associated with 30-day CV events (OR 2.20, 95%-CI: 1.38 to 3.52), as shown in *Table 3 (Model 2*).

Table 3 **Multivariate association between CCA-IMT and 30-day follow-up**

		Model 1 *		Model 2 **	
	[N=508]	OR	[95%-CI]	OR	[95%-CI]
Cardiovascular events					
RCR index ***					
1 risk factor	34/250	1.00		1.00	
2 risk factors	35/146	1.96	1.12-3.43	1.86	1.06-3.28
≥3 risk factors	53/112	6.43	3.66-11.28	5.70	3.21-10.11
CCA-IMT					
<1.25	66/363	-	-	1.00	
≥1.25	56/145	-	-	2.20	1.38-3.52
All-cause mortality					
RCR index ***					
1 risk factor	6/250	1.00	0.90-8.22	1.00	
2 risk factors	9/146	2.73	1.32-12.21	2.42	0.80-7.37
≥3 risk factors	10/112	4.02	0.90-8.22	2.92	0.93-9.15
CCA-IMT					
<1.25	10/363	-	-	1.00	
≥1.25	15/145	-	-	3.76	1.44-8.93

** Model 1: predictive value of RCR index for adverse outcome. Multivariate analyses were adjusted for age, gender, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, current smoking, β-blocker use, statin use, and aspirin use.*

*** Model 2: additional value of CCA-IMT for prediction of adverse outcome additionally to clinical risk factors. Multivariate analysis adjusted for RCR risk factors and risk factors described in model 1. *** RCR risk factors: heart failure, ischemic heart disease, cerebrovascular disease, diabetes mellitus, renal dysfunction, and high-risk surgery.*

Confidence interval (CI), common carotid artery intimamedia thickness (CCA-IMT), odds ratio (OR), revised cardiac risk (RCR).

Long-term outcome

During long-term follow-up, 81 (16%) patients died due to a CV cause. Of these patients, 24 (7%) had a CCA-IMT <1.25 mm and 57 (39%) had an increased CCA-IMT (*Table 2*). Cumulative 5-year survival (log rank $p < 0.01$) is shown in *Figure 2*. Multivariate analyses showed that the RCR index was predictive for CV mortality for patients with 2 and ≥3 risk factors with HRs of 2.02 (95%-CI: 1.05 to 3.88) and 3.81 (95%-CI: 1.95 to 7.45), respectively (*Table 4, Model 1*). When including CCA-IMT in the model (*Table 4, Model 2*), an increased CCA-IMT was independently associated with CV mortality with an HR of 6.57 (95%-CI: 3.93 to 10.96). The incremental value of CCA-IMT in the prediction of CV events is further illustrated in *Figure 3*.

Table 4 **Multivariate association between CCA-IMT and long-term mortality**

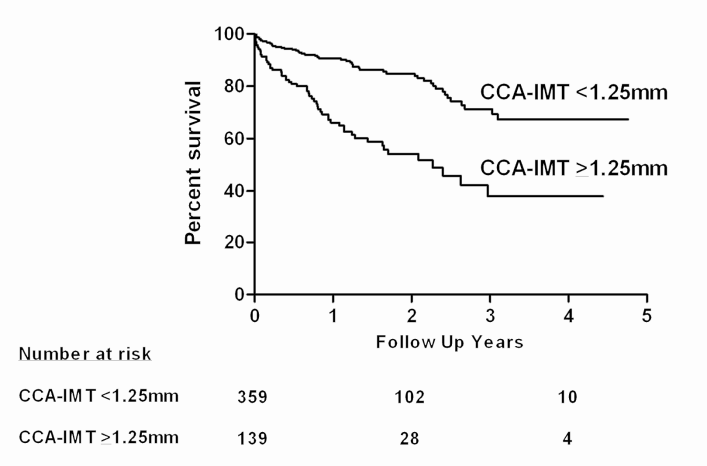
		Model 1 *		Model 2 **	
	[N=508]	HR	[95%-CI]	HR	[95%-CI]
Cardiovascular events					
RCR index ***					
1 risk factor	27/250	1.00		1.00	
2 risk factors	24/146	1.84	1.02-3.35	1.74	0.95-3.19
≥ 3 risk factors	35/112	3.66	2.08-6.43	2.97	1.67-5.29
CCA-IMT					
<1.25	24/363	-	-	1.00	
≥1.25	57/145	-	-	6.88	4.11-11.50
All-cause mortality					
RCR index ***					
1 risk factor	48/250	1.00		1.00	
2 risk factors	37/146	1,53	0.94-2.50	1.50	0.92-2.44
≥3 risk factors	40/112	2.49	1.53-4.04	2.14	1.31-3.49
CCA-IMT					
<1.25	53/363	-	-	1.00	
≥1.25	69/145	-	-	2.88	1.94-4.27

** Model 1: predictive value of RCR index for adverse outcome. Multivariate analyses were adjusted for age, gender, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, current smoking, β-blocker use, statin use, and aspirin use.*

*** Model 2: additional value of CCA-IMT for prediction of adverse outcome additionally to clinical risk factors. Multivariate analysis adjusted for RCR risk factors and risk factors described in model 1. *** RCR risk factors: heart failure, ischemic heart disease, cerebrovascular disease, diabetes mellitus, renal dysfunction, and high-risk surgery.*

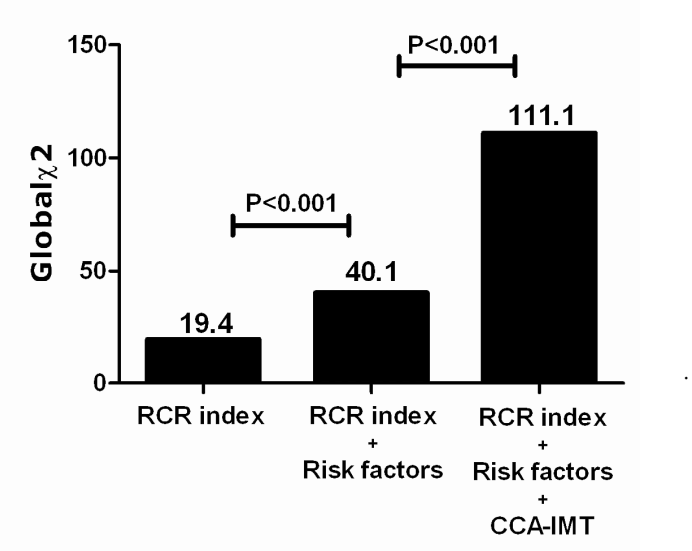
Confidence interval (CI), common carotid artery intimamedia thickness (CCA-IMT), hazard ratio (HR), revised cardiac risk (RCR).

Figure 2: Cumulative long-term survival.



Common carotid artery intimamedia thickness (CCA-IMT).

Figure 3: Incremental value of CCA-IMT in the prediction of postoperative cardiovascular mortality.



Risk factors: age, gender, current smoking, hypercholesterolemia, chronic obstructive pulmonary disease. Common carotid artery intimamedia thickness (CCA-IMT), revised cardiac risk (RCR).

DISCUSSION

To our knowledge, our study is the first to describe the prognostic value of an increased CCA-IMT in patients undergoing vascular surgery. We have found a cut off value (maximum CCA-IMT) of 1.25 mm, using receiver operating characteristic curve analysis, to be most indicative for the prediction of 30-day CV events and long-term CV mortality. In patients with an increased CCA-IMT, the occurrence of 30-day CV events was more than twice as high compared with patients with a CCA-IMT <1.25 mm. The occurrence of long-term CV mortality was more than five times higher in patients with an increased CCA-IMT compared with patients with a CCA-IMT <1.25 mm.

Atherosclerosis, a systemic inflammatory disease, is known to affect multiple sections of the arterial tree simultaneously. Previous studies have demonstrated a correlation between an increased CCA-IMT with cardiac risk factors and coronary atherosclerosis.[12-14] However, the extent of the atherosclerotic process is thought to differ between the vascular beds. In the general population, the median carotid IMT ranges from 0.5 to 1.0 mm,[15] and the CCA-IMT is considered increased being >1.0 mm.[16] In the prediction of myocardial infarction and stroke, The Rotterdam Study found the average maximum CCA-IMT to be 1.03 ± 0.22 and divided the carotid IMT into quartiles based on the population distribution. Using maximal CCA-IMT cut off values of 0.88, 0.99, and 1.12 mm, they have defined mild, moderate, and severe thickening of the carotid wall, respectively.[12, 17] The Multi-Ethnic Study of Atherosclerosis

study also divided the maximal common carotid IMT in quartiles and found cut off values of 0.74, 0.84, 0.97, and 2.45 mm, respectively.[18] Our study population consisted of major vascular surgery patients, which are prone to have atherosclerosis. In comparison, the Rotterdam study and Multi-Ethnic Study of Atherosclerosis study were population-based studies. As patients with operable vascular disease may have more diffuse and more severe vascular disease, this might explain our relatively high cut off value for CCA-IMT to predict future CV events.

The carotid IMT is increasingly used as a surrogate marker of early atherosclerosis, which is associated with CV diseases such as myocardial infarction, stroke and peripheral arterial disease. Several studies have demonstrated that carotid IMT is associated with risk of CV events.[5, 19] This study was performed to evaluate the predictive value of the CCA-IMT for preclinical stages of atherosclerosis. Therefore, focal thickened regions in the carotid arteries were excluded, as they reflect later stages of atherosclerosis. A meta-analysis performed by Lorenz *et al*,[12] in which 37,197 patients were included, provided data on the use of carotid IMT to predict myocardial infarction and stroke in the general population. In this study an absolute carotid IMT difference of 0.1 mm was associated with an increased risk for myocardial infarction of 10 to 15% and an increased risk for stroke of 13 to 18%. However, as reported in the Mannheim Carotid IMT Consensus statement, the Food and Drug Administration does not yet approve carotid IMT as a surrogate marker of vascular events. Although, it is stated that carotid IMT is the most important candidate to be studied, as an independent marker for CV events.[7] To our knowledge, the prognostic value of an increased CCA-IMT has not been previously described in patients undergoing vascular surgery. Only limited information is available regarding the prognostic value of CCA-IMT in patients undergoing cardiac interventions. Lacroix *et al*.[20] evaluated whether CCA-IMT thickening was related to an increased risk of CV events after percutaneous transluminal coronary angioplasty. Univariate analysis demonstrated that a CCA-IMT >0.7 mm was associated with increased CV events after percutaneous transluminal coronary angioplasty ($p = 0.03$). They concluded CCA-IMT could be useful to identify high-risk patients. Aboyans *et al*.[21] enrolled 609 patients undergoing coronary artery bypass grafting and hypothesized CCA-IMT could be used for perioperative and long-term risk stratification. However, in multivariate analysis, CCA-IMT failed to be an independent predictor for secondary CV events after coronary artery bypass grafting. Both studies mentioned above included patients with known coronary artery disease and long-term follow-up included nonfatal CV events as well. This might explain our relatively high cut off value for CCA-IMT to predict future CV events.

The 'American Society of Echocardiography Carotid IMT task force' have stated that carotid IMT imaging should not be performed in patients with established atherosclerotic vascular disease or if the results would not be expected to alter therapy. They recommend prospective studies to investigate the effectiveness of carotid ultrasound imaging in support to improve CV outcome.[5] It is suspected that 95% of the episodes of perioperative myocardial infarction and ischemia are asymptomatic,[1, 22-25] and subsequently, these patients do not receive

adequate treatment. We have shown that an increased CCA-IMT is an independent predictor of perioperative myocardial infarction and ischemia and could therefore contribute to optimize medical treatment as well. With current ultrasound scanners, CCA-IMT can be easily used in clinical routine for objective and reproducible cardiac risk assessment. Importantly, CCA-IMT has an additional value, incremental to subjective cardiac risk assessment using the RCR index. Validation of our results in future studies is needed to justify the recommendation of standard CCA-IMT measurements in preoperative risk stratification of vascular surgery patients.

Potential limitations of these data merit consideration. First, the study population consisted of patients referred to a tertiary referral center and may not fully represent a general population scheduled for elective major vascular surgery. Second, although two experienced investigators performed offline assessments of the obtained ultrasound images, we cannot rule out interobserver variability to have had minor influence on our results.[26] Third, we did not validate the CCA-IMT cut off point in a prospective group of patients undergoing vascular surgery.

In conclusion, the present study shows that an increased CCA-IMT of ≥1.25 mm has a prognostic value in vascular surgery patients to predict 30-day CV events and long-term, incremental to the widely used RCR index.

REFERENCES

1. Mangano DT. Perioperative medicine: NHLBI working group deliberations and recommendations. *J Cardiothorac Vasc Anesth.* 2004;18(1):1-6.

2. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med.* 1977;297(16):845-850.

3. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation.* 1999;100(10):1043-1049.

4. de Groot E, Hovingh GK, Wiegman A, et al. Measurement of arterial wall thickness as a surrogate marker for atherosclerosis. *Circulation.* 2004;109(23 Suppl 1):III33-38.

5. Dickstein. ESC Guidelines for the diagnosing and treatment of acute and chronic heart failure 2008. *Eur Heart J.* 2008;10:1093.

6. Bots ML, Hoes AW, Koudstaal PJ, et al. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation.* 1997;96(5):1432-1437.

7. Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. *Cerebrovasc Dis.* 2007;23(1):75-80.

8. Poldermans D, Bax JJ, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: The Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur Heart J.* 2009.

9. Wendelhag I, Gustavsson T, Suurkula M, et al. Ultrasound measurement of wall thickness in the carotid artery: fundamental principles and description of a computerized analysing system. *Clin Physiol.* 1991;11(6):565-577.

10. Aviles RJ, Askari AT, Lindahl B, et al. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. *N Engl J Med.* 2002;346(26):2047-2052.

11. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *Eur Heart J.* 2007;28(20):2525-2538.

12. Lorenz MW, Markus HS, Bots ML, et al. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation.* 2007;115(4):459-467.

13. Bots ML, Baldassarre D, Simon A, et al. Carotid intima-media thickness and coronary atherosclerosis: weak or strong relations? *Eur Heart J.* 2007;28(4):398-406.

14. Baldassarre D, Amato M, Pustina L, et al. Measurement of carotid artery intima-media thickness in dyslipidemic patients increases the power of traditional risk factors to predict cardiovascular events. *Atherosclerosis.* 2007;191(2):403-408.

15. Howard G, Sharrett AR, Heiss G, et al. Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. ARIC Investigators. *Stroke.* 1993;24(9):1297-1304.

16. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. *Arterioscler Thromb.* 1991;11(5):1245-1249.

17. van der Meer IM, Bots ML, Hofman A, et al. Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction: the Rotterdam Study. *Circulation.* 2004;109(9):1089-1094.

18. Folsom AR, Kronmal RA, Detrano RC, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). *Arch Intern Med.* 2008;168(12):1333-1339.

19. Touboul PJ, Hernandez-Hernandez R, Kucukoglu S, et al. Carotid artery intima media thickness, plaque and Framingham cardiovascular score in Asia, Africa/Middle East and Latin America: the PARC-AALA study. *Int J Cardiovasc Imaging.* 2007;23(5):557-567.

20. Lacroix P, Aboyans V, Espaliat E, et al. Carotid intima-media thickness as predictor of secondary events after coronary angioplasty. *Int Angiol.* 2003;22(3):279-283.

21. Aboyans V, Guilloux J, Lacroix P, et al. Common carotid intima-media thickness measurement is not a pertinent predictor for secondary cardiovascular events after coronary bypass surgery. A prospective study. *Eur J Cardiothorac Surg.* 2005;28(3):415-419.

22. McCann RL, Clements FM. Silent myocardial ischemia in patients undergoing peripheral vascular surgery: incidence and association with perioperative cardiac morbidity and mortality. *J Vasc Surg.* 1989;9(4):583-587.

23. Badner NH, Knill RL, Brown JE, et al. Myocardial infarction after noncardiac surgery. *Anesthesiology.* 1998;88(3):572-578.

24. Haagensen R, Steen PA. Perioperative myocardial infarction. *Br J Anaesth.* 1988;61(1):24-37.

25. Ouyang P, Gerstenblith G, Furman WR, et al. Frequency and significance of early postoperative silent myocardial ischemia in patients having peripheral vascular surgery. *Am J Cardiol.* 1989;64(18):1113-1116.

26. Velazquez F, Berna JD, Abellan JL, et al. Reproducibility of sonographic measurements of carotid intima-media thickness. *Acta Radiol.* 2008;49(10):1162-1166.

Chapter 13

Asymptomatic low ankle-brachial index in vascular surgery patients: a predictor of perioperative myocardial damage

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ABSTRACT

Objectives This study evaluated the prognostic value of asymptomatic low ankle-brachial index (ABI) to predict perioperative myocardial damage, incremental to conventional cardiac risk factors imbedded in preoperative cardiac risk indices (Revised Cardiac Risk index and Adapted Lee index).

Methods Preoperative ABI measurements were performed in 627 consecutive vascular surgery patients (carotid artery or abdominal aortic aneurysm repair). An ABI <0.90 was considered abnormal. Patients with ABI >1.40 or (a history of) intermittent claudication were excluded. Serial troponin T measurements were performed routinely before and after surgery. The main study endpoint was perioperative myocardial damage, the composite of myocardial ischemia and infarction. Multivariate regression analyses, adjusted for conventional risk factors, evaluated the relation between asymptomatic low ABI and perioperative myocardial damage.

Results In total, 148 (23%) patients had asymptomatic low ABI (mean 0.73, standard deviation ± 0.13). Perioperative myocardial damage was recorded in 107 (18%) patients. Multivariate regression analyses demonstrated that asymptomatic low ABI was associated with an increased risk of perioperative myocardial damage (OR 2.4, 95%-CI: 1.4 to 4.2).

Conclusions This study demonstrated that asymptomatic low ABI has a prognostic value to predict perioperative myocardial damage in vascular surgery patients, incremental to risk factors imbedded in conventional cardiac risk indices.

INTRODUCTION

Cardiac complications form the leading cause of postoperative morbidity or mortality, with a prevalence reported to range between 2.2 an 19.0% in vascular surgery patients.[1] The high incidence of perioperative cardiac complications reflects the high prevalence of underlying ischemic heart disease.[2, 3] Adequate preoperative evaluation is inevitable in vascular surgery patients to (i) identify patients at increased cardiac risk (ii) initiate risk-reduction therapy and (iii) select optimal surgical and anaesthesia techniques. In conventional preoperative cardiac risk indices (Revised Cardiac Risk index and Adapted Lee index), age, heart failure, ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus, and high-risk surgery have been identified as independent predictors of perioperative cardiovascular events.[4, 5]

Peripheral arterial disease (PAD) is associated with an increased risk of cardiovascular mortality and morbidity. The ankle-brachial index (ABI) is a simple noninvasive test to screen patients with suspected PAD.[6, 7] In the nonsurgical setting, a resting low ABI (<0.90) has been associated with a two- to fourfold increased risk of cardiovascular mortality or severe cardiovascular events compared with normal ABI.[7-10] Low ABI has demonstrated to improve risk prediction for cardiovascular mortality and major nonfatal myocardial infarction (nonsurgical setting), even beyond risk prediction properties using cardiac risk scores.[9, 11] However, the predictive value of asymptomatic low ABI for perioperative myocardial damage has not been studied yet. The current study evaluated if asymptomatic low ABI has a predictive value for perioperative myocardial damage, independent from conventional risk factors imbedded in cardiac risk indices.

MATERIAL AND METHODS

Study population

The original study population consisted of 1,113 consecutive patients undergoing vascular surgery during the period between 2002 and 2009. The study was performed at the Erasmus Medical Center in Rotterdam, a tertiary hospital in the Netherlands. After exclusion of (i) lower extremity arterial or abdominal aortic stenosis repair patients, (ii) patients with (a history of or current) intermittent claudication assessed with the Edinburgh questionnaire,[12] and (iii) patients with asymptomatic ABI >1.40,[13] a total 627 patients were included (*Figure 1*). The study was approved by the hospital's ethics committee and performed with the informed consent of all patients.

Baseline characteristics

Before surgery, a detailed history was obtained from every patient. Clinical data included: age, sex, ischemic heart disease (defined as a history myocardial infarction, coronary

revascularization or the presence of pathologic Q-waves on preoperative electrocardiogram), cerebrovascular disease (defined as a history of ischemic or haemorrhagic stroke), renal dysfunction (serum creatinine >2.0 mg/dL), diabetes mellitus (fasting blood glucose ≥6.1 mmol/L or requirement of anti-diabetic medication), hypertension (blood pressure ≥140/90 mmHg in non-diabetic patients and ≥130/80 mmHg in diabetics or requirement of antihypertensive medication), hypercholesterolemia (history of hypercholesterolemia or low-density lipoprotein cholesterol >3.5 mmol/L), chronic obstructive pulmonary disease (history of chronic obstructive pulmonary disease or according the Global Initiative on Obstructive Lung Diseases classification), and smoking status. The use of the prescription medication was recorded and included β-blockers, statins, angiotensin-converting enzyme inhibitors, aspirin and, oral anticoagulants. Preoperatively, transthoracic echocardiography was performed in all patients using a hand-held Acuson Cypress Ultrasound System (7V3c transducer) manufacturers address 1220 Charleston Road, Mountain View, CA 94043. Standard parasternal and apical two- and four-chamber views were obtained during rest with the patient in the left lateral decubitus position, as recommended.[14] Left ventricular end-systolic and end-diastolic volumes were determined and left ventricular ejection fraction was calculated using the biplane Simpson's technique.[15] Systolic left ventricular dysfunction was defined as left ventricular ejection fraction <50%.

Ankle-brachial index

The ABI at rest was measured in each patient by trained technicians, using a Doppler ultrasonic instrument with an 8-MHz vascular probe (Imexdop CT+ Vascular Doppler; Nicolet Vascular, Madison, WI, USA). The ABI in the right and left leg was calculated by dividing the right and the left ankle pressures by the brachial pressure. The higher of the two brachial blood pressures was used if a discrepancy in systolic blood pressure was present. Further, the higher of the dorsalis pedis and posterior tibial artery pressures was used if a discrepancy in systolic blood pressure between the two arteries was measured.[16] Asymptomatic low ABI was defined as an ABI <0.90 with an inter- and intraobserver agreement of 97 and 98%, as shown previously.[17]

Study outcomes

The main study endpoints were perioperative myocardial damage (defined as nonfatal myocardial ischemia or infarction up to 30 days after surgery) and long-term mortality. Serial electrocardiograms and troponin T measurements were obtained from all patients before surgery, postoperatively on days 1, 3, 7 and before discharge. Myocardial ischemia was present in patients with normal preoperative and elevated (>0.03 ng/mL) troponin T levels postoperatively.[18] Elevated troponin T levels in combination with electrocardiographic changes (new-onset ST-T changes and pathological Q-waves) or symptoms of angina pectoris defined myocardial infarction.[19] Patients with elevated troponin T levels before surgery were not included in the study. Long-term mortality was assessed by approaching the municipal civil registries. Median follow-up was 2 years (interquartile range [IQR] 1 to 3).

Statistical analysis

Dichotomous data are described as numbers and percentages. Continuous variables are described as mean ± standard deviation (SD). Continuous data were compared using one-way ANOVA and categorical data were compared using a χ^2 test. Logistic regression analyses were performed to evaluate the relationship between asymptomatic low ABI and perioperative myocardial damage. Cox regression analyses were performed to evaluate the relationship between asymptomatic low ABI and long-term mortality. Cumulative long-term survival was determined using the Kaplan-Meier method. Multivariate regression analyses were adjusted for sex, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease, current smoking and risk factors imbedded in conventional cardiac risk indices (age, ischemic heart disease, symptomatic heart failure, cerebrovascular disease, renal dysfunction, diabetes mellitus, and high-risk surgery). We report both the crude and the adjusted odds ratio (OR) and hazard ratio (HR) with their 95% confidence intervals (95%-CI). For all tests, a *p*-value <0.05 (two-sided) was considered significant. All analyses were performed using SPSS version 15.0 statistical software (SPSS, Inc., Chicago, IL, USA).

RESULTS

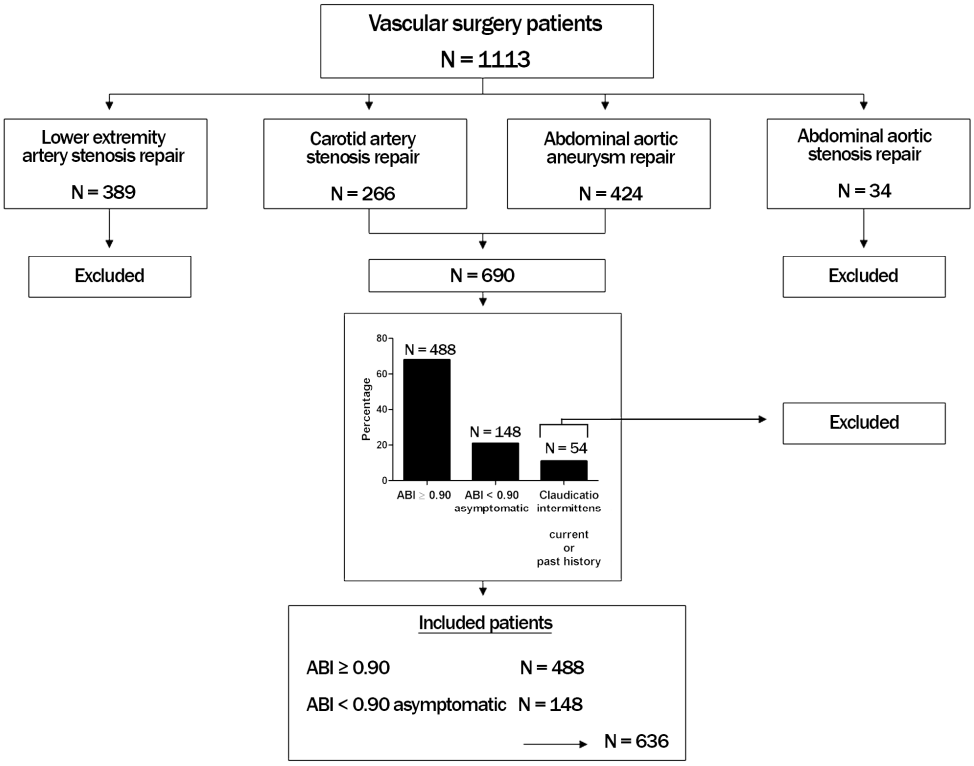
Prevalence of PAD and baseline characteristics

The initial study population consisted of 690 patients. In total, 54 patients with (a history of) intermittent claudication and nine patients with an asymptomatic ABI >1.40 were excluded from the analyses. Therefore, 627 patients, without (a history of) intermittent claudication, undergoing carotid artery stenosis (N=241), or abdominal aortic aneurysm (N=386) repair were included in the study. In total, 148 (23%) patients had asymptomatic low ABI (mean 0.73, SD ± 0.13). The distribution of asymptomatic low ABI values is demonstrated in *Figure 2*. In addition, baseline characteristics stratified to ABI are shown in *Table 1*. The majority of patients were males (82%) and the mean age was 70 (SD ± 8.6) years. Asymptomatic low ABI was associated with ischemic heart disease, renal dysfunction, smoking and a left ventricular ejection fraction <50%.

Perioperative myocardial damage

The study endpoint perioperative myocardial damage, was reached in 107 (17%) patients, as shown in *Table 2*. Of these patients, 76 (71%) had myocardial ischemia and 31 (29%) had myocardial infarction. Symptoms of angina pectoris were reported in only six (6%) patients. As demonstrated in *Table 2*, the prevalence of perioperative myocardial damage was the highest in patients undergoing abdominal aortic aneurysm repair or open surgery. In addition, 32% (47/148) of patients with asymptomatic low ABI had perioperative myocardial damage, compared with 13% (60/479) of patients with normal ABI.

Figure 1: Overview of the selected patient population.



Ankle-brachial index (ABI).

Multivariate analyses showed that risk factors imbedded in the Revised Cardiac Risk index and Adapted Lee index (combined risk factors) were predictive for perioperative myocardial damage, as shown in *Table 3A, Model 1*. When including ABI in the model (*Table 3A Model 2 + 3*), asymptomatic low ABI was independently associated with an increased risk of perioperative myocardial damage with an OR of 2.4 (95%-CI: 1.4 to 4.2). The risk for developing myocardial damage was higher in patients with asymptomatic ABI <0.70 (OR 2.6, 95%-CI: 1.4 to 5.1) compared with patients with asymptomatic ABI 0.70-0.89 (OR 2.3, 95%-CI: 1.3 to 4.4). In addition, patients with low ABI and (a history of) intermittent claudication had the highest risk for developing perioperative myocardial damage (OR 2.8, 95%-CI: 1.2 to 6.4). Multivariate sub-analyses performed in patients undergoing abdominal aortic aneurysm repair, and patients undergoing carotid repair separately, demonstrated that asymptomatic low ABI was associated with an increased risk for myocardial damage in both groups with ORs of 1.9 (95-CI: 1.1 to 3.6) and 5.3 (95%-CI: 2.4 to 19.8), respectively.

Table 1 **Baseline characteristics of the study population**

	ABI ≥0.9	ABI <0.9	*p*-value
	[N=479]	[N=148]	
Demographics			
Age (± SD)	70 (9)	69 (8)	0.91
Body mass index (± SD)	26 (3)	26 (4)	0.94
Male (%)	378 (79)	130 (88)	0.02
Medical history (%)			
Ischemic heart disease	183 (37)	71 (48)	0.01
Clinical heart failure	48 (10)	19 (13)	0.30
Cerebrovascular disease	231 (48)	69 (47)	0.73
Renal dysfunction	67 (14)	33 (23)	0.03
Diabetes mellitus	117 (24)	38 (29)	0.57
Hypertension	278 (63)	82 (65)	0.61
Hypercholesterolemia	287 (61)	67 (62)	0.78
Chronic obstructive pulmonary disease	155 (32)	56 (38)	0.22
Smoking, current	162 (34)	69 (46)	0.01
Echocardiography (%)			
Left ventricular ejection fraction <50%	79 (17)	50 (34)	<0.01
Medication (%)			
β-blockers	368 (77)	121 (82)	0.21
Statins	357 (75)	99 (67)	0.08
Angiotensin-converting enzyme inhibitors	120 (27)	40 (32)	0.37
Aspirin	287 (60)	81 (55)	0.26
Oral anticoagulants	57 (12)	26 (18)	0.08

Ankle-brachial index (ABI), standard deviation (SD).

Table 2 **Ankle-brachial index and postoperative outcome**

		ALL		ABI ≥0.9		ABI <0.9		*p*-value
		[N=627]		[N=479]		[N=148]		
Perioperative myocardial damage								
All	procedures	107/6	(17)	60/479	(13)	47/148	(21)	<0.01
AAA	open procedures	67/20	(32)	42/148	(28)	25/60	(42)	<0.01
	endovascular procedures	20/17	(11)	9/138	(6)	11/40	(28)	<0.01
Carotid	open procedures	16/15	(10)	8/125	(7)	8/31	(26)	<0.01
	endovascular procedures	4/85	(5)	1/68	(2)	3/17	(18)	<0.01
Long-term mortality								
All	procedures	111/6	(18)	74/479	(15)	43/148	(27)	<0.01
AAA	open procedures	60/20	(29)	36/148	(24)	24/60	(40)	<0.01
	endovascular procedures	33/17	(19)	23/138	(17)	10/40	(25)	<0.01
Carotid	open procedures	13/15	(8)	10/125	(8)	6/31	(19)	<0.01
	endovascular procedures	5/85	(6)	2/68	(3)	3/17	(18)	<0.01

Abdominal aortic aneurysm (AAA), ankle-brachial index (ABI).

Long-term mortality

In total, 111 (18%) patients died during follow-up (*Table 2*) and the prevalence of long-term mortality was the highest in patients undergoing abdominal aortic aneurysm repair. Of the

patients who died, 36% (40/111) had perioperative myocardial damage and 39% (43/111) patients had asymptomatic low ABI. Cumulative 6-year survival (log rank $p < 0.01$) is shown in *Figure 3*. Survival rates in patients with normal ABI and asymptomatic low ABI were (i) 87 ± 2% and 72 ± 5% during a two-year follow-up, (ii) 76 ± 3% and 59 ± 6% during a four-year follow-up, and (iii) 60 ± 6% and 48 ± 9% during six-year follow-up, respectively.

Multivariate analyses showed that the combined risk factors were predictive for long-term mortality, as shown in *Table 3B, Model 1*. When including ABI in the model (*Table 3B Model 2 + 3*), asymptomatic low ABI was independently associated with an increased risk of long-term mortality with an HR of 1.9 (95%-CI: 1.2 to 2.8). The risk of long-term mortality was higher in patients with asymptomatic ABI <0.70 (HR 2.4, 95%-CI: 1.5 to 3.8) compared with patients with asymptomatic ABI 0.70 to 0.89 (HR 1.6, 95%-CI: 1.1 to 2.6). In addition, patients with low ABI and (a history of) intermittent claudication had the highest risk of long-term mortality (HR 3.0, 95%-CI: 1.2 to 3.4).

Multivariate sub-analyses performed in patients undergoing abdominal aortic aneurysm repair and patients undergoing carotid repair separately, demonstrated that asymptomatic low ABI was associated with an increased risk for long-term mortality in both groups with HRs of 1.8 (95%-CI: 1.2 to 3.0) and 2.3 (95%-CI: 1.7 to 7.9), respectively.

Table 3A **Multivariate association between ABI and myocardial damage**

	Model 1[a]		Model 2[b]		Model 3[c]	
	OR	[95%-CI]	OR	[95%-CI]	OR	[95%-CI]
Combined risk factors						
Age (>70 years)	1.6	2.1-5.2	1.4	1.9-5.0	1.4	1.9-4.8
Symptomatic heart failure	3.2	1.7-5.5	3.1	1.6-5.8	3.1	1.6-6.0
Ischemic heart disease	2.4	1.3-4.6	2.6	1.5-5.2	2.7	1.7-5.3
Cerebrovascular disease	1.4	1.9-6.1	1.6	1.9-6.7	1.7	2.0-6.9
Renal dysfunction	1.7	1.8-7.7	1.5	1.6-7.3	1.5	1.6-7.2
Diabetes mellitus[d]	1.2	1.1-3.0	1.3	1.2-3.3	1.3	1.2-3.4
High-risk surgery	7.3	3.6-14.6	8.4	3.8-18.4	9.2	4.0-21.0
ABI						
≥0.90	-	-	reference		reference	
<0.90 asymptomatic	-	-	2.4	1.4-4.1	2.4	1.4-4.2
<0.90 intermittent claudication	-	-	2.7	1.2-6.0	2.8	1.2-6.4

[a] Model 1: Predictive value of combined risk factors derived from the Revised Cardiac Risk and Adapted Lee Risk indices: multivariate analyses adjusted for: sex, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease and current smoking. [b] Model 2: Predictive value of low ABI: multivariate analyses adjusted for combined risk factors, sex, left ventricular ejection fraction <40%, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease and current smoking. [c] Model 3: Predictive value of low ABI: multivariate analyses adjusted as in model 2 and for medication use (β-blockers, statins, aspirin, oral anticoagulants, and angiotensin-converting enzyme inhibitors). [d] insulin dependent. Ankle-brachial index (ABI), confidence interval (CI), odds ratio (OR).

Table 3B **Multivariate association between ABI and long-term mortality**

	Model 1[a]		Model 2[b]		Model 3[c]	
	HR	[95%-CI]	HR	[95%-CI]	HR	[95%-CI]
Combined risk factors						
Age (>70 years)	3.2	1.3-4.2	3.0	1.2-4.3	3.0	1.2-4.2
Symptomatic heart failure	2.6	1.6-3.4	2.5	1.6-4.0	2.3	1.4-3.7
Ischemic heart disease	2.0	1.2-4.9	1.8	1.1-5.2	1.7	1.1-5.4
Cerebrovascular disease	1.2	1.1-3.2	1.3	1.2-3.8	1.3	1.1-3.9
Renal dysfunction	2.3	1.6-4.0	1.9	1.1-3.7	1.9	1.1-3.6
Diabetes mellitus [d]	1.2	1.2-3.5	1.7	1.4-3.7	1.7	1.4-3.8
High-risk surgery	2.9	1.6-3.4	2.0	1.2-3.8	1.9	1.1-3.7
ABI						
≥0.90	-	-		reference		reference
<0.90 asymptomatic	-	-	2.0	1.3-3.0	1.9	1.2-2.8
<0.90 intermittent claudication	-	-	3.1	1.2-3.6	3.0	1.2-3.4

[a] Model 1: Predictive value of combined risk factors derived from the Revised Cardiac Risk and Adapted Lee Risk indices: multivariate analyses adjusted for: sex, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease and current smoking. [b] Model 2: Predictive value of low ABI: multivariate analyses adjusted for combined risk factors, sex, left ventricular ejection fraction <40%, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease and current smoking. [c] Model 3: Predictive value of low ABI: multivariate analyses adjusted as in model 2 and for medication use (β-blockers, statins, aspirin, oral anticoagulants, and angiotensin-converting enzyme inhibitors). [d] insulin dependent. ankle-brachial index (ABI), confidence interval (CI), hazard ratio (HR).

Figure 2: Distribution of ankle-brachial index (ABI) <0.90 in asymptomatic patients.

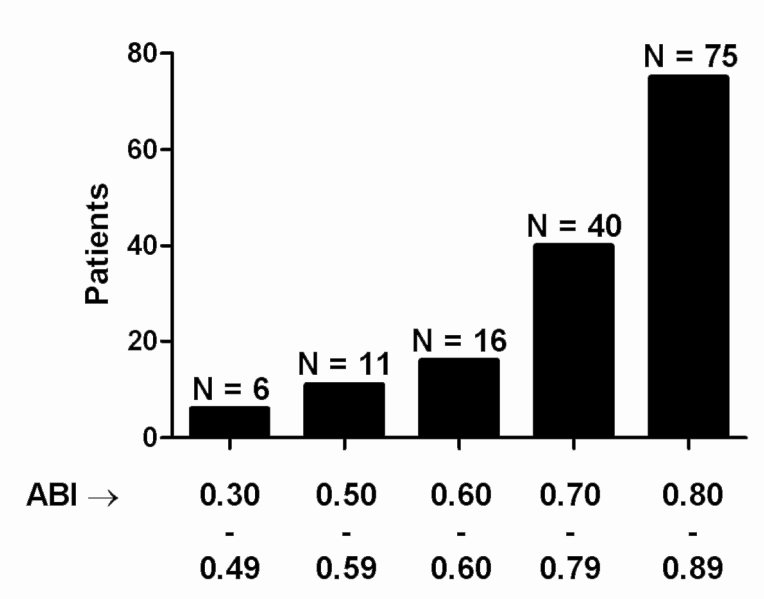
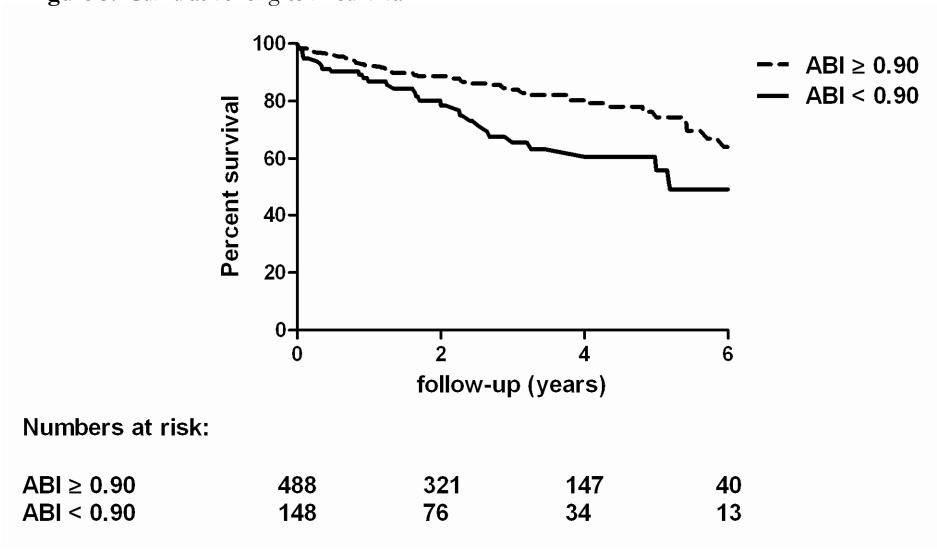


Figure 3: Cumulative long-term survival.



Ankle-brachial index (ABI).

DISCUSSION

The current study demonstrated that asymptomatic low ABI was present in around one out of four patients undergoing carotid artery stenosis or abdominal aortic aneurysm repair. To our knowledge, this study is the first to demonstrate that asymptomatic low ABI has prognostic value to predict perioperative myocardial damage in vascular surgery patients, incremental to risk factors imbedded in conventional cardiac risk indices.

Ischemic heart disease, cerebrovascular disease, and PAD result from atherosclerotic arterial disease. Atherosclerosis is a systemic inflammatory disease of the vasculature and a response to injury, lipid peroxidation, and inflammation. The process of atherosclerosis is known to affect multiple sections of the arterial tree simultaneously.[20] Large international registries, such as the REACH registry, have shown a high prevalence of multiple-affected vascular beds in patients with PAD (around 20%) indicating that these patients often have concomitant ischemic heart or cerebrovascular disease.[21] The ABI is a noninvasive and reliable indicator for the atherosclerotic status of the lower leg vasculature.[6, 7] Multiple studies have demonstrated that the majority of patients with PAD, defined as ABI <0.90, are asymptomatic.[10, 22, 23] Patients with asymptomatic PAD have an increased risk for cardiovascular disease, equal to patients with intermittent claudication.[8] The high prevalence of asymptomatic PAD suggests that ABI should be systematically measured in high-risk hospitalized patients to ensure that appropriate secondary prevention programs are initiated.[24]

In our patients population, three out of four patients with low ABI did not have (a history of) intermittent claudication.

The current study is the first to demonstrate that, after adjusting for risk factors imbedded in conventional cardiac risk indices, asymptomatic low ABI was associated with an increased risk of perioperative myocardial damage in vascular surgery patients. The prevalence of myocardial ischemia has been evaluated in the nonsurgical setting that focused on patients with symptomatic PAD and without clinical ischemic heart disease. In a study conducted by Raby *et al,* the prevalence of myocardial ischemia detected with Holter monitoring was around 18% and was demonstrated to be an independent predictor of two-year prognosis.[25] The ABI collaboration group demonstrated that low ABI has the potential to improve risk prediction for major nonfatal myocardial infarction, beyond the Framingham Risk Score.[11] Recently, Mostaza *et al.* evaluated silent myocardial ischemia, detected with exercise stress tests, in 85 patients with asymptomatic low ABI. Although the sample size in this study was limited, the authors found that a positive exercise test was present in 16% of patients with asymptomatic low ABI, compared with 3.5% in control patients.[26] As the authors themselves state, the real prevalence of ischemic heart disease in these patients remains unknown, because no additional tests were performed in patients with a positive exercise test. To our knowledge, the impact of asymptomatic low ABI on perioperative myocardial damage in vascular surgery patients has not been studied yet. The current study demonstrated that the risk of patients with asymptomatic low ABI to develop perioperative myocardial damage was more than twice as high compared with patients with normal ABI. In line with previous studies, endovascular surgery was associated with a reduced incidence of perioperative myocardial damage, possibly explained by reduced myocardial stress during endovascular procedures.[27, 28]

Perioperative myocardial damage is most often silent and the great majority of these patients (95%) remain untreated, which might contribute to an increased risk of long-term cardiovascular mortality.[25, 27, 29-31] Multiple studies have demonstrated that low ABI has the potential to improve prediction of long-term mortality over and above conventional risk factors.[9,11] In line with these studies, we found that after adjusting for conventional risk factors, imbedded in conventional cardiac risk indices, asymptomatic low ABI was associated with increased risk of long-term mortality after vascular surgery.

Our results indicate that preoperative counselling of vascular surgery patients undergoing carotid stenosis or aortic aneurysm repair should include systematic screening for asymptomatic lower extremity PAD by measuring the ABI. A recent study conducted by Hoeks *et al.* has observed a care gap between guideline recommendations and clinical practice in PAD patients.[32] Standard screening for asymptomatic PAD could reduce this observed care gap by initiating recommended medical treatment with (i) statins, (ii) antiplatelet therapy to reduce the risk of adverse cardiovascular ischemic events, and (iii) angiotensin-converting enzyme inhibition, which may be considered for cardiovascular risk reduction.[33] The presence

of asymptomatic lower-extremity PAD creates the need for optimal lifestyle modification and screening for additional risk factors. Our results indicate that asymptomatic lower-extremity PAD is associated with an increased risk for systolic left ventricular dysfunction and ischemic heart disease. Standard cardiac evaluation during preoperative counselling should therefore be considered in asymptomatic lower-extremity PAD patients. Asymptomatic systolic left ventricular dysfunction with an ejection fraction <40% should be treated with an angiotensin-coverting enzyme inhibitor or, in case of intolerance, an angiotensin receptor blocker. In patients with a history of ischemic heart disease, β-blocker treatment should be initiated as well.[34] Patients with asymptomatic lower-extremity PAD are at increased risk for perioperative myocardial damage. Perioperative montoring with cardiac biomarkers, such as troponin T, could be justified since the majority of perioperative myocardial damage is silent and patients therefore remain untreated. Available evidence suggests that β-blockers reduce perioperative ischemia and the latest American College of Cardiology / American Heart Accociation (ACC/AHA) guidelines on perioperative care provide a (class IIa, level of evidence B) recommendation to initiate β-blocker treatment in patients with one or more cardiovascular risk factors.[35]

Potential limitations of these data merit consideration. First, the study population consisted of patients referred to a tertiary referral center and may not fully represent a general population scheduled for elective vascular surgery. Second, we did not address nonfatal cardiovascular events during long-term follow-up. Third, we included both open and endovascular surgical procedures. The number of endovascular procedures has increased in the past three years, which has influenced the median follow-up period.

In conclusion, the current study demonstrated that asymptomatic low ABI has prognostic value to predict perioperative myocardial damage in vascular surgery patients, incremental to conventional risk factors imbedded in the RCR and Adapted Lee Risk indices. These data suggest that ABI measurements should be systematically performed in patients scheduled for carotid artery stenosis or abdominal aortic aneurysm repair to ensure that appropriate perioperative treatment is initiated.

REFERENCES

1. Mangano DT, Goldman L. Preoperative assessment of patients with known or suspected coronary disease. *N Engl J Med.* 1995;333(26):1750-1756.

2. Kannel WB, Abbott RD. Incidence and prognosis of unrecognized myocardial infarction. An update on the Framingham study. *N Engl J Med.* 1984;311(18):1144-1147.

3. Nabel EG, Rocco MB, Barry J, et al. Asymptomatic ischemia in patients with coronary artery disease. *Jama.* 1987;257(14):1923-1928.

4. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation.* 1999;100(10):1043-1049.

5. Boersma E, Kertai MD, Schouten O, et al. Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index. *Am J Med.* 2005;118(10):1134-1141.

6. Criqui MH, Denenberg JO, Bird CE, et al. The correlation between symptoms and non-invasive test results in patients referred for peripheral arterial disease testing. *Vasc Med.* 1996;1(1):65-71.

7. McKenna M, Wolfson S, Kuller L. The ratio of ankle and arm arterial pressure as an independent predictor of mortality. *Atherosclerosis.* 1991;87(2-3):119-128.

8. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med.* 1992;326(6):381-386.

9. Lee AJ, Price JF, Russell MJ, et al. Improved prediction of fatal myocardial infarction using the ankle brachial index in addition to conventional risk factors: the Edinburgh Artery Study. *Circulation.* 2004;110(19):3075-3080.

10. Diehm C, Lange S, Darius H, et al. Association of low ankle brachial index with high mortality in primary care. *Eur Heart J.* 2006;27(14):1743-1749.

11. Fowkes FG, Murray GD, Butcher I, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *Jama.* 2008;300(2):197-208.

12. Leng GC, Fowkes FG. The Edinburgh Claudication Questionnaire: an improved version of the WHO/Rose Questionnaire for use in epidemiological surveys. *J Clin Epidemiol.* 1992;45(10):1101-1109.

13. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg.* 2007;33 Suppl 1:S1-75.

14. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. *Eur J Echocardiogr.* 2006;7(2):79-108.

15. Stamm RB, Carabello BA, Mayers DL, et al. Two-dimensional echocardiographic measurement of left ventricular ejection fraction: prospective analysis of what constitutes an adequate determination. *Am Heart J.* 1982;104(1):136-144.

16. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med.* 2001;344(21):1608-1621.

17. Feringa HH, Karagiannis SE, Schouten O, et al. Prognostic significance of declining ankle-brachial index values in patients with suspected or known peripheral arterial disease. *Eur J Vasc Endovasc Surg.* 2007;34(2):206-213.

18. Aviles RJ, Askari AT, Lindahl B, et al. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. *N Engl J Med.* 2002;346(26):2047-2052.

19. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *Eur Heart J.* 2007;28(20):2525-2538.

20. Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. *Circulation.* 2004;109(21 Suppl 1):II2-10.

21. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *Jama.* 2006;295(2):180-189.

22. Fowkes FG, Housley E, Cawood EH, et al. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol.* 1991;20(2):384-392.

23. Meijer WT, Hoes AW, Rutgers D, et al. Peripheral arterial disease in the elderly: The Rotterdam Study. *Arterioscler Thromb Vasc Biol.* 1998;18(2):185-192.

24. Mourad JJ, Cacoub P, Collet JP, et al. Screening of unrecognized peripheral arterial disease (PAD) using ankle-brachial index in high cardiovascular risk patients free from symptomatic PAD. *J Vasc Surg.* 2009.

25. Raby KE, Goldman L, Cook EF, et al. Long-term prognosis of myocardial ischemia detected by Holter monitoring in peripheral vascular disease. *Am J Cardiol.* 1990;66(19):1309-1313.

26. Mostaza JM, Gonzalez-Juanatey JR, Castillo J, et al. Prevalence of carotid stenosis and silent myocardial ischemia in asymptomatic subjects with a low ankle-brachial index. *J Vasc Surg.* 2009;49(1):104-108.

27. Schouten O, Dunkelgrun M, Feringa HH, et al. Myocardial damage in high-risk patients undergoing elective endovascular or open infrarenal abdominal aortic aneurysm repair. *Eur J Vasc Endovasc Surg.* 2007;33(5):544-549.

28. Elkouri S, Gloviczki P, McKusick MA, et al. Perioperative complications and early outcome after endovascular and open surgical repair of abdominal aortic aneurysms. *J Vasc Surg.* 2004;39(3):497-505.

29. Ouyang P, Gerstenblith G, Furman WR, et al. Frequency and significance of early postoperative silent myocardial ischemia in patients having peripheral vascular surgery. *Am J Cardiol.* 1989;64(18):1113-1116.

30. Pasternack PF, Grossi EA, Baumann FG, et al. Beta blockade to decrease silent myocardial ischemia during peripheral vascular surgery. *Am J Surg.* 1989;158(2):113-116.

31. Wallace A, Layug B, Tateo I, et al. Prophylactic atenolol reduces postoperative myocardial ischemia. McSPI Research Group. *Anesthesiology.* 1998;88(1):7-17.

32. Hoeks SM, Scholte op Reimer, WJM, van Gestel, YRBM, et al. Medication Underuse During Long-Term Follow-Up in Patients With Peripheral Arterial Disease. *Circulation Cardiovascular Quality and Outcome.* 2009;10:1161.

33. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation.* 2006;113(11):e463-654.

34. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J.* 2008;29(19):2388-2442.

35. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *Circulation.* 2007;116(17):1971-1996.

Chapter 14

Objective assessment of atherosclerosis in the carotid and lower limb arteries to predict adverse cardiac events and mortality after vascular surgery

Submitted

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ABSTRACT

Background Asymptomatic low ankle-brachial index (ABI) and subclinical increased common carotid artery intimamedia thickness (CCA-IMT) are predictors of cardiac events. This study is the first to evaluate the separate and combined prognostic values of these markers in one cohort of vascular surgery patients.

Methods 400 patients undergoing abdominal aortic aneurysm repair, without intermittent claudication, a history of lower extremity revascularization or cerebrovascular disease, were included. In all patients, preoperative CCA-IMT measurements (using high-resolution B-mode ultrasonography) and ABI measurements were performed. CCA-IMT >1.25 mm was considered increased and an ABI <0.9 was considered low. Study endpoints were 30-day myocardial damage (defined as troponin T release >0.03 ng/mL) and long-term mortality. Multivariate regression analyses, adjusted for conventional cardiac risk factors, evaluated the prognostic value of ABI and CCA-IMT towards the study endpoints. Mean follow-up was 2.5 ± 2.2 years.

Results Of the included patients, 75 (19%) patients had an ABI <0.9, 59 (15%) patients had a CCA-IMT>1.25 and 34 (9%) patients had both. In total, 82 (21%) patients had 30-day myocardial damage and 77 (19%) patients died during follow-up. An ABI <0.9 and CCA-IMT >1.25 were separately associated with 30-day myocardial damage (OR 2.6, 95%-CI: 1.4 to 6.2 and OR 2.1, 95%-CI: 1.3 to 7.4) and long-term mortality (HR 3.2, 95%-CI: 1.6 to 6.7 and HR 3.9, 95%-CI: 1.8 to 8.8). However, the combination of an ABI <0.9 + CCA-IMT >1.25 was associated with the highest risk (30-day myocardial damage: OR 5.2, 95%-CI: 2.0 to 11.1 and long-term mortality: HR 5.6, 95%-CI: 2.5 to 12.5), compared with patients with an ABI >0.9 + CCA-IMT <1.25.

Conclusions Although asymptomatic ABI <0.9 and subclinical CCA-IMT >1.25 independently predict 30-day myocardial damage and long-term mortality in patients undergoing abdominal aortic aneurysm repair, a combination of these markers is associated with the highest risk.

INTRODUCTION

Atherosclerosis is a systemic, chronic inflammatory disease affecting the intima layer of the vessel wall. During the earlier phases of atherosclerosis, symptoms do not occur and remain absent for several decades. Atherosclerosis is known to affect multiple sections of the arterial tree simultaneously, such as the coronary-, lower extremity-, and carotid arteries. Therefore, individuals with one manifestation of atherosclerosis are more likely to have concomitant disease in other vascular territories as well.

Patients undergoing abdominal aortic aneurysm repair are at significant risk for both perioperative and long-term cardiovascular events, related to a high prevalence of underliying coronary artery disease. However, preoperative risk stratification for adverse cardiac outcome using traditional cardiac risk factors is suboptimal indicating the necessity to improve cardiac evaluation before surgery.[1-2] Preoperative evaluation of subclinical manifestations of the atherosclerotic process could be considered to improve the prediction of cardiac outcome.

Surrogate markers reflecting the severity and extent of the atherosclerotic process, such as the ankle-brachial index (ABI) and the common carotid artery intimamedia thickness (CCA-IMT), have demonstrated to predict adverse cardiac events. However, the predictive value of these two markers combined has not been evaluated in one cohort of patients undergoing abdominal aortic aneurysm repair. The present study was performed to evaluate the separate and combined prognostic values of low ABI and increased CCA-IMT towards postoperative outcome of patients undergoing abdominal aortic aneurysm repair.

MATERIAL AND METHODS

Study population

The original study population consisted of 499 patients undergoing abdominal aortic aneurysm repair during the period between 2002 and 2009. After exclusion of patients with a history of or current (i) intermittent claudication assessed with the Edinburgh questionnaire,[3] (ii) asymptomatic ABI >1.40,[4] (iii) lower extremity revascularization, or (iv) cerebrovascular disease, 400 patients were included in the study. The study was performed at the Erasmus Medical Center in Rotterdam, a tertiary hospital in the Netherlands. The study was approved by the hospital's ethics committee and performed with the informed consent of all patients.

Baseline characteristics

Before surgery, a detailed history was obtained from every patient. Clinical data included age, sex, ischemic heart disease (defined as a history of myocardial infarction, coronary revascularization, or the presence of pathologic Q-waves on preoperative electrocardiogram), renal dysfunction (serum creatinine >2.0 mg/dL), diabetes mellitus (fasting blood glucose ≥6.1 mmol/L or requirement of anti-diabetic medication), hypertension (blood pressure ≥140/90 mmHg in non-diabetic patients and ≥130/80 mmHg in diabetics or requirement of antihypertensive medication), hypercholesterolemia (history of hypercholesterolemia or low-density lipoprotein cholesterol >3.5 mmol/L), chronic obstructive pulmonary disease (history of chronic obstructive pulmonary disease or according the Global Initiative on Obstructive Lung Diseases classification), and smoking status. The use of the prescription medications was recorded and included β-blockers, statins, inhibitors of the renin-angiotensin-aldosterone system (RAAS inhibitors: ACE inhibitors, angiotensin-II receptor blockers, renin inhibitors, aldosterone antagonists), aspirin, and oral anticoagulants.

Ankle-brachial index

The ABI at rest was measured in each patient by trained technicians, using a Doppler ultrasonic instrument with an 8-MHz vascular probe (Imexdop CT+ Vascular Doppler; Nicolet Vascular, Madison, WI, USA). The ABI in the right and the left leg was calculated by dividing the right and the left ankle pressures by the brachial pressure. The higher of the two brachial blood pressures was used if a discrepancy in systolic blood pressure was present. Further, the higher of the dorsalis pedis and posterior tibial artery pressures was used if a discrepancy in systolic blood pressure between the two arteries was measured.[16] Asymptomatic low ABI was defined as an ABI <0.90 with an inter- and intraobserver agreement of 97 and 98%, as described previously.[5-6]

Common carotid artery intimamedia thickness

The CCA-IMT was measured according to the 'Mannheim Carotid Intima-Media Thickness Consensus' scanning and reading protocol recommendations.[7-8] Measurements were taken at 10 mm proximal to the carotid bifurcation in the near and far wall of the left and right common carotid artery. Repeated measurements were performed along a minimum of 10 mm length. Four measurements were taken from both the left and right common carotid artery, two of which in the near and of which two in the far wall. The maximal measurement, of these eight measurements, was used. Plaques (defined as a focal structure encroaching into the arterial lumen of at least 0.5 mm)[7] when present, were not used in the CCA-IMT measurements. Measurements were electrocardiogram-gated at the peak of the QRS complex to control for changes in CCA-IMT during the cardiac cycle. Two sonographers, unaware of the clinical information for each patient, performed the measurements with an interobserver correlation of the 96.2%, as shown previously.[9] In addition, a cut off value of CCA-IMT of 1.25 mm was used to predict the occurrence of the study endpoints.[9]

Left ventricular ejection fraction

Preoperatively, transthoracic echocardiography was performed in all patients using a hand-held Acuson Cypress Ultrasound System (7V3c transducer), manufacturers address 1220 Charleston Road, Mountain View, CA 94043. Standard parasternal and apical two- and four-chamber views were obtained at rest with the patient in the left lateral decubitus position, as recommended.[10] Left ventricular end-systolic and end-diastolic volumes were determined and left ventricular ejection fraction was calculated using the biplane Simpson's technique.[11] Systolic left ventricular dysfunction was defined as left ventricular ejection fraction <50%.

Study outcomes

The main study endpoints were perioperative myocardial damage (defined as nonfatal myocardial ischemia or infarction up to 30 days after surgery) and long-term mortality. Serial electrocardiograms and troponin T measurements were obtained from all patients before surgery, postoperatively on days 1, 3, 7, and before discharge. Myocardial ischemia was present in patients with normal preoperative and elevated (>0.03 ng/mL) troponin T levels postoperatively.[12] Elevated troponin T levels in combination with electrocardiographic changes (new-onset ST-T changes and pathological Q-waves) or symptoms of angina pectoris defined myocardial infarction.[13] Patients with elevated troponin T levels before surgery were not included in the study. Long-term mortality was assessed by approaching the municipal civil registries. Mean follow-up was 2.5 ± 2.2 years.

Statistical analysis

Dichotomous data are described as numbers and percentages. Continuous variables are described as mean ± standard deviation (SD). Continuous data were compared using one-way ANOVA and categorical data were compared using a χ^2 test. Logistic regression analyses were performed to evaluate the relationship between asymptomatic low ABI, subclinical increased CCA-IMT and perioperative myocardial damage. Cumulative long-term survival was determined using the Kaplan-Meier method. Cox regression analyses were performed to evaluate the relationship between asymptomatic low ABI, subclinical increased CCA-IMT and long-term mortality. Multivariate regression analyses were adjusted for sex, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease, current smoking, and risk factors imbedded in conventional cardiac risk indices (age, ischemic heart disease, symptomatic heart failure, renal dysfunction, diabetes mellitus, and high-risk surgery),[14-15] and medication use. We report both the crude and the adjusted odds ratio (OR) and hazard ratio (HR) with their 95% confidence intervals (95%-CIs). For all tests, a *p*-value <0.05 (two-sided) was considered significant. All analyses were performed using SPSS version 15.0 statistical software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics

The initial study population consisted of 499 patients. Patients with (a history of) or current intermittent claudication (N=21), ABI >1.40 (N=6), lower extremity revascularization (N=14), or cerebrovascular disease (N=58) were excluded from the analyses. Therefore, 400 patients undergoing abdominal aortic aneurysm repair were included in the study. In total, 197 patients (49%) underwent open and 203 patients (51%) underwent endovascular surgery. Of the 400 patients, 75 (19%) patients had asymptomatic low ABI, 59 (15%) patients had subclinical CCA-IMT >1.25 mm, and 34 (9%) patients had asymptomatic low ABI + subclinical CCA-IMT >1.25 mm.

Table 1 **Baseline characteristics according to ABI and CCA-IMT**

	ABI >0.9 CCA-IMT <1.25 [N=232]	Low ABI CCA-IMT <1.25 [N=75]	ABI >0.9 INCREASED CCA-IMT [N=59]	Low ABI INCREASED CCA-IMT [N=34]	*P* for trend
Demographics (mean ± SD)					
Age	69 (12)	72 (7)	74 (7)	73 (8)	0.008
Male (%)	199 (86)	65 (87)	53 (87)	30 (88)	0.564
Heart rate	71 (14)	72 (17)	70 (13)	75 (14)	0.550
Medical history (%)					
Ischemic heart disease	79 (34)	42 (56)	34 (58)	20 (59)	0.034
Heart failure	12 (5)	7 (10)	8 (13)	4 (12)	0.002
Renal dysfunction	35 (15)	16 (21)	13 (22)	8 (24)	0.042
Diabetes mellitus	30 (13)	19 (25)	14 (24)	4 (12)	0.262
Hypertension	131 (57)	51 (68)	42 (71)	22 (65)	0.120
Hypercholesterolemia	89 (38)	30 (40)	26 (44)	13 (38)	0.897
COPD	115 (50)	41 (55)	32 (54)	19 (56)	0.465
Smoker, current	78 (34)	34 (45)	17 (29)	16 (47)	0.508
Surgery type (%)					
Open	115 (50)	38 (51)	25 (42)	20 (58)	0.695
Echocardiography (%)					
LVEF < 50% *	25 (11)	21 (28)	16 (27)	15 (44)	<0.001
Medication (%)					
β-blockers	195 (84)	70 (93)	48 (81)	31 (91)	0.454
Statins	165 (71)	51 (68)	35 (59)	21 (62)	0.150
Aspirin	118 (51)	47 (63)	33 (56)	16 (47)	0.845
Oral anticoagulants	23 (10)	9 (12)	11 (19)	6 (18)	0.166
RAAS inhibitors	88 (38)	35 (47)	25 (42)	16 (47)	0.312
Diuretics	49 (21)	13 (17)	14 (24)	6 (18)	0.892

** No heart failure symptoms. Ankle-brachial index (ABI), common carotid artery intimamedia thickness (CCA-IMT), left ventricular ejection fraction (LVEF).*

Baseline characteristics stratified to ABI and CCA-IMT are demonstrated in *Table 1*. The majority of patients were males (82%) and the mean age was 70 (SD ± 8.6) years. Asymptomatic low ABI, subclinical CCA-IMT >1.25 mm, or a combination these two markers were associated with a history of ischemic heart disease, heart failure, and renal dysfunction. In addition, asymptomatic low ABI, subclinical CCA-IMT >1.25 mm, or a combination these two markers were associated with a left ventricular ejection fraction <50%.

A contingency table sub-analysis was performed to compare patients with (i) asymptomatic low ABI or subclinical CCA-IMT >1.25 mm to patients with (ii) a combination these two markers. Although a history of ischemic heart disease, symptomatic heart failure, and renal dysfunction were equally present in the two groups (with *p*-values of 0.541, 0.975 and 0.618, respectively), the presence of left ventricular ejection fraction <50% was significantly increased in patients with asymptomatic low ABI + subclinical CCA-IMT >1.25 mm ($p < 0.001$).

Perioperative myocardial damage

The study endpoint perioperative myocardial damage was reached in 82 (21%) patients, of whom 61 (74%) had myocardial ischemia and 21 (26%) had myocardial infarction. In total, 25/203 (12%) of the patients undergoing endovascular, and 57/197 (29%) of the patients undergoing open procedures had perioperative myocardial damage. These results are demonstrated in *Table 2*. The prevalence of perioperative myocardial damage was the lowest (11%) in patients with an ABI >0.9 + CCA-IMT <1.25 mm and the highest (44%) in patients with asymptomatic low ABI + subclinical CCA-IMT >1.25 mm.

Table 2 **ABI, CCA-IMT and postoperative outcome after abdominal aortic aneurysm repair**

			Open procedures [N=197]		Endovascular procedures [N=203]	
Perioperative myocardial damage (N=82)						
ABI >0.9	CCA-IMT <1.25	33/232 (11%)	23/115	20%	10/117	9%
Low ABI	CCA-IMT <1.25	20/75 (27%)	14/38	37%	6/37	16%
ABI >0.9	increased CCA-IMT	14/59 (24%)	9/25	36%	5/34	15%
Low ABI	increased CCA-IMT	15/34 (44%)	11/20	55%	4/14	36%
Long-term mortality (N=77)						
ABI >0.9	CCA-IMT <1.25	24/232 (12%)	12/115	10%	12/117	10%
Low ABI	CCA-IMT <1.25	22/75 (27%)	13/38	34%	9/37	24%
ABI >0.9	increased CCA-IMT	16/59 (29%)	8/25	32%	8/34	24%
Low ABI	increased CCA-IMT	15/34 (44%)	9/20	45%	6/14	43%

Ankle-brachial index (ABI), common carotid artery intimamedia thickness (CCA-IMT).

Multivariate analyses demonstrated that risk factors imbedded in conventional cardiac risk indices were predictive for perioperative myocardial damage, as presented in *Table 3, Model 1*. When including ABI and CCA-IMT in the model (*Table 3 Model 2 + 3 and Figure 1*), the presence of asymptomatic low ABI + CCA-IMT <1.25 or ABI >0.9 + subclinical CCA-IMT >1.25 mm were both independently associated with an increased risk of perioperative myocardial damage with ORs of 2.6 (95%-CI: 1.4 to 6.2) and 2.1 (95%-CI: 1.3 to 7.4). However, the risk for developing myocardial damage was the highest in patients with asymptomatic low ABI + subclinical CCA-IMT >1.25 mm (HR 5.2, 95%-CI: 2.0 to 11.1).

Table 3 **Multivariate association between ABI, CCA-IMT and perioperative events**

		Model 1[a]		Model 2[b]		Model 3[c]	
		HR	[95%-CI]	HR	[95%-CI]	HR	[95%-CI]
Cardiac risk factors							
Age (>70 years)		1.6	1.2-3.6	1.5	1.2-3.6	1.6	1.3-4.0
Symptomatic heart failure		3.0	1.5-5.6	3.0	1.6-5.7	3.2	1.6-5.8
Ischemic heart disease		2.4	1.2-4.4	2.5	1.1-4.4	2.6	1.2-4.6
Renal dysfunction		1.5	1.1-6.5	1.5	1.3-7.2	1.6	1.3-7.5
Diabetes mellitus [d]		1.2	1.3-4.9	1.2	1.4-4.1	1.3	1.4-4.2
High-risk surgery		3.3	1.1-3.9	3.4	1.2-4.3	3.5	1.2-4.6
ABI >0.9	CCA-IMT <1.25						
Low ABI	CCA-IMT <1.25			2.6	1.3-5.5	2.6	1.4-6.2
ABI >0.9	increased CCA-IMT			1.9	1.2-6.4	2.1	1.3-7.4
Low ABI	increased CCA-IMT			4.1	1.6-9.8	5.2	2.0-11.1

[a] *Model 1: Predictive value of risk factors imbedded in preoperative cardiac risk indices: multivariate analysis adjusted for: gender, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease, and current smoking*

[b] *Model 2: Predictive value of ABI <0.9 and/or CCA-IMT > 1.25: multivariate analyses adjusted for risk factors imbedded in preoperative cardiac risk indices + gender, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease and current smoking*

[c] *Model 3: Predictive value of ABI <0.9 and/or CCA-IMT > 1.25: multivariate analyses adjusted as in model 2 and for medication use (β-blockers, statins, aspirin, oral anticoagulants and RAAS inhibitors).*

Ankle-brachial index (ABI), common carotid artery intimamedia thickness (CCA-IMT), rennin-angiotensin-aldosteron system (RAAS).

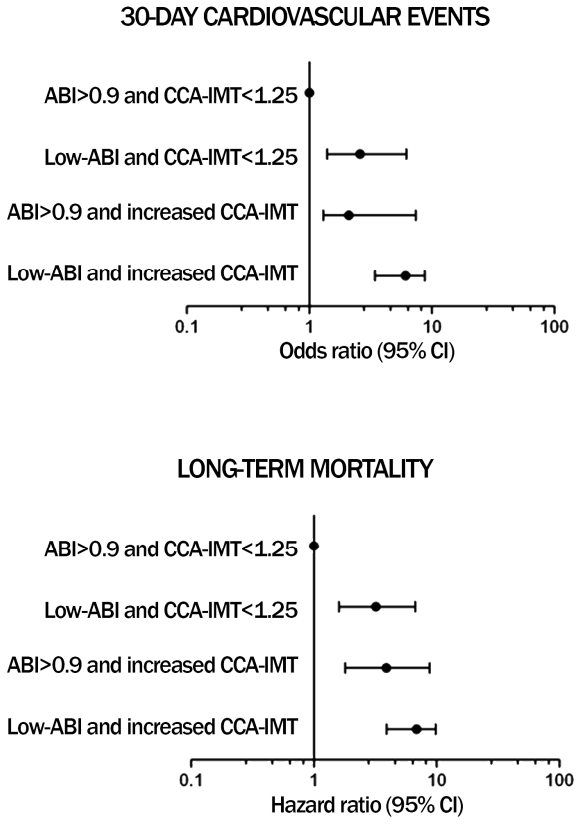
Long-term mortality

In total 77 patients (19%) died during follow-up (*Table 2*). In total, 42 (21%) of the 197 patients who had open surgery died, compared with 35 (17%) of the 203 patients who had endovascular surgery. As demonstrated in *Table 2*, the lowest incidence of long-term mortality (11%) was noted in patients with ABI >0.9 + CCA-IMT <1.25 mm. In addition, the highest

incidence of long-term mortality (44%) was noted in patients with asymptomatic low ABI + subclinical CCA-IMT >1.25 mm.

Multivariate analyses demonstrated that risk factors imbedded in conventional cardiac risk indices were predictive for long-term mortality, as presented in *Table 4, Model 1*. When including ABI and CCA-IMT in the model (*Table 4 Model 2 + 3 and Figure 1*), the presence of asymptomatic low ABI + CCA-IMT <1.25 mm or ABI >0.9 + subclinical CCA-IMT >1.25 mm were both independently associated with long-term mortality with HRs of 3.2 (95%-CI: 1.6 to 6.7) and 3.9 (95%-CI: 1.8 to 8.8). However, the risk for long-term mortality was the highest in patients with asymptomatic low ABI + subclinical CCA-IMT >1.25 mm (HR 5.6, 95%-CI: 2.5 to 12.5).

Figure 1: Ankle-brachial index (ABI), common carotid artery intimamedia thickness (CCA-IMT) and postoperative outcome



DISCUSSION

This study demonstrated that asymptomatic low ABI, subclinical CCA-IMT >1.25 mm, or a combination of asymptomatic low ABI + subclinical CCA-IMT >1.25 mm were all associated with an increased risk for perioperative myocardial damage and long-term mortality. However, a combination of asymptomatic low ABI + subclinical CCA-IMT >1.25 mm was associated with the highest risk for the study endpoints.

Table 4 **Multivariate association between ABI, CCA-IMT and long-term mortality**

		Model 1[a]		Model 2[b]		Model 3[c]	
		HR	[95%-CI]	HR	[95%-CI]	HR	[95%-CI]
Cardiac risk factors							
Age (>70 years)		3.0	1.2-4.5	3.2	1.2-4.6	3.2	1.2-4.6
Symptomatic heart failure		2.5	1.3-5.1	2.6	1.4-5.2	2.6	1.4-5.4
Ischemic heart disease		1.9	1.1-5.3	2.1	1.2-5.4	2.0	1.2-5.4
Renal dysfunction		2.1	1.2-6.9	2.0	1.4-7.4	2.1	1.4-7.9
Diabetes mellitus [d]		1.3	1.3-4.1	1.4	1.3-4.5	1.4	1.4-4.9
High-risk surgery		1.4	0.8-4.0	1.5	0.8-4.2	1.5	0.9-4.6
ABI >0.9	CCA-IMT <1.25						
Low ABI	CCA-IMT <1.25			2.9	1.4-5.9	3.2	1.6-6.7
ABI >0.9	increased CCA-IMT			3.2	1.5-6.9	3.9	1.8-8.8
Low ABI	increased CCA-IMT			4.6	2.1-10.1	5.6	2.5-12.5

[a] *Model 1: Predictive value of risk factors imbedded in preoperative cardiac risk indices: multivariate analysis adjusted for: gender, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease, and current smoking*

[b] *Model 2: Predictive value of ABI <0.9 and/or CCA-IMT > 1.25: multivariate analyses adjusted for risk factors imbedded in preoperative cardiac risk indices + gender, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease and current smoking*

[c] *Model 3: Predictive value of ABI <0.9 and/or CCA-IMT > 1.25: multivariate analyses adjusted as in model 2 and for medication use (β-blockers, statins, aspirin, oral anticoagulants and RAAS inhibitors).*

Ankle-brachial index (ABI), common carotid artery intimamedia thickness (CCA-IMT), rennin-angiotensin-aldosteron system (RAAS).

Adequate risk stratification of patients undergoing noncardiac surgery is of utmost importance to identify patients at risk for perioperative cardiac events. Over the years, several cardiac risk indices have been developed to identify those patients at risk, however, the Revised Cardiac Risk (RCR) index is nowadays widely used and considered to be the best available cardiac risk index for patients undergoing noncardiac surgery.[15] Cardiac risk factors imbedded in the RCR index are (i) ischemic heart disease, (ii) symptomatic heart failure, (iii)

cerebrovascular disease, (iv) insulin dependent diabetes mellitus, (v) renal dysfunction, and (vi) high-risk surgery. Several noninvasive assessment techniques, such as measuring the ABI or CCA-IMT, have been evaluated to determine whether they increase the accuracy of preoperative risk assessment.

The ABI is a noninvasive test to screen for patients with possible peripheral arterial disease. Low ABI (ABI <0.90) at rest has been associated with an increased risk of cardiovascular events and mortality, compared with a normal ABI.[16-19] In addition, low ABI demonstrated to improve risk prediction for cardiovascular events and mortality in nonsurgical [17, 20] and surgical [5] settings, even beyond the risk prediction properties of conventional cardiac risk scores such as the RCR index.[15]

The CCA-IMT is a direct marker to quantify the atherosclerotic process in the carotid artery. Several studies in the nonsurgical population demonstrated that carotid IMT is associated with an increased risk of cardiovascular events and that measuring the CCA-IMT increases the power of traditional risk factors to predict cardiovascular events.[21-24] Of note, an increased CCA-IMT demonstrated to predict adverse cardiac events in patients undergoing cardiac interventions [25-26] or vascular surgery [9] as well.

In 1994, Bots *et al.* were the first to evaluate the association between an increased CCA-IMT and asymptomatic low ABI within the general population. The authors concluded that increased CCA-IMT reflects generalized atherosclerosis, as indicated by its association with asymptomatic low ABI.[27] This finding has been confirmed in several studies [28-30] and in 2008 Hayashi *et al.* stated that measurements of the ABI and CCA-IMT might provide good prognostic indicators for the prevalence of coronary heart disease. However, the prognostic value of low ABI, increased CCA-IMT or the combination of low ABI + increased CCA-IMT has not been evaluated in one cohort of patients undergoing vascular surgery.

In the present study we found that low ABI and increased CCA-IMT >1.25 mm were both associated with 30-day cardiovascular events and long-term mortality. However, patients with a combination of low ABI + increased CCA-IMT >1.25 mm constituted the highest risk for the study endpoints. Interestingly, a history of ischemic heart disease, symptomatic heart failure, or renal dysfunction, documented during preoperative visits at the outpatients clinic, were equally present in patients with asymptomatic ABI <0.9 and/or subclinical CCA-IMT >1.25 mm. However, transthoratic echocardiography was performed in all patients before surgery and the prevalence of systolic left ventricular dysfunction was evaluated. Interestingly, the prevalence of asymptomatic systolic left ventricular dysfunction with a left ventricular ejection fraction <50% was increased in patients with a combination of asymptomatic low ABI + subclinical CCA-IMT >1.25 mm compared with patients with solely a low ABI or an increased CCA-IMT >1.25 mm ($p < 0.001$). This notion could explain why patients with a

combination of low ABI + increased CCA-IMT >1.25 mm constituted the highest risk for the study endpoints.

In the latest 'European Society of Cardiology'perioperative guidelines, symptomatic heart failure symptoms are considered a well acknowledged risk factor for adverse cardiac outcome [31]. In most recent 'European Society of Cardiology guidelines for the diagnosing and treatment of acute and chronic heart failure', it is stated that asymptomatic left ventricular dysfunction is associated with high mortality as well.[32] In vascular surgery patients, this notion is supported by a study conducted by Flu *et al*, demonstrating that asymptomatic left ventricular dysfunction is associated with increased 30-day cardiovascular events and long-term cardiovascular mortality.[33] Based on a cost-effectiveness consideration, however, routine preoperative echocardiography might not be applicable. The association of low ABI, increased CCA-IMT, and especially the combination these markers with asymptomatic systolic left ventricular dysfunction, could indicate that routine ABI and CCA-IMT measurements may play an important role to detect asymptomatic left ventricular dysfunction in patients undergoing abdominal aneurysm repair. Especially, in patients with a combination of low ABI + increased CCA-IMT, the presence of left ventricular dysfunction should be excluded with cardiac echo. In addition, in patients with asymptomatic systolic left ventricular dysfunction with a left ventricular ejection fraction <50%, treatment with β-blockers and angiotensin blocking agents should be initiated as recommended.[32]

Potential limitations of these data merit consideration. First, the study population consisted of patients referred to a tertiary referral center and may not fully represent a general population scheduled for elective vascular surgery. Second, although two experienced investigators performed off-line assessments of the obtained ultrasound images, we cannot rule out interobserver variability to have had minor influence on our results [34]. Third, we did not validate the CCA-IMT cut off point in a prospective group of patients undergoing vascular surgery. Third, we included both open and endovascular surgical procedures. The number of endovascular procedures has increased the last three years, which has influenced the median follow-up period.

In conclusion, asymptomatic low ABI and subclinical CCA-IMT >1.25 mm independently predict 30-day myocardial damage and long-term mortality in patients undergoing abdominal aortic aneurysm repair. Interestingly, a history of ischemic heart disease, symptomatic heart failure, or renal dysfunction was equally present in patients with asymptomatic low ABI and/or subclinical CCA-IMT >1.25 mm. However, a combination of asymptomatic low ABI + subclinical CCA-IMT >1.25 mm was associated with the highest risk for the study endpoints, possibly related to an increased incidence of asymptomatic systolic left ventricular dysfunction.

REFERENCES

1. Utoh J, Goto H, Hirata T, et al. Routine coronary angiography prior to abdominal aortic aneurysm repair: incidence of silent coronary artery disease. *Panminerva Med.* 1998;40(2):107-109.

2. Bayazit M, Gol MK, Battaloglu B, et al. Routine coronary arteriography before abdominal aortic aneurysm repair. *Am J Surg.* 1995;170(3):246-250.

3. Leng GC, Fowkes FG. The Edinburgh Claudication Questionnaire: an improved version of the WHO/Rose Questionnaire for use in epidemiological surveys. *J Clin Epidemiol.* 1992;45(10):1101-1109.

4. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg.* 2007;33 Suppl 1:S1-75.

5. Feringa HH, Karagiannis SE, Schouten O, et al. Prognostic significance of declining ankle-brachial index values in patients with suspected or known peripheral arterial disease. *Eur J Vasc Endovasc Surg.* 2007;34(2):206-213.

6. Flu WJ, van Kuijk JP, Voute MT, et al. Asymptomatic low ankle-brachial index in vascular surgery patients: a predictor of perioperative myocardial damage. *Eur J Vasc Endovasc Surg.*39(1):62-69.

7. Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. *Cerebrovasc Dis.* 2007;23(1):75-80.

8. Wendelhag I, Gustavsson T, Suurkula M, et al. Ultrasound measurement of wall thickness in the carotid artery: fundamental principles and description of a computerized analysing system. *Clin Physiol.* 1991;11(6):565-577.

9. Flu WJ, van Kuijk JP, Hoeks SE, et al. Intima media thickness of the common carotid artery in vascular surgery patients: a predictor of postoperative cardiovascular events. *Am Heart J.* 2009;158(2):202-208.

10. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. *Eur J Echocardiogr.* 2006;7(2):79-108.

11. Stamm RB, Carabello BA, Mayers DL, et al. Two-dimensional echocardiographic measurement of left ventricular ejection fraction: prospective analysis of what constitutes an adequate determination. *Am Heart J.* 1982;104(1):136-144.

12. Aviles RJ, Askari AT, Lindahl B, et al. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. *N Engl J Med.* 2002;346(26):2047-2052.

13. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *Eur Heart J.* 2007;28(20):2525-2538.

14. Boersma E, Kertai MD, Schouten O, et al. Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index. *Am J Med.* 2005;118(10):1134-1141.

15. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation.* 1999;100(10):1043-1049.

16. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med.* 1992;326(6):381-386.

17. Lee AJ, Price JF, Russell MJ, et al. Improved prediction of fatal myocardial infarction using the ankle brachial index in addition to conventional risk factors: the Edinburgh Artery Study. *Circulation.* 2004;110(19):3075-3080.

18. McKenna M, Wolfson S, Kuller L. The ratio of ankle and arm arterial pressure as an independent predictor of mortality. *Atherosclerosis.* 1991;87(2-3):119-128.

19. Diehm C, Lange S, Darius H, et al. Association of low ankle brachial index with high mortality in primary care. *Eur Heart J.* 2006;27(14):1743-1749.

20. Fowkes FG, Murray GD, Butcher I, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *Jama.* 2008;300(2):197-208.

21. Lorenz MW, Markus HS, Bots ML, et al. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation.* 2007;115(4):459-467.

22. Bots ML, Baldassarre D, Simon A, et al. Carotid intima-media thickness and coronary atherosclerosis: weak or strong relations? *Eur Heart J.* 2007;28(4):398-406.

23. Baldassarre D, Amato M, Pustina L, et al. Measurement of carotid artery intima-media thickness in dyslipidemic patients increases the power of traditional risk factors to predict cardiovascular events. *Atherosclerosis.* 2007;191(2):403-408.

24. Touboul PJ, Hernandez-Hernandez R, Kucukoglu S, et al. Carotid artery intima media thickness, plaque and Framingham cardiovascular score in Asia, Africa/Middle East and Latin America: the PARC-AALA study. *Int J Cardiovasc Imaging.* 2007;23(5):557-567.

25. Lacroix P, Aboyans V, Espaliat E, et al. Carotid intima-media thickness as predictor of secondary events after coronary angioplasty. *Int Angiol.* 2003;22(3):279-283.

26. Aboyans V, Guilloux J, Lacroix P, et al. Common carotid intima-media thickness measurement is not a pertinent predictor for secondary cardiovascular events after coronary bypass surgery. A prospective study. *Eur J Cardiothorac Surg.* 2005;28(3):415-419.

27. Bots ML, Hofman A, Grobbee DE. Common carotid intima-media thickness and lower extremity arterial atherosclerosis. The Rotterdam Study. *Arterioscler Thromb.* 1994;14(12):1885-1891.

28. Allan PL, Mowbray PI, Lee AJ, et al. Relationship between carotid intima-media thickness and symptomatic and asymptomatic peripheral arterial disease. The Edinburgh Artery Study. *Stroke.* 1997;28(2):348-353.

29. Gutierrez F, Bernal E, Padilla S, et al. Relationship between ankle-brachial index and carotid intima-media thickness in HIV-infected patients. *AIDS*. 2008;22(11):1369-1371.

30. Hayashi C, Ogawa O, Kubo S, et al. Ankle brachial pressure index and carotid intima-media thickness as atherosclerosis markers in Japanese diabetics. *Diabetes Res Clin Pract.* 2004;66(3):269-275.

31. Poldermans D, Bax JJ, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: The Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur Heart J.* 2009.

32. Dickstein. ESC Guidelines for the diagnosing and treatment of acute and chronic heart failure 2008. *Eur Heart J.* 2008;10:1093.

33. Flu WJ, Van Kuijk JP, Hoeks S, et al. Prognostic implications of asymptomatic left ventricular dysfunction in patients undergoing vascular surgery. *Anesthesiology.* 2010; in press.

34. Velazquez F, Berna JD, Abellan JL, et al. Reproducibility of sonographic measurements of carotid intima-media thickness. *Acta Radiol.* 2008;49(10):1162-1166.

Chapter 15

Metabolic syndrome is an independent predictor of cardiovascular events in high-risk patients with occlusive and aneurysmatic peripheral arterial disease

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ABSTRACT

Objective Metabolic syndrome (MetSyn) is a well-known risk factor for cardiovascular (CV) disease in the general population; however, the additional predictive value for CV events in high-risk patients with peripheral arterial disease (PAD) is unknown. The aims of the current study were to assess and compare: (i) prevalence of MetSyn, and (ii) predictive value of MetSyn for CV events, in patients with either occlusive or aneurysmatic PAD.

Methods We screened 2069 patients scheduled for lower occlusive arterial revascularization (N=1,031) or abdominal aortic aneurysm repair (N=1,038) for the presence of MetSyn. Adult Treatment Panel III report (ATP III) was used for defining MetSyn. Central obesity was defined as body-mass-index >30 kg/m2. Main outcomes were the occurrence of CV events and CV mortality during a median follow-up of 6 years (IQR 2 to 9 yrs).

Results Metabolic syndrome was diagnosed in 421 (41%) and 432 (42%) patients with occlusive and aneurysmatic PAD, respectively (p = 0.72). Patients with occlusive or aneurysmatic PAD and MetSyn had an increased risk for the development of CV events, when compared with patients without MetSyn (27 vs 18% and 27 vs 19%, $p < 0.001$, respectively). In occlusive and aneurysmatic PAD, MetSyn was independently associated with an increased risk of CV events (HR 1.6, 95%-CI: 1.2 to 2.1 and HR 1.4, 95%-CI: 1.1 to 1.8). No significant association between the presence of MetSyn and CV mortality was observed.

Conclusions Metabolic syndrome is highly prevalent in high-risk PAD patients. In occlusive and aneurysmatic PAD patients, MetSyn is an independent predictor of long-term CV events.

INTRODUCTION

The metabolic syndrome (MetSyn), also known as the insulin resistance syndrome or Syndrome X, is the concurrence of multiple metabolic abnormalities associated with cardiovascular (CV) disease. The prevalence of MetSyn in the general healthy population is 9-22%, and increases up to 50% in patients with known cerebrocardiovascular disease.[1-3] Importantly, the prevalence depends on the definition of MetSyn.[4]

In 1988, Raeven was the first who defined MetSyn, based on the fundamental pathogenic process of insulin resistance.[5] In 1999, the World Health Organization (WHO) defined specific metabolic components and laboratory thresholds for the definition of MetSyn, primarily based on the presence of insulin resistance.[6] The U.S. National Cholesterol Education Program (NCEP) redefined the MetSyn in 2003, in an attempt to simplify the clinical application of its criteria.[7] Of note, the fundamental pathogenic mechanism was not longer insulin resistance, but the presence of abdominal obesity.[8]

Metabolic syndrome was primarily developed as a predictor of CV disease in healthy populations, however, only recently studies have indeed demonstrated the association between MetSyn and increased risk of CV events.[1, 9-11] Important to notice is that these studies had different definitions of MetSyn and varying study populations. In patients with known cerebrocardiovascular disease it has been demonstrated that MetSyn was associated with increased risk for CV events and CV mortality.[9] However, the prevalence and predictive value of MetSyn in patients with occlusive peripheral arterial disease (PAD) or abdominal aortic aneurysms (AAA) has been examined only in low to intermediate risk patients or small groups of AAA patients.[1, 12-15]

Therefore, the primary aim of the current study was to assess the prevalence of MetSyn in these two high-risk populations. In addition, as data about the predictive value of MetSyn in these high-risk patients is scarce,[3, 11] the secondary aim of the current study was to assess the long-term predictive value of MetSyn in patients with either established occlusive or aneurysmatic PAD which has not been previously examined.

METHODS

Study design and population

This retrospective study included a total of 2933 patients with PAD, scheduled for elective lower extremity revascularization (N=1,031), abdominal aortic aneurysm surgery (N=1,038) and carotid endarterectomy (N=864) during the time period 1990 to 2008. The focus of the current study was to examine the prevalence and predictive value of MetSyn in patients with occlusive lower extremity arterial disease (symptomatic PAD requiring surgical intervention) or

aneurysmatic PAD (N=2,069). Patients undergoing surgery for occlusive disease with a history of aneurysmatic PAD were regarded as occlusive disease (3%), while patients undergoing surgery for aneurysmatic PAD and a history of occlusive disease were regarded as aneurysmatic PAD (10%). Patient enrolment was performed after approval of the hospital's ethics committee.

Patient data

At baseline all medical records were reviewed to determine the presence of documented ischemic heart disease and cerebrovascular disease. Ischemic heart disease was defined as a composite of previous angina pectoris, myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting. In addition, all (cardiac) risk factors were determined at baseline, including age, gender, body-mass-index (BMI), smoking status, chronic obstructive pulmonary disease (according to the Global Initiative on Obstructive Lung Diseaseas-classification)[16] and chronic renal insufficiency (serum creatinine >2.0 mg/dL). During preoperative evaluation fasting glucose and lipid-profiles (total cholesterol, HDL, LDL, triglycerides) were measured. Finally, the use of the following medication was recorded: aspirin, statins, β-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitor, oral anticoagulants and ticlopidines.

Metabolic syndrome

The presence of MetSyn was defined according the National Cholesterol Education Program's (NCEP) Adult Treatment Panel III report (ATP III), which identified the MetSyn as a multiplex risk factor for CV disease.[17] According the ATP III report, diagnosis of MetSyn can be made when 3 out of 5 of the following characteristics are present: (i) abdominal obesity (waist circumference men >102 cm, women >88 cm), (ii) triglycerides ≥150 mg/dL (>1.695 mmol/L), (iii) HDL cholesterol in men <40 mg/dL (<0.9 mmol/L) or in women <50 mg/dL (<1.0 mmol/L), (iv) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, and (v) fasting glucose ≥110 mg/dL (>6.1 mmol/L). For the current study we defined abdominal obesity as BMI >30 kg/m2.[18]

Follow-up and endpoints

The median follow-up of all patients was 6 years (interquartile (IQR) range 2 to 9). Primary study endpoint was the occurrence of CV events, defined as a composite of myocardial infarction, percutaneous coronary intervention / coronary artery bypass grafting or cerebrovascular accident / transient ischemic attack. Follow-up data were recorded by reviewing the medical records. Secondary endpoint included CV mortality. Survival status was completed by reviewing the municipal civil registries. Cause of death was ascertained by examining the death certificates, and otherwise by reviewing the medical records. Cardiovascular death was defined as any death with a cerebro-cardiovascular complication as the primary or secondary cause and included death following myocardial infarction, serious cardiac arrhythmias (defined as the presence of a sustained cardiac rhythm disturbance that

required urgent medical intervention), congestive heart failure, stroke (cerebrovascular event or transient ischemic attack), surgery related bleeding complications (only a postoperative cause of death), and others. Sudden unexpected death was classified as a CV death as well.

Statistics

Continuous data were compared using analyses of variance, and are expressed as mean ± Standard Deviation (SD). Categorical data are presented as percentage frequencies and compared using a χ^2 test. Cumulative estimated event rates of patients with or without MetSyn were determined by the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate Cox regression models were used to investigate the association between MetSyn (patients without MetSyn as reference group) and pre-specified endpoints. Multivariate analyses were adjusted for potential confounders (age, gender, smoking, heart failure, chronic renal insufficiency, and history of cerebrocardiovascular disease). We used interaction terms to study a possible interaction between these potential confounders and the primary endpoint for both groups of patients. Statistical analyses were performed using SPSS software (SPSS version 15.0; SPSS, Inc., Chicago, Illinois). Hazard ratios (HR) were calculated from these models along with their 95% confidence intervals (95%-CI.). A two-sided *p*-value <0.05 was considered statistically significant.

Figure 1: Distribution of the metabolic syndrome components among patients with occlusive or aneurysmatic peripheral arterial disease.

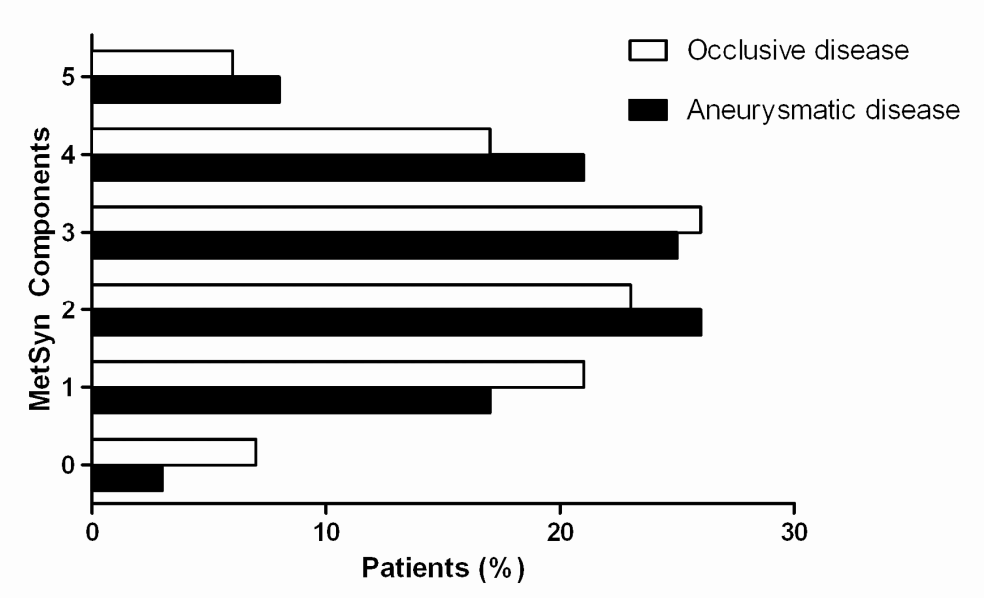


Table 1 **Baseline characteristics of the study population**

	Metabolic Syndrome				MetSyn in group 1 vs MetSyn in group 2
	Group 1 occlusive disease		Group 2 aneurysmatic disease		
	yes	no	yes	no	
	[N=421]	[N=610]	[N=432]	[N=606]	*p*-value
Demographics (%)					
Age >70 years	142 (34)	254 (42)	207 (48)	355 (39)	<0.001
Male (%)	372 (65)	442 (73)	365 (85)	505 (83)	<0.001
Medical history (%)					
Ischemic heart disease	215 (51)	239 (39)	239 (55)	277 (46)	0.19
CVA/TIA	80 (19)	64 (11)	81 (19)	71 (12)	0.90
Metabolic syndrome components					
Abdominal obesity (%)	89 (21)	32 (5)	388 (68)	141 (30)	0.21
Triglycerides ≥150mg/dL	394 (94)	123 (20)	433 (76)	50 (11)	0.05
HDL Cholesterol					
men <40 mg/dL	255 (94)	81 (18)	369 (75)	39 (10)	0.09
women <50 mg/dL	140 (94)	27 (16)	67 (81)	10 (12)	0.25
Blood pressure ≥130/85	409 (94)	433 (71)	537 (94)	334 (72)	0.22
Fasting glucose 6.1 mmol/L	112 (27)	55 (9)	324 (57)	131 (28)	<0.001
Additional risk factors (%)					
Smoking					0.08
no	120 (29)	260 (43)	148 (34)	249 (41)	
current	185 (44)	233 (38)	158 (37)	220 (36)	
history	116 (27)	117 (19)	126 (29)	137 (23)	
Renal insufficiency	69 (16)	51 (8)	60 (14)	67 (11)	0.29
Chronic heart failure	54 (11)	37 (7)	36 (8)	45 (7)	0.10
COPD	69 (16)	101 (17)	124 (29)	171 (28)	<0.001
Medication at discharge (%)					
Aspirin	223 (53)	192 (32)	215 (50)	219 (36)	0.31
Statin	255 (61)	121 (20)	223 (52)	159 (26)	0.01
β-blocking agents	237 (56)	167 (27)	260 (60)	261 (43)	0.25
ACE-inhibitors	142 (34)	136 (22)	143 (33)	132 (22)	0.87
Diuretics	138 (33)	124 (20)	131 (30)	129 (21)	0.46
Oral anticoagulants	201 (48)	382 (63)	115 (27)	191 (32)	<0.001
Ticlopidines	30 (7)	15 (3)	14 (3)	19 (3)	0.01

Angiotensin coverting enzyme (ACE), cerebrovascular accident/transient ischemic attack (CVA/TIA), chronic obstructive pulmonary disease (COPD), high density lipoprotein (HDL), metabolic syndrome (MetSyn), peripheral arterial disease (PAD).

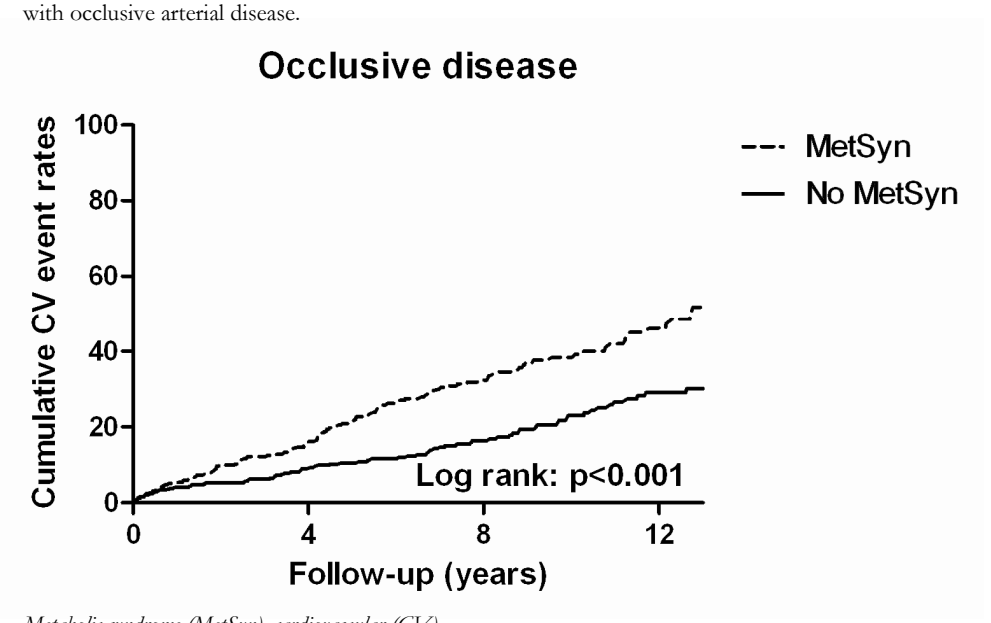
RESULTS

Baseline characteristics of the total study population

A total of 2,069 eligible patients, referred for lower extremity revascularization (N=1,031) or abdominal aortic aneurysm repair (N=1,038) comprised the study population (*Table 1*). Diagnosis of MetSyn was established in 421 (41%) and 432 (42%) patients with occlusive and

aneurysmatic PAD, respectively (p = 0.72). The distribution of the number of MetSyn components among occlusive and aneurysmatic PAD patients with or without MetSyn is shown in *Figure 1*. In addition, baseline characteristics of patients with occlusive and aneurysmatic PAD and MetSyn are shown in *Table 1*.

Figure 2a: Kaplan-Meier estimated of cardiovascular event rates during long-term follow-up in patients with occlusive arterial disease.



Metabolic syndrome (MetSyn), cardiovascular (CV).

Occlusive peripheral arterial disease

Patients with occlusive PAD and MetSyn were more likely to have a history of cerebrocardiovascular disease (ischemic heart disease/cerebrovascular disease), smoking habits (current or history), chronic renal insufficiency and chronic heart failure ($p < 0.001$), compared with patients without MetSyn. Lipid spectrum disorders and hypertension were the most often present components in patients with MetSyn. Medical treatment with aspirin, statins and β-blockade was higher in patients with MetSyn ($p < 0.001$). In addition, patients with MetSyn were more often treated with antihypertensive drugs ($p < 0.001$). During a median follow-up of 6 years (IQR 2 to 9), 228 (22%) occlusive disease patients developed CV events. Patients with MetSyn had an increased risk for the occurrence of CV events, compared with patients without MetSyn (27 vs 19%, p = 0.001). Kaplan-Meier estimates for long-term CV event rates showed that patients with MetSyn had higher event rates compared with patients without MetSyn (*Figure 2a*). Moreover, the presence of MetSyn proved to be an independent prognostic factor for long-term cardiovascular events (HR 1.61, 95%-CI: 1.2 to 2.1). For the occurrence of late cardiovascular events, diabetes mellitus, and BMI >30 kg/m^2 were the independent prognostic

factors contributing to the MetSyn (*Table 2*). Furthermore, age (HR 1.02, 95%-CI: 1.0 to 1.1), ischemic heart disease (HR 2.16, 95%-CI: 1.6 to 2.9) and chronic renal insufficiency (HR 2.93, 95%-CI: 2.1 to 4.2) were independent predictors for long-term cardiovascular events. No interaction between age, gender, smoking, heart failure, chronic renal insufficiency, and history of cerebrocardiovascular disease and the occurrence of cardiovascular events in patients with MetSyn was observed. The secondary endpoint CV mortality occurred in 337 (33%) patients. Regression analyses demonstrated no association between the presence of MetSyn and the occurrence of all-cause or CV mortality.

Table 2 **Long-term cardiovascular events in occlusive of aneurysmatic peripheral arterial disease**

	HR	[95%-CI]
Occlusive peripheral arterial disease		
Metabolic syndrome	1.61	1.23-2.11
Abdominal obesity	1.79	1.25-2.58
Triglycerides ≥150 mg/dL	1.10	0.80-1.52
HDL cholesterol	1.31	0.88-1.96
Blood pressure ≥130/85	1.15	0.77-1.71
Fasting glucose ≥6.1 mmol/L	2.07	1.49-2.86
Aneurysmatic peripheral arterial disease		
Metabolic syndrome	1.36	1.05-1.76
Abdominal obesity	0.95	0.57-1.60
Triglycerides ≥150 mg/dL	1.50	1.09-2.07
HDL cholesterol	0.98	0.71-1.35
Blood pressure ≥130/85	0.88	0.61-1.25
Fasting glucose ≥6.1 mmol/L	1.10	0.84-1.44

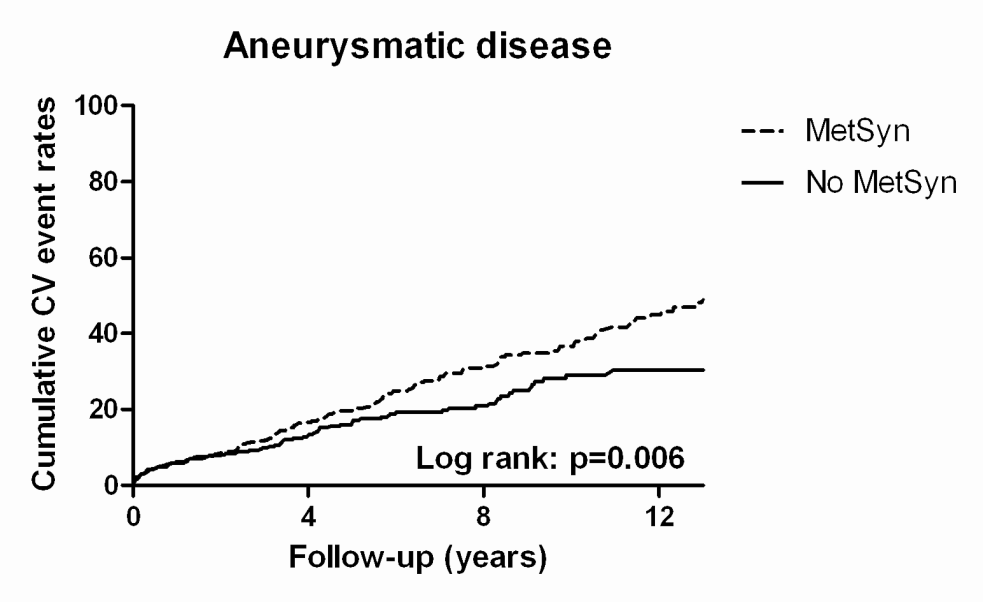
Long-term cardiovascular events in occlusive or aneurysmatic peripheral arterial disease. Confidence interval (CI), hazard ratio (HR), high density lipoprotein (HDL).

Aneurysmatic peripheral arterial disease

Aneurysmatic PAD patients with MetSyn were significantly younger and had more often a history of cerebrocardiovascular disease ($p < 0.05$). At discharge, patients with MetSyn were more often treated with aspirin, statins and β-blocking agents, compared with aneursymatic patients without MetSyn ($p < 0.001$). Hypertension was the most frequent component of MetSyn and medical treatment was in line with this finding as the majority of the MetSyn patients were treated with diuretics or ACE-inhibitors ($p < 0.001$). Cardiovascular events occurred in 153 (27%) aneurysmatic PAD patients with MetSyn, compared with 88 (19%) of the patients without MetSyn ($p = 0.001$). Estimates for long-term CV event rates according the Kaplan-Meier curves, demonstrated that patients with MetSyn had significantly higher event rates compared with patients without MetSyn (Log rank test, $p = 0.006$) (*Figure 2b*). Using multivariate analyses, the presence of MetSyn in patients with aneurysmatic PAD was an independent predictor for long-term CV events (HR 1.36, 95%-CI: 1.1 to 1.8). Of the components contributing to the MetSyn, only elevated triglycerides were significantly

associated with an increased risk of long-term CV events. In line with occlusive disease patients, age (HR 1.03, 95%-CI: 1.0 to 1.1), Ischemic heart disease (HR 1.45, 95%-CI: 1.1 to 1.9) and chronic renal insufficiency (HR 3.60, 95%-CI: 2.6 to 4.9) were independent predictors for long-term cardiovascular events. Using interaction terms, no significant interaction for age, gender, smoking, heart failure, chronic renal insufficiency, and history of cerebrocardiovascular disease were demonstrated.

Figure 2b: Kaplan-Meier estimated of cardiovascular event rates during long-term follow-up in patients with aneurysmatic peripheral arterial disease.



Metabolic Syndrome (MetSyn), cardiovascular (CV).

Of note, during long-term follow-up 324 (31%) patients died due to a CV cause. However, no association between the presence of MetSyn and CV mortality was observed in patients with aneurysmatic PAD. Additional analyses were performed to study the predictive usefulness of MetSyn in patients without diabetes. After excluding the patients with known DM (N=362, 17%), and those with a fasting glucose >7.0 mmol/L (N=142), there was a remaining population of 1,564 patients (76%). Using multivariate Cox regression analysis, MetSyn remained to be an independent predictor of adverse cardiovascular events with a HR of 1.4 (95%-CI: 1.09 to 1.81). Furthermore, we evaluated the predictive value of MetSyn using three (N=563, 27%), four (N=256, 12%) or five (N=34, 1,6%) criteria for the diagnosis of MetSyn. In multivariate analyses, MetSyn defined with the three, four and five criteria were all independently associated with a 1.3 (95%-CI: 1.1 to 1.6), 1.8 (95%-CI: 1.3 to 2.3) and 2.2-fold (95%-CI: 1.2 to 4.1) increased risk of CV events.

DISCUSSION

To our knowledge, this is the first study demonstrating the predictive value of MetSyn on the occurrence of CV events in patients with symptomatic occlusive and aneurysmatic PAD. We found a high prevalence of MetSyn in both groups of patients. In addition, in both occlusive and aneurysmatic PAD patients, MetSyn was an independent predictor for the occurrence of CV events during long-term follow-up, compared with PAD patients without MetSyn. No association between the presence of MetSyn and the occurrence of CV mortality was observed.

Metabolic syndrome has 2 potential pathophysiological processes, including (i) insulin resistance, and (ii) obesity and disorders of adipose tissue. In line with Raeven *et al.*[5] who proposed the first definition of MetSyn, the WHO identified insulin resistance as the fundamental mechanism. Insulin resistance and hyperinsulinemia directly causes other metabolic risk factors, including an increased body fat content.[6] The emphasis of insulin resistance as the basic pathophysiological mechanism is based on the presence of reduced insulin sensitivities throughout several degrees of obesity.[10] In contrast, by the NCEP expert panel [7, 17] the rising prevalence of MetSyn was considered to be a direct consequence of the "obesity epidemic", as obesity directly or indirectly contributes to hypertension, high serum cholesterol, low HDL cholesterol and hyperglycemia. Although there is no definite consensus about the leading pathophysiological mechanism of MetSyn, a combined process of increased obesity and insulin resistance with a strong interaction seems most appropriate mechanism.

A direct consequence of the lack of consensus about the pathogenic mechanisms of MetSyn, are the differences in clinical criteria for the diagnosis recommended by at least 3 organizations, including the ATP III [17], the WHO [6] and the American Association of Clinical Endocrinologists (AACE).[19] Although their criteria are similar in several aspects, they reveal fundamental differences in positioning of the predominant causes of the syndrome. In the ATP III criteria, priority is given to abdominal obesity as a contributor of MetSyn, recognized by increased waist circumference.[17] In contrast, the WHO regarded insulin resistance as a required component for diagnosis, while this was not explicitly required in the ATP III definition.[6] Furthermore, abdominal obesity was defined as a BMI >30 kg/m^2. The AACE criteria appear to be a hybrid of the ATP III and WHO criteria. In this set of criteria, abdominal obesity is a major criteria and is defined as BMI >30 kg/m^2.[19] These different abdominal obesity parameters could influence the prevalence of MetSyn and its predictive value for CV events. However, a meta-analysis by Gami *et al.* demonstrated that the heterogeneity between the predictive values of the WHO and ATP III criteria was not explained by the use of different obesity metrics. Currently, ATP III criteria are most commonly used as they provide a practical tool to identify patients at increased risk for CV disease.[20] Furthermore, WHO and AACE criteria require additional oral glucose tolerance testing if impaired fasting glucose and diabetes are absent.

The prevalence of MetSyn is strongly related to the definition of MetSyn, but to the target population as well. The impact of MetSyn as a growing and pressing problem for the general population is reflected by the high prevalence of the condition in healthy subjects (9-22%).[1, 2] The current study showed a prevalence of 41 and 42% of MetSyn in patients with symptomatic occlusive and aneurysmatic PAD, respectively. Previous studies reported that the prevalence of MetSyn in PAD patients can be up to 58%, which is even higher than in patients with coronary heart disease (41%) or cerebrovascular disease (43%).[3, 11] These findings have important clinical implications, considering that PAD is highly prevalent in the adult population and is associated with an increased risk of CV events.[21, 22] The current study observed no difference in prevalence of MetSyn in patients with aneurysmatic compared with patients with occlusive PAD. These findings have not been examined by previous studies, however, the difference in prevalence might be a result of the small sample size of previous studies compared with the present study.[3, 23] In addition, the use of different criteria for defining MetSyn could have influenced the observed prevalence. In the present study we used ATP III criteria as these provide a practical tool to identify patients at increased risk for CV events and have been acknowledge as a reliable prognostic indicator of adverse cardiac outcome.[20]

In this study the presence of MetSyn in patients with established occlusive or aneurysmatic PAD was independently associated with an increased risk for the occurrence of CV events during long-term follow-up. Although patients undergoing vascular surgery are classified as being a high-risk population for perioperative and long-term adverse cardiac outcome, the present study demonstrated that diagnosing MetSyn has an additional value for long-term prognosis. Therefore, based on our results we support the clinical use of MetSyn as a prognostic factor for long-term cardiac outcome in both patients with occlusive and aneurysmatic PAD. Despite the high prevalence of MetSyn in patients with aneurysmatic PAD, the correlation between MetSyn and CV events seemed to be less strong compared with patients with occlusive disease. The most reasonable explanation for this low correlation could be the difference in risk factors and the pathophysiological processes. Occlusive arterial disease is a direct consequence of atherosclerotic wall damage, while aneurysmatic PAD is an inflammatory process of the arterial wall with subsequent weakening of the aortic wall as a result of connective tissue degradation.[24] In the present study these differences were underlined by different risk factor patterns, especially lower age at presentation in patients with occlusive disease and high prevalence of COPD (a connective tissue disease as well) in patients with aneurysmatic PAD.

Some studies have demonstrated no additional effect of MetSyn above its individual components for the prediction of cardiovascular events.[20] In the present study of patients with occlusive PAD, obesity and elevated fasting glucose levels were independent predictors. In aneurysmatic PAD patients, only hypertriglyceridemia was an independent predictor of adverse outcome. MetSyn is a unique and uniform entity, requiring at least three out of five diagnostic

components; therefore, it is reasonable that the combination of components (MetSyn) has an additional value in the current study. In addition, using only the significant individual components for predicting future cardiovascular events, the importance of the non-significant components would be under-estimated. To study the specific influence of diabetes as an individual component on the predictive value of MetSyn, we performed additional analyses in which we excluded patients with known DM and/or fasting glucose levels >7.0 mmol/L. Importantly, MetSyn remained to be an independent predictor of cardiovascular events during long-term follow-up. The kind, magnitude and number of the diagnostic components are likely to influence the prognostic information of MetSyn; therefore, future studies should be performed using MetSyn as a weighted-risk model in which each component has its own predictive value. Previous studies in patients with PAD have been performed and observed a predictive value of MetSyn for future vascular events.[12-15] However, most of these studies included patients out of the general population [12, 13] (low-risk) or patients with symptomatic PAD (intermediate-risk).[14, 15] Of note, one study included a small number of patients with AAA, but no association between the presence of MetSyn and future vascular events or all-cause mortality was detected.[15] In contrast, the current study included high-risk patients and a large cohort of AAA patients.

No relation between the presence of MetSyn and CV mortality was observed in patients with either occlusive or aneurysmatic PAD. According to the WHO and ATP III definition, the primary clinical outcome of MetSyn as a multiplex risk factor is the development of CV disease in patients free of cardiac history.[6, 17] A meta-analysis addressing MetSyn and CV risk showed an increased risk for the development of CV events (RR 2.18, 95%-CI: 1.6 to 2.9) and CV death (RR 1.91, 95%-CI: 1.5 to 2.5).[25] However, this meta-analysis included a diversity of study populations evaluating studies with and without previous histories of CV disease. In addition, definitions of MetSyn were different between the included studies. We performed additional analyses using a diagnosis of MetSyn based on three, four or even five diagnostic criteria for MetSyn to explore whether the risk estimates changed with the number of criteria. These analyses demonstrated that with an increased number of diagnostic criteria the risk of cardiovascular events increased as well, however; the accuracy of the risk estimates diminished. Importantly, the current study included high-risk PAD patients of which almost 50% had a history of CV disease. This could be a possible explanation for the absence of a relation between the presence of MetSyn and the risk of CV mortality as well. Patients with PAD are known to be at increased risk of CV mortality, and based on the present study the presence of MetSyn had no incremental risk for CV mortality in these patients. Therefore, the presence of MetSyn only has an additional value as a predictor for CV events in high-risk PAD patients. Finally, patients with MetSyn received more optimal medical treatment. Although this did not influence the risk of developing CV events, medical treatment could possibly be related to a stabilization of the risk for CV mortality.

Potential limitations of the current study merit consideration. First, we used the ATP III criteria for the definition of MetSyn; however, abdominal obesity was defined as BMI >30 kg/m^2 instead of increased waist circumference. Although this abdominal obesity parameter could have influenced the outcome parameters, the meta-analysis discussed above demonstrated that obesity metrics did not influence the predictive value of MetSyn.[25] Second, for the current study we used ATP III criteria for defining MetSyn. As there are other definitions using different combinations of diagnostic criteria, this could have influenced the prognostic information in this study. Third, this study has the inherent limitations of a retrospective study design. Although the present study found no association between MetSyn and increased CV mortality risk, other studies did show this relation. This might be related to the associations between target population, cardiovascular disease history, and the prevalence of MetSyn. Finally, although medication at discharge was recorded, no data on medication during the follow-up period were available.

CONCLUSION

Patients with occlusive or aneurysmatic PAD have a high prevalence of metabolic syndrome. In both patients with occlusive or aneurysmatic PAD, the presence of metabolic syndrome was independently associated with an increased risk for the occurrence of CV events during long-term follow-up. Concomitant presence of metabolic syndrome in patients with occlusive or aneurysmatic PAD was not associated with an increased long-term risk of CV mortality.

REFERENCES

1. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. Jama. 2002; 288: 2709-2716.

2. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. Jama. 2002; 287: 356-359.

3. Gorter PM, Olijhoek JK, van der Graaf Y, Algra A, Rabelink TJ, Visseren FL. Prevalence of the metabolic syndrome in patients with coronary heart disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm. Atherosclerosis. 2004; 173: 363-369.

4. Grundy SM, Brewer HB, Jr., Cleeman JI, Smith SC, Jr., Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation. 2004; 109: 433-438.

5. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988; 37: 1595-1607.

6. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998; 15: 539-553.

7. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). Jama. 2001; 285: 2486-2497.

8. Lim HS, Patel JV, Lip GY. Metabolic syndrome: a definition in progress. Circulation. 2004; 110: e35; author reply e35.

9. Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyorala K. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. Arch Intern Med. 2004; 164: 1066-1076.

10. Abbasi F, Brown BW, Jr., Lamendola C, McLaughlin T, Reaven GM. Relationship between obesity, insulin resistance, and coronary heart disease risk. J Am Coll Cardiol. 2002; 40: 937-943.

11. Brevetti G, Schiano V, Sirico G, Giugliano G, Laurenzano E, Chiariello M. Metabolic syndrome in peripheral arterial disease: relationship with severity of peripheral circulatory insufficiency, inflammatory status, and cardiovascular comorbidity. J Vasc Surg. 2006; 44: 101-107; discussion 107.

12. Conen D, Rexrode KM, Creager MA, Ridker PM, Pradhan AD. Metabolic syndrome, inflammation, and risk of symptomatic peripheral artery disease in women: a prospective study. Circulation. 2009; 120: 1041-1047.

13. Jacobs M, van Greevenbroek MM, van der Kallen CJ, et al. Low-grade inflammation can partly explain the association between the metabolic syndrome and either coronary artery disease or severity of peripheral arterial disease: the CODAM study. Eur J Clin Invest. 2009; 39: 437-444.

14. Vlek AL, van der Graaf Y, Sluman MA, Moll FL, Visseren FL. Metabolic syndrome and vascular risk in patients with peripheral arterial occlusive disease. J Vasc Surg. 2009; 50: 61-69.

15. Wassink AM, van der Graaf Y, Olijhoek JK, Visseren FL. Metabolic syndrome and the risk of new vascular events and all-cause mortality in patients with coronary artery disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm. Eur Heart J. 2008; 29: 213-223.

16. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007; 176: 532-555.

17. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002; 106: 3143-3421.

18. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation. 2003; 107: 391-397.

19. Einhorn D, Reaven GM, Cobin RH, et al. American College of Endocrinology position statement on the insulin resistance syndrome. Endocr Pract. 2003; 9: 237-252.

20. Wang J, Ruotsalainen S, Moilanen L, Lepisto P, Laakso M, Kuusisto J. Metabolic syndrome and incident end-stage peripheral vascular disease: a 14-year follow-up study in elderly Finns. Diabetes Care. 2007; 30: 3099-3104.

21. Meijer WT, Hoes AW, Rutgers D, Bots ML, Hofman A, Grobbee DE. Peripheral arterial disease in the elderly: The Rotterdam Study. Arterioscler Thromb Vasc Biol. 1998; 18: 185-192.

22. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. Jama. 2001; 286: 1317-1324.

23. Olijhoek JK, van der Graaf Y, Banga JD, Algra A, Rabelink TJ, Visseren FL. The metabolic syndrome is associated with advanced vascular damage in patients with coronary heart disease, stroke, peripheral arterial disease or abdominal aortic aneurysm. Eur Heart J. 2004; 25: 342-348.

24. Lindblad B, Borner G, Gottsater A. Factors associated with development of large abdominal aortic aneurysm in middle-aged men. Eur J Vasc Endovasc Surg. 2005; 30: 346-352.

25. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol. 2007; 49: 403-414.

Chapter 16

The interrelationship between preoperative anemia and N-terminal pro-B-type natriuretic peptide: effect on predicting postoperative cardiac outcome in vascular surgery patients

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ABSTRACT

Introduction N-terminal pro-B-type natriuretic peptide (NT-proBNP) predicts adverse cardiac outcome in patients undergoing vascular surgery. However, several conditions might influence this prognostic value, including anemia. In this study, we evaluated whether anemia confounds the prognostic value of NT-proBNP for predicting cardiac events in patients undergoing vascular surgery.

Methods A detailed cardiac history, resting echocardiography, hemoglobin and NT-proBNP levels were obtained in 666 patients before vascular surgery. Anemia was defined as serum hemoglobin <13 g/dL for men and <12 g/dL for women. Troponin T measurements and 12-lead electrocardiograms were performed on postoperative days 1, 3, 7 and 30 and whenever clinically indicated. The primary endpoint of the study was the composite of 30-day postoperative cardiovascular death, nonfatal myocardial infarction, and troponin T release. Receiver operating characteristic curve analysis was used to assess the optimal cut off value of NT-proBNP for the prediction of the composite endpoint. Multivariate regression analysis was used to assess the additional value of NT-proBNP for the prediction of postoperative cardiac events in nonanemic and anemic patients.

Results Anemia was present in 206 patients (31%) before surgery. Hemoglobin level was inversely related with the NT-proBNP levels (β coefficient = -2.242, $p = 0.025$). The optimal predictive cut off value of NT-proBNP for predicting the composite cardiovascular outcome was 350 pg/mL. After adjustment for clinical cardiac risk factors, both anemia (OR 1.53, 95%-CI: 1.07 to 2.99) and elevated levels of NT-proBNP (OR 4.09, 95%-CI: 2.19 to 7.64) remained independent predictors for postoperative cardiac events. However, elevated levels of NT-proBNP were not predictive for the risk of adverse cardiac events in the subgroup of anemic patients (OR 2.16, 95%-CI: 0.90 to 5.21).

Conclusions Both anemia and NT-proBNP are independently associated with an increased risk for postoperative cardiac events in patients undergoing vascular surgery. NT-proBNP has less predictive value in anemic patients.

INTRODUCTION

In patients with extensive comorbidities, scheduled for major vascular surgery, a simple screening biomarker associated with adverse cardiac events would be useful for identifying those patients who might benefit from additional cardiac diagnostic testing or therapeutic interventions. N-terminal pro-B-type natriuretic peptide (NT-proBNP) is synthesized in the ventricular myocardium in response to ventricular wall stress, such as in heart failure and coronary artery disease.[1, 2] It has been suggested that measurement of NT-proBNP levels might improve preoperative cardiac risk stratification for surgical patients.[3-5] Anemia is independently related to both elevated NT-proBNP levels,[6-8] and adverse cardiac outcome after vascular surgery.[9] It is unknown whether the association between anemia and elevated NT-proBNP levels is attributable to subclinical ventricular dysfunction, coronary artery disease, or both. Nonetheless, anemia may be an important confounding variable that may affect the prognostic value of NT-proBNP levels for predicting cardiac risk for surgical patients. To further increase the diagnostic accuracy of NT-proBNP for preoperative screening, it is important to identify factors that influence NT-proBNP levels and their interaction with identifying risk for adverse events. The purpose of this study was to evaluate whether anemia influences the prognostic value of preoperative NT-proBNP levels for identifying patients undergoing vascular surgery at risk for adverse cardiac events.

METHODS

The study population consisted of 666 consecutive patients undergoing elective vascular surgery at the Erasmus Medical Center, Rotterdam, the Netherlands, during the period between June 2004 and April 2008. These patients were identified in a prospectively maintained database of all patients undergoing vascular surgery at this institution. The Medical Ethics Committee of the hospital was informed about the study, and all procedures of this retrospective study met with the approval of the Medical Ethics Committee of the Erasmus Medical Center.

Study procedures

Before surgery, a detailed cardiac history was obtained including the use of cardiovascular medication and the presence of cardiac risk factors. The latter included age, angina pectoris, prior myocardial infarction, history of heart failure or current congestive heart failure, prior stroke or transient ischemic attack, diabetes mellitus (fasting glucose level ≥7.0 mmol/L or medication to control diabetes), renal dysfunction (defined as an estimated glomerular filtration rate <60 mL·min^{-1}·1.73 m^{-2} using the Modification of Diet in Renal Disease formula),[10] hypertension (arterial blood pressure ≥140/90 mmHg or medical therapy to control hypertension), and hypercholesterolemia (plasma cholesterol level ≥5.5 mmol/L or treatment

with lipid-lowering drugs). Other data collected included history of chronic obstructive pulmonary disease (defined as a forced expiratory volume in 1 second <70% of age and gender predictive value), site of surgery (abdominal aortic, peripheral, or carotid), and type of procedure (endovascular or open). Peripheral venous blood samples were obtained for measurement of hemoglobin and NT-proBNP levels in all patients during the preoperative outpatient clinic visit or at hospital admission. The NT-proBNP concentration was determined using an electrochemoluminescence assay on an Elecsys 2010 (Hoffman-La Roche, Basel, Switzerland). The method is a "sandwich"-type quantitative immunoassay based on polyclonal antibodies against epitopes in the N-terminal part of proBNP. The lower detection limit was 5 pg/mL. Intraassay coefficients of variance at 271 and 6,436 pg/mL were 1.9 and 0.9%, respectively. Assays were performed by a laboratory technician blinded to the patients' clinical data. The preoperative hemoglobin value was defined as the last measurement obtained before surgery. Preoperative anemia was defined based on World Health Organization criteria as a serum hemoglobin level <12 g/dL for men and <12 g/dL for women.[11]

Preoperatively, patients underwent a two-dimensional transthoracic echocardiographic examination at rest. Left ventricular (LV) ejection fraction (LVEF) was assessed in the apical, 4- or 2-chamber views. Quantification of the LV volumes was performed using the modified Simpson's rule. The LVEF was calculated as (LV end systolic volume – LV end diastolic volume) x 100/ LV end diastolic volume. Impaired LV systolic function was considered when the LVEF was <40%. Congestive heart failure was defined as suggestive clinical signs and symptoms with pulmonary congestion on chest radiograph in the presence of impaired LV function.

Twelve-lead electrocardiography (ECG) and serum cardiac troponin T measurements were performed immediately before surgery and on postoperative days 1, 3, 7, and 30 or at hospital discharge and whenever clinically indicated. ECG data were initially processed by a technician and analyzed by 2 experienced investigators who were blinded to patients' clinical data. Troponin T level was measured using a whole blood rapid test (TropT version 2, Roche Diagnostics, Mannheim, Germany). The upper limit of normal for this assay is 0.03 ng/mL.

Study endpoints

The primary endpoint of this study was the composite outcome of death within 30 days of surgery because of cardiac events, nonfatal myocardial infarction, and increased serum cardiac troponin T levels, which was considered to be a non-Q wave myocardial infarction. Cardiovascular death was defined as any death with a cardiovascular cause, including those deaths after a cardiac procedure, cardiac arrest, myocardial infarction, pulmonary embolus, stroke, or sudden deaths not ascribed to other causes. A myocardial infarction was defined as the presence of two of the following three criteria: (i) characteristic ischemic symptoms lasting >20 min, (ii) ECG changes including acute ST elevation, followed by appearance of Q waves or loss of R waves, new left bundle-branch block, new persistent T wave inversion for at least

24 h, or new ST segment depression that persisted >24 h, or (iii) a positive value for troponin T, defined as >0.10 ng/mL.[12]

Data analysis

Continuous data with a normal distribution are expressed as means and were compared using Student's *t*-test. Continuous data with a significant skewed distribution are expressed as medians and were compared using the Mann-Whitney *U*-statistic test. Data are presented as percentages unless otherwise indicated. The association between hemoglobin and NT-proBNP plasma levels and the composite cardiovascular outcome was assessed using multivariate linear regression analysis adjusted for age (per decade), angina pectoris, myocardial infarction, heart failure, stroke, diabetes mellitus, renal dysfunction, and site and type of surgery. Receiver operating characteristic curve analysis was used to assess the optimal cut off value of NT-proBNP for the prediction of the composite endpoint. The optimal value of NT-proBNP for predicting the postoperative composite cardiac outcome was defined as the concentration with the largest sum of sensitivity plus specificity. Univariate and multivariate logistic regression analyses were used to evaluate the relationship among anemia, increased levels of NT-proBNP, and the study endpoint. Interaction between anemia and NT-proBNP was evaluated by forcing this interaction term in the multivariate regression model. Subgroup analyses for the prognostic value of elevated levels of NT-proBNP were conducted when there was a statistically significant interaction term. We report crude and adjusted odds ratios (ORs) and their 95% confidence interval (95%-CI). For all tests, a p-value < 0.05 (two-sided) was considered significant. All analyses were performed using SPSS version 15.0 statistical software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Of the 666 patients, 250 underwent abdominal aortic aneurysm repair, 218 underwent lower limb arterial reconstructions, and 198 underwent carotid artery surgery. Baseline characteristics of the patients are presented in *Table 1*. Endovascular procedures comprised 30% of the studied surgical procedures (40% abdominal aortic, 8% lower limb, and 43% carotid artery). The majority of patients were men (76.6%), and the mean age was 68.2 ± 10.5 yr. Anemia was present in 206 patients (31%). Univariate factors associated with anemia were diabetes mellitus ($p = 0.001$), a history of a myocardial infarction ($p = 0.010$), previous coronary intervention ($p < 0.001$), renal dysfunction ($p < 0.001$), and heart failure ($p = 0.002$). Notably, patients with a history of stroke were less likely to have anemia ($p = 0.002$). Except for diuretics ($p = 0.018$), no association was seen between medication use and the incidence of anemia. Importantly, median levels of NT-proBNP were significantly higher in anemic compared with nonanemic patients (624.8 pg/mL and 141.4 pg/mL, respectively; $p < 0.001$). Hemoglobin levels were

inversely related to NT-proBNP levels (β coefficient for log-NT-proBNP for each 0.1-point increase in hemoglobin level was –0.063; $p < 0.001$).

Table 1 **Baseline characteristics according to the presence or absence of anemia**

	All patients	No anemia [a]	Anemia	*p*-value
	[N=666]	[N=460]	[N=206]	
Demographics				
Age [b]	68.2 (±10.5)	67.1 (±10.4)	70.6 (±10.4)	<0.001
Men (%)	76.6	75.7	78.6	0.429
Body mass index (kg/m²) [b]	25.8 (±4.0)	26.0 (±3.9)	25.3 (±4.3)	0.037
Medical history (%)				
Hypertension	50.6	52.6	46.1	0.131
Diabetes mellitus	24.7	19.6	35.9	0.001
Angina pectoris	23.5	22.7	25.2	0.489
Myocardial infarction	29.5	26.4	36.4	0.010
Coronary intervention	19.8	15.7	29.1	<0.001
Renal dysfunction	11.0	5.2	23.8	<0.001
Heart failure	6.4	4.2	11.2	0.002
Cerebrovascular accident	38.9	42.9	30.1	0.002
COPD	23.6	25.3	20.0	0.166
Hypercholesterolemia	37.9	40.0	33.7	0.317
Surgery (%)				
Site				0.221
carotid	29.7	34.8	18.0	
abdominal aortic	37.6	38.3	36.1	
lower extremity	32.7	25.7	45.4	
Type				0.122
endovascular	69.3	32.6	26.3	
open	30.7	67.4	73.7	
Medication (%)				
ACE inhibitors	32.4	31.7	34.0	0.589
Diuretics	27.2	24.4	33.5	0.018
Calcium-antagonists	22.4	21.6	24.1	0.480
Aspirin	67.4	68.2	65.5	0.529
β-blockers	84.7	83.9	86.7	0.412
Statins	76.4	78.0	72.9	0.165
Laboratory				
Hemoglobin (g/dL) [c]	13.7 (12.5-14.7)	14.4 (13.6-15.2)	11.5 (10.6-12.6)	<0.001
NT-proBNP (pg/mL) [c]	209.8 (91.4-560.1)	141.3 (68.5-313.9)	624.8 (230.3-1487.5)	<0.001

[a] defined as a serum hemglobin level <13 g/dL for men and a level <12 g/dL for women [b] mean (SD) [c] median (interquartile range)

Ninety-one patients (14.3%) experienced the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or non-Q wave myocardial infarction. Of these patients, 41 (6.2%) experienced ECG changes compatible with myocardial infarction. Thirteen patients (1.9%) had a cardiovascular death.

Anemia was more frequent in patients with the composite cardiovascular endpoint compared with those without postoperative cardiac events (51.6 and 27.8%, respectively; $p < 0.001$). Moreover, baseline NT-proBNP levels in the patients with a postoperative cardiac event were significantly higher than in those without an event (763.1 pg/mL and 169.2 pg/mL, respectively; $p < 0.001$). Using receiver operating characteristic curve analysis, the optimal value of NT-proBNP for predicting an adverse cardiac event was 350 pg/mL. The sensitivity and specificity of predicting this event for patients with a serum NT-proBNP level ≥350 pg/mL were 71 and 72%, respectively (area under the curve: 0.78, 95%-CI: 0.72 to 0.83) (*Figure 1*). In separate adjusted multivariate logistic regression models, the presence of preoperative anemia and elevated levels of NT-proBNP were both predictive of postoperative cardiac events with ORs of 1.53 (95%-CI: 1.07 to 2.99) and 4.09 (95%-CI: 2.19 to 7.64), respectively (*Table 2*). The sensitivity of anemia for detecting the postoperative outcome is 56.0% and specificity is 91.4%. Importantly, because the interaction term between anemia and NT-proBNP was significant ($p = 0.004$) for the prediction of the study endpoint, we conducted a subgroup analysis for nonanemic and anemic patients. *Figure 2* shows that, after adjustment for clinical cardiac risk factors, and site and type of surgery, an increased level of NT-proBNP has no predictive value of the composite outcome in anemic (OR 2.16, 95%-CI: 0.90 to 5.21) compared with nonanemic patients (OR 5.59, 95%-CI: 2.23 to 13.97).

Table 2 **Odds ratios for postoperative cardiac events**

	OR [95%-CI]	*p*-value
Anemia		
Unadjusted model	2.78 (1.77 - 4.37)	<0.001
Multivariate model [a]	1.53 (1.07 - 2.99)	0.038
NT-proBNP ≥350 pg/mL		
Unadjusted model	7.07 (4.28 - 11.68)	<0.001
Multivariate model [a]	4.09 (2.19 - 7.64)	<0.001

[a] *adjusted for age, angina pectoris, myocardial infarction, heart failure, stroke, diabetes mellitus, renal dysfunction, site of surgery, and type of surgery.*

DISCUSSION

In this study, an association was observed between increased preoperative NT-proBNP levels and the risk for postoperative cardiac events in patients undergoing vascular surgery. However, our results demonstrate that anemia is a confounding factor in this relationship. Although preoperative NT-proBNP levels were additive to clinical risk factors for identifying risk for postoperative cardiovascular events in patients without anemia, NT-proBNP had less predictive value in those with anemia.

Figure 1: Receiver operating characteristic curve of N-terminal pro-B-type natriuretic peptide levels to predict postoperative cardiac events. Sensitivity and 1-specificity are plotted for various levels. The ideal cut off value is indicated by the arrow.

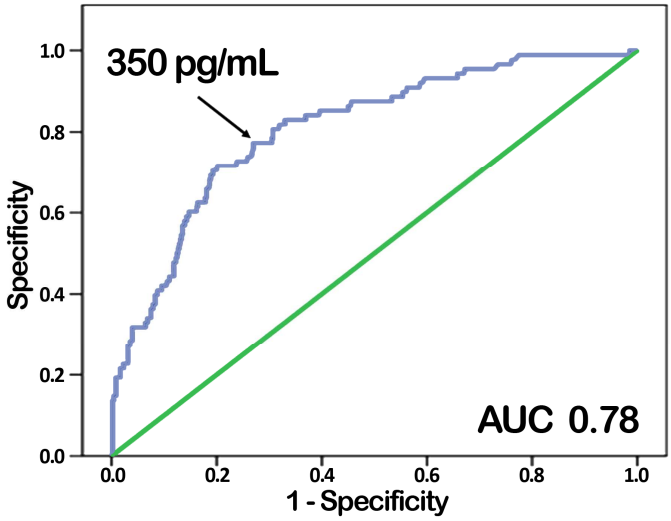
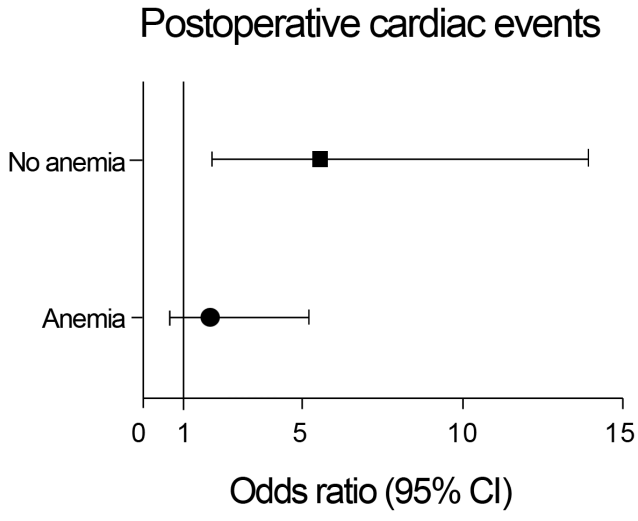


Figure 2: Screening value of N-terminal pro-B-type natriuretic peptide (≥350 pg/mL) for the prediction of postoperative cardiac events in nonanemic, and anemic patients. * Adjusted for age, angina pectoris, myocardial infarction, heart failure, stroke, diabetes mellitus, renal dysfunction, site of surgery, and type of surgery.



Postoperative cardiac events in patients undergoing vascular surgery are more common in patients with preoperative myocardial ischemia, LV dysfunction, and valve abnormalities compared with patients without these conditions.[13, 14] Several studies have shown that serum NT-proBNP is an independent predictor of postoperative cardiac events.[3-5] Because NT–proBNP is synthesized in the ventricular myocardium in response to ventricular wall stress,[1, 2] the most obvious explanation for this association is increased ventricular pressure in response to myocardial ischemia and/or systolic dysfunction in patients prone to adverse postoperative cardiac events. In addition, noncardiac factors, such as renal dysfunction, pulmonary hypertension, chronic obstructive pulmonary disease, and body mass index, might influence NT-proBNP levels.[15, 16] In these patients with extensive comorbidities, an inexpensive, simple, and objective screening test can identify patients at increased risk.

Previous studies have shown that the presence of preoperative anemia increases the risk of death or serious morbidity,[17, 18] especially in patients with a history of cardiovascular disease.[19] Recently, Dunkelgrun *et al.*[9] studied the contribution of anemia to the risk of perioperative and long-term cardiac outcome in 1,211 patients undergoing elective noncardiac open vascular surgery. They found that the presence and severity of anemia are significant predictors of 30-day and 5-yr cardiac events, regardless of underlying heart failure or renal dysfunction. Our findings that also included patients undergoing endovascular procedures seem to confirm these findings.

Anemia is common in patients with chronic heart failure and chronic renal insufficiency and is related to adverse outcomes in these populations.[20, 21] The cause of anemia is largely uncertain and is likely to be multifactorial. Lower hemoglobin levels can be associated with hemodilution (pseudoanemia) in heart failure [20] or can be caused and/or worsened by various different mechanisms, such as malnutrition,[22] iron or vitamin deficiencies,[22] and bone marrow depression due to increased levels of proinflammatory cytokines.[23] However, anemia may also enhance subclinical cardiac risk factors, such as mild coronary artery disease and LV dysfunction, because cardiac oxygen extraction ratio may be limited.[24, 25] In addition, heart failure can cause renal dysfunction as a consequence of forward failure leading to a reduction of renal perfusion and subsequently anemia by a reduction of erythropoietin production.[26, 27]

In our study population using World Health Organization criteria for anemia,[11] more than 30% of patients were anemic before surgery. Because NT-proBNP is released in response to ventricular plasma overload,[28] NT-proBNP levels are higher in anemic compared with nonanemic patients. The effect of anemia on the plasma concentration of NT-proBNP has been reported in patients with heart failure and established coronary artery disease.[29, 30] Nonetheless, hemoglobin seems to be inversely associated with NT-proBNP even after adjustment for these factors.[31] In this study, we found that anemia in vascular surgery patients was an independent predictor of NT-proBNP when adjusted for known confounders. Using multivariate analyses, we adjusted for heart failure and renal dysfunction, both factors

frequently associated with fluid retention. Thus, one explanation for our findings of an independent association between anemia with NT-proBNP levels is that anemia may result in tissue hypoxemia [32] or subclinical fluid retention resulting in hemodilution.[33, 34] These results raise the possibility that anemia may be associated with increased ventricular pressure and myocardial strain even before evidence of clinical ventricular dysfunction can be detected. This might confound the screening value of NT-proBNP to predict postoperative cardiac events, as is shown in our results.

The clinical implications of our findings are that patients scheduled for major vascular surgery could potentially be screened for adverse cardiac outcome with a relatively simple and objective test, NT-proBNP. However, especially in those patients that might benefit most, i.e., those with heart failure and renal disease in whom American College of Cardiology/American Heart Association guidelines recommend additional noninvasive testing,[35] the prognostic value is reduced in the presence of anemia, whereas in nonanemic patients, the prognostic value is excellent.

The potential limitations of these data merit consideration. First, the study population consisted of patients referred to a tertiary referral center and may not fully represent a general population scheduled for elective vascular surgery. Second, our analyses are based on single baseline determinations of NT-proBNP and hemoglobin levels. As such, we could not address the potential importance of hemoglobin change over time, especially in patients with heart failure and renal dysfunction. Furthermore, the effects of unmeasured confounding variables or complex interactions between covariates, such as perioperative in-stent thrombosis, on the observed association and endpoints cannot be excluded. Third, we did not have enough information on preoperative blood transfusion to justly incorporate this in our analysis. Previous studies have shown divergent views regarding pre- and postoperative blood transfusion in vascular surgery, cardiac surgery and patients with acute coronary syndromes.[36-39] Further research is needed to assess the effect of preoperative correction of anemia in vascular surgery patients for the reduction of postoperative cardiac events. Regardless of these limitations, our study suggests that anemia should be considered during the interpretation of preoperative NT-proBNP levels. Moreover, it confirms the previous reports regarding the influence of anemia on NT-proBNP levels.

REFERENCES

1. Kragelund C, Gronning B, Kober L, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. *N Engl J Med.* 2005;352(7):666-675.

2. Yasue H, Yoshimura M, Sumida H, et al. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. *Circulation.* 1994;90(1):195-203.

3. Yeh HM, Lau HP, Lin JM, et al. Preoperative plasma N-terminal pro-brain natriuretic peptide as a marker of cardiac risk in patients undergoing elective non-cardiac surgery. *Br J Surg.* 2005;92(8):1041-1045.

4. Dernellis J, Panaretou M. Assessment of cardiac risk before non-cardiac surgery: brain natriuretic peptide in 1590 patients. *Heart.* 2006;92(11):1645-1650.

5. Feringa HH, Bax JJ, Elhendy A, et al. Association of plasma N-terminal pro-B-type natriuretic peptide with postoperative cardiac events in patients undergoing surgery for abdominal aortic aneurysm or leg bypass. *Am J Cardiol.* 2006;98(1):111-115.

6. Wold Knudsen C, Vik-Mo H, Omland T. Blood haemoglobin is an independent predictor of B-type natriuretic peptide (BNP). *Clin Sci (Lond).* 2005;109(1):69-74.

7. Wu AH, Omland T, Wold Knudsen C, et al. Relationship of B-type natriuretic peptide and anemia in patients with and without heart failure: a substudy from the Breathing Not Properly (BNP) Multinational Study. *Am J Hematol.* 2005;80(3):174-180.

8. Ralli S, Horwich TB, Fonarow GC. Relationship between anemia, cardiac troponin I, and B-type natriuretic peptide levels and mortality in patients with advanced heart failure. *Am Heart J.* 2005;150(6):1220-1227.

9. Dunkelgrun M, Hoeks SE, Welten GM, et al. Anemia as an independent predictor of perioperative and long-term cardiovascular outcome in patients scheduled for elective vascular surgery. *Am J Cardiol.* 2008;101(8):1196-1200.

10. Froissart M, Rossert J, Jacquot C, et al. Predictive performance of the modification of diet in renal disease and Cockcroft-Gault equations for estimating renal function. *J Am Soc Nephrol.* 2005;16(3):763-773.

11. Nutritional anaemias. Report of a WHO scientific group. *World Health Organ Tech Rep Ser.* 1968;405:5-37.

12. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *J Am Coll Cardiol.* 2007;50(22):2173-2195.

13. Boersma E, Poldermans D, Bax JJ, et al. Predictors of cardiac events after major vascular surgery: Role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. *Jama.* 2001;285(14):1865-1873.

14. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation.* 1999;100(10):1043-1049.

15. DeFilippi C, van Kimmenade RR, Pinto YM. Amino-terminal pro-B-type natriuretic peptide testing in renal disease. *Am J Cardiol.* 2008;101(3A):82-88.

16. de Lemos JA, Hildebrandt P. Amino-terminal pro-B-type natriuretic peptides: testing in general populations. *Am J Cardiol.* 2008;101(3A):16-20.

17. Wu WC, Schifftner TL, Henderson WG, et al. Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. *Jama.* 2007;297(22):2481-2488.

18. Beattie WS, Karkouti K, Wijeysundera DN, et al. Risk associated with preoperative anemia in noncardiac surgery: a single-center cohort study. *Anesthesiology.* 2009;110(3):574-581.

19. Carson JL, Duff A, Poses RM, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet.* 1996;348(9034):1055-1060.

20. Horwich TB, Fonarow GC, Hamilton MA, et al. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. *J Am Coll Cardiol.* 2002;39(11):1780-1786.

21. Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol.* 2001;38(4):955-962.

22. Anker SD, Negassa A, Coats AJ, et al. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. *Lancet.* 2003;361(9363):1077-1083.

23. Weiss G. Pathogenesis and treatment of anaemia of chronic disease. *Blood Rev.* 2002;16(2):87-96.

24. Levy PS, Chavez RP, Crystal GJ, et al. Oxygen extraction ratio: a valid indicator of transfusion need in limited coronary vascular reserve? *J Trauma.* 1992;32(6):769-773; discussion 773-764.

25. Levy PS, Kim SJ, Eckel PK, et al. Limit to cardiac compensation during acute isovolemic hemodilution: influence of coronary stenosis. *Am J Physiol.* 1993;265(1 Pt 2):H340-349.

26. Anand IS, Ferrari R, Kalra GS, et al. Edema of cardiac origin. Studies of body water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure. *Circulation.* 1989;80(2):299-305.

27. Westenbrink BD, Visser FW, Voors AA, et al. Anaemia in chronic heart failure is not only related to impaired renal perfusion and blunted erythropoietin production, but to fluid retention as well. *Eur Heart J.* 2007;28(2):166-171.

28. Nakagawa O, Ogawa Y, Itoh H, et al. Rapid transcriptional activation and early mRNA turnover of brain natriuretic peptide in cardiocyte hypertrophy. Evidence for brain natriuretic peptide as an "emergency" cardiac hormone against ventricular overload. *J Clin Invest.* 1995;96(3):1280-1287.

29. Brucks S, Little WC, Chao T, et al. Relation of anemia to diastolic heart failure and the effect on outcome. *Am J Cardiol.* 2004;93(8):1055-1057.

30. Mockel M, Muller R, Vollert JO, et al. Role of N-terminal pro-B-type natriuretic peptide in risk stratification in patients presenting in the emergency room. *Clin Chem.* 2005;51(9):1624-1631.

31. Desai AS, Bibbins-Domingo K, Shlipak MG, et al. Association between anaemia and N-terminal pro-B-type natriuretic peptide (NT-proBNP): findings from the Heart and Soul Study. *Eur J Heart Fail.* 2007;9(9):886-891.

32. Goetze JP, Gore A, Moller CH, et al. Acute myocardial hypoxia increases BNP gene expression. *Faseb J.* 2004;18(15):1928-1930.

33. Androne AS, Katz SD, Lund L, et al. Hemodilution is common in patients with advanced heart failure. *Circulation.* 2003;107(2):226-229.

34. Westenbrink BD, de Boer RA, Voors AA, et al. Anemia in chronic heart failure: etiology and treatment options. *Curr Opin Cardiol.* 2008;23(2):141-147.

35. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol.* 2007;50(17):1707-1732.

36. Bursi F, Barbieri A, Politi L, et al. Perioperative Red Blood Cell Transfusion and Outcome in Stable Patients after Elective Major Vascular Surgery. *Eur J Vasc Endovasc Surg.* 2008.

37. Aronson D, Dann EJ, Bonstein L, et al. Impact of red blood cell transfusion on clinical outcomes in patients with acute myocardial infarction. *Am J Cardiol.* 2008;102(2):115-119.

38. Reeves BC, Murphy GJ. Increased mortality, morbidity, and cost associated with red blood cell transfusion after cardiac surgery. *Curr Opin Anaesthesiol.* 2008;21(5):669-673.

39. Karkouti K, Wijeysundera DN, Beattie WS. Risk associated with preoperative anemia in cardiac surgery: a multicenter cohort study. *Circulation.* 2008;117(4):478-484.

Chapter 17

Screening for abdominal aortic aneurysms using a dedicated portable ultrasound system: early results

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ABSTRACT

Aims Abdominal aortic aneurysms (AAA) are often diagnosed at time of (impending) rupture leading to a dramatic increase of morbidity and mortality. A simple screening device might be the key solution for widespread AAA screening. This study evaluated the diagnostic accuracy of a new portable ultrasound scanner (Aortascan BVI 9600) developed for automatic AAA detection.

Methods A total of 150 patients with presumed aneurysmatic peripheral atherosclerotic disease were included in the study. Patients were first scanned with conventional ultrasound (US), serving as reference technique. An infra-renal abdominal aorta diameter of ≥30 mm was defined as an AAA. Hereafter, the aorta was scanned using the Aortascan BVI 9600. Statistical analyses were performed using SPSS version 15.0 statistical software.

Results Abdominal aortic aneurysms were detected with conventional US in 78 (52%) patients, compared with 74 (49%) AAA's detected with Aortascan BVI 9600. The Aortascan BVI 9600 demonstrated a sensitivity, specificity, positive and negative predictive value of 90, 94, 95 and 89%, respectively, in the detection of AAA's.

Conclusions The Aortascan BVI 9600 automatically detects the aortic diameter with a 90% sensitivity without the need for a trained operator. Because of these unique capabilities, it can be used for AAA screening outside the hospital.

INTRODUCTION

The prevalence of abdominal aortic aneurysm (AAA), in patients aged above 55 years, ranges from 4.1 to 14.2% in men and 0.35 to 6.2% in women.[1] The incidence of AAA is known to increase, due to an increased life expectancy.[2] Effective screening programs for detecting AAA are currently not available. Therefore AAA's are often diagnosed at time of (impending) rupture[3] which leads to a dramatic increase of morbidity and mortality. Abdominal ultrasound (US) and computerized tomography (CT) are the most frequently used noninvasive imaging tests to detect or exclude the presence of an AAA. These imaging techniques are expensive and require trained staff. In case of CT, the patient is exposed to a fair amount of radiation. Hence these techniques are not ideal for screening purposes. A simple screening device, which is less expensive and offers the possibility for use outside the hospital, might be the key solution for widespread AAA screening. In 2006, a pilot study conducted by Vidakovic *et al.*[4] demonstrated the diagnostic potential of an automatic bladder volume scanner (BVI 6400, Verathon Medical, Bothell, USA) to detect AAA. The current study evaluated the diagnostic accuracy of a new portable ultrasound scanner [Aortascan BVI 9600 (BVI 9600), Verathon Medical] developed for automatic AAA detection.

MATERIAL AND METHODS

Study population

The study population consisted of 150 consecutive patients referred to the outpatient clinic of the Department of Vascular Surgery of the Erasmus Medical Center (Rotterdam, The Netherlands) for presumed aneurysmatic peripheral atherosclerotic disease. Patient enrolment was performed from January until December 2008, after approval of the hospital's Ethics Committee. All patients gave informed consent at time of inclusion. Patients with abdominal aortic stents or a previous open aortic reconstruction were excluded from the study.

Baseline characteristics

A detailed history was obtained from every patient and the following characteristics were recorded; age, gender, body mass index, heart failure (defined as the presence of heart failure symptoms according the New York Heart Association classification or previous hospital admission for decompensated heart failure), ischemic heart disease (defined as history of angina pectoris, coronary revascularization or myocardial infarction), cerebrovascular disease (defined as a history of ischemic or hemorrhagic stroke), lower extremity arterial disease (defined as ankle brachial index <0.9), renal dysfunction (defined as creatinin clearance >2.0 mg/dL), diabetes mellitus (fasting blood glucose ≥7.0 mmol/L or requirement for insulin and/or anti-diabetic medication), hypertension (blood pressure was measured during preoperative evaluation at the outpatient clinic and hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg in non-diabetics, systolic blood pressure ≥130

mmHg, diastolic blood pressure ≥80 mmHg in diabetics or the use of antihypertensive medication), hypercholesterolemia (low-density lipoprotein cholesterol >3.5 mmol/L and the requirement of lipid-lowering medication), chronic obstructive pulmonary disease (according to the Global Initiative on Obstructive Lung Diseases classification) and smoking status.

Measurement of the abdominal aortic diameter

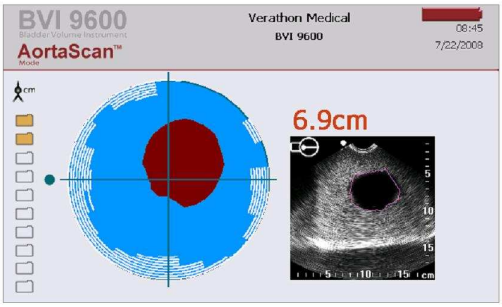
All patients were first scanned with conventional US and measurements obtained with conventional US served as the reference value. An infra-renal abdominal aorta diameter (either anterior-posterior or transverse) of ≥30 mm was defined as an AAA.[5] Hereafter, the aorta was scanned using the Aortascan BVI 9600. The examinations were performed and reviewed by 2 physicians, both skilled and experienced in abdominal US. The interobserver variability between the two echocardiographists was up to 95% for the measured aortic diameter.

Conventional abdominal ultrasound

A handheld US device (SonoSite Titan, SonoSite Inc., Bothell, Washington) with a C11/8-5MHz broadband slightly curved array transducer was used for US evaluation of the abdominal aorta. Both anterior-posterior and transverse diameters at the largest portion of the abdominal aorta were measured. The aortic diameters were obtained using on-screen callipers from the outer edge to edge of the aortic wall, including intraluminal thrombus if present. The maximal obtained diameter, measured in the xiphoid to umbilical traject, was used for analysis.

Figure 1: The Aortascan BVI 9600.

Figure 2: Screenplay Aortascan BVI 9600.



The 3D dimensional scan is obtained as a set of 12 mechanically rotated two dimensional scans, 15 degrees apart. Each planar scan is obtained by mechanically sweeping a single element transducer through a 120º arc. The transducer is used for transmission and reception of ultrasonic waves at 3.7 MHz. Echoes originating from a depth up to 20 cm were included for analysis. Dedicated detection software uses the data obtained from the 3D scan to create a 3D geometry of the abdominal aorta. From this 3D geometry, the maximum diameter is deduced and displayed as result for the user. The user is also provided with a B-mode image representing the cross-sectional scan plane. Electronic callipers are provided to manually redefine the maximum diameter when necessary. Each Aortascan BVI 9600 assessment consisted of four consecutive scans, located at the midline of the abdomen, starting ~2.5 cm below the xiphoid. Scanning locations are shown in *Figure 3*. Abdominal aortic diameter measurements <30 mm were displayed solely as being <3.0 cm. An estimated diameter in mm was provided by the Aortascan, when the abdominal aorta diameter was assumed to be $\geq$30 mm. The maximal abdominal aorta diameter was used for the hypothesis on the presence of AAA.

Statistics

Dichotomous data are described as numbers and percentages. The continuous variables age and BMI are described as mean ± standard deviation (SD). Differences in baseline characteristics between patients with abdominal aorta diameter <30 or $\geq$30 mm, detected with conventional US, were evaluated using χ^2 tests for categorical data. Continuous data were compared using one-way ANOVA. For all tests, a *p*-value less than 0.05 (two sided) was considered significant. All analyses were performed using SPSS version 15.0 statistical software (SPSS, Inc., Chicago, IL, USA).

Figure 3: Scanning locations of the Aortascan BVI 9600.

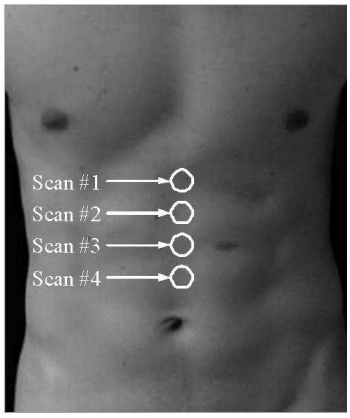
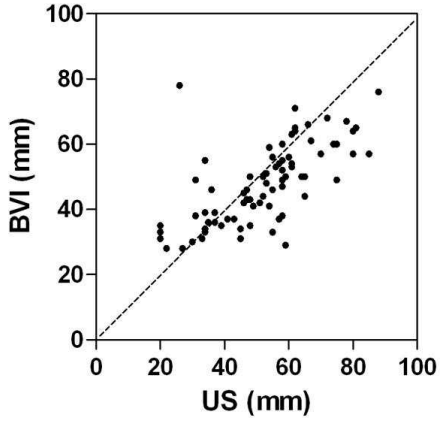


Figure 4: Correlation between conventional ultrasound and Aortascan BVI 9600 (abdominal aorta size <30 mm are not included because not measured with Aortascan BVI 9600).



Ultrasound (US).

RESULTS

A total of 150 patients with presumed aneurysmatic peripheral atherosclerotic disease were included in the study. Abdominal aortic aneurysms were detected with conventional US in 78 (52%) patients, compared with 74 (49%) presumed AAA's detected with Aortascan BVI 9600. Mean abdominal aortic size was 39 mm, measured with conventional US. Patients with aneurysmatic disease were older (70 vs. 65 years), more likely to be male (89 vs 59%, $p < 0.01$)

and more often a BMI >25 compared with patients with normal abdominal aortic size. Other factors associated with an AAA were heart failure, renal dysfunction, and smoking. Baseline characteristics are shown in *Table 1*.

Table 1 **Baseline characteristics of the study population**

	Conventional ultrasound		
	No AAA	AAA	*p*-value
	[N=72]	[N=78]	
Demographics			
Age (± SD)	65 (10)	70 (10)	0.022
Male (%)	43 (59)	72 (89)	<0.01
Body mass index (± SD)	25 (3)	27 (4)	0.008
Medical history (%)			
Clinical heart failure	4 (6)	16 (20)	0.009
Ischemic heart disease	20 (27)	33 (41)	0.082
Cerebrovascular disease	27 (37)	19 (24)	<0.01
Lower extremity arterial disease	42 (58)	27 (33)	0.003
Renal dysfunction	4 (6)	18 (23)	0.003
Diabetes mellitus	20 (25)	13 (18)	0.300
Hypertension	44 (61)	53 (66)	0.510
Hypercholesterolemia	37 (51)	45 (56)	0.548
Chronic obstructive pulmonary disease	11 (15)	13 (16)	0.870
Smoking, current	28 (39)	20 (25)	0.066

Abdominal aortic aneurysm (AAA), standard deviation (SD), ultrasound (US).

In total, 70 (90%) AAA patients measured with conventional US were detected with the Aortascan BVI 9600 as well. Furthermore, 68 (95%) patients with normal abdominal aorta observed with conventional US had a normal abdominal aorta, measured with the Aortascan BVI 9600 as well. False-positive measurements, i.e. a presumed AAA detected with the Aortascan BVI 9600, which was not present with conventional US was observed in four patients (5%). False-negative measurements, i.e. an AAA detected with conventional US and missed with the Aortascan BVI 9600 was present in eight (10%) patients. We have found sensitivity, specificity, positive-predictive value and negative-predictive values of 90, 94, 95 and 89%, respectively (*Table 2*). Furthermore, the correlation, in measured AAA diameter, between conventional US and the Aortascan BVI 9600 is demonstrated in *Figure 4*.

Table 2 **Conventional ultrasound vs. aortascan BVI 9600**

Conventional ultrasound	Aortascan BVI 9600 AAA yes	AAA no	*p*-value	
AAA yes	70 (95)	8 (10)	<0.01	sensitivity[a]: 90
AAA no	4 (5)	68 (90)	<0.01	specificity[a]: 94

[a] *Aortascan BVI 9600. Abdominal aortic aneurysm (AAA).*

DISCUSSION

The current study provides early results on the detection of AAA with the Aortascan BVI 9600, compared with conventional US. The main finding of this study was that the Aortascan BVI 9600 detects abdominal aortic aneurysms with a sensitivity and specificity of 90 and 94%, respectively. In addition to this, the positive- and negative- predictive values were 95 and 89%, respectively.

The development of aortic aneurysmatic disease is associated with alterations of connective tissue in the aortic wall, in which the process of atherosclerosis is regarded an important factor.[6] The formation of an AAA is initiated when vascular endothelium is injured and AAA progression is influenced by factors such as (i) infection and complement activation, (ii) shear stress forces, and (iii) increased oxidative stress and cytokine release leading to endothelial activation and dysfunction.[7, 8] The prevalence and incidence of AAA has been widely investigated and a population-based study including 6,386 patients showed a prevalence of AAA in 263 (8.9%) men and 74 (2.2%) women.[9] Approximately 6% of men have an aortic diameter of more than 2.9 cm by the age of 65 years.[10] A meta-analysis performed by Cornuz *et al.* in 2004 included around 110,000 patients screened for AAA and concomitant risk factors.

The prevalence of AAA in Europe and America ranged from 4.1 to 14.2% in men and from 0.35 to 6.2% in women with all patients aged above 55 years.[1] In patients with symptomatic atherosclerotic disease, the prevalence of aneurysmatic disease is much higher, as data of our own population showed prevalence up to 25%. Therefore, the use of a quick and efficient AAA screening tool in this high-risk population, could add significantly to complete the patients risk profile. Patients with ruptured AAA have a worse prognosis, as up to 55% of the patients that reach the hospital alive will still die in the first 30 postoperative days.[11, 12] Therefore, screening of patients at increased risk for developing AAA and subsequent elective surgical interventions may improve outcome. As noted by Hailey *et al,*[13] the non-availability of an echo-system and/or operator at the point-of-care may lead to a delay in diagnosis and patient management. Although the first portable echo devices were developed in the 1970s,[14, 15] portable echo has become commercially available since 1996.[16] In 2003, for instance,

portable cardiac US (or echo-stethoscope) broadened the application of echocardiography to the patient's bedside.[17] The use of portable US for AAA detection was first described by Vidakovic *et al*,[4] using the automatic BVI 6400 system.

Ultrasonography provides the possibility to diagnose or rule-out AAA rapidly and accurately.[18, 19] However, finding the correct cross-sectional scan plane with the maximum aortic diameter remains the most difficult part in AAA screening. Small errors in the angle of cross-section causes direct errors in the found diameter and may lead to wrong diagnosis. Therefore, only well-trained echocardiographists should perform conventional US for the detection of AAA. Hence Vidakovic *et al*.[4] proposed to use the automatic BVI 6400 system for AAA screening because of (i) potential widespread availability, (ii) low costs (~10.000 €) compared with expensive conventional US equipment, and (iii) steep learning curve compared with more intensive training required for conventional US. They concluded that the BVI 6400 is simpler for use, requires a less intensive training period and therefore can be used by a nurse or a technician. Furthermore, the BVI 6400 is roughly four times less expensive compared with conventional US. In the pilot study conducted by Vidakovic *et al,* volume measurements of the infrarenal abdominal aorta were performed with the BVI 6400 and compared with conventional US. On the basis of the technical characteristics of the BVI 6400, they estimated that a volume of 14 mL measured with the BVI 6400 corresponded with an abdominal aortic diameter of 30 mm, which is considered an AAA. Using the cut off value of >14 mL for the presence of AAA, they demonstrated a sensitivity of 94% and specificity of 82% of the BVI 6400 in the detection of AAA. Furthermore, positive- and negative-predictive values for the BVI 6400 to detect AAAs were 88 and 92%, respectively. However, although these data look promising, the use of volume measurements, which have to be recalculated, remains questionable.

In our study, the Aortascan BVI 9600 directly measured the maximum abdominal aortic diameter and therefore, we did not have to estimate a volume cut off value corresponding with the abdominal aortic diameter in mm. Consequently, results obtained from the Aortascan BVI 9600 can be directly compared with conventional US. With the use of these new types of measurements, we found a sensitivity of 90% and an increased specificity of 94% compared with the BVI 6400. Furthermore we found a negative-predictive value of 89% and an increased positive-predictive value of 95% compared with the BVI 6400. The Aortascan BVI 9600 provides a scan depth of 20 cm, which was sufficient for the patient population. Hence, no false negatives occurred due to a limited field of view. However, although the Aortascan BVI 9600 seems to detect AAA with a sufficient accuracy, the use of the system should not be extended as a replacement for conventional US. Patients with AAA detected by the Aortascan BVI 9600 should be referred to a radiologist to perform a conventional abdominal US.

Although we have used conventional US as the reference technique, we are aware that the sensitivity and specificity of conventional US is not 100%. This is mainly due to the difficulty of finding the right cross-sectional plane and location of the aorta, even for experienced operators. The 3D acquisition of the Aortascan BVI 9600 is likely to overcome the problems associated with two dimensional US. This was demonstrated in a patient with a curved aortic shape (including an AAA) not located at the midline of the abdomen. The measurement with conventional US initially produced a false-negative result, where the Aortascan BVI 9600 did detect an AAA. The presence of a true AAA was confirmed with a second conventional US measurement. This case underlines the need for future studies, evaluating the accuracy of the Aortascan BVI 9600, using angio-CT as the reference technique.

In conclusion, the Aortascan BVI 9600 automatically detects and calculates the aortic diameter with a 90% sensitivity without the need for a trained operator. Because of these unique capabilities, it can be used for AAA screening outside the hospital and allows for AAA detection in patients who would not have been examined otherwise. However, final diagnosis and subsequent treatment requires additional medical examination.

REFERENCES

1. Cornuz J, Sidoti Pinto C, Tevaearai H, et al. Risk factors for asymptomatic abdominal aortic aneurysm: systematic review and meta-analysis of population-based screening studies. *Eur J Public Health.* 2004;14(4):343-349.

2. Barba A, Estallo L, Rodriguez L, et al. Detection of abdominal aortic aneurysm in patients with peripheral artery disease. *Eur J Vasc Endovasc Surg.* 2005;30(5):504-508.

3. Daly KJ, Torella F, Ashleigh R, et al. Screening, diagnosis and advances in aortic aneurysm surgery. *Gerontology.* 2004;50(6):349-359.

4. Vidakovic R, Schouten O, Feringa HH, et al. Abdominal aortic aneurysm screening using non-imaging hand-held ultrasound volume scanner--a pilot study. *Eur J Vasc Endovasc Surg.* 2006;32(6):615-619.

5. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *J Am Coll Cardiol.* 2006;47(6):1239-1312.

6. Ross R. Atherosclerosis--an inflammatory disease. *N Engl J Med.* 1999;340(2):115-126.

7. Shah PK. Inflammation, metalloproteinases, and increased proteolysis: an emerging pathophysiological paradigm in aortic aneurysm. *Circulation.* 1997;96(7):2115-2117.

8. Van Kuijk JP, Flu WJ, Dunckelgrun M, et al. Coronary artery disease in patients with abdominal aortic aneurysm: a review article. *J Cardiovasc Surg (Torino).* 2009;50(1):93-107.

9. Singh K, Bonaa KH, Jacobsen BK, et al. Prevalence of and risk factors for abdominal aortic aneurysms in a population-based study : The Tromso Study. *Am J Epidemiol.* 2001;154(3):236-244.

10. Powell JT, Greenhalgh RM. Clinical practice. Small abdominal aortic aneurysms. *N Engl J Med.* 2003;348(19):1895-1901.

11. Akkersdijk GJ, van der Graaf Y, van Bockel JH, et al. Mortality rates associated with operative treatment of infrarenal abdominal aortic aneurysm in The Netherlands. *Br J Surg.* 1994;81(5):706-709.

12. Dardik A, Burleyson GP, Bowman H, et al. Surgical repair of ruptured abdominal aortic aneurysms in the state of Maryland: factors influencing outcome among 527 recent cases. *J Vasc Surg.* 1998;28(3):413-420; discussion 420-411.

13. Hailey D, Topfer LA. Hand-carried ultrasound units for point-of-care cardiac examinations. *Issues Emerg Health Technol.* 2002(41):1-4.

14. Ligtvoet C, Rijsterborgh H, Kappen L, et al. Real time ultrasonic imaging with a hand-held scanner. Part I--technical description. *Ultrasound Med Biol.* 1978;4(2):91-92.

15. Roelandt J, Wladimiroff JW, Baars AM, et al. Ultrasonic real time imaging with a hand-held-scanner. Part II--initial clinical experience. *Ultrasound Med Biol.* 1978;4(2):93-97.

16. Bom N, van der Steen AF, de Jong N, et al. Early, recent and future applications of echocardiography. *Clin Physiol Funct Imaging.* 2004;24:141-146.

17. Vourvouri EC, Koroleva LY, Ten Cate FJ, et al. Clinical utility and cost effectiveness of a personal ultrasound imager for cardiac evaluation during consultation rounds in patients with suspected cardiac disease. *Heart.* 2003;89(7):727-730.

18. Giaconi S, Lattanzi F, Orsini E, et al. Feasibility and accuracy of a rapid evaluation of the abdominal aorta during routine transthoracic echocardiography. *Ital Heart J Suppl.* 2003;4(4):332-336.

19. Kuhn M, Bonnin RL, Davey MJ, et al. Emergency department ultrasound scanning for abdominal aortic aneurysm: accessible, accurate, and advantageous. *Ann Emerg Med.* 2000;36(3):219-223.

PART III

Prevention and treatment

Chapter 18

Prevention of acute coronary events in major vascular surgery: the value of β-blocker therapy and coronary revascularization

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ABSTRACT

During major vascular surgery, patients are at high risk for developing myocardial infarction and myocardial ischemia, and two risk-reduction strategies can be considered before surgery: pharmacological treatment and prophylactic coronary revascularization. β-blockers are established therapeutic agents for patients with hypertension, heart failure and coronary artery disease. There is still considerable debate concerning the protective effect of β-blocker therapy towards perioperative coronary events, which will be outlined it this article. Two randomized controlled trials suggest that coronary revascularization of cardiac-stable patients provides no benefits in the postoperative outcome. In the current American College of Cardiology/American Heart Association guidelines for 'Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery', routine prophylactic coronary revascularization is not recommended in patients with stable coronary artery disease. However, a recent retrospective, observational study suggests that intermediate-risk patients may benefit from preoperative coronary revascularization. The present article provides an extended overview of leading observational studies, randomized, controlled trials, meta-analyses and guidelines assessing perioperative β-blocker therapy and prophylactic coronary revascularization.

INTRODUCTION

Among the 30 million patients undergoing noncardiac surgery in the USA annually, cardiac complications are the leading cause of perioperative morbidity and mortality.[1] A pooled analysis of several large studies found an incidence of 2.5% for perioperative cardiac events in patients over the age of 40 years (Range: 2.0 to 3.7%).[2] These cardiac events were more common among vascular surgery patients, with an incidence of 6.2% (Range: 2.2 to 19.0%).[3] Symptoms of perioperative cardiac events are uncommon and it is suspected that 95% of the episodes are asymptomatic.[1, 4-8] The high frequency of perioperative cardiac complications reflects the high prevalence of underlying coronary artery disease (CAD).[9] According to the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines on Perioperative Care, patients with active cardiac conditions need to be evaluated and treated before surgery.[10] Two risk-reduction strategies can be performed to reduce the incidence of cardiac complications: pharmacological treatment and prophylactic coronary revascularization. The present article provides an extended and detailed overview of leading observational studies, randomized, controlled trials and guidelines assessing perioperative β-blocker therapy and prophylactic revascularization. The randomized trials are summarized, allowing the readers to place their strengths and weaknesses into perspective. Based on the current available literature and our own experience, treatment recommendations in patients scheduled for noncardiac surgery are also provided

CURRENT CONCEPTS IN PERIOPERATIVE β-BLOCKER THERAPY

β-blockers are established therapeutic agents for patients with hypertension,[11] heart failure,[12] and CAD.[13] In the nonsurgical setting, β-blockers are widely used for the prevention and treatment of ischemic heart disease and heart failure, which are major determinants of the occurrence of perioperative cardiovascular complications. Pharmacological risk reduction plays an important role in the reduction of perioperative cardiovascular complications, and multiple studies have been performed to assess the risk-reduction value of β-blockers. β-blockers are known to exert anti-arrhythmic, anti-inflammatory and anti-renin-angiotensin effects, as well as shifting energy metabolism.[14-16] During surgery, high catecholamine production is responsible for vasoconstriction and hemodynamic stress, leading to an increased oxygen-demand[1], which (in combination with perioperative tachycardia and increased myocardial contractility) can result in an oxygen supply–demand mismatch, causing myocardial infarction (MI) or ischemia.[17, 18] β-blockers have been demonstrated to reduce heart rate and contractile force and, therefore, tend to reduce the myocardial oxygen-demand.

Several observational studies have demonstrated the beneficial effects of perioperative β-blocker treatment in reducing perioperative cardiovascular complication. Wallace *et al.* showed that treatment with the long-acting β-blocker atenolol resulted in a

reduced incidence of postoperative ischemia by 30 to 50%.[19] A retrospective study performed by Redelmeier *et al.* evaluated 37,151 elderly surgery patients treated with atenolol, using the database of the Canadian Institutes for Health Information. They demonstrated that atenolol treatment was associated with greater cardioprotective benefits perioperatively, compared with treatment with short-acting β-blockers, such as metoprolol tartrate.[20] Lindenauer *et al.* conducted a retrospective cohort study of 782,969 patients, using the Premier's Perspective database for 'small-to-midsize nonteaching hospitals' in the USA and concluded that preoperative β-blocker therapy was associated with a reduced risk of inhospital death in high-risk (but not in low-risk) patients undergoing vascular surgery. However, patients with moderate risk for CAD did not derive any benefits from β-blocker treatment and may experience worse outcomes compared with controls.[21] An observational study conducted by Feringa *et al.* showed that bisoprolol treatment was associated with a reduced incidence of perioperative myocardial ischemia, detected with Holter monitoring (hazard ratio [HR], 2.49, 95% confidence interval [95%-CI]: 1.79 to 3.48), and troponin T release (HR 1.53, 95%-CI: 1.16 to 2.03). They conclude that high-dose bisoprolol and concomitant tight heart-rate control may lead to reduced perioperative myocardial ischemia and troponin T release, thereby improving long-term outcome.[22] Several randomized, controlled trials have demonstrated beneficial effects of perioperative β-blocker treatment on the postoperative outcomes of surgery patients, of which the most important trials will be discussed in the following sections.

Mangano *et al.*

In 1996, Mangano *et al.* randomized 200 patients with either known or suspected CAD who were undergoing high-risk noncardiac surgery to receive atenolol 50 or 100 mg, or placebo.[23] They hypothesized that intensive perioperative β-blockade and strict heart rate control may limit the development of ischemia. Treatment was initiated before the induction of anesthesia, administered immediately following surgery and continued once-daily throughout the patients' hospital stay for up to 7 days after surgery (*Table 1*).[23] In most patients, atenolol treatment was continued for up to 2 years following surgery. Although the study only demonstrated a perioperative effect towards ischemia (detected using Holter monitoring), atenolol use was associated with significantly lower mortality rates at 6 months after discharge (0 vs. 8%; $p = 0.005$), and after 2 years (10 vs. 21%; $p = 0.019$).

Raby *et al.*

In 1999, Raby *et al.* were the first to demonstrate the beneficial effect of strict heart rate control immediately after surgery.[24] They included 26 major vascular surgery (MVS) patients with preoperative ischemia detected by Holter monitoring. These patients were randomized to receive β-blockade with esmolol or placebo immediately following MVS (*Table 1*).[24] This study demonstrated that a reduction of postoperative heart rate to 20% below the ischemic threshold markedly reduced postoperative ischemia.

DECREASE-I trial

Poldermans *et al.* performed a randomized, controlled Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE)-I trial to assess the effect of perioperative bisoprolol treatment on the incidence of death from cardiac causes and nonfatal MI within 30 days following MVS (*Table 1*).[25] With the use of preoperative dobutamine stress-echocardiography, 112 patients with evidence of myocardial ischemia were included in the study and defined as high-risk for cardiac events. A total of 59 patients were randomly assigned to receive bisoprolol, and 53 to receive standard care. Bisoprolol treatment was started an average of 37 days before MVS (*Table 2*), and careful titration was performed to prevent adverse side effects, such as hypotension and bradycardia. Compared with placebo, a reduction in the incidence of perioperative cardiovascular death and MI, from 34 to 3.4% ($p < 0.001$) was demonstrated in patients treated with bisoprolol.[25]

POISE trial

In 2008, the randomized, controlled Perioperative ischemic evaluation (POISE) trial was published and prompted discussion regarding β-blocker use in perioperative care. A total of 8,351 patients were randomized to receive either metoprolol succinate or placebo (*Table 1*). Metoprolol succinate was administered at high dosages using the following treatment protocol: 100 mg was given 2-4 h before surgery, another 100 mg within 6 h, and followed by another 200 mg 12-18 h post-surgery if permitted by heart rate and blood pressure. Therefore, the maximum recommended daily dose of 400 mg was administered on the day of surgery and treatment was continued with 200 mg daily doses for 30 days post-surgery. The primary endpoint of cardiac death, MI or cardiac arrest was reduced in the metoprolol group, compared with placebo (5.8 vs. 6.9%, respectively; HR 0.83, 95%-CI: 0.70 to 0.99; $p = 0.04$). However, the 30% decrease in nonfatal MI (3.6 vs. 5.1%, $p < 0.01$) was accompanied by a 33% increase in total mortality (3.1 vs. 2.3%, $p = 0.03$) and a twofold increased risk in stroke (1.0 vs. 0.5%, $p < 0.01$).[26] Metoprolol succinate did lower the incidence of MI by more than a quarter (5.7% to 4.2%); however, this benefit was outweighed by the previously mentioned increased incidence of stroke and death.[26] Stroke was associated with perioperative bradycardia, hypotension, and bleeding complications. *Post hoc* analysis also showed that hypotension had the largest population-attributable risk for death and stroke. Importantly, hypotension can be related to the use of a high dose of metroprolol without dose titration.

There is still considerable debate concerning the protective effect of β-blocker therapy towards perioperative coronary events, and several randomized, controlled trials have demonstrated negative results. We will discuss the most important trials to have questioned the use of perioperative β-blockade in the following sections.

Table 1 **Randomized, controlled trials demonstrating a beneficial effect of perioperative β-blockade towards cardiovascular complications**

TRIAL	TRIAL PROTOCOL	MAIN FINDINGS
Mangano *et al.* 1996 [N=200]	**Inclusion criteria:** • Noncardiac surgery • Presence of CAD [a] or ≥ 1 CAD risk factors [b] **Treatment:** Atenolol: treatment continued up to 7 days after surgery • 5-10 mg intravenously 30 min before and after surgery • 50-100 mg orally once a day, from day 1-7 following surgery	Atenolol treatment can reduce mortality and the incidence of cardiovascular complications for as long as 2 years after surgery
Raby *et al.* 1999 [N=26]	**Inclusion criteria:** • Vascular surgery **Main exclusion criteria:** • LBBB or left ventricular hypertrophy • ST-T changes precluding accurate Holter interpretation **Treatment:** Esmolol: initiation immediately after surgery • 100-300 µg/kg/min intravenously for 48 h	Esmolol can reduce perioperative myocardial ischemia
DECREASE-I 1999 [N=112]	**Inclusion criteria:** • Vascular surgery • Patients with ≥1 cardiac risk factor [c] and ischemia during cardiac stress testing **Main exclusion criteria:** • Current β-blocker use or history of intolerance • Extensive wall motion abnormalities (WMI > 1.7 at rest) • Strong evidence during stress testing of left main or severe three-vessel disease **Treatment:** Bisoprolol: initiation at least 1 week before surgery, treatment continued 30 days after surgery • 5-10 mg orally once-daily for 30 days	Bisoprolol reduces the perioperative incidence of cardiovascular mortality and nonfatal MI
POISE 2008 [N=8351]	**Inclusion criteria:** • Noncardiac surgery • Expected hospital stay >24 h • Age ≥45 years • At least 1 of the following criteria: history CAD, PAD, stroke or hospitalization for CHF in previous 3 years, undergoing MVS or any 3 of 7 risk criteria [d] **Main exclusion criteria:** • Current β-blocker use or history of intolerance • Bradycardia, 2nd or 3rd-degree AV block • Low-risk surgical procedure **Treatment:** Metoprolol: initiation 2-4 h before surgery, treatment continued for 30 days after surgery • 100 mg 2-4 hours before surgery, • 100 mg up to 6 h after surgery and 200 mg 12 hours later • 200 mg orally once-daily for 30 days	Metoprolol prevents nonfatal MI but increases the risk of nonfatal stroke

[a] Previous MI, typical angina pectoris or atypical angina pectoris with a positive stress-test. [b] Age >65 years, hypertension, current smoking, hypercholesterolemia or DM. [c] Age >70 years, angina pectoris, previous MI (on basis of history, pathologic Q-waves on ECG), CHF (history or compensated), current treatment for ventricular arrhythmias, current treatment for DM, limited exercise capacity. [d] Undergoing intrathoracic or intraperitoneal surgery, history of CHF, transient ischemic attack, DM, serum creatinine >175 µmol/L, age >70 years or undergoing emergency or urgent surgery. Atrioventricular (AV), coronary artery disease (CAD), chronic heart failure (CHF), Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE), diabetes mellitus (DM), left bundle branch block (LBBB), myocardial infarction (MI), major vascular surgery (MVS), peripheral arterial disease (PAD), Perioperative Ischemic Evaluation (POISE), wall motion index (WMI).

POBBLE trial

The randomized, placebo-controlled Perioperative β-Blockade (POBBLE) trial included low-risk patients (history of ischemic heart disease was an exclusion criteria) scheduled for MVS.[27] In total, 103 patients were randomized to receive either metoprolol 25 or 50 mg, or placebo (*Table 2*). Treatment began 1 day before surgery and continued until 7 days postoperatively. Although the POBBLE trial was designed to evaluate the effect of perioperative β-blockade in low-risk patients, they found a remarkable number of perioperative events (i.e., MI, unstable angina pectoris, ventricular tachycardia or stroke) in more than 30% of all patients who were supposed to have a low prevalence of pre-existing heart disease. Furthermore, this trial did not show a difference in the incidence of perioperative cardiovascular events between the two small, randomized groups (placebo: 34%, metoprolol 32%; relative risk 0.87, 95%-CI: 0.48 to 1.55). However, the duration of hospitalization was shorter for those patients receiving metoprolol vs. placebo (10 vs. 12 days). It should be mentioned that the POBBLE trial only included 103 patients over a period of nearly 3 years and was discontinued because of poor recruitment and lack of funding.

MAVS trial

The Metoprolol After Vascular Surgery (MAVS) trial randomized 496 patients to receive metoprolol or placebo. Medical treatment started 2 h before surgery and continued until hospital discharge or 5 days after surgery (*Table 2*).[28] In the MAVS trial, there was no difference between the metoprolol- and placebo-treated groups for the occurrence of cardiovascular death, MI, heart failure, arrhythmias or stroke 30 days postoperatively (10 and 12% respectively; $p = 0.057$).

DIPOM trial

The randomized, controlled Diabetic Postoperative Mortality and Morbidity (DIPOM) trial also did not show a difference in 30-day morbidity and mortality between metoprolol- and placebo-treated groups (21 vs. 20%; $p = 0.66$). This trial included 921 diabetic patients, randomized to receive metoprolol 100 mg or placebo. Treatment was started the evening before major noncardiac surgery (*Table 2*). The DIPOM trial concluded that perioperative metoprolol did not significantly affect mortality and cardiac morbidity in patients with diabetes.[29]

BBSA trial

The double-blinded, placebo-controlled Swiss Beta Blocker in Spinal Anesthesia (BBSA) trial noted that bisoprolol therapy did not affect cardiovascular outcomes in elderly patients undergoing surgery with neuraxial blockade (*Table 2*).[30] The lack of benefit of β-blocker treatment could be explained by the varying cardiac risk profiles of the patients included and the fact that it was an underpowered study. Interestingly, the authors suggest that pholymorphisms in β1-adrenergic receptor genotypes could be associated with different

responses to β-blocker therapy and may be of use to optimize therapy by maximizing efficacy and limiting toxicity.[30]

Table 2 **Randomized, controlled trials demonstrating no beneficial effect of perioperative β-blockade towards cardiovascular complications**

TRIAL	TRIAL PROTOCOL	MAIN FINDINGS
POBBLE 2005 [N=103]	**Inclusion criteria:** • Vascular surgery patients **Main exclusion criteria:** • Current β-blocker use or history of intolerance • MI, unstable AP or AP with a positive cardiac stress test **Treatment:** Metoprolol: initiation 1 day before surgery, treatment continued 7 days after surgery • 2-4 mg intravenously 5-10 min before intubation • 25-50 mg orally twice a day from day 1 to 7	Metoprolol did not seem to reduce 30-day cardiovascular events. In patients receiving metoprolol treatment, time from surgery to discharge was decreased.
MAVS 2006 [N=496]	**Inclusion criteria:** • Vascular surgery patients • ASA ≤ 3 **Main exclusion criteria:** • Current β-blocker use or history of intolerance • History of CHF or AV block **Treatment:** Metoprolol: initiation day of surgery, treatment continued 5 days after surgery • 25-100 mg orally 2 h before and after surgery • 25-100 mg orally twice a day, from day 1 to 5	Metoprolol was not effective in reducing the 30-day and 6-month postoperative cardiac event rates
DIPOM 2006 [N=921]	**Inclusion criteria:** • Noncardiac surgery patient with diabetes mellitus • Age ≥ 40 years **Main exclusion criteria:** • Current β-blocker use or history of intolerance • CHF New York Heart Association Class IV **Treatment:** Metoprolol: initiation 30 min before surgery, treatment continued up to 6 days after surgery • 50 mg orally evening before surgery • 100 mg orally 2 h before surgery • 100 mg orally once a day from day 1 to 6	Metoprolol did not significantly affect mortality and cardiac morbidity
BBSA 2007 [N=224]	**Inclusion criteria:** • Surgery with spinal block, in-hospital stay > 24 h • Presence of CAD or ≥2 CAD risk factors [a] **Main exclusion criteria:** • Current β-blocker use or history of intolerance • History of CHF, • High-degree heart block or LBBB **Treatment:** Bisoprolol: initiation at least 3 h before surgery, treatment continued up to 10 days after surgery • 5-10 mg orally 3 h before and 6 h after surgery • 2-10 mg orally once a day from day 1 to 10	Bisoprolol did not affect cardiovascular outcome

[a] *Age >65 years, hypertension, current smoking, hypercholesterolemia or diabetes mellitus. Angina pectoris (AP), American Society of Anaesthesiologists (ASA), atrioventricular (AV), β-blocker in Spinal Anaesthesia (BBSA), coronary artery disease (CAD), chronic heart failure (CHF), Diabetic Postoperative Mortality and Morbidity (DIPOM),left bundle branch block (LBBB), Metoprolol After Vascular Surgery (MAVS), myocardial infarction (MI), Perioperative β-blockade (POBBLE).*

A meta-analysis performed by Bangalore *et al.* was published in the *Lancet* in 2008 and included 33 randomized trials, with a total of 12,306 patients, evaluating perioperative β-blocker therapy. They concluded that β-blocker treatment resulted in 16 fewer nonfatal MIs per 1000 patients, but at the expense of three nonfatal, disabling strokes and possibly three fatal cardiac or noncardiac complications.[31] Based on these results, the main conclusion was that evidence does not support the use perioperative β-blocker therapy in surgery patients. However, the authors acknowledged that results derived from the POISE trial had the greatest influence on their results.

A comment from Boersma and Poldermans was published in the same edition of the *Lancet*, in which they concluded that the general mechanism underlying the excess cerebral complications is unknown and additional hemodynamic data are needed. They stated that these data will be crucial to future updates of treatment guidelines.[32]

DISCUSSION: PERIOPERATIVE β-BLOCKADE

There are different explanations regarding the conflicting evidence for perioperative β-blocker use. Important factors that may relate to the effectiveness of β-blocker therapy are the patients' underlying cardiac risk and variations of treatment protocols in initiation time, β-blocker type, starting dose, dose adjustments for heart-rate control and duration of treatment.

Patients' cardiac risk profiles

Boersma *et al.* have suggested that the absolute risk reduction associated with β-blocker treatment is most pronounced in patients who are at high risk for coronary events.[33] The MAVS trial and DIPOM trial both included many patients at low risk for cardiovascular complications. In the MAVS trial, almost 60% of the patients had a Lee Risk index of only one. This is in contrast to the DECREASE-I trial, which randomized vascular surgery patients with a positive dobutamine echocardiography, so that only 112 patients from an initial population of 1,351 patients met the entrance criteria of inducible myocardial ischemia. The high incidence of perioperative cardiovascular events could be explained by the selection of high-risk cardiac patients, in which bisoprolol treatment was highly effective in reducing perioperative cardiovascular mortality and nonfatal MI.

Treatment protocols

The initiation time of β-blocker treatment may be related to the effectiveness of β-blocker therapy. In the DECREASE-I trial, the mean time between initiation of β-blocker treatment and surgery was 37 days and the largest effect of perioperative β-blocker treatment was demonstrated.[25] By contrast, the POBBLE, MAVS, DIPOM and BBSA trials began treatment either 1 day before or on the day of surgery.

The type of β-blocker used may influence the effectiveness of β-blocker therapy. Negative inotropic and chonotropic effects derived from selective β_1-blockade are thought to exert the most beneficial perioperative effects towards cardiovascular outcome. This may be the reason why treatment with the highly β_1-selective β-blocker bisoprolol was associated with better results compared with metoprolol or atenolol, which are moderately β_1-selective.

Aside from the initiation time, the administrated dosage of β-blocker was also different among the randomized studies we assessed. In the POISE trial, metoprolol succinate could have been administered on the first day of surgery at a dose of up to 400 mg, which is 100% of the maximum daily therapeutic dose. In the nonsurgical setting, much lower starting doses are recommended; for instance, in patients with New York Heart Association Class II heart failure, starting doses of 12.5 to 25 mg daily are administered for 2 weeks, and for hypertension, the initial dose is between 25 and 100 mg, and usually increased at weekly intervals. In the editorial to the publication of the POISE trial, Fleisher and Poldermans compared the POISE trial results with results from the DECREASE-I trial, in which patients undergoing MVS were treated with low-dose bisoprolol (between 5 and 10 mg once-daily).[34] The incidence of stroke in the DECREASE-I trials was 0,4%, which is comparable with placebo, while maintaining a significant reduction in cardiac death and nonfatal MI from 34% in the standard-care group to 3.4% in the bisoprolol-treated group in the first DECREASE-I trial.[25, 34] The DECREASE-I trial has demonstrated that low-dose bisoprolol treatment is associated with overall benefits compared with risk.

To maximize the benefit a patient will receive from β-blocker treatment, tight heart-rate control is paramount, without over-treating the patient. Analyzing the safety and tolerability of β-blockers is as important as assessing the beneficial effects of β-blockers regarding efficacy. The most important side effects to be expected with β-blocker treatment are bradycardia and hypotension, which usually occur dose-dependently. The use of a fixed vs. an individualized dose titrated to the patients' heart rate may also be of importance. As recommended by the guidelines for treatment of congestive heart failure and shown in β-blocker studies for treatment of heart failure, such as the Cardiac Insufficiency Bisoprolol Study (CIBIS), β-blocker treatment should begin with a very low dose and then be uptitrated to the maximum tolerated dose.[12, 35] Titration according to tolerance is of utmost importance to obtain tight heart-rate control and prevent adverse side effects such as hypotension. The value of adequate heart-rate control in improving cardiovascular outcome is not only confirmed in a recent large meta-analysis,[36] the latest 2007 ACC/AHA guidelines on perioperative care also strongly recommend achieving a heart rate of 65-70 beats per minute.[10]

A factor that could also influence the effect of β-blockers in surgical patients is the duration of β-blocker treatment. Withdrawal of β-blocker therapy shortly before surgery or in the immediate postoperative period may contribute to adverse myocardial effects resulting from a 'rebound' effect, thereby inducing increased arterial blood pressures, heart rates and

plasma noradrenalin concentrations.[37] Discontinuation of β-blocker therapy immediately after MVS could increase the risk of postoperative cardiovascular mortality,[38] and early withdrawal of β-blockers after surgery is associated with a higher 1-year mortality compared with continuous β-blocker therapy, which highlights the importance of continuing β-blocker therapy in the perioperative period.[39] Recently, it has been suggested that the long-term beneficial effects of β-blocker therapy may be explained by a decrease in the progress of coronary atherosclerosis.[40] In contrast to the instant effect on heart-rate control, the effect of β-blockers on plaque stabilization may, therefore, only be achieved after prolonged treatment. As demonstrated by Mangano *et al,* treatment with atenolol during hospitalization can reduce mortality and the incidence of cardiovascular complications for as long as 2 years following noncardiac surgery.[23] In most patients, atenolol treatment was indeed continued up to 2 years after surgery.

Guidelines

Current recommendations concerning perioperative β-blocker use, as provided in the ACC/AHA 2006 Guideline Update on 'Perioperative Cardiovascular Evaluation for Noncardiac Surgery: Focused Update on Perioperative β-blocker Therapy', are illustrated in *Table 3*.[41] Although these guidelines advocate perioperative β-blocker use, data from observational studies and registries observe a poor compliance with guidelines in pharmacological treatment. Several studies have demonstrated that there is still an underuse of β-blockers in patients undergoing MVS, even when patients are considered to be at high risk for cardiovascular events and despite a worldwide increase in β-blocker prescription.[39, 42]

CURRENT CONCEPTS IN PROPHYLACTIC REVASCULARIZATION

In patients undergoing MVS surgery, there is a high prevalence of significant CAD. A classification of 1000 coronary angiograms in peripheral arterial disease patients, performed by Hertzer *et al,* demonstrated a prevalence of 18% for patients with severe three-vessel disease and 4% for patients with left main disease. In patients undergoing MVS, preoperative cardiac-risk evaluation by means of risk-factor assessment and noninvasive testing may often identify patients at increased cardiac risk. These patients may either have documented symptomatic involvement or be fully asymptomatic. Therefore, in patients requiring MVS within weeks or a few months, the need for diagnostic evaluation and subsequent revascularization will have to be questioned. When the presence of CAD is confirmed by angiography or cardiac computed tomography, coronary revascularization via percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) can be considered as prophylactic therapy before noncardiac surgery in these patients.[9] However, the cumulative risk of prophylactic coronary revascularization and MVS needs to be weighed up against the risk of the surgical procedure performed without preoperative interventions. Several observational studies have evaluated the

Table 3 **American College of Cardiology/American Heart Association recommendations, focussed on perioperative β-blocker therapy**

Class I
• β-blockers should be continued in patients undergoing surgery who are receiving β-blockers to treat angina, symptomatic arrhythmias, heart failure, hypertension or other Class I guideline indications (Level of Evidence: C)
• β-blockers should be given to patients undergoing vascular surgery at high cardiac risk owing to the finding of ischemia on preoperative testing (Level of Evidence: B).
Class IIa
• β-blockers are probable recommended for patients in whom preoperative assessment identifies coronary artery disease or high cardiac risk, as defined by the presence of multiple clinical risk factors [a] (Level of Evidence: B).
• β-blockers are probable recommended for patients in whom preoperative assessment for vascular surgery identifies high cardiac risk as defined by the presence of multiple clinical risk factors [a] (Level of Evidence: B).
• β-blockers are probable recommended for patients in whom preoperative assessment identifies coronary artery disease or high cardiac risk as defined by the presence of multiple clinical risk factors [a] and who are undergoing intermediate- or high-risk procedures (Level of Evidence: B).
Class IIb
• β-blockers may be considered for patients who are undergoing intermediate- of high-risk procedures, including vascular surgery, in whom preoperative assessment identifies intermediate cardiac risk as defined by the presence of a single clinical risk factor [a] (Level of Evidence: C).
• β-blockers may be considered for patients undergoing vascular surgery with low cardiac risk who are not currently taking β-blockers (Level of Evidence: C).
Class III
• β-blockers should not be given to patients undergoing surgery who have absolute contraindications to β-blockade (Level of Evidence: C).

[a] *Clinical predictors of increased perioperative risk: major - unstable coronary syndromes, decompensated heart failure, significant arrhythmias and severe valvular disease; Intermediate - mild angina pectoris, previous myocardial infarction, compensated or prior heart failure, diabetes mellitus and renal dysfunction; minor - advanced age, abnormal ECG, rhythm other than sinus, low functional capacity, history of stroke, and uncontrolled systemic hypertension.*[41]

value of prophylactic revascularization to prevent adverse cardiovascular events after noncardiac surgery.[43-48] In 1997, Eagle *et al.* evaluated 24,959 participants with suspected CAD in the Coronary Artery Surgery Study (CASS) database. They demonstrated that, among the 1,961 patients undergoing higher-risk surgery, prior CABG was associated with fewer postoperative deaths compared with medically managed coronary disease.[48] The value of PCI before MVS was retrospectively evaluated by Gottlieb *et al,* who found a low rate of perioperative cardiovascular events.[45] Fleisher *et al.* retrospectively included 6,895 patients, a random sample of the Medicare population, and demonstrated a reduced long-term mortality among patients who had previously undergone revascularization (i.e., PCI or CABG) and underlined the need for a randomized trial to determine the value of preoperative revascularization.[46] Back *et al.* concluded that previous coronary revascularization, defined as CABG fewer than 5 years or PCI fewer than 2 years before surgery, may only have a modest beneficial effect in preventing adverse cardiovascular events, and stated that further evaluation by randomized trial was needed.[47] Two prospective, randomized trials have provided new insights concerning preoperative interventions; the Coronary Artery Revascularization Prophylaxis (CARP) trial and the DECREASE-V trial.

CARP trial

The CARP trial, conducted by McFalls *et al,* screened 5,859 patients at 18 Veterans Affairs US hospitals and was the first prospectively, randomized study to investigate the benefit of coronary revascularization before elective MVS.[49] In total, 510 patients with significant coronary artery stenosis were randomized to either revascularization or no revascularization before MVS (*Table 4*). The main finding of the CARP trial was that there was no difference in the primary outcome of long-term mortality (median follow-up 2.7 years) in patients who underwent preoperative coronary revascularization compared with patients who received optimized medical therapy (22 vs. 23%, relative risk 0.98, 95%-CI: 0.70 to 1.37). No reduction in the number of MIs, deaths or length of hospital stay was observed within 30 days. Although the study was not powered to test the short-term benefit of prophylactic revascularization, results point to the suggestion that prophylactic revascularization may not provide additional benefits in reducing the incidence of perioperative and long-term cardiac morbidity and mortality in cardiac-stable MVS patients. As the majority of patients in the CARP trial had only one or two-vessel disease with a preserved left ventricular function, the optimal preoperative management for patients with left main disease, severe left ventricular dysfunction, unstable angina pectoris and aortic stenosis was not determined yet. As already noted, the CARP trial included 5,859 patients from which 1,048 patients underwent coronary angiography before vascular surgery. These patients were used by the CARP investigators in a sub-analysis to determine the impact of prophylactic coronary revascularization on long-term survival in patients with multi-vessel CAD.[50] They have demonstrated that 382 (36.5%) of the 1,048 patients presented with multi-vessel CAD without previous CABG. No long-term survival benefit was observed in patients with two- and three-vessel disease. However, in a cohort of 48 patients (4.6%) with left main coronary artery stenosis, preoperative revascularization did seem to have an improved 2.5-year survival (84 vs. 52%, $p < 0.01$). A secondary analysis of the CARP trial that solely evaluated patients with significant CAD and either critical limb ischemia or intermittent claudication indicated that mortality and morbidity were not improved by coronary artery revascularization before vascular surgery.[51] Another subgroup analysis of the CARP trial, performed by Ward *et al,* demonstrated that rates of perioperative and long-term MIs were lower in patients who had undergone CABG before vascular surgery, compared with patients with preoperative PCI. In the CABG group, the length of hospital stay was also decreased, and the authors concluded that this observation may be related to more complete revascularization in the CABG group.[52]

Table 4	Randomized, controlled trials evaluating the use of prophylactic revascularization before vascular surgery	
TRIAL	TRIAL PROTOCOL	MAIN FINDINGS
CARP 2004 [N=510]	**Inclusion criteria:** • Elective vascular surgery patients • CAG: stenosis of at least 70% in one or more major coronary arteries suitable for revascularization **Main exclusion criteria:** • Prior revascularization without evidence of recurrent ischemia • CAG: stenosis of left main coronary artery of at least 50% • LVEF <20% or severe aortic stenosis	In patients with stable CAD, coronary-artery revascularization does not improve long-term survival
DECREASE-V 101 [N=101]	**Inclusion criteria:** • Elective vascular surgery patients • ≥ three cardiac risk factors [a] • Extensive stress-induced ischemia during cardiac stress testing **Main exclusion criteria:** • Emergency surgery patients	Preoperative coronary revascularization was not associated with an improved outcome

[a] *Age > 65 years, hypertension, current smoking, hypercholesterolemia, or diabetes mellitus. Coronary artery disease (CAD), coronary angiography (CAG), Coronary Artery Revascularization Prophylaxis (CARP), Dutch Echocardiographic Cardiac Risk Index (DECREASE), left ventricular ejection fraction (LVEF).*

DECREASE-V trial

In the prospectively randomized DECREASE-V trial, comparable results to the CARP trial were obtained; however, this trial mainly included patients with three-vessel disease.[53] Cardiac-stable, elective MVS patients were screened for the following risk factors: age of more than 70 years, history of MI, presence of angina pectoris, congestive heart failure, diabetes mellitus or renal dysfunction, and history of cerebrovascular events (*Table 4*). In total, 430 patients with three or more clinical risk factors underwent cardiac-stress testing, from which 101 (23%) patients showed extensive stress-induced ischemia. The patients with extensive stress-induced ischemia were randomly assigned to receive either no-revascularization (N=52) or revascularization (N=49). Of the 49 patients assigned for revascularization, 12 (24%) had two-vessel disease, 33 (67%) had three-vessel disease and four (8%) had left main disease. Although the study population in the DECREASE-V trial reflects MVS patients at highest cardiac risk, revascularization did not improve cardiovascular outcomes. The incidence of the composite endpoint of 30-day cardiovascular mortality and MI was 43 vs. 33% (OR 1.4, 95%-CI: 0.7 to 2.8). Furthermore, no benefit was observed during 1-year follow-up after coronary revascularization, 49 vs. 44% (OR 1.2, 95%-CI: 0.7 to 2.3; p = 0.48). Comparable with the DECREASE-I trial, a high incidence of perioperative cardiovascular events was observed.[25] This could be explained by the selection of high-risk cardiac patients with extensive ischemia during cardiac stress testing.

In 2007, Landesberg *et al.* included 502 patients in a retrospective observational study, in which thallium scanning was performed before MVS. They demonstrated improved long-term survival in patients with moderate-to-severe ischemia who were undergoing preoperative revascularization.[54] Furthermore, Landesberg *et al.* constructed a long-term survival score

(LTSS) for the prediction of cardiac risk in patients undergoing MVS. On the basis of the following risk factors, MVS patients were stratified to be at low, intermediate or high cardiac risk: age of more than 65 years, presence of diabetes mellitus or congestive heart failure, history of MI, chronic renal dysfunction, cerebrovascular disease and ST-segment depression on ECG. Intermediate-risk patients (two or three LTSS risk factors) were most likely to benefit from preoperative coronary revascularization (3-year mortality: OR 0.45, 95%-CI: 0.21 to 0.97, and long-term mortality: HR 0.48, 95%-CI: 0.31 to 0.75; $p = 0.001$). Patients with a low-risk LTSS score (0 or 1) had good long-term survival that was not affected by revascularization. High-risk patients (LTSS >4) had poor long-term survival, which was also unaffected by revascularization.[55, 56]

DISCUSSION: PROPHYLACTIC REVASCULARIZATION

The main difference between the CARP trial and the retrospective study conducted by Landesberg *et al,* was the criteria for patients inclusion. In the CARP trial, patients with left main disease were excluded and 33% of the enrolled patients had three-vessel disease. By comparison, in the study conducted by Landesberg *et al,* 73% of the enrolled patients had left main or three-vessel disease.[54] In the DECREASE-V trial, preoperative dobutamine stress echocardiography, stress nuclear imaging and cardiac-risk scores were used to identify cardiac high-risk patients. Therefore, the DECREASE-V trial mainly included patients with three-vessel disease, the group most likely to benefit from prophylactic revascularization. The majority of patients in the CARP trial had one- or two-vessel disease.[53] In an editorial paper by Garcia and McFalls, it was reported that patients with major risk factors (i.e., unstable coronary syndromes, decompensated congestive heart failure, severe valvular abnormalities and life-threatening arrhythmias) were not included in the major randomized trials because the unstable cardiac status would probably influence postoperative cardiovascular outcome.[50] No trials exist investigating the role of prophylactic revascularization in patients with unstable angina pectoris requiring MVS. However, if MVS can be postponed safely, diagnosis and treatment for these patients should be in line with the recent guidelines on unstable angina management.[13]

Guidelines

In the current ACC/AHA guidelines for 'Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery', it is stated that coronary revascularization before noncardiac surgery is useful in patients with acute ST-elevation MI, non-ST-elevation MI, high-risk unstable angina or stable angina in combination with significant left main coronary artery stenosis, two- or three-vessel disease with significant proximal left anterior descending stenosis and either an ejection fraction of less than 50% or ischemia during noninvasive testing.[10] Furthermore, it is stated that the usefulness of preoperative coronary revascularization is not well established for high-risk ischemic patients (with an abnormal dobutamine stress echocardiogram with wall motion abnormalities in at least five segments) or low-risk ischemic patients (wall motion

abnormalities in up to four segments).[10] In patients with stable CAD, routine prophylactic coronary revascularization is not recommended before noncardiac surgery.[10] In patients who undergo coronary angiography without stent placement, noncardiac surgery should be postponed for at least two weeks.[57] Regarding the management of patients with previous coronary stenting undergoing noncardiac surgery, a time window to surgery of at least 6 weeks for bare-metal stents and 1 year for drug-eluting stents is recommended.[58] For CABG, noncardiac surgery should be postponed for at least 1 month.[57]

EXPERT COMMENTARY AND FIVE-YEAR VIEW

The value of perioperative β-blocker therapy and preoperative prophylactic coronary revascularization has been widely debated over the years. Garcia and McFalls state in their editorial paper that it is time for clinicians to shift the emphasis from extensive preoperative testing to evidence-based medical therapies, including β-blocker treatment.[59]

We agree with this statement and propose that all patients undergoing high-risk surgical procedures, such as open vascular surgery, should be treated with low dose β-blockade, preferable the β_1-selective β-blocker bisoprolol. Treatment should be initiated at least 30 days before surgery, and to maximize the beneficial effects, titration according to tolerance and heart-rate control between 65 and 70 beats per minute is of utmost importance. Furthermore, we promote the idea of prolonged treatment after surgery. Next to β-blockers, patients should also receive statins and aspirin, to optimize medical treatment. In all patients with unstable angina and coronary artery stenosis, prophylactic revascularization should be performed, preferably before surgery if surgery can be safely postponed. Asymptomatic patients or patients with one- or two-vessel coronary disease (not including left main disease) should receive optimal medical treatment without the need for coronary revascularization. Asymptomatic patients with left main, two or three-vessel disease with significant proximal left anterior descending stenosis and either an ejection fraction of less than 50% or ischemia during noninvasive testing should receive coronary revascularization, next to optimal medical therapy. If noncardiac surgery can be postponed, coronary revascularization should be performed before surgery. If noncardiac surgery cannot be postponed, coronary revascularization should still be performed after surgery.

Future randomized trials are needed to further evaluate the value of β-blocker therapy and prophylactic revascularization. Withdrawal of β-blocker therapy shortly before surgery, or in the immediate postoperative period, may contribute to adverse myocardial effects resulting from a rebound effect, leading to increases in arterial blood pressure, heart rate and plasma noradrenalin concentrations. Intraoperative infusion with esmolol may be effective in preventing intraoperative tachycardia and reduce intraoperative left ventricular contractile force. The short-acting character of esmolol and continuous hemodynamic monitoring during

surgery limit adverse side effects, such as hypotension or bradycardia. The beneficial effect of intraoperative esmolol treatment next to pre- and postoperative treatment with low-dose bisoprolol may further improve postoperative outcome, which should be evaluated in randomized, controlled trials. Prophylactic treatment of high-risk patients with CABG or PCI apparently provides insufficient extra protection on top of β-blocker treatment as demonstrated in the CARP and DECREASE-V trials. Retrospective data indicate that prophylactic revascularization may be the most effective option in intermediate-risk cardiac patients. To assess the addition value of prophylactic revascularization next to optimal medical therapy, future randomized trials are needed, focussing on coronary revascularization and low-dose β-blocker treatment in low-, intermediate- and high-risk patients groups.

REFERENCES

1. Mangano DT. Perioperative cardiac morbidity. *Anesthesiology.* 1990;72(1):153-184.

2. Mangano DT. Adverse outcomes after surgery in the year 2001--a continuing odyssey. *Anesthesiology.* 1998;88(3):561-564.

3. Mangano DT, Goldman L. Preoperative assessment of patients with known or suspected coronary disease. *N Engl J Med.* 1995;333(26):1750-1756.

4. McCann RL, Clements FM. Silent myocardial ischemia in patients undergoing peripheral vascular surgery: incidence and association with perioperative cardiac morbidity and mortality. *J Vasc Surg.* 1989;9(4):583-587.

5. Mangano DT, Browner WS, Hollenberg M, et al. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. *N Engl J Med.* 1990;323(26):1781-1788.

6. Badner NH, Knill RL, Brown JE, et al. Myocardial infarction after noncardiac surgery. *Anesthesiology.* 1998;88(3):572-578.

7. Haagensen R, Steen PA. Perioperative myocardial infarction. *Br J Anaesth.* 1988;61(1):24-37.

8. Ouyang P, Gerstenblith G, Furman WR, et al. Frequency and significance of early postoperative silent myocardial ischemia in patients having peripheral vascular surgery. *Am J Cardiol.* 1989;64(18):1113-1116.

9. Hertzer NR, Beven EG, Young JR, et al. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Ann Surg.* 1984;199(2):223-233.

10. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *Circulation.* 2007;116(17):1971-1996.

11. Mancia G, De Backer G, Dominiczak A, et al. [ESH/ESC 2007 Guidelines for the management of arterial hypertension]. *Rev Esp Cardiol.* 2007;60(9):968 e961-994.

12. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J.* 2008;29(19):2388-2442.

13. Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J.* 2007;28(13):1598-1660.

14. Yeager MP, Fillinger MP, Hettleman BD, et al. Perioperative beta-blockade and late cardiac outcomes: a complementary hypothesis. *J Cardiothorac Vasc Anesth.* 2005;19(2):237-241.

15. Stanley WC, Lopaschuk GD, Hall JL, et al. Regulation of myocardial carbohydrate metabolism under normal and ischemic conditions. Potential for pharmacological interventions. *Cardiovasc Res.* 1997;33(2):243-257.

16. Cruickshank JM. Beta-blockers continue to surprise us. *Eur Heart J.* 2000;21(5):354-364.

17. Sun JZ, Maguire D. How to prevent perioperative myocardial injury: the conundrum continues. *Am Heart J.* 2007;154(6):1021-1028.

18. Priebe HJ. Perioperative myocardial infarction--aetiology and prevention. *Br J Anaesth.* 2005;95(1):3-19.

19. Wallace A, Layug B, Tateo I, et al. Prophylactic atenolol reduces postoperative myocardial ischemia. McSPI Research Group. *Anesthesiology.* 1998;88(1):7-17.

20. Redelmeier D, Scales D, Kopp A. Beta blockers for elective surgery in elderly patients: population based, retrospective cohort study. *Bmj.* 2005;331(7522):932.

21. Lindenauer PK, Pekow P, Wang K, et al. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med.* 2005;353(4):349-361.

22. Feringa HH, Bax JJ, Boersma E, et al. High-dose beta-blockers and tight heart rate control reduce myocardial ischemia and troponin T release in vascular surgery patients. *Circulation.* 2006;114(1 Suppl):I344-349.

23. Mangano DT, Layug EL, Wallace A, et al. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. *N Engl J Med.* 1996;335(23):1713-1720.

24. Raby KE, Brull SJ, Timimi F, et al. The Effect of Heart Rate Control on Myocardial Ischemia Among High-Risk Patients After Vascular Surgery. *Anesth Analg.* 1999;88(3):477-482.

25. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med.* 1999;341(24):1789-1794.

26. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet.* 2008;371(9627):1839-1847.

27. Brady AR, Gibbs JS, Greenhalgh RM, et al. Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. *J Vasc Surg.* 2005;41(4):602-609.

28. Yang H, Raymer K, Butler R, et al. The effects of perioperative beta-blockade: results of the Metoprolol after Vascular Surgery (MaVS) study, a randomized controlled trial. *Am Heart J.* 2006;152(5):983-990.

29. Juul AB, Wetterslev J, Gluud C, et al. Effect of perioperative beta blockade in patients with diabetes undergoing major non-cardiac surgery: randomised placebo controlled, blinded multicentre trial. *Bmj.* 2006;332(7556):1482.

30. Zaugg M, Bestmann L, Wacker J, et al. Adrenergic receptor genotype but not perioperative bisoprolol therapy may determine cardiovascular outcome in at-risk patients undergoing surgery with spinal block: the Swiss Beta Blocker in Spinal Anesthesia (BBSA) study: a double-blinded, placebo-controlled, multicenter trial with 1-year follow-up. *Anesthesiology.* 2007;107(1):33-44.

31. Bangalore S, Wetterslev J, Pranesh S, et al. Perioperative beta blockers in patients having non-cardiac surgery: a meta-analysis. *Lancet.* 2008;372(9654):1962-1976.

32. Boersma E, Poldermans D. Beta blockers in non-cardiac surgery: haemodynamic data needed. *Lancet.* 2008;372(9654):1930-1932.

33. Boersma E, Poldermans D, Bax JJ, et al. Predictors of cardiac events after major vascular surgery: Role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. *Jama.* 2001;285(14):1865-1873.

34. Fleisher LA, Poldermans D. Perioperative beta blockade: where do we go from here? *Lancet.* 2008;371(9627):1813-1814.

35. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet.* 1999;353(9146):9-13.

36. Beattie WS, Wijeysundera DN, Karkouti K, et al. Does tight heart rate control improve beta-blocker efficacy? An updated analysis of the noncardiac surgical randomized trials. *Anesth Analg.* 2008;106(4):1039-1048, table of contents.

37. Maling TJ, Dollery CT. Changes in blood pressure, heart rate, and plasma noradrenaline concentration after sudden withdrawal of propranolol. *Br Med J.* 1979;2(6186):366-367.

38. Shammash JB, Trost JC, Gold JM, et al. Perioperative beta-blocker withdrawal and mortality in vascular surgical patients. *Am Heart J.* 2001;141(1):148-153.

39. Hoeks SE, Scholte Op Reimer WJ, van Urk H, et al. Increase of 1-year Mortality After Perioperative Beta-blocker Withdrawal in Endovascular and Vascular Surgery Patients. *Eur J Vasc Endovasc Surg.* 2007;33(1):13-19.

40. Sipahi I, Tuzcu EM, Wolski KE, et al. Beta-blockers and progression of coronary atherosclerosis: pooled analysis of 4 intravascular ultrasonography trials. *Ann Intern Med.* 2007;147(1):10-18.

41. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2006 guideline update on perioperative cardiovascular evaluation for noncardiac surgery: focused update on perioperative beta-blocker therapy: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society for Vascular Medicine and Biology. *J Am Coll Cardiol.* 2006;47(11):2343-2355.

42. Siddiqui AK, Ahmed S, Delbeau H, et al. Lack of physician concordance with guidelines on the perioperative use of beta-blockers. *Arch Intern Med.* 2004;164(6):664-667.

43. Hertzer NR, Young JR, Beven EG, et al. Late results of coronary bypass in patients presenting with lower extremity ischemia: the Cleveland Clinic Study. *Ann Vasc Surg.* 1987;1(4):411-419.

44. Hertzer NR, Young JR, Beven EG, et al. Late results of coronary bypass in patients with infrarenal aortic aneurysms. The Cleveland Clinic Study. *Ann Surg.* 1987;205(4):360-367.

45. Gottlieb A, Banoub M, Sprung J, et al. Perioperative cardiovascular morbidity in patients with coronary artery disease undergoing vascular surgery after percutaneous transluminal coronary angioplasty. *J Cardiothorac Vasc Anesth.* 1998;12(5):501-506.

46. Fleisher LA, Eagle KA, Shaffer T, et al. Perioperative- and long-term mortality rates after major vascular surgery: the relationship to preoperative testing in the medicare population. *Anesth Analg.* 1999;89(4):849-855.

47. Back MR, Stordahl N, Cuthbertson D, et al. Limitations in the cardiac risk reduction provided by coronary revascularization prior to elective vascular surgery. *J Vasc Surg.* 2002;36(3):526-533.

48. Eagle KA, Rihal CS, Mickel MC, et al. Cardiac risk of noncardiac surgery: influence of coronary disease and type of surgery in 3368 operations. CASS Investigators and University of Michigan Heart Care Program. Coronary Artery Surgery Study. *Circulation.* 1997;96(6):1882-1887.

49. McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med.* 2004;351(27):2795-2804.

50. Garcia S, Moritz TE, Ward HB, et al. Usefulness of revascularization of patients with multivessel coronary artery disease before elective vascular surgery for abdominal aortic and peripheral occlusive disease. *Am J Cardiol.* 2008;102(7):809-813.

51. Raghunathan A, Rapp JH, Littooy F, et al. Postoperative outcomes for patients undergoing elective revascularization for critical limb ischemia and intermittent claudication: a subanalysis of the Coronary Artery Revascularization Prophylaxis (CARP) trial. *J Vasc Surg.* 2006;43(6):1175-1182.

52. Ward HB, Kelly RF, Thottapurathu L, et al. Coronary artery bypass grafting is superior to percutaneous coronary intervention in prevention of perioperative myocardial infarctions during subsequent vascular surgery. *Ann Thorac Surg.* 2006;82(3):795-800; discussion 800-791.

53. Poldermans D, Schouten O, Vidakovic R, et al. A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: the DECREASE-V Pilot Study. *J Am Coll Cardiol.* 2007;49(17):1763-1769.

54. Landesberg G, Mosseri M, Wolf YG, et al. Preoperative thallium scanning, selective coronary revascularization, and long-term survival after major vascular surgery. *Circulation.* 2003;108(2):177-183.

55. Landesberg G, Berlatzky Y, Bocher M, et al. A clinical survival score predicts the likelihood to benefit from preoperative thallium scanning and coronary revascularization before major vascular surgery. *Eur Heart J.* 2007;28(5):533-539.

56. Landesberg G, Mosseri M. PRO: Preoperative coronary revascularization in high-risk patients undergoing vascular surgery. *Anesth Analg.* 2008;106(3):759-763.

57. Damen J, Hagemeijer JW, van den Broek L, et al. [Prevention of perioperative cardiac complications in non-cardiac surgery: an evidence-based guideline]. *Ned Tijdschr Geneeskd.* 2008;152(48):2612-2616.

58. Brilakis ES, Banerjee S, Berger PB. Perioperative management of patients with coronary stents. *J Am Coll Cardiol.* 2007;49(22):2145-2150.

59. Garcia S, McFalls EO. CON: Preoperative coronary revascularization in high-risk patients undergoing vascular surgery. *Anesth Analg.* 2008;106(3):764-766.

Chapter 19

Long-term outcome of prophylactic coronary revascularization in cardiac high-risk patients undergoing major vascular surgery (from the randomized DECREASE-V pilot study)

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ABSTRACT

Background Prophylactic coronary revascularization in vascular surgery patients with extensive coronary artery disease was not associated with an improved immediate postoperative outcome. However, the potential long-term benefit was unknown. This study was performed to assess the long-term benefit of prophylactic coronary revascularization in these patients.

Methods Of 1,880 patients scheduled for major vascular surgery, 430 had ≥3 risk factors (>70 yrs, angina pectoris, myocardial infarction, heart failure, stroke, diabetes mellitus, and renal failure). All underwent cardiac testing using dobutamine echocardiography or nuclear stress imaging. Patients with extensive stress-induced ischemia (≥5 segments or ≥3 walls) were randomly assigned to additional revascularization.

Results In total, 101 patients showed extensive ischemia and were assigned to revascularization (N=49) or no-revascularization (N=52). After 2.8 years, the overall survival was 64% for patients randomly assigned to no preoperative coronary revascularization vs. 61% for patients assigned to preoperative coronary revascularization (hazard ratio [HR] 1.18, 95% confidence interval [95%-CI]: 0.63 to 2.19, $p = 0.61$). Rates for survival free of all-cause death, nonfatal myocardial infarction, and coronary revascularization were similar in both groups at 49% and 42% for patients allocated to medical treatment or coronary revascularization, respectively (HR 1.51, 95%-CI: 0.89 to 2.57, $p = 0.13$). Only two patients assigned to medical treatment required coronary revascularization during follow-up. Also, in patients who survived the first 30 days after surgery there was no apparent benefit of revascularization on cardiac events (HR 1.35, 95%-CI: 0.72 to 2.52, $p = 0.36$).

Conclusions Preoperative coronary revascularization in high-risk patients undergoing major vascular surgery was not associated with an improved postoperative or long-term outcome compared with the best medical treatment.

INTRODUCTION

According to the guidelines of the American College of Cardiology /American Heart Association, it is recommended to perform coronary angiography in patients with high-risk noninvasive test results. Subsequently, myocardial revascularization should be performed in patients with prognostic high-risk anatomy in whom long-term outcome is likely to be improved.[1] However in both the Coronary Artery Revascularization Prophylaxis (CARP) trial and Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) V trial, prophylactic preoperative coronary revascularization was not associated with improved immediate postoperative outcome.[2, 3] As recently shown, early surgery after coronary stent placement might lead to an increase in adverse cardiac events caused by in-stent thrombosis or bleeding complications.[4] This might explain the lack of perioperative benefit. However, it was expected that at least long-term outcome, such as after the potentially hazardous perioperative period, should be improved in these patients. Therefore, we analyzed the long-term outcome of the randomized DECREASE V trial to assess whether there was a long-term benefit of prophylactic coronary revascularization in high-risk patients undergoing major vascular surgery.

METHODS

The study design and the perioperative results of the original DECREASE V trial have been published previously.[2] In brief, patients were considered eligible for the study if they were scheduled for elective open abdominal aortic or infrainguinal arterial reconstruction. Patients were screened for the prevalence of cardiac risk factors including age >70 years, angina pectoris, previous myocardial infarction, compensated congestive heart failure or history of congestive heart failure, drug therapy for diabetes mellitus, renal dysfunction (serum creatinine >160 μmol/L), and prior stroke or transient ischemic attack. All patients with ≥3 risk factors underwent cardiac stress testing before surgery. Those who experienced extensive stress-induced ischemia were enrolled in the DECREASE V trial. All patients provided informed consent, and the Erasmus MC (Rotterdam, The Netherlands) medical ethics committee and local research ethics committees approved the study. Out of 1,880 screened patients, 101 (5.3%) were considered eligible, had ≥3 risk factors, had extensive stress induced myocardial ischemia and were subsequently randomized. A total of 49 patients were allocated to best medical treatment and preoperative coronary revascularization and 52 patients to best medical treatment only.

Cardiac stress testing was performed using dobutamine echocardiography or dobutamine or dipyridamole perfusion scintigraphy, as previously described.[5, 6] Test results were scored according to the extent of stress-induced ischemia using a 17-segment model for dobutamine echocardiography and a 6-wall model for stress perfusion scintigraphy. Limited

ischemia was defined by the presence of 1 to 4 ischemic segments or 1 to 2 ischemic walls, whereas extensive ischemia was defined as ≥5 ischemic segments or ≥3 ischemic walls.

All patients were monitored for cardiac events after screening. The 12-lead electrocardiogram and serum troponin T level were systematically assessed 1, 3, 7, and 30 days after surgery. Outpatient follow-up was performed at 30 days if a patient had been discharged from the hospital. At the outpatient clinic, all patients were screened at 3-month intervals for cardiac events using clinical history and 12-lead electrocardiogram and additional tests were performed when indicated by the treating physicians. For this report, outcomes were long-term all-cause death and a combined endpoint of all-cause death, nonfatal myocardial infarction, and coronary revascularization during follow-up.

Myocardial infarction was defined as the presence of two of the three criteria of (i) characteristic ischemic symptoms lasting >20 minutes, (ii) electrocardiographic changes, including acute ST elevation followed by the appearance of Q waves or loss of R waves; new left bundle branch block or new persistent T-wave inversion for ≥24 hours; or new ST segment depression that persisted >24 hours, and (iii) a positive troponin T (i.e. >0.10 ng/mL) or peak creatinine kinase-MB >8% of increased total creatinine kinase with characteristic increase and decrease.

Continuous data were presented as median and corresponding 25th and 75th percentiles, whereas dichotomous data are presented as percentages. Differences in clinical and surgical characteristics between patients allocated to revascularization or no revascularization were evaluated by Wilcoxon's nonparametric tests, χ^2 or Fisher's exact tests, as appropriate. The incidence of outcome events over time was examined by the Kaplan-Meier method. Multivariate (Cox) regression was used to compare differences in overall survival and cardiac event free survival between the allocated treatment strategies, adjusted for baseline clinical risk factors. Patients who had an event before surgery but after screening were included in the analyses as the day of screening was considered to be baseline. Analyses were performed according to the intention-to-treat principle. All statistical tests were two-sided and a $p < 0.05$ was considered significant.

RESULTS

Baseline variables in patients who underwent preoperative coronary revascularization (N=49) or best medical treatment only (N=52) are shown in *Table 1*. In patients allocated to coronary revascularization, 32 underwent a percutaneous coronary intervention (PCI), with a bare-metal stent in two and drug-eluting stent in 30. Patients continued with dual-antiplatelet therapy during surgery. After surgery, patients with bare-metal stents stopped dual-antiplatelet therapy after three months and continued with aspirin afterward. Patients with drug-eluting stent

continued dual-antiplatelet therapy during follow-up. A bypass procedure was performed in 17 patients. The impact of drug-eluting stents vs. bare-metal stents could not be assessed because of the number of patients included in the study.

Table 1 **Baseline characteristics**

	Revascularization		
	Yes	No	*p*-value
	[N=49]	[N=52]	
Demographics			
Age (yrs)	71 (64,7)	70 (63,8)	
Men (%)	42 (86)	47 (90)	0.55
Medical history (%)			
Diabetes mellitus	18 (37)	15 (29)	0.53
Current angina pectoris	25 (51)	22 (42)	0.43
Previous myocardial infarction	49 (100)	50 (96)	0.50
Previous heart failure	23 (47)	24 (46)	1.0
Previous cerebrovascular accident	20 (41)	13 (25)	0.14
Previous renal failure	9 (18)	11 (21)	0.81
Medication (%)			
aspirin	37 (76)	30 (58)	0.09
ß-blocker	34 (70)	36 (69)	1.0
ACE - inhibitor	28 (57)	22 (42)	0.17
statin	34 (69)	30 (58)	0.30
Cororary artery narrowed >50% (%)			
right coronary	39 (80)	–	
left artery descending	46 (94)	–	
left circumflex	37 (76)	–	
Number of narrowed arteries (%)			
1	0 (0)	–	
2	12 (24)	–	
3	33 (67)	–	
left main	4 (8)	–	

Angiotensin converting enzyme (ACE).

The 30-day outcome of the study population has been described in detail previously.[2] Two patients died before vascular surgery because of a ruptured aneurysm after successful bypass surgery and 1 patient experienced myocardial infarction after unsuccessful coronary revascularization. Revascularization did not improve 30-day outcome after vascular surgery. The incidence of all-cause death or nonfatal myocardial infarction for patients with preoperative revascularization or medical treatment only was 43 vs. 33% respectively (hazard ratio [HR] 1.4, 95% confidence interval [95%-CI]: 0.7 to 2.8 $p = 0.30$).

During a median follow-up of 2.8 years (interquartile range 0.9 to 4.2 years) 42 of 101 patients died. After 2.8 years, the overall survival rate was 64% for patients randomly assigned to no preoperative coronary revascularization vs. 61% for patients assigned to preoperative

coronary revascularization (HR 1.18, 95%-CI: 0.63 to 2.19, p = 0.61; *Figure 1*). As shown in *Figure 2*, the incidence of all-cause death, nonfatal myocardial infarction, and coronary revascularization was similar in both groups. Event-free survival after 2.8 years were 49% and 42% for patients allocated to medical treatment or coronary revascularization, respectively (HR 1.51, 95%-CI: 0.89 to 2.57, p = 0.14). In the no-revascularization group, two patients (4%) underwent coronary revascularization during follow-up; one patient underwent coronary artery bypass surgery 12 months after vascular surgery because of unstable angina pectoris, and one patient underwent PCI using drug-eluting stents 27 months after vascular surgery because of progressive angina pectoris symptoms.

Figure 1: Overall survival in 101 randomly assigned patients.

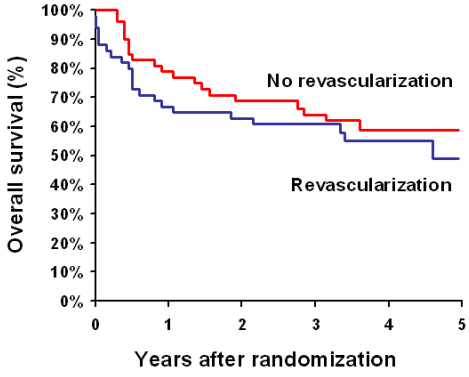
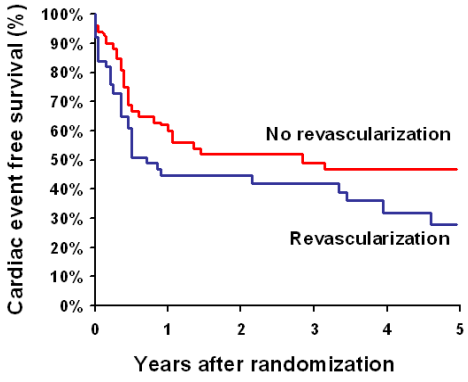


Figure 2: Cardiac event-free survival in 101 randomly assigned patients.



It might be argued that preoperative coronary revascularization, in particular, stent placement, might lead to an increased 30-day risk for in-stent thrombosis or bleeding after discontinuation or continuation of antiplatelet therapy.[4] Therefore, we performed a separate analysis including only patients who survived ≥30 days after surgery (N=36 and N=46 for revascularization and medical treatment only, respectively). As shown in *Figures 3 and 4*, in these survivors, no apparent benefit of revascularization was observed. Of patients who underwent revascularization, 47% had an event within a median of 2.8 years of follow-up vs. 44% in those who did not undergo preoperative coronary revascularization (HR 1.35, 95%-CI: 0.72 to 2.52, $p = 0.36$). In addition, all-cause mortality did not differ between groups (HR 0.79, 95%-CI: 0.35 to 1.78, $p = 0.57$).

Figure 3: Overall survival in patients who survived the first 30 days after surgery.

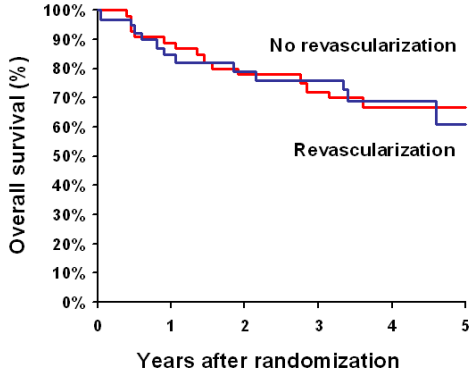
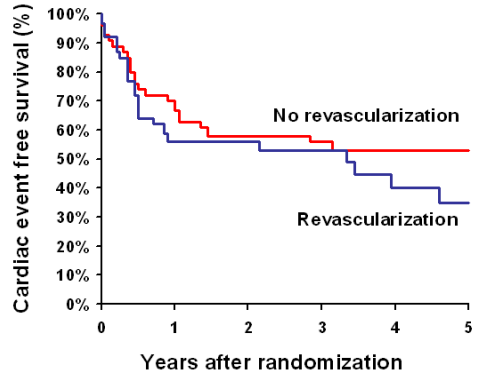
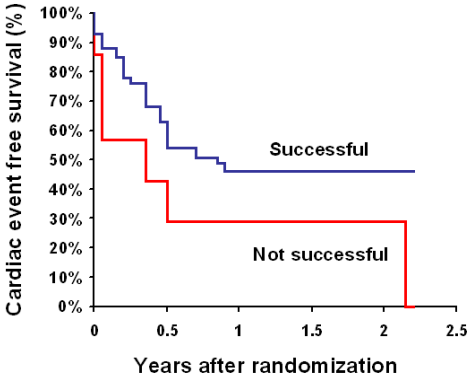


Figure 4: Cardiac event-free survival of patients who survived the first 30 days after surgery.



There was no difference in long-term event free survival between patients who underwent preoperative PCI or coronary artery bypass grafting (HR 0.91, 95%-CI: 0.44 to 1.88, p = 0.80). After a median of 2.8 years, event-free survival was 41 vs. 44% for PCI and coronary artery bypass grafting, respectively. In addition, for the endpoint of all-cause death, no significant difference was observed (HR 0.81, 95%-CI: 0.33 to 1.96, p = 0.64). However, patients with an incomplete revascularization procedure had the worst outcome; six of seven (86%) patients died within two years after the attempted revascularization compared with 13 of 42 (31%) with complete revascularization (HR 4.07, 95%-CI: 1.53 to 10.82, p = 0.005, *Figure 5*).

Figure 5: Cardiac event-free survival after successful or not successful preoperative revascularization.



DISCUSSION

The DECREASE-V study did not show a long-term benefit of prophylactic preoperative coronary revascularization in stable patients with multiple cardiac risk factors and extensive stress-induced myocardial ischemia scheduled for major vascular surgery.

The current findings were in line with results of large randomized trials in the nonsurgical population. Patients with stable multivessel coronary artery disease did not have better survival after coronary stent placement or bypass grafting compared with medical treatment only. The recent published Medicine, Angioplasty, or Surgery Study (MASS II) was the first randomized controlled clinical trial to report 5-year outcomes of nonsurgical patients with stable multivessel coronary artery disease treated with either bare-metal stent placement, coronary artery bypass grafting, or best medical treatment only.[7] That study showed that optimal medical therapy in patients with stable multivessel coronary artery disease resulted in

similar long-term outcomes in terms of cardiac-related death or all-cause mortality. The investigators concluded that "patients with mild to moderate angina can be safely managed medically, whereas PCI or [coronary artery bypass grafting] CABG is appropriate if symptoms are not adequately controlled by medication or other high-risk features are apparent."[7] The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial also found no additional benefit of coronary revascularization in addition to optimal medical therapy in 2,287 patients with objective evidence of myocardial ischemia and significant coronary artery disease.[8] During a median follow-up of 4.6 years, cumulative event rate of all-cause death and myocardial infarction were 19.0% in the PCI group and 18.5% in the medical-therapy group. As discussed by the COURAGE trialists, these findings may be explained by differences in atherosclerotic plaque morphologic characteristics and vascular remodeling associated with acute coronary syndromes compared with stable coronary artery disease. Medical treatment in both MASS II and COURAGE included rigorous statin and aspirin therapy. This might have prevented vulnerable plaques, which are usually difficult to detect and impossible to treat using coronary angioplasty or bypass, to rupture and cause acute coronary syndromes. It is important to realize that vulnerable coronary lesions are not necessarily severely stenotic, and severely stenotic lesions are not necessarily unstable. Focal management of severely stenotic coronary lesions using PCI in both MASS II and COURAGE did not reduce the rate of death and myocardial infarction, presumably because the treated, severely stenotic lesions were not likely to trigger an acute coronary event.[8]

Remarkably, in MASS II and COURAGE, annual mortality rates were approximately 1 to 2% whereas in CARP and DECREASE V the annual mortality rates in patients who survived surgery were 6.8 and 8.2%, respectively. Baseline angiographic cardiac status in MASS II and COURAGE was not significantly better or worse than in CARP and DECREASE V: 3-vessel disease was present in 58 and 31% vs. 33 and 75%, respectively. In line with these findings, it was recently shown that patients with so-called "polyvascular" disease, i.e. multiple vascular beds affected, have a significant worse outcome compared with patients with coronary artery disease only.[9] In Reduction of Atherothrombosis for Continued Health (REACH), event rates (cardiovascular death, MI, stroke, or hospitalization for a cardiovascular event) increased with the number of symptomatic vascular beds: 5.3% of patients with risk factors only to 12.6 with one, 21.1 with two, and 26.3% with three disease locations.[9] Because all patients in DECREASE V and CARP had proven coronary artery disease and were planned for noncardiac vascular surgery, these patients can be considered to have polyvascular disease. This indicated that patients scheduled for vascular surgery with extensive coronary artery disease should be considered to be a different population than patients without peripheral arterial disease, but with coronary artery disease only. However, also in this patient population with stable severe coronary artery disease, optimal medical therapy seems to be equal to coronary revascularization in addition to best medical treatment.

The findings of both CARP and DECREASE V support the current guidelines of the American College of Cardiology/American Heart Association for perioperative management in high-risk patients to reserve revascularization for cardiac unstable patients. Considering the high long-term mortality and cardiac event rates, these patients should be regularly screened for the presence of ischemic symptoms, and aggressive anti-ischemic medical therapy must be used.

REFERENCES

1. Eagle KA, Berger PB, Calkins H, Chaitman BR et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery---executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation* 2002;105:1257-1267.
2. Poldermans D, Schouten O, Vidakovic R et al. A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: the DECREASE-V Pilot Study. *J Am Coll Cardiol* 2007;49:1763-1769.
3. McFalls EO, Ward HB, Moritz TE et al. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med* 2004;351:2795-2804.
4. Schouten O, Van Domburg RT, Bax JJ et al. Noncardiac Surgery After Coronary Stenting: Early Surgery and Interruption of Antiplatelet Therapy Are Associated With an Increase in Major Adverse Cardiac Events. *J Am Coll Cardiol* 2007;49:122-124.
5. Poldermans D, Arnese M, Fioretti PM, et al. Improved cardiac risk stratification in major vascular surgery with dobutamine-atropine stress echocardiography. *J Am Coll Cardiol* 1995;26:648-653.
6. Schinkel AF, Bax JJ, Elhendy A et al. Long-term prognostic value of dobutamine stress echocardiography compared with myocardial perfusion scanning in patients unable to perform exercise tests. *Am J Med* 2004;117:1-9.
7. Hueb W, Lopes NH, Gersh BJ et al. Five-year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation* 2007;115:1082-1089.
8. Boden WE, O'Rourke RA, Teo KK et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503-1516.
9. Steg PG, Bhatt DL, Wilson PW et al. One-year cardiovascular event rates in outpatients with atherothrombosis. *Jama* 2007;297:1197-1206.

Chapter 20

Timing of noncardiac surgery after coronary artery stenting with bare metal or drug-eluting stents

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ABSTRACT

Background The current guidelines recommend postponing noncardiac surgery (NCS) for ≥6 weeks after bare metal stent (BMS) placement and 1 year after drug-eluting stent (DES) placement. However, much debate has ensued about these intervals. The aim of the present study was to assess the influence of different intervals between stenting and NCS and the use of dual antiplatelet therapy on the occurrence of perioperative major adverse cardiac events (MACEs).

Methods We identified 550 patients (376 with a DES and 174 with a BMS) by cross-matching the Erasmus Medical Center percutaneous coronary intervention (PCI) database with the NCS database. The following intervals between PCI-BMS (<30 days, <3 months, >3 months) or PCI-DES (<30 days, <3 months, 3-6 months, 6-12 months and >12 months) and NCS were studied. MACEs included death, myocardial infarction and repeated revascularization.

Results In the PCI-BMS group, the rates of MACEs during the intervals of <30, 30 days–3 months, and >3 months was 50, 14, and 4%, respectively (overall $p < 0.001$). In the PCI-DES group, the rate of MACE changed significantly with the interval after PCI (35, 13, 15, 6, and 9% for patients undergoing NCS <30 days, 30 days to 3months, 3 to 6 months, 6 to 12 months, and >12 months after PCI-DES respectively, overall $p < 0.001$). Of the patients who experienced a MACE, 45 and 55% were receiving single and dual antiplatelet therapy at NCS, respectively ($p = 0.92$). The risk of severe bleeding in patients with single and dual therapy at NCS was 4 and 21%, respectively ($p < 0.001$).

Conclusions We found an inverse relation between the interval from PCI to NCS and perioperative MACEs. Continuation of dual antiplatelet therapy until NCS did not provide complete protection against MACEs.

INTRODUCTION

Approximately 5% of patients who undergo coronary stenting require some form of noncardiac surgery (NCS) within one year.[1] Surgery increases the risk of thrombosis owing to a perioperative stress response; including sympathetic activation promoting reduced fibrinolytic activity, platelet activation, and hypercoagulability. In addition, dual antiplatelet therapy is often interrupted because of the fear of excessive perioperative bleeding complications. The prevention of cardiac complications vs. the risk of severe bleeding creates a double-edged sword on the timing of surgery and the antiplatelet regimen. The current guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) have recommend delaying NCS for ≥6 weeks after PCI with a bare metal stent (BMS) and ≥1 year after PCI with a drug-eluting stent (DES).[2, 3] However, in a recent large study including patients with DES placement these recommendations could not be confirmed.[4] Therefore, the aim of the present study was to assess the relation among the interval to NCS after PCI, medical therapy and the occurrence of perioperative major adverse cardiovascular events (MACEs).

METHODS

The present study included 1,000 patients who had undergone cardiac surgery or NCS after successful PCI because of severe ischemia from January 2000 to December 2007. The final study population included 550 patients who had undergone NCS. The patients were identified by cross matching the Erasmus Medical Centre PCI database with the NCS database (including 78,000 procedures). The PCI database is a prospectively maintained registry of 13,000 procedures performed from January 2000 to December 2007.[5]

All patients underwent PCI using either a BMS (2000 to March 2002) or DES (April 2002 to 2007; sirolimus or paclitaxel). The patient characteristics were prospectively collected directly after the PCI procedure and included the PCI-indication, number of affected and stented coronary arteries, left ventricular ejection fraction, and medication use during and after PCI. Patients with a BMS were prescribed lifelong aspirin and clopidogrel (loading dose 300 mg, followed by 75mg daily) for ≥30 days. Patients with a DES usually were prescribed lifelong aspirin and clopidogrel for ≥3 months (sirolimus) to 6 months (paclitaxel), or longer, at the discretion of the treating physician. The treating physician determined the type of used stent at the PCI procedure.

All data on the surgical procedure were retrospectively collected by screening the medical charts. The type of surgery was classified and categorized according to the surgical risk, determined using the ACC/AHA classification.[6] In addition, cardiac history and cardiac risk factors were assessed at stenting and surgery. Medication use was assessed during the initial PCI procedures and was updated at the point of surgery. The use of proton pump inhibitors concomitantly with clopidogrel was also noted. No standard protocol for

perioperative antiplatelet therapy was used in the present study population, becuse this was an observational study and the surgical procedures included all types of NCS. Consequently, some patients received aspirin and/or clopidogrel throughout the surgical procedure, but for other patients, aspirin and/or clopidogrel were discontinued five to ten days before surgery. All medical records were reviewed to categorize the maintenance of antiplatelet therapy (i.e. no therapy, aspirin, clopidogrel or dual antiplatelet therapy) in the period before NCS as discontinued >30 days, discontinued 7 to 30 days, or continued to within <7 days before NCS.

The perioperative complications were defined as the occurrence of MACEs (i.e. death, myocardial infarction [either ST-elevation or non-ST-elevation myocardial infarction], stent thrombosis, repeated revascularization) within 30 days after NCS. Perioperative myocardial infarction was defined according to the European Society of Cardiology/ACC criteria.[7] Bleeding complications were categorized as life-threatening or moderate bleedings, during the first 30 postoperative days. Life-threatening bleeding was defined as fatal bleeding, intracranial bleeding, or bleeding requiring surgical intervention or transfusion of ≥4 U of blood or blood products. Moderate bleeding was defined as bleeding requiring transfusion of 1 to 3 U of blood or blood products.[8]

Statistical analyses were performed using the Statistical Package for Social Sciences, version 15.0 (SPSS, Chicago, Illinois). Continuous data were compared using Student's t test and are expressed as mean ± SD. Categorical data are presented as percentages, and differences between proportions were compared using the χ^2 test. To assess whether the risk of the occurrence of MACEs after NCS was associated with the interval from PCI to NCS, the interval from PCI to NCS was assessed as a categorical variable. Determined by the current guidelines and recommendations, the intervals used for patients with a BMS were <30days, <3 months, and >3 months and for a DES were <30 days, 30 days to 3 months, 3 to 6 months, 6 to 12 months, and >12 months.[3, 4, 9] Logistic regression analyses were used to calculate the association between the intervals from PCI to NCS and MACEs. Logistic regression analyses were also used to determine possible associations between the presence of cardiac risk factors and the development of MACEs. Adjustments were made for age, gender, and all baseline cardiac risk factors (history of myocardial infarction, PCI/coronary artery bypass grafting, congestive heart failure, renal dysfunction, smoking, hypertension, diabetes mellitus, hypercholesterolemia, positive family history of cardiovascular (CV) disease), vessel/stent-diameter, lesion length and use of proton pump inhibitors during clopidogrel treatment. In all analyses, two-tailed tests were performed, and statistical significance was inferred at $p \leq 0.05$.

RESULTS

A total of 1,000 PCI procedures with stent placement followed by a surgical procedure were identified. NCS was performed in 550 patients either after PCI-BMS (N=174) or PCI-DES (N=376). No difference was found in the cardiac history or type of indication for PCI between the patients undergoing PCI-BMS and PCI-DES (*Table 1*). Most patients underwent intermediate to high-risk surgery; a trend was found for more emergency surgical procedures in patients with a DES ($p = 0.054$; *Table 2*).

Table 1 **Baseline characteristics**

	Total	BMS	DES	*p*-value
	[N=550]	[N=174]	[N=376]	
Demographics				
Age (yrs), mean ± SD	62.6	61.2	63.3	0.04
Male	74.9%	75.3%	74.7%	0.89
Medical histroy (%)				
Myocardial infarction	179 (33)	56 (32)	123 (33)	0.77
CABG	66 (12)	23 (13)	43 (12)	0.61
PCI	161 (30)	52 (30)	109 (30)	0.95
Risk factors (%)				
Smoking				
current	253 (46)	65 (37)	188 (50)	<0.001
history	86 (16)	10 (6)	76 (20)	<0.001
Hypertension	118 (22)	39 (22)	79 (21)	0.71
Diabetes mellitus	119 (22)	26 (15)	93 (25)	0.01
Dyslipidemia	296 (54)	81 (47)	215 (57)	0.02
Renal failure	47 (9)	7 (4)	40 (11)	0.01
LVEF <50%	236 (44)	170 (46)	66 (38)	0.07
PCI indications (%)				0.31
Stable angina pectoris	245 (45)	175 (47)	70 (40)	
Instable angia pectoris	174 (32)	112 (30)	62 (36)	
Acute myocardial infarction	131 (24)	89 (24)	42 (24)	
Discharge medication (%)				
Aspirin	503 (92)	160 (92)	343 (91)	0.78
Statin	318 (58)	90 (52)	228 (61)	0.05
ß-blocking agents	502 (91)	158 (91)	344 (92)	0.79
ACE-inhibitors	149 (27)	40 (23)	109 (29)	0.14
Diuretics	48 (9)	10 (6)	38 (10)	0.09
Calcium antagonists	182 (33)	84 (48)	98 (26)	<0.001
Nitrates	56 (10)	13 (8)	43 (11)	0.15
Ticloxpidines	477 (87)	151 (87)	326 (87)	0.98
Clopidogrel use (monthly)				<0.001
median	3	2	6	
interquartile range	1-6	1-3	1-6	

Angiotensin converting enzyme (ACE), bare metal stent (BMS), coronary artery bypass grafting (CABG), drug eluting stent (DES), percutaneous coronary intervention (PCI), left ventricular ejection fraction (LVEF).

Table 2	Surgical Group*	
	BMS	DES
	[N=174]	[N=376]
High-risk (%)		
Vascular system	23 (13)	41 (11)
Emergency	4 (2)	40 (11)
Intermediate-risk (%)		
Nose, mouth, pharynx	13 (8)	15 (4)
Eye	29 (17)	42 (11)
Digestive system	16 (9)	48 (13)
Musculoskeletal system	20 (12)	39 (10)
Respiratory system	4 (2)	11 (3)
Nervous system	6 (3)	23 (6)
Endocrine system	-	2 (1)
Oncology	1 (1)	1 (1)
Low-risk (%)		
Urinary system	28 (16)	49 (13)
Cosmetic surgery	9 (5)	18 (5)
Dermatologic	9 (5)	17 (5)
Miscellaneous	12 (7)	30 (8)

** Categorized according to ACC/AHA classification. Bare metal stent (BMS), drug-eluting stent (DES).*

The median interval between PCI–BMS and NCS was 3.6 years (interquartile range 1.8 to 5.4). Of the patients who underwent NCS after PCI-BMS, 8 (5%) patients had NCS within 30 days, 7 (4%) between 30 days and 3 months, and 159 (91%) after 3 months. During the first 30 days after NCS, 11 patients (6%) with PCI-BMS experienced a MACE (10 cardiovascular death and 1 myocardial infarction). An inverse relation was found between the rate of postoperative MACEs and the interval to NCS after PCI-BMS. The rate of MACEs for intervals of <30, 30 days to 3 months, and >3 months was 50, 14, and 4%, respectively (overall $p < 0.001$; *Figure 1* and *Table 3*). When NCS was postponed for ≥3 months after PCI with a BMS, the lowest risk of perioperative MACE was observed (*Figure 1*).

Dual antiplatelet therapy was used in 100 and 75% of the patients who underwent NCS within 30 days or 30 days to 3 months after PCI-BMS, respectively. Overall, at NCS, 157 (91%) and 16 (9%) patients were receiving single and dual antiplatelet therapy, respectively. Of the patients who experienced a MACE, 5 (46%) and 6 (55%) had been receiving single or dual antiplatelet therapy at NCS ($p = 0.92$). All patients who underwent NCS within 30 days after PCI-BMS and experienced a MACE were receiving dual antiplatelet therapy until NCS. Patients with concomitant use of proton pump inhibitors and clopidogrel at NCS seemed to have greater rates of MACE than patients without proton pump inhibitor use (46 vs 20%); however, this was not statistically significance ($p = 0.33$). Of the patients undergoing PCI-BMS, 81% had a large stent/vessel diameter (>3.0 mm) or a short lesion length (<25 mm). No association was found between the stent/vessel diameter or lesion length and the risk of MACEs in these patients.

The median time between PCI–DES and NCS was 1.4 years (interquartile range 0.5 to 2.6). NCS after PCI-DES was performed within 30 days, at 30 days to 3 months, 3 to 6 months, 6 to 12 months, and >12 months in 45 (12%), 25 (6%), 27 (7%), 47 (13%) and 232 (62%) patients, respectively. A total of 48 patients (13%) experienced a MACE within the first 30 postoperative days (36 [82%] cardiovascular death, 4 [9%] noncardiovascular death, 2 [5%] myocardial infarction, 6 [14%] stent thrombosis). The MACE rate changed significantly with the interval after PCI-DES (35, 13, 15, 6, and 9% for patients undergoing NCS <30 days, 30 days to 3 months, 3 to 6 months, 6 to 12 months, and >12 months after PCI-DES respectively; overall $p < 0.001$; *Figure 1* and *Table 3*). In line with the ACC/AHA guidelines, NCS within one year after PCI-DES was associated with an increased rate of MACEs (18 vs 10%, $p = 0.015$). On multivariate analysis, patients undergoing NCS within one year after PCI-DES, had an increased risk of perioperative MACEs (hazard ratio 2.0, 95% confidence interval: 1.1 to 3.5) compared with patients undergoing NCS >1 year after PCI-DES.

Table 3 **30-day MACEs stratified by interval between PCI and NCS**

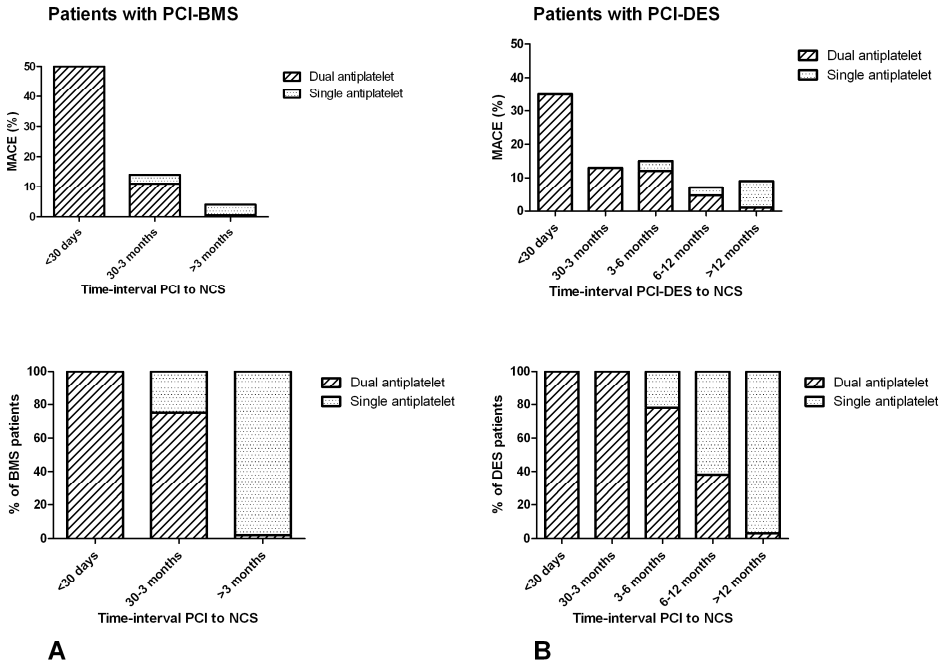
PCI to NCS interval		N (%)	*p*-value
BMS [N=174]			
0 - 30 days	[N=8]	4 (50)	<0.001
31 - 90 days	[N=7]	1 (14)	
>91 days	[N=159]	6 (4)	
<30 days	[N=8]	4 (50)	<0.001
≥30 days	[N=166]	7 (4)	
<3 months	[N=15]	5 (33)	<0.001
≥3 months	[N=159]	6 (4)	
DES [N=376]			
<30 days	[N=46]	16 (35)	<0.001
30d – 3 months	[N=24]	3 (13)	
3 – 6 months	[N=27]	4 (15)	
6 – 12 months	[N=47]	3 (6)	
>12 months	[N=232]	22 (9)	
<1years	[N=144]	26 (18)	0.015
≥1 years	[N=232]	22 (9)	

Bare metal stent (BMS), drug eluting stent (DES), major adverse cardiovascular events (MACEs), noncardiac surgery (NCS), percutaneous coronary intervention (PCI).

Dual antiplatelet therapy was used in 100 and 80% of the patients during the first 3 and 6 months after PCI-DES, respectively. Overall, dual antiplatelet therapy was continued until NCS in 112 (30%) patients, and 264 (70%) patients received single antiplatelet therapy. Of the patients who experienced a perioperative MACE, 56 and 44% had received dual or single antiplatelet therapy, respectively ($p = 0.72$). Because all patients were receiving dual antiplatelet therapy during the first 3 to 6 months after PCI-DES, the risk of perioperative MACE was only related to the interval to NCS after PCI. No relation was found between the

concomitant use of clopidogrel and proton pump inhibitors and the risk of perioperative MACEs (28 vs 21% $p = 0.38$), compared with patients without proton pump inhibitor use. Patients in the PCI-DES group more often had a small stent-vessel diameter, but an increased lesion length, compared with those in the PCI-BMS group (84 vs 16% and 78 vs 22%, $p < 0.001$), respectively. No association was found between the stent/vessel diameter or lesion length and the risk of perioperative MACEs (12 vs 15%, $p = 0.4$, and 11 vs 15%, $p = 0.2$), respectively.

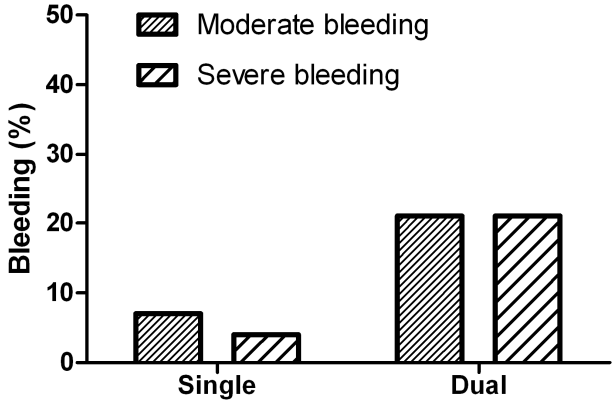
Figure 1: Perioperative major adverse cardiac events and antiplatelet regimen in (A) PCI-BMS and (B) PCI-DES. Risk of perioperative major adverse cardiac events during prespecified intervals between PCI and NCS. Antiplatelet regimens (single or dual antiplatelet therapy) subdivided according to occurrence of perioperative major adverse cardiac events



Bare metal stent (BMS), drug eluting stent (DES), noncardiac surgery (NCS), percutaneous coronary intervention (PCI).

Moderate and severe bleeding after surgery occurred in 56 (10%) and 42 (8%) patients, respectively. A strong association was found between the use of single or dual antiplatelet therapy at NCS and the risk of moderate, severe or any bleeding ($p < 0.001$; *Figure 2*). The risk of severe bleeding in patients receiving single or dual therapy at NCS was 4 and 21%, respectively ($p < 0.001$). Additionally, the risk of bleeding was associated with interval from PCI to NCS.

Figure 2: Bleeding risk according to antiplatelet regimen (single or dual antiplatelet therapy).



DISCUSSION

The results of the present study revealed an inverse relation between the interval from PCI to NCS and the occurrence of MACEs within 30 days after NCS in patients with PCI-BMS or PCI-DES. Irrespective of dual antiplatelet therapy continuation until NCS, early surgery after stenting was associated with an increased risk of MACEs. In addition, dual antiplatelet therapy at NCS increased the bleeding risk. Therefore, elective NCS should preferably be postponed for 90 days after PCI-BMS; however, if more urgent surgery is needed, a minimum interval of 30 days should be recommended. After PCI-DES, NCS should be delayed for ≥1 year.

In response to several small studies that reported cases of late stent thrombosis,[10, 11] the first European Society of Cardiology guidelines recommended dual antiplatelet therapy for a minimum of three to four weeks after PCI-BMS. The most recent scientific advisory of the ACC/AHA on the discontinuation of dual antiplatelet therapy for patients with coronary stents proposed an interval of 6 weeks after PCI-BMS.[2, 3] In the present study, the strongest decrease in the risk of perioperative MACEs in patients undergoing NCS after PCI-BMS was reached when NCS was postponed for a minimum of 30 days from PCI. In contrast, only a small additional effect was realized if NCS was postponed until six weeks after PCI compared with 30 days. Previous studies of patients undergoing NCS after PCI-BMS reported high rates of MACEs when NCS was performed within two weeks after PCI,[12, 13] and others have recommended a delay of ≥6 weeks.[14, 15] Recent studies have shown the greatest risk of ischaemic events when NCS was performed within 30 days of PCI, and the lowest after 90 days.[9] In line with these studies, our study found the same high risk of perioperative MACE with NCS within 30 days of PCI-BMS. However, the number of events in the present study

was greater (10.7 vs 5.4%), possibly because of the intensive and close follow-up of our patient population. As mentioned by Nutall *et al.*[9] they used no protocol for the detection of perioperative MACE.

The occurrence of stent thrombosis is a multifactorial process that includes device-related factors (e.g. surface coating, stent diameter, stent length) and patient- or lesion-specific factors (e.g. interval from PCI to NCS, stent/vessel diameter, antiplatelet therapy, proton pump inhibitor use and left ventricular ejection fraction).[16] In the present study, only the interval from PCI to NCS was independently associated with an increased risk of perioperative MACEs after NCS. The continuation of dual antiplatelet therapy until NCS in PCI-BMS patients was not associated with lower rates of MACEs in the perioperative phase but was, however, associated with an increased risk of bleeding complications. Nuttall *et al.*[9] found no association between the different intervals after PCI-BMS and the frequency of bleeding events. After an interval of ≥30 days, they found a bleeding event rate of 4.6%, in line with our rate of (4%).

A significant association between the interval from PCI-DES to NCS and the risk of perioperative MACEs was detected, confirming the ACC/AHA advisory to postpone elective NCS for ≥1 year after PCI.[3] Although stabilization for the occurrence of MACEs was detected at a 6-month interval between PCI and NCS, other studies have shown catastrophic effects of early discontinuation.[17] The value of at least a 1-year continuation of dual antiplatelet therapy after DES placement was also shown.[18] In addition, more recent studies have shown that even if clopidogrel is stopped after the previous recommended three to six months, those who continue dual antiplatelet therapy have better survival and less late in-stent thrombosis than those with single or no antiplatelet therapy.[18, 19] Rabbits *et al.*[4] performed the largest trial in patients with PCI-DES before NCS, and observed a nonsignificant trend-wise decrease in the rate of MACEs with an increasing interval after PCI.[4] From these cited studies, prolonged dual antiplatelet therapy for ≥1 year is supported for patients with PCI-DES. Although our study demonstrated stabilization for the risk of MACEs after an interval of six months after PCI, an overall reduction in the incidence of MACEs was seen when NCS was performed ≥1 year after PCI-DES.

The continuation of dual antiplatelet therapy until surgery was not associated with a reduced risk of perioperative MACEs, compared with the discontinuation of dual antiplatelet therapy. In patients who underwent NCS within three months after PCI-DES, continuation of dual antiplatelet therapy was not sufficiently protective to prevent perioperative MACEs. Although this finding surprised us, Rabbitts *et al.*[4] detected the same association. They even found that use of thienopyridine <7 days from NCS was associated with an increased rate of MACEs, compared with the use of single antiplatelet therapy. In contrast, other studies showed the adverse effects of stopping dual antiplatelet too early.[12, 19, 20] In our study, all patients who developed a MACE during dual antiplatelet therapy had undergone surgery within three months after PCI. A possible explanation for the occurrence of MACEs in this specific subset

of patients is minimal early re-endothelization of the coronary arteries at the stent-location. The combination of aspirin and thienopyridines during the hypercoagulable state during NCS seemed insufficient to reduce the risk of in-stent thrombosis during this vulnerable period.

Although the overall bleeding risk was in line with that reported by previous studies[4], an increased rate of severe bleeding episodes occurred in the PCI-DES patients that was related to (i) the use of dual antiplatelet therapy at NCS, (ii) high-risk NCS, and (iii) NCS within 30 days after PCI. Harder *et al.*[21] concluded that monotherapy with aspirin or clopidogrel usually does not need to be discontinued during surgery, which was confirmed in a meta-analysis by Burger *et al.*[21] However, an increased risk of severe bleeding was shown by the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial for patients receiving dual antiplatelet therapy.[22] Although the use of dual antiplatelet therapy has the disadvantage of an increased bleeding risk, the long-term survival effects of thienopyridines seem to outweigh these short-term negative effects.

The potential limitations of the present study merit consideration. First, a referral bias was possible, because we did not include patients who underwent NCS elsewhere. Second, although the present sample size represented a very small part of both databases, a minor susceptibility to chance remained. Third, a selection bias for the occurrence of MACEs during dual antiplatelet therapy was possible, because these patients were more prone to undergo nonelective NCS early after PCI. Although no independent events' committee adjudicated clinical events, this was performed by 2 of us. Finally, we were unable to determine whether PCI was performed specifically for the subsequent surgery; however, almost 80% of PCI procedures were performed in a stable cardiac setting.

In conclusion, after PCI-BMS, NCS should preferably be postponed 90 days; however, if more urgent surgery is needed, a minimum interval of 30 days should be recommended. In patients with PCI-DES, elective NCS should be postponed for ≥1 year after PCI.

REFERENCES

1. Vicenzi MN, Ribitsch D, Luha O, et al. Coronary artery stenting before noncardiac surgery: more threat than safety? *Anesthesiology.* 2001;94(2):367-368.
2. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol.* 2007;50(17):e159-241.
3. Grines CL, Bonow RO, Casey DE, Jr., et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association,

American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *J Am Coll Cardiol.* 2007;49(6):734-739.

4. Rabbitts JA, Nuttall GA, Brown MJ, et al. Cardiac risk of noncardiac surgery after percutaneous coronary intervention with drug-eluting stents. *Anesthesiology.* 2008;109(4):596-604.

5. Lemos PA, Lee CH, Degertekin M, et al. Early outcome after sirolimus-eluting stent implantation in patients with acute coronary syndromes: insights from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *J Am Coll Cardiol.* 2003;41(11):2093-2099.

6. Eagle KA, Berger PB, Calkins H, et al. ACC/AHA Guideline Update for Perioperative Cardiovascular Evaluation for Noncardiac Surgery--Executive Summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Anesth Analg.* 2002;94(5):1052-1064.

7. Alpert JS, Thygesen K, Antman E, et al. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol.* 2000;36(3):959-969.

8. Anand S, Yusuf S, Xie C, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med.* 2007;357(3):217-227.

9. Nuttall GA, Brown MJ, Stombaugh JW, et al. Time and cardiac risk of surgery after bare-metal stent percutaneous coronary intervention. *Anesthesiology.* 2008;109(4):588-595.

10. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet.* 2004;364(9444):1519-1521.

11. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation.* 2004;109(6):701-705.

12. Kaluza GL, Joseph J, Lee JR, et al. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. *J Am Coll Cardiol.* 2000;35(5):1288-1294.

13. Leibowitz D, Cohen M, Planer D, et al. Comparison of cardiovascular risk of noncardiac surgery following coronary angioplasty with versus without stenting. *Am J Cardiol.* 2006;97(8):1188-1191.

14. Reddy PR, Vaitkus PT. Risks of noncardiac surgery after coronary stenting. *Am J Cardiol.* 2005;95(6):755-757.

15. Wilson SH, Fasseas P, Orford JL, et al. Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. *J Am Coll Cardiol.* 2003;42(2):234-240.

16. Honda Y, Fitzgerald PJ. Stent thrombosis: an issue revisited in a changing world. *Circulation.* 2003;108(1):2-5.

17. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *Jama.* 2005;293(17):2126-2130.

18. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *Jama.* 2007;297(2):159-168.

19. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol.* 2006;48(12):2584-2591.

20. Schouten O, van Domburg RT, Bax JJ, et al. Noncardiac surgery after coronary stenting: early surgery and interruption of antiplatelet therapy are associated with an increase in major adverse cardiac events. *J Am Coll Cardiol.* 2007;49(1):122-124.

21. Burger W, Chemnitius JM, Kneissl GD, et al. Low-dose aspirin for secondary cardiovascular prevention - cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation - review and meta-analysis. *J Intern Med.* 2005;257(5):399-414.

22. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med.* 2001;345(7):494-502.

Chapter 21

Timing of preoperative β-blocker treatment in vascular surgery patients: influence on postoperative outcome

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ABSTRACT

Objectives The present study evaluated timing of β-blocker initiation before surgery and its relationship with (i) preoperative heart rate and high-sensitive C-reactive-protein (hs-CRP) levels and (ii) postoperative outcome.

Background Perioperative guidelines recommend β-blocker initiation days to weeks before surgery, based on expert opinions.

Methods In 940 vascular surgery patients, preoperative heart rate and hs-CRP levels were recorded, as well as timing of β-blocker initiation before surgery (0-1,>1-4,>4 weeks). Pre- and postoperative troponin T measurements and ECGs were performed routinely. Endpoints were 30-day cardiac events (composite of myocardial infarction and cardiac mortality) and long-term mortality. Multivariate regression analyses, adjusted for cardiac risk factors, evaluated the relation between duration of β-blocker treatment and outcome.

Results Treatment was initiated 0-1, >1 to 4, and >4 weeks before surgery in 158 (17%), 393 (42%), and 389 (41%) patients, respectively. Median heart rate was 74 (±17), 70 (±16), and 66 (±15) beats per minute ($p < 0.001$; comparing heart rate of treatment initiation >1 with <1 week preoperatively) and hs-CRP was 4.9 (±7.5), 4.1 (±.6.0), and 4.5 (±6.3) mg/L ($p = 0.782$), respectively. Multivariate regression analyses demonstrated that treatment initiated >1 to 4 or >4 weeks before surgery was associated with a lower incidence of 30-day cardiac events (OR 0.46, 95%-CI: 0.27 to 0.76, OR 0.48, 95%-CI: 0.29 to 0.79) and long-term mortality (HR 0.52, 95%-CI: 0.21 to 0.67, HR 0.50, 95%-CI: 0.25 to 0.71) compared with treatment initiated <1 week preoperatively.

Conclusions Our results indicate that β-blocker treatment initiated >1 week before surgery is associated with lower preoperative heart rate and improved outcome, compared with treatment initiated <1 week preoperatively. In addition, no reduction of median hs-CRP levels was observed, also not in patients receiving β-blocker treatment >1 week before surgery.

INTRODUCTION

β-blockers are established therapeutic agents for patients with hypertension,[1] heart failure,[2] and coronary artery disease.[3] In the nonsurgical setting, β-blockers are widely used for the prevention and treatment of coronary heart disease and heart failure, both important determinants of perioperative cardiovascular complications. Over the years, multiple observational studies and randomized, controlled trials have been performed to evaluate the effect of perioperative β-blocker treatment in patients undergoing noncardiac surgery.[4-15] The majority of these studies have demonstrated cardioprotection derived from perioperative β-blocker treatment.

Proposed mechanisms by which β-blockers exert intraoperative cardioprotective effects include (i) heart rate control, (ii) reduction of systolic pressure and ventricular contractile force, and (iii) its anti-arrhythmic properties. Long-term; β-blockers reduce mechanical stress imposed to coronary plaques preventing plaque rupture.[16] Patients receiving β-blockers tend to have lower plasma concentrations of C-Reactive Protein (CRP) than those not receiving β-blockers, and the anti-inflammatory properties of β-blockers are thought to stabilize coronary plaques.[17-19] In addition, β-blockers are known to lessen adverse cardiac remodelling in patients with impaired left ventricular function, which is highly prevalent in the vascular surgery population, by inhibiting the sympathetic nervous system and hormone activation (A-type and B-type natriuretic peptides and norepinephrine).[20-22] Potential side effects associated with β-blocker treatment are bradycardia, hypotension and stroke.

Factors that may relate to the effectiveness of β-blocker therapy and the occurrence of side effects are variations in treatment protocols, such as (i) β-blocker type, (ii) β-blocker dose, and (iii) timing of β-blocker initiation before surgery. However, the duration of β-blocker treatment before surgery and its effect on cardiovascular outcome has not been evaluated yet in a cohort of vascular surgery patients. The present study was conducted to evaluate timing of β-blocker initiation and its influence on preoperative heart rate, preoperative high-sensitive CRP (hs-CRP) levels, and postoperative outcome of vascular surgery patients.

MATERIAL AND METHODS

Study population

The original study population consisted of 940 vascular surgery patients undergoing (open or endovascular) lower extremity artery, carotid artery, or abdominal aortic repair, receiving preoperative β-blocker treatment. Open abdominal aortic aneurysm repair and lower extremity revascularization were considered procedures with high cardiac risk. Carotid surgery and endovascular surgery were considered procedures with intermediate-cardiac risk. [23] Patients (i) undergoing emergency surgery (ii) randomized for β-blocker treatment in previous

randomized, controlled trials, and (iii) with preoperative heart rate <50 beats per minute were not included in the present study. The study was performed at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period between 2002 and 2008. The study was approved by the hospital's ethics committee and performed with informed consent of all patients.

Baseline characteristics

Before surgery, a detailed history was obtained from every patient. Clinical data included: age, gender, ischemic heart disease (defined as a history myocardial infarction, coronary revascularization or the presence of pathologic Q-waves on preoperative electrocardiogram), heart failure (defined as the presence of heart failure symptoms according the New York Heart Association classification or previous hospital admission for decompensated heart failure) and cerebrovascular disease (defined as a history of ischemic or hemorrhagic stroke). In addition, kidney dysfunction (serum creatinine >2.0 mg/dL), diabetes mellitus (fasting blood glucose ≥6.1 mmol/L or requirement of anti-diabetic medication), hypertension (blood pressure ≥140/90 mmHg in non diabetic patients and ≥130/80 mmHg in diabetics, or requirement of antihypertensive medication), hypercholesterolemia (low density lipoprotein cholesterol >3.5 mmol/L or requirement of lipid-lowering medication), chronic obstructive pulmonary disease (according to the Global Initiative on Obstructive Lung Diseases classification), and smoking status were recorded as well. Peripheral blood samples for hs-CRP in mg/L, measured by a nephelometric assay on a Beckman-Immage analyzer (Beckman-Coulter, Fullerton, California, USA) were routinely performed one day before surgery.

Medication use

The use of the prescription medications was recorded at baseline and included β-blockers, statins, aspirin, oral anticoagulants, inhibitors of the renin-angiotensin-aldosterone system (RAAS inhibitors: ACE inhibitors, angiotensin-II receptor blockers, renin inhibitors, aldosterone antagonists), and diuretics. During the first preoperative visit at the outpatient clinic preoperative β-blocker use was established in patients already receiving β-blockers and in patients not already receiving β-blockers, preoperative β-blocker treatment was initiated. Preoperative β-blocker use was subdivided according to initiation time of treatment 0 to 1, >1 to 4, or >4 weeks before surgery. All patients returned to the outpatients clinic after 1 week and β-blocker dosage, if needed, was adjusted and titrated according to tolerance to obtain a preoperative heart rate between 60 to 70 beats per minute.[24] This protocol could not be followed in patients in whom β-blocker treatment was initiated <1 week before surgery.

Study outcomes

Main study endpoints were 30-cardiovascular events and long-term mortality. 30-day cardiovascular events was the composite of myocardial damage (defined as myocardial ischemia or infarction), stroke and mortality up to 30 days after surgery. Serial electrocardiograms and troponin T measurements were obtained from all patients before

surgery, postoperatively on day 1, 3, 7, and before discharge. Perioperative myocardial ischemia was defined as patients with normal preoperative and elevated (>0.03 ng/mL) troponin T levels postoperatively. Elevated troponin T levels in combination with electrocardiographic changes (new onset ST-T changes and pathological Q waves) or symptoms of angina pectoris defined myocardial infarction.[25] Patients with elevated troponin T levels before surgery were not included in the study. Long-term mortality was assessed by approaching the municipal civil registries. Mean follow-up was 2.2 ± 1.8 years. Secondary endpoints were preoperative heart rate (beats per minute) and hs-CRP levels (mg/L). Peripheral blood samples for hs-CRP were routinely performed one day before surgery. Optimal specificity and sensitivity of hs-CRP to predict postoperative outcome was calculated using receiver operating curve analyses and a cut off value >6.5 mg/L was used in the analyses.

Statistical analysis

Dichotomous data are described as numbers and percentages and categorical data are compared using the χ^2 test. The continuous variable age is described as mean ± standard deviation (SD) and compared using ANOVA. The continuous variables heart rate and hs-CRP are described as medians ± interquartile range (IQR) and compared using the Mann–Whitney U test. The relation between β-blocker use and postoperative outcome was evaluated with regression analyses with propensity score adjustment for β-blocker use. The relation between β-blocker use and perioperative myocardial damage was evaluated with logistic regression analyses. In addition, the relation between β-blocker use and long-term follow-up was evaluated with Cox regression analysis. Multivariate analyses were adjusted for demographics (age and gender), cardiovascular risk factors (ischemic heart disease, cerebrovascular disease, heart failure, renal dysfunction, diabetes mellitus, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, and smoking status), type of surgery and medication use (statins, aspirin and RAAS inhibitors). We report crude and adjusted odds and hazard ratios (OR and HR) with their 95% confidence interval (95%-CI). For all tests, a *p*-value <0.05 (two-sided) was considered significant. All analyses were performed using SPSS version 15.0 statistical software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics

The baseline study population consisted of 940 patients undergoing carotid artery stenosis (N=215), abdominal aortic aneurysm (N=405), and lower extremity artery (N=153) repair and receiving preoperative β-blocker treatment. A total of 661 (70%) patients received bisoprolol, 186 (20%) received metoprolol succinate, 49 (5%) received atenolol, and 44 (5%) patients received other β-blockers. Clinical parameters, stratified by timing between β-blocker initiation and vascular surgery, are demonstrated in *Table 1*. The majority of patients were males (77%) and the mean age was 67 ±10 years. Patients receiving β-blocker treatment >1 week before

surgery more often had a history of ischemic heart disease, kidney dysfunction, hypertension, and more often received RAAS inhibitors and diuretics, compared with patients who received β-blocker treatment <1 week before surgery.

Table 1 Baseline characteristics

	Timing of β-blocker initiation before surgery			
	0-1 week	>1-4 weeks	>4 weeks	*p*-value*
	[N=158]	[N=393]	[N=389]	
Demographics				
Age (± SD)	68 (11)	67 (10)	67 (10)	0.920
Median heart rate at day of surgery (± IQR)	74 (17)	70 (16)	66 (15)	<0.001
Male (%)	117 (74)	310 (79)	279 (76)	0.437
Medical history (%)				
Ischemic heart disease	56 (35)	142 (36)	208 (54)	<0.01
Heart failure	12 (8)	35 (9)	50 (13)	0.090
Cerebrovascular disease	69 (44)	118 (30)	137 (35)	0.009
Renal dysfunction	28 (18)	55 (14)	87 (22)	0.010
Diabetes mellitus	48 (30)	100 (26)	126 (33)	0.100
Hypertension	101 (64)	236 (60)	290 (75)	<0.01
Hypercholesterolemia	79 (50)	165 (42)	198 (51)	0.032
Smoker, current	75 (58)	167 (43)	157 (40)	0.313
Chronic obstructive pulmonary disease	42 (27)	136 (35)	134 (34)	0.154
Surgery type (%)				
Open	91 (58)	260 (66)	247 (63)	0.170
lower extremity revascularization	29 (18)	92 (23)	110 (28)	0.153
abdominal aorta repair	29 (18)	110 (28)	95 (24)	0.163
carotid artery repair	33 (22)	58 (15)	42 (11)	0.973
Endovascular	67 (42)	133 (34)	142 (37)	0.170
lower extremity revascularization	16 (10)	30 (8)	43 (11)	0.244
abdominal aorta repair	27 (17)	83 (21)	61 (16)	0.091
carotid artery repair	24 (15)	20 (5)	38 (10)	0.107
Echocardiography (%)				
Left ventricular ejection fraction <40%	26 (17)	71 (18)	84 (22)	0.312
Laboratory (IQR)				
Median hs-CRP (mg/L) 1 day before surgery	4.9 (7.5)	4.1 (6.0)	4.5 (6.3)	0.782
Medication (%)				
Statins	118 (75)	289 (74)	296 (76)	0.271
Aspirin	95 (60)	228 (58)	239 (61)	0.187
Oral anticoagulants	25 (16)	57 (15)	71 (18)	0.360
RAAS inhibitors	57 (36)	138 (35)	197 (51)	<0.01
Diuretics	40 (25)	85 (22)	116 (30)	0.030

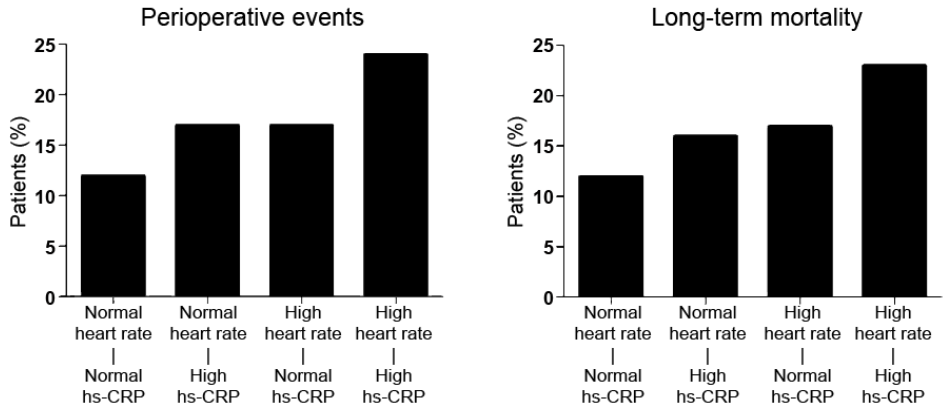
** p-value: comparison of groups >1-4 weeks and >4 weeks with group 0-1 week. High-sensitive C-reactive-protein (hs-CRP), renin-angiotensin-aldosterone system (RAAS).*

Preoperative heart rate, preoperative hs-CRP and postoperative outcome

As demonstrated in *Table 1*, patients receiving β-blocker treatment >1 week before surgery had lower median rest heart rate at day of surgery, compared with patients receiving β-blocker treatment <1 week preoperatively ($p < 0.001$). No significant difference was observed in median preoperative hs-CRP levels between these groups ($p = 0.782$). A sub-analysis demonstrated that median hs-CRP concentrations were significantly lower in patients receiving statin treatment >1 week before surgery (median hs-CRP = 4.0 mg/L), compared with patients receiving no statin treatment before surgery (median hs-CRP = 5.7 mg/L, *p*-value of 0.043).

The influence of median preoperative heart rate and hs-CRP towards postoperative outcome is demonstrated in *Figure 1*. An increased heart rate >70 bpm (42/243 or 17%) or an hs-CRP concentration >6.5 mg/L (24/139 or 17%) were both associated with an increased incidence of perioperative events (*Figure 1*), compared with patients with normal heart rate (60 to 70 bpm) in combination with a hs-CRP concentration ≤6.5 mg/L (53/438 or 12%). In addition, an increased heart rate >70 bpm (38/243 or 16%) or hs-CRP concentration >6.5 mg/L (23/139 or 17%) were both associated with an increased incidence of long-term mortality (*Figure 1*), compared with patients with normal heart rate (60 to 70 bpm) in combination with a hs-CRP concentration ≤6.5 mg/L (27/120 or 23%). Patients with high heart rate (>70 bpm) in combination with an hs-CRP >6.5 mg/L had the highest incidence of perioperative events (29/120 or 24%) and long-term mortality (27/120 or 23%).

Figure 1: Influence of preoperative heart rate and hs-CRP towards postoperative outcome.



High-sensitive C-Reactive Protein (hs-CRP).

Initiation of β-blocker treatment and postoperative outcome

During the first 30 days after surgery 150 (16%) patients had troponin T release, of which 114 (76%) patients had myocardial ischemia and 36 (24%) patients had myocardial infarction. The study endpoint 30-day cardiovascular events (composite of troponin T release, stroke, and 30-day mortality) was reached by 162 patients, as demonstrated in *Table 2*. In total, 27% (52/158) of patients receiving β-blocker treatment <1 week before surgery had a perioperative 30-day cardiovascular event, compared with 15% (120/782) of patients who received preoperative β-blocker treatment >1 week before surgery (*Table 3*). Multivariate analyses demonstrated that β-blocker treatment initiated >4 and >1 to 4 weeks before surgery were both associated with a reduced incidence of 30-day cardiovascular events with ORs of 0.46 (95%-CI: 0.27 to 0.48) and 0.48 (95%-CI: 0.29 to 0.79), compared with patients in whom β-blocker treatment was initiated <1 week preoperatively (*Table 3*). Sub analyses performed in patients undergoing vascular surgery associated with high- and intermediate-cardiac risk are demonstrated in *Table 3*.

Table 2 **The influence of timing of β-blocker initiation before vascular surgery and postoperative outcome**

	Timing of β-blocker initiation before surgery			
	0-1 week	>1-4 weeks	>4 weeks	*p*-value*
	[N=158]	[N=393]	[N=389]	
30-day outcome				
Troponin T release	40 (22)	54 (12)	56 (15)	0.032
Mortality	6 (4)	8 (2)	11 (3)	0.495
Stroke	3 (1.9)	2 (0.5)	2 (0.5)	0.021
Cardiovascular events	42 (27)	58 (15)	62 (16)	<0.001
Long-term outcome				
Diuretics	30 (19)	55 (14)	57 (15)	0.039

During long-term follow-up 142 (15%) patients died. Cumulative postoperative survival stratified to β-blocker treatment initiation time is demonstrated in *Figure 2* (log rank $p < 0.01$). Of the patients who died, 33% (47/142) had perioperative myocardial damage. In total, 19% (30/158) of patients receiving β-blocker treatment <1 week before surgery died, compared with 15% (112/782) of patients who received preoperative β-blocker treatment >1 week before surgery (*Table 4*). Of the patients who died, 72 patients (51%) had myocardial damage during 30-day follow-up. Multivariate analyses demonstrated that β-blocker treatment initiated >4 and >1 to 4 weeks before surgery was associated with a reduced incidence of long-term mortality with HRs of 0.52 (95%-CI: 0.21 to 0.67) and 0.50 (95%-CI: 0.25 to 0.71) compared with patients in β-blocker treatment was initiated <1 week preoperatively (*Table 4*). Sub analyses performed in patients undergoing surgery associated with high- and intermediate-cardiac risk are demonstrated in *Table 4*.

Table 3 **Association of time between β-blocker initiation before vascular surgery and the presence of 30-day cardiovascular events**

			Univariate		Multivariate	
All procedures	**N**	**(%)**	**OR**	**[95%-CI]**	**OR**	**[95%-CI]**
Timing of β-blocker initiation	162/940					
0-1 week preoperatively	42/158	(27)	reference		reference	
>1-4 weeks preoperatively	58/393	(15)	0.48	0.30 - 0.78	0.46	0.27 - 0.76
>4 weeks preoperatively	62/389	(16)	0.54	0.40 - 0.88	0.48	0.29 - 0.79
High-risk procedures	**N**	**(%)**	**HR**	**[95%-CI]**	**HR**	**[95%-CI]**
Timing of β-blocker initiation	125/469					
0-1 week preoperatively	25/58	(43)	reference		reference	
>1-4 weeks preoperatively	44/204	(22)	0.35	0.18 - 0.66	0.38	0.19 - 0.79
>4 weeks preoperatively	56/207	(27)	0.66	0.36 - 0.97	0.58	0.29 - 0.91
Intermediate-risk procedures						
Timing of β-blocker initiation	37/471					
0-1 week preoperatively	17/100	(17)	reference		reference	
>1-4 weeks preoperatively	14/189	(7)	0.49	0.23 - 0.97	0.51	0.13 - 0.79
>4 weeks preoperatively	6/182	(3)	0.10	0.03 - 0.34	0.12	0.02 - 0.25

Table 4 **Association of time between β-blocker initiation before vascular surgery and long-term mortality**

			Univariate		Multivariate	
All procedures	**N**	**(%)**	**OR**	**[95%-CI]**	**OR**	**[95%-CI]**
Timing of β-blocker initiation	142/940					
0-1 week preoperatively	30/158	(19)	reference		reference	
>1-4 weeks preoperatively	55/393	(14)	0.57	0.32 - 0.91	0.52	0.21 - 0.67
>4 weeks preoperatively	57/389	(15)	0.62	0.35 - 0.94	0.50	0.25 - 0.71
High-risk procedures	**N**	**(%)**	**HR**	**[95%-CI]**	**HR**	**[95%-CI]**
Timing of β-blocker initiation	93/469					
0-1 week preoperatively	17/58	(29)	reference		reference	
>1-4 weeks preoperatively	38/204	(19)	0.31	0.17 - 0.57	0.37	0.20 - 0.69
>4 weeks preoperatively	43/207	(20)	0.47	0.27 - 0.83	0.46	0.26 - 0.83
Intermediate-risk procedures						
Timing of β-blocker initiation	49/471					
0-1 week preoperatively	13/100	(13)	reference		reference	
>1-4 weeks preoperatively	17/189	(9)	0.59	0.27 - 0.91	0.46	0.21 - 0.94
>4 weeks preoperatively	13/182	(7)	0.37	0.16 - 0.88	0.37	0.15 - 0.91

DISCUSSION

The present study evaluated the influence of time, between β-blocker treatment initiation before vascular surgery, and postoperative outcome. Our results indicate that β-blocker treatment initiated >1 week before surgery is associated with a reduction of preoperative heart rate compared with treatment initiated <1 week before surgery. Of note, no reduction of hs-CRP levels was observed. Importantly, our results indicate that β-blocker treatment initiated

>1 week before surgery is associated with an improved postoperative outcome, compared with treatment initiated <1 week before surgery. This could be related to adequate heart rate control.

Surgical procedures are associated with tachycardia and increased myocardial contractility leading to an increased oxygen-demand.[26] Maintaining a balance between the myocardial oxygen-demand and supply is key to prevent perioperative cardiac events. Proposed mechanisms by which β-blockers exert intraoperative cardioprotective effects are (i) heart rate control with subsequent prolongation of coronary diastolic filling time and (ii) anti-arrhythmic properties reducing the risk for tachycardia.[17] In addition, β-blockers are known to reduce systolic pressure and ventricular contractile force.[17, 19]

Long-term; β-blockers reduce mechanical stress imposed to coronary plaques preventing plaque rupture.[16] In addition, the anti-inflammatory properties of β-blockers are thought to stabilize coronary plaques.[17, 19] Recently, it is suggested that left ventricular dysfunction is highly present in the vascular surgery population.[27] Long-term β-blocker therapy is known to reduce adverse cardiac remodelling in patients with impaired left ventricular function by inhibiting the sympathetic nervous system and hormone activation (A-type and B-type natriuretic peptides and norepinephrine).[20, 22]

Over the years, multiple randomized, controlled trials evaluated the effectiveness of perioperative β-blocker use and provided conflicting evidence regarding its benefit.[4-15] In 1996, Mangano *et al.* hypothesized that strict perioperative heart rate control with atenolol may limit the development of perioperative ischemia in high-risk surgery patients.[9] In addition, Raby *et al.* demonstrated a beneficial effect of heart rate control, using the short acting β-blocker esmolol immediately after vascular surgery.[11] In the present study, β-blocker treatment >1 week before surgery was associated with lower mean preoperative heart rate and improved postoperative outcome.

In 2002, Jenkins *et al.* evaluated the association between β-blocker treatment and plasma CRP levels in patients with symptomatic coronary artery disease.[18] The authors found that patients who were treated with β-blockers had lower plasma concentrations of CRP than those not receiving β-blockers, however no differences among types or dosages of β-blockers were evident. In our study, all patients received β-blocker treatment and our results indicate that longer duration of β-blocker therapy is not associated with an additional reduction of hs-CRP levels. However, patients receiving statin treatment >1 week before surgery did have lower median hs-CRP levels before surgery than those not receiving statin treatment, in line with previous studies.[28-30] The Novel Approaches for Preventing or Limiting Events (NAPLES)-II trial demonstrated that even a single high loading-dose (80 mg) of atorvastatin reduced the incidence of periprocedural myocardial infarction in patients undergoing elective percutaneous coronary intervention.[29]

In 2008, the perioperative ischemic evaluation (POISE)-trial randomized patients to receive either high dosage metoprolol succinate on the day of surgery or placebo, without titration of the dose according to heart rate.[5] Although a 30% decrease in nonfatal myocardial infarction was found in patients treated with high-dose metoprolol succinate, this beneficial effect was accompanied by a 33% increase in total mortality and a twofold increased risk of stroke, compared with placebo. Metoprolol is metabolized via the CYP 2D6 pathway and might interact with other drugs, administered intraoperatively and metabolized via the CYP 2D6 pathway as well, underlining the importance for adequate β-blocker dosage.[31] Poldermans *et al.* performed the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE)-I trial and evaluated the effect of low-dose bisoprolol on postoperative outcome after vascular surgery.[10] Bisoprolol treatment was started an average of 37 days before surgery with careful titration according to heart rate to prevent adverse side effects. In contrast to the POISE-trial, the incidence of stroke in the DECREASE-I trial was comparable with placebo, while reducing the incidence of cardiac death and nonfatal myocardial infarction from 34% in the standard-care group to 3.4% in the bisoprolol-treated group. Interestingly, in all clinical trials who did not demonstrate a difference in postoperative outcome between β-blocker- and placebo-treated groups, β-blocker treatment was initiated <1 week before surgery.[4, 7, 14-15] This could provide an explanation for the conflicting results regarding the effect of perioperative β-blocker treatment in the literature up to now.

The most recent 'European Society of Cardiology' guidelines, addressing perioperative care, recommend that β-blocker treatment should be initiated between 30 days and at least 1 week before surgery.[24] This recommendation is based on an expert opinion with a level of evidence C. In addition, in the 2009 'American College of Cardiology Foundation/American Heart Association Focused Update on Perioperative β-blockade for noncardiac surgery' it is suggested that when possible and where indicated, β-blockers should be started days to weeks before elective surgery.[32] The results from the present study underline the importance of β-blocker initiation >1 week before vascular surgery. One of the reasons we did not observe better survival of patients in whom β-blocker treatment was initiated >4 weeks, compared with patients in whom β-blocker treatment was initiated >4 weeks before surgery, is an increased prevalence of ischemic heart disease and renal dysfunction present in this group of patients.

Regarding perioperative β-blocker treatment, the following questions could be asked. First, could one give just a slightly higher β-blocker dose in order to achieve adequate heart rate control and routinely start the treatment <1 week before surgery to reach an improved postoperative outcome as well? As we have learned from the POISE-trial, treatment with high β-blocker dosage and without up-titration according to tolerance, is accompanied with an increased incidence of side effects (bradycardia, hypotension, and stroke). In the present study, the incidence of stroke was increased in patients receiving β-blocker treatment <1 week before surgery compared with patients receiving β-blocker treatment >1 week before surgery. In

patients in whom β-blocker therapy is initiated shortly before surgery, there might be an increased risk of side effects, because treatment is initiated too aggressively and the response to β-blocker therapy cannot be adequately monitored during this short period of time leading to a danger of overdosing.[33] In addition, as recently described by Beattie *et al,* β-blocked patients do not seem to tolerate surgical anaemia when compared with patients who are naive to β-blockers.[34] Although, one could assume that high β-blocker dosage may prevent compensatory mechanisms evoked by perioperative anaemia, such as an increase in heart rate, optimal β-blocker titration in anaemic patients remains to be elucidated. A second question to be asked is: what to do with β-blocker naïve patients in urgent need for vascular surgery, i.e. should surgery be postponed to obtain adequate heart rate control first? The results of this study have demonstrated that β-blocker initiation >1 week before surgery is not associated with a reduction of hs-CRP concentrations, which might indicate that anti-inflammatory effects are achieved within days. In addition, β-blocker initiation at day of surgery is known to reduce preoperative heart rate as well, as demonstrated by Mangano *et al.*[9] and Raby *et al.*[11] Therefore, it seems to be justified to state that β-blockers treatment should be ideally initiated >1 week before surgery, to perform heart rate titration before surgery.

Potential limitations of these data merit consideration. First, the study population consisted of patients referred to a tertiary referral center and may not fully represent a general population scheduled for elective vascular surgery. Second, although more than 900 patients were included in the study, the observational and retrospective nature of the study remains a limitation. Third, nonfatal cardiovascular events during long-term follow-up were not addressed, however the study focused on the hard endpoint of long-term mortality. Fourth, data in the current study are not randomized according to initiation time of β-blocker treatment. Although multivariate analyses were adjusted for known confounders, the possibility of unsuspected or uncaptured confounders persists.

The present study provides an indication that β-blocker therapy initiated >1 week before surgery is associated with reduced preoperative heart rate and improved postoperative outcome, compared with patients in whom β-blocker was initiated <1 week before vascular surgery. In addition, no reduction of median hs-CRP levels was observed, also not in patients receiving β-blocker treatment >1 week before surgery. Improved postoperative outcome of patients receiving β-blocker treatment >1 week before vascular surgery could therefore be related to adequate heart rate control.

REFERENCES

1. Mancia G, Laurent S, Agabiti-Rosei E, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens*. 2009.

2. European Society of C, Heart Failure Association of the ESC, European Society of Intensive Care M, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for

the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail.* 2008;10(10):933-989.

3. Fox K, Garcia MA, Ardissino D, et al. Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. *Eur Heart J.* 2006;27(11):1341-1381.

4. Brady AR, Gibbs JS, Greenhalgh RM, et al. Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. *J Vasc Surg.* 2005;41(4):602-609.

5. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet.* 2008;371(9627):1839-1847.

6. Feringa HH, Bax JJ, Boersma E, et al. High-dose beta-blockers and tight heart rate control reduce myocardial ischemia and troponin T release in vascular surgery patients. *Circulation.* 2006;114(1 Suppl):I344-349.

7. Juul AB, Wetterslev J, Gluud C, et al. Effect of perioperative beta blockade in patients with diabetes undergoing major non-cardiac surgery: randomised placebo controlled, blinded multicentre trial. *Bmj.* 2006;332(7556):1482.

8. Lindenauer PK, Pekow P, Wang K, et al. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med.* 2005;353(4):349-361.

9. Mangano DT, Layug EL, Wallace A, et al. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. *N Engl J Med.* 1996;335(23):1713-1720.

10. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med.* 1999;341(24):1789-1794.

11. Raby KE, Brull SJ, Timimi F, et al. The Effect of Heart Rate Control on Myocardial Ischemia Among High-Risk Patients After Vascular Surgery. *Anesth Analg.* 1999;88(3):477-482.

12. Redelmeier D, Scales D, Kopp A. Beta blockers for elective surgery in elderly patients: population based, retrospective cohort study. *Bmj.* 2005;331(7522):932.

13. Wallace A, Layug B, Tateo I, et al. Prophylactic atenolol reduces postoperative myocardial ischemia. McSPI Research Group. *Anesthesiology.* 1998;88(1):7-17.

14. Yang H, Raymer K, Butler R, et al. The effects of perioperative beta-blockade: results of the Metoprolol after Vascular Surgery (MaVS) study, a randomized controlled trial. *Am Heart J.* 2006;152(5):983-990.

15. Zaugg M, Bestmann L, Wacker J, et al. Adrenergic receptor genotype but not perioperative bisoprolol therapy may determine cardiovascular outcome in at-risk patients undergoing surgery with spinal block: the Swiss Beta Blocker in Spinal Anesthesia (BBSA) study: a double-blinded, placebo-controlled, multicenter trial with 1-year follow-up. *Anesthesiology.* 2007;107(1):33-44.

16. Lopez-Sendon J, Swedberg K, McMurray J, et al. Expert consensus document on beta-adrenergic receptor blockers. *Eur Heart J.* 2004;25(15):1341-1362.

17. Cruickshank JM. Are we misunderstanding beta-blockers. *Int J Cardiol.* 2007;120(1):10-27.

18. Jenkins NP, Keevil BG, Hutchinson IV, et al. Beta-blockers are associated with lower C-reactive protein concentrations in patients with coronary artery disease. *Am J Med.* 2002;112(4):269-274.

19. Yeager MP, Fillinger MP, Hettleman BD, et al. Perioperative beta-blockade and late cardiac outcomes: a complementary hypothesis. *J Cardiothorac Vasc Anesth.* 2005;19(2):237-241.

20. de Groote P, Delour P, Lamblin N, et al. Effects of bisoprolol in patients with stable congestive heart failure. *Ann Cardiol Angeiol (Paris).* 2004;53(4):167-170.

21. Flu WJ, van Kuijk JP, Galal W, et al. Prevalence and pharmacological treatment of left ventricular dysfunction in patients undergoing vascular surgery. *Eur J Heart Fail.* 2010;12(3):288-293.

22. Kukin ML. Beta-blockers in chronic heart failure: considerations for selecting an agent. *Mayo Clin Proc.* 2002;77(11):1199-1206.

23. Boersma E, Kertai MD, Schouten O, et al. Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index. *Am J Med.* 2005;118(10):1134-1141.

24. Poldermans D, Bax JJ, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: the Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur Heart J.* 2009;30(22):2769-2812.

25. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *Eur Heart J.* 2007;28(20):2525-2538.

26. Priebe HJ. Perioperative myocardial infarction--aetiology and prevention. *Br J Anaesth.* 2005;95(1):3-19.

27. Flu. Prevalence of LV dysfunction in vascular surgery patients. 2009.
28. Albert MA, Danielson E, Rifai N, et al. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *Jama.* 2001;286(1):64-70.
29. Briguori C, Visconti G, Focaccio A, et al. Novel approaches for preventing or limiting events (Naples) II trial: impact of a single high loading dose of atorvastatin on periprocedural myocardial infarction. *J Am Coll Cardiol.* 2009;54(23):2157-2163.
30. Ridker PM, Rifai N, Pfeffer MA, et al. Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators. *Circulation.* 1999;100(3):230-235.
31. Brodde OE, Kroemer HK. Drug-drug interactions of beta-adrenoceptor blockers. *Arzneimittelforschung.* 2003;53(12):814-822.
32. Fleisher LA, Beckman JA, Brown KA, et al. 2009 ACCF/AHA Focused Update on Perioperative Beta Blockade Incorporated Into the ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery. *J Am Coll Cardiol.* 2009;54(22):e13-e118.
33. Poldermans D, Schouten O, van Lier F, et al. Perioperative strokes and beta-blockade. *Anesthesiology.* 2009;111(5):940-945.
34. Beattie WS, Wijeysundera DN, Karkouti K, et al. Acute surgical anemia influences the cardioprotective effects of beta-blockade: a single-center, propensity-matched cohort study. *Anesthesiology.*112(1):25-33.

Chapter 22

β-blockade in noncardiac Surgery

Hot Topics in Cardiology 2009; 4(16):5-6

Willem-Jan Flu
Don Poldermans

Dr A Margonato and Dr D Gerosa have provided us with a thorough and well-written review article 'β-blockers in noncardiac surgery; do they really work?' addressing a central question in perioperative medicine: do β-blockers sufficiently protect patients for the development of perioperative cardiovascular complications? The value of β-blockers has been debated for many years and the relevance of this topic will only expand. Cardiac complications are the leading cause of perioperative morbidity and mortality [1] in 2020 the number of patients eligible for surgery will increase by 25%.[2] This Review article provides the reader a clear insight of (i) mechanisms of action and characteristic of β-blockers, (ii) pathophysiology of perioperative cardiovascular complications, and (iii) provides an extended literature overview of β-blocker use in noncardiac and vascular surgery.

Two randomized controlled trials evaluating the protective value of β-blockers, which are discussed thoroughly, are the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE)-1 trial performed in Rotterdam [3] and the multi-centre Perioperative Ischemic Evaluation (POISE)-trial.[4] In DECREASE-I trial, vascular surgery patients were treated with the highly selective β 1-adrenoreceptor-antagonist bisoprolol titrated to achieve a heart rate between 60-65 beats per minute. Bisoprolol treatment reduced the occurrence peri- and postoperative cardiovascular complications.[3, 5] The DECREASE-I trial included high-risk vascular surgery patients, however promising results in the DECREASE-IV trial show beneficial effects of bisoprolol treatment in intermediate risk patients as well.[6] The incidence of stroke was comparable between patients receiving bisoprolol or placebo. In the POISE trial, patients were treated with a relative high dosage of the long-acting β-blocker metoprolol succinate. Metoprolol succinate did lower the incidence of myocardial infarction, however this benefit was outweighed by an increased incidence of stroke and death.

Different treatment protocols of the DECREASE-I trial, POISE trial and other studies are elegantly summarized by the authors and differ in (i) initiation time of therapy, (ii) β-blocker type, (iii) mode of administration, and (iv) risk profile of the patients. Dr A Margonato and Dr D Gerosa note that the question whether β-blocker use is effective in reducing preoperative cardiovascular complication without excessive side effect has not been answered yet. They propose that a future randomized, double-blind, placebo-controlled trial is needed, which should include a sufficient number of patients with a revised cardiac risk index of at least $\geq$2, scheduled for vascular and major noncardiac surgery. We propose low dose treatment with a highly selective long-acting β-blocker, initiated al least a month before surgery. Up-titration according to tolerance to obtain heart rates between 65 and 70 beats per minute could demonstrate maximal protection of β-blockers without over treating the patients. Intraoperatively, the ultra short β-blocker esmolol, administered via a continuous infusion, could be considered as well to maximally prevent the occurrence of adverse myocardial events. A randomized double-blind placebo-controlled trial of this kind could provide the final answer to the question: β-blockers in noncardiac surgery; do they really work?

REFERENCES

1. Mangano DT. Perioperative cardiac morbidity. *Anesthesiology.* 1990;72(1):153-184.

2. Mangano DT. Perioperative medicine: NHLBI working group deliberations and recommendations. *J Cardiothorac Vasc Anesth.* 2004;18(1):1-6.

3. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med.* 1999;341(24):1789-1794.

4. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet.* 2008;371(9627):1839-1847.

5. Feringa HH, Bax JJ, Schouten O, et al. Protecting the heart with cardiac medication in patients with left ventricular dysfunction undergoing major noncardiac vascular surgery. *Semin Cardiothorac Vasc Anesth.* 2006;10(1):25-31.

6. Dunkelgrun M, Boersma E, Koopman-Van Gemert A, et al. Fluvastatin and bisoprolol for cardiac risk reduction in intermediate-risk patients undergoing non-cardiovascular surgery; a randomised controlled trial. *European Heart Journal.* 2008;29 (supplement):602-603.

Chapter 23

Summary and conclusions
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SUMMARY AND CONCLUSIONS

In this thesis, the influence of asymptomatic manifestations of atherosclerosis towards perioperative and long-term outcome (myocardial damage and survivial) is described in patients undergoing vascular surgery. In general, the influence of asymptomatic left ventricular dysfunction, low ankle-brachial index, and increased intimamedia thickness of the common carotid artery were evaluated. In addition, the predictive value of the metabolic syndrome and biomarkers, such as N-terminal pro-B-type natriuretic peptide, will be discussed. Furthermore, the possibility to screen for asymptomatic abdominal aortic aneurysms with a handheld ultrasound devise has been explored. The last part of the thesis has focussed on the value of perioperative β-blocker use and prophylactic revascularization in order to reduce the incidence of perioperative cardiac events en improve long-term outcome.

Part I: Left ventricular function

In **Chapter 2**, the most frequently used tests for preoperative cardiac risk stratification are discussed. Stress echocardiography is recommended (class 1 recommendation, level of evidence C) in patients with ≥3 Revised Cardiac Risk factors undergoing high-risk surgery. In addition, for patients with 0-2 Revised Cardiac Risk factors undergoing high-risk vascular surgery (class IIb recommendation, level of evidence B) or patients undergoing intermediate-risk vascular surgery (class IIb recommendation, level of evidence C), stress echocardiography may be considered. In addition, rest echocardiography should be considered in all patients undergoing high-risk vascular surgery (class IIa recommendation, level of evidence C).[1]

Coronary artery disease is the most common cause of myocardial disease, being the initial cause in 70% of patients with predominantly systolic heart failure. In order to identify patients with coronary artery disease, regional and global wall motion assessment with echocardiography plays a pivotal role. As described in **Chapter 3**, two-dimensional echocardiography has the advantage of being (i) safe, (ii) widely available, (iii) noninvasive and (iv) feasible in almost all circumstances at low costs, compared with cardiac computed tomography, magnetic resonance imaging, or nuclear imaging techniques.

Druing the period between 2002 and 2008, 1,005 patients undergoing vascular surgery at the Erasmus Medical Center underwent standard preoperative evaluation using echocardiography, regardless the presence of heart failure symptoms. As described in **Chapter 4**, left ventricular (LV) dysfunction was diagnosed in 506, or 50% of the patients included. Interestingly, 403 patients (80%) had asymptomatic LV dysfunction and 103 patients (20%) had symptomatic heart failure. Half of the patients with asymptomatic LV dysfunction had an LV ejection fraction <50%. Importantly, pharmacological treatment with angiotensin blocking agents, β-blockers or diuretics, as recommended in European Society of Cardiology guidelines [2] could be

initiated or improved in one third of patients with LV dysfunction (symptomatic or asymptomatic). The prognostic implications of asymptomatic LV dysfunction on postoperative outcome of patients undergoing vascular surgery are discussed in **Chapter 5**. In patients undergoing open vascular surgery, asymptomatic LV dysfunction was associated with increased risk for 30-day cardiovascular events (composite of 30-day myocardial ischemia, myocardial infarction and mortality) and long-term cardiovascular mortality. In patients undergoing endovascular surgery, the presence of symptomatic heart failure was associated with an increased risk for these study endpoints.

Chronic lung diseases, such as chronic obstructive pulmonary disease (COPD), and cardiovascular disease are common co-morbidities in surgery patients, associated with poor outcome. In **Chapter 6**, we hypothesized that (i) COPD would be independently associated with LV dysfunction and that (ii) the presence of asymptomatic LV dysfunction would significantly increase the risk of pospoperative mortality of COPD patients. Of the 1005 included patients, approximately 1 out of 3 patients had COPD detected with spirometry and more than half of these patients had LV dysfunction detected with echocardiography. Both mild and moderate to severe COPD patients who had asymptomatic LV dysfunction were at increased risk for all-cause mortality, compared with COPD patients with normal LV function.

Elevated C-reactive protein (CRP) plasma levels reflect an inflammatory state associated with atherosclerosis. Since elevated high-sensitive CRP levels are associated with an increased risk for cardiac events in patients with or without coronary artery disease, we evaluated the prognostic value of LV dysfunction assessed using the wall motion score index (WMSI) in patients with normal or increased high-sensitive CRP in **Chapter 7**. Results described in this chapter indicate that WMSI >1.5 is associated with an increased risk for 30-day myocardial damage and long-term mortality in patients with high-sensitive CRP >6.5 or ≤6.5 mg/L. In addition, patients with WMSI >1.5 + high-sensitive CRP >6.5 mg/L had the highest risk for the study endpoints.

In **Chapter 8**, dobutamine stress echocardiography was performed before vascular surgery and transesophageal echocardiography was performed intraoperatively in 54 patients. The study was conducted to compare the location of (i) wall motion abnormalities induced during preoperative dobutamine stress echocardiography with (ii) intraoperative wall motion abnormalities detected with transesophageal echocardiography. In these patients, an excellent correlation between pre- and intraoperative rest wall motion abnormalities was observed, however, poor agreement correlations were found between pre- and intraoperative locations of new wall motion abnormalities during stress.

Chapter 9 provides a brief discussion regarding the accuracy of three- vs. two-dimensional speckle tracking echocardiography for measuring end-systolic and end-diastolic LV volumes. Recently it has been demonstrated that inter- and intraobserver variability of measurements performed with three-dimensional speckle tracking was lower and less spread, compared with two-dimensional speckle tracking echocardiography.[3] This might imply that three-dimensional speckle tracking echocardiography could be an attractive new method for the assessment of LV volumes and perhaps function.

Part II: Asymptomatic atherosclerosis in patients with symptomatic peripheral arterial disease

A systematic Medline search was undertaken in **Chapter 10**, to identify studies addressing perioperative myocardial damage, assessed with troponin I or T, in patients undergoing elective peripheral vascular surgery published during the period between 2000 and 2010. The incidence of perioperative myocardial ischemia ranged from 14 to 47% and the incidence of perioperative myocardial infarction (troponin release + angina pectoris or electrocardiographic changes) ranged from 1 to 26%. In addition, hazard ratios describing the prognostic value of troponin T or I towards postoperative mortality or the occurrence of major adverse cardiac events varied from 1.9 to 9.0.

The prevalence and prognostic implications of polyvascular disease in patients undergoing vascular surgery at the Erasmus Medical Center during the period between 1990 and 2008 is described in **Chapter 11**. Single, two and three affected vascular beds were detected in 1.369 (46%), 1.249 (43%) and 315 (11%) patients, respectively. Compared with patients with one affected vascular beds, patients with two- or three affected vascular beds had significantly higher rates of all-cause and cardiovascular mortality during long-term follow-up.

In **Chapter 12**, the impact of subclinical increased intimamedia thickness of the common carotid artery (CCA-IMT) was evaluated in patients undergoing abdominal aortic- or lower extremity artery repair. The optimal predictive value of CCA-IMT, using receiver-operating characteristic curve analysis, for the prediction of CV events was calculated to be 1.25 mm (sensitivity 70%, specificity 80%). Importantly, an increased CCA-IMT was independently associated with 30-day cardiovascular events and long-term cardiovascular mortality. **Chapter 13** evaluates the predictive value of asymptomatic low ankle-brachial index (ABI) towards postoperative outcome of patients undergoing abdominal aortic- or carotid artery stenos repair. Asymptomatic low ABI has prognostic value towards perioperative myocardial damage and long-term mortality, incremental to risk factors imbedded in conventional cardiac risk indices such as the Revised Cardiac Risk index. The separate and combined prognostic values of asymptomatic low ABI (<0.9) or increased CCA-IMT (>1.25 mm) is evaluated in **Chapter 14**, in a cohort of patients undergoing abdominal aortic aneurysm repair. Although asymptomatic

ABI <0.9 and subclinical CCA-IMT >1.25 independently predict 30-day myocardial damage and long-term mortality, a combination of these markers is associated with the highest risk towards the occurrence of the study endpoints.

Chapter 15 illustrates that metabolic syndrome, defined according the National Cholesterol Education Program's Adult Treatment Panel III report,[4] is highly prevalent in vascular surgery patients. Metabolic syndrome was diagnosed in 41% of patients with occlusive and 42% of patients with aneurysmatic peripheral arterial disease. Both in occlusive as in aneurysmatic peripheral arterial disease patients, metabolic syndrome constituted to be an independent predictor of long-term cardiovascular events.

The interrelationship between preoperative anemia and N-terminal Pro-B-type natriuretic peptide and its effect in predicting postoperative cardiac events in vascular surgery patients is evaluated in **Chapter 16**. The optimal predictive value of N-terminal Pro-B-type natriuretic peptide, using receiver-operating characteristic curve analysis, for the prediction of postoperative cardiac events was calculated to be 350 pg/mL. Anemia was defined as serum hemoglobin <13 g/dL for men and <12 g/dL for women. Both N-terminal Pro-B-type natriuretic peptide and anemia were independently associated with an increased risk for postoperative cardiac events. However, N-terminal Pro-B-type natriuretic peptide was less predictive in anemic patients.

In **Chapter 17**, the diagnostic accuracy of a new portable ultrasound scanner (Aortascan BVI 9600) developed for automated abdominal aortic aneurysm detection is discussed. 150 patients were first scanned with conventional ultrasound, serving as the reference technique. An abdominal aortic diameter ≥30 mm defined an aneurysm. The Aortascan BVI 9600 automatically detects and calculates the aortic diameter ≥30 mm with a 90% sensitivity.

PART III: Prevention and treatment

In **Chapter 18**, leading randomized controlled trials addressing the value of preoperative β-blocker treatment or prophylactic coronary revascularization are discussed. The value of preoperative β-blocker treatment has been widely debated. Important factors that may relate to the effectiveness of β-blocker therapy are the patients' underlying cardiac risk and variations of treatment protocols in (i) initiation time, (ii) β-blocker type, (iii) starting dose, (iv) dose adjustments for heart-rate control, and (v) duration of treatment, as discussed in this chapter. Prophylactic coronary revascularization of patients with ≥3 Revised Cardiac Risk factors apparently provides insufficient extra protection on top of β-blocker treatment as demonstrated. Retrospective data indicate that prophylactic coronary revascularization may be the most effective option patients with 1-2 Revised Cardiac Risk factors.

Long-term outcome of prophylactic coronary revascularization in cardiac high-risk patients undergoing major vascular surgery is evaluated in **Chapter 19**. Included patients in the study had ≥3 Revised Cardiac Risk factors + extensive ischemia induced during stress echocardiography. Patients were randomized in the following groups: (i) best medical treatment or (ii) preoperative coronary revascularization + best medical treatment. Rates for survival free of all-cause death, nonfatal myocardial infarction, and coronary revascularization were similar in both groups at 49% and 42% for patients allocated to medical treatment or coronary revascularization, respectively. Therefore, preoperative coronary revascularization in high-risk patients undergoing major vascular surgery was not associated with an improved postoperative long-term outcome compared with the best medical treatment.

The aim of **Chapter 20** was to assess the influence of (i) different intervals between coronary stent placement (drug-eluting or bare metal stents) and noncardiac surgery and (ii) the use of dual antiplatelet therapy towards the occurrence of perioperative major adverse cardiac events. An inverse relation between the interval from coronary stent placement to noncardiac surgery, and the occurrence of perioperative major adverse cardiac events was demonstrated. Continuation of dual antiplatelet therapy did not provide complete protection against major adverse cardiac events. Based on these results, elective noncardiac surgery should be preferably postponed 90 days after placement of a drug-eluting stent and ≥1 year after placement of a bare metal stent.

The study described in **Chapter 21** was conducted to evaluate the relation between timing of β-blocker treatment initiation 0-1, >1-4, and >4 weeks before surgery and (i) preoperative heart rate and high-sensitive C-reactive protein levels and (ii) postoperative outcome. The results from these studies indicate that β-blocker treatment initiated >1 week before surgery is associated with lower preoperative heart rate and improved cardiac outcome after vascular surgery, compared with treatment initiated <1 week before surgery. No reduction of median hs-CRP levels was observed, also not in patients receiving β-blocker treatment >1 week before surgery. The results underline the importance of adequate perioperative heart rate control between 60-70 beats per minute, which is discussed in **Chapter 22** as well.

REFERENCES

1. Poldermans D, Bax JJ, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: the Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur Heart J.* 2009;30(22):2769-2812.

2. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J.* 2008;29(19):2388-2442.

3. Nesser HJ, Mor-Avi V, Gorissen W, et al. Quantification of left ventricular volumes using three-dimensional echocardiographic speckle tracking: comparison with MRI. *Eur Heart J*. 2009;30(13):1565-1573.

4. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106(25):3143-3421.

SAMENVATTING EN CONCLUSIES

Dit proefschrift beschrijft de invloed die asymptomatische aderverkalking, of atherosclerose, heeft op de perioperatieve- en lange-termijn resultaat (myocard schade en overleving) van patiënten die een perifeer vaatheelkundige ingreep ondergaan. De voorspellende waarde van asymptomatische linker ventrikel dysfunctie, asymptomatische verlaagde enkel-arm index en een toegenomen intimamedia dikte in de halsslagader op het ontstaan van cardiale complicaties en lange-termijn resultaten zijn hiertoe geëvalueerd. Tevens wordt de voorspellende waarde van het metabool syndroom en van biomarkers, zoals N-terminal pro-B-type natriuretic peptide, besproken. Daarnaast wordt de mogelijkheid tot screening van asymptomatische aneurysma's van de abdominale aorta via het gebruik van een draagbaar echo apparaat onderzocht. Het laatste deel van het proefschrift beschrijft de invloed van perioperatief bètablokker gebruik en profylactische revascularisatie voorafgaand aan de vaatingreep, op de incidentie van perioperatieve cardiale complicaties en de lange-termijn resultaten.

Deel I: Linker ventrikel functie

Hoofdstuk 2 beschrijft de meest gebruikte diagnostische testen die gebruikt worden bij de preoperatieve inschatting van het cardiale risico tijdens en na de operatie. In perioperatieve richtlijnen wordt stress echocardiografie aanbevolen (aanbeveling van klasse 1, niveau van bewijs C) bij patiënten met ≥3 'Revised Cardiac Risk' risicofactoren die een 'high-risk' perifere vaatheelkundige ingreep ondergaan. Daarnaast kan stress echocardiografie worden overwogen bij patiënten met 0-2 'Revised Cardiac Risk' risicofactoren die een 'high-risk' perifere vaatheelkundige ingreep ondergaan (Klasse IIb aanbeveling, niveau van bewijs B) of patiënten die een 'intermediate-risk' perifere vaatheelkundige ingreep ondergaan (klasse IIb aanbeveling, niveau van bewijs C). Verder kan een rust echo worden overwogen bij alle patiënten die een 'high-risk' perifere vaatingreep ondergaan (klasse IIa aanbeveling, het niveau van bewijs C).[1]

Coronair vaatlijden is de meest voorkomende oorzaak van aandoeningen van het myocard en tevens de oorzaak van systolisch hartfalen bij 70% van de patiënten. Echocardiografie speelt een centrale rol in de diagnostiek van coronair vaatlijden, via de beoordeling van regionale en globale wandbewegingen van het myocard. Zoals in **Hoofdstuk 3** is beschreven, heeft twee-dimensionale echocardiografie het voordeel (i) veilig, (ii) op grote schaal beschikbaar, (iii) niet invasief en (iv) relatief goedkoop te zijn, dit vergeleken met cardiale 'computed tomography', 'magnetic resonance imaging', of nucleaire beeldvormende technieken.

Gedurende de periode van 2002 tot en met 2008 zijn 1005 patiënten die een perifere vaatingreep in het Erasmus Medisch Centrum ondergingen, onderworpen aan standaard preoperatieve evaluatie met behulp van echocardiografie, ongeacht de aanwezigheid van

symptomen van hartfalen. Zoals beschreven in **Hoofdstuk 4,** werd linker ventrikel (LV) dysfunctie vastgesteld bij 506 patiënten, dit is 50% van de patiënten. Van deze groep, hadden 403 patiënten (80%) asymptomatische LV dysfunctie en 103 patiënten (20%) symptomatisch hartfalen. De helft van de patiënten met asymptomatische LV dysfunctie had een LV ejectiefractie <50%. Een belangrijke constatering is dat medicamenteuze behandeling zoals aanbevolen in de richtlijnen van de Europese Vereniging voor Cardiologie,[2] met bijvoorbeeld ACE-remmers, β-blokkers of diuretica, kon worden opgestart of verbeterd bij één derde van de patiënten met LV dysfunctie (zowel symptomatisch als asymptomatisch). De prognostische waarde van asymptomatische LV dysfunctie op de postoperatieve resultaten van patiënten die een vaatheelkundige ingreep ondergingen wordt besproken in **Hoofdstuk 5**. Bij patiënten die een open open vaatheelkundige ingreep ondergingen, bleek de aanwezigheid van een asymptomatische LV dysfunctie gerelateerd te zijn aan een verhoogd risico voor (i) cardiovasculaire complicaties (myocardischemie, myocardinfarct en cardiale mortaliteit) gedurende de eerste 30 dagen na de ingreep en (ii) een verhoogd risico op cardiovasculair overlijden gedurende de lange-termijn follow-up. Echter, bij patiënten die een endovasculaire ingreep ondergingen was alleen de aanwezigheid van symptomatisch hartfalen geassocieerd met een verhoogd risico voor de hierbovengenoemde studie eindpunten.

Hart-en vaatziekten en chronische longziekten, zoals 'chronic obstructive pulmonary disease' (COPD), vormen een veel voorkomende co-morbiditeit bij de chirurgische patiënten populatie en zijn geassocieerd met een minder goed postoperatief resultaat. In **Hoofdstuk 6** hebben we de hypothese gevormd dat (i) COPD onafhankelijk geassocieerd is met LV dysfunctie en (ii) dat de aanwezigheid van een asymptomatische LV dysfunctie bij COPD patiënten het risico op postoperatieve sterfte aanzienlijk verhoogd. In deze studie zijn 1005 patiënten geincludeerd. Met behulp van spirometrie is COPD gediagnosticeerd in ongeveer één derde van de patiënten. Echocardiografie toonde dat in meer de helft van de 1005 patiënten een LV dysfunctie aanwezig was. Patiënten die zowel milde COPD of matig tot ernstige COPD als een asymptomatische LV dysfunctie hadden, hadden een verhoogd risico op postoperatieve mortaliteit, vergeleken met COPD patiënten met een normale LV functie.

Een verhoogde 'high-sensitive C-reactive protein' (hs-CRP) waarde in het plasma is een weerspiegeling van het ontstekingsproces dat samenhangt met atherosclerose. Verhoogde hs-CRP waarden zijn geassocieerd met een verhoogd risico op cardiale complicaties, zowel bij patiënten mét als bij patiënten zónder coronair vaatlijden. In **Hoofdstuk 7** is de prognostische waarde van LV dysfunctie, beoordeeld met behulp van de 'wall motion score index' (WMSI), onderzocht bij patiënten met een normaal of een verhoogd hs-CRP. Uit de resultaten zoals beschreven in dit hoofdstuk blijkt dat patiënten met een WMSI >1.5 een verhoogd risico hebben op (i) het ontstaan van hartschade binnen 30 dagen na een perifere vaatheelkunde ingreep en (ii) mortaliteit gedurende lange-termijn follow-up, zowel bij een hs-CRP >6.5 als ≤6.5 mg/L. Verder hadden patiënten met een WMSI> 1.5 + hs-CRP >6.5 mg/L het hoogste risico op het ontstaan van één van de studie eindpunten.

Hoofdstuk 8 beschrijft een studie waarin, bij 54 patiënten, dobutamine stress echocardiografie is verricht voorafgaand aan een perifere vaatingreep gevolgd door transoesofageale echocardiografie gedurende de operatie. De locatie van wandbewegingsstoornissen gedetecteerd gedurende dobutamine stress echocardiografie voorafgaand aan de operatie zijn vergeleken met wandbewegingsstoornissen gedetecteerd gedurende de operatie. Bij deze patiënten is een zeer goede correlatie gevonden tussen pre- en intraoperatieve wandbewegingsstoornissen aanwezig in rust. Echter, de correlatie was slecht tussen pre- en intraoperatieve locaties van nieuw ontstane wandbewegingsstoornissen gedurende stress.

Hoofdstuk 9 geeft een kort overzicht over de nauwkeurigheid van de drie- vs. tweedimensionale 'speckle tracking' echocardiografie voor het meten van eind-systolische en eind-diastolische LV volumes. Recent is aangetoond dat de inter- en intraobserver variabiliteit lager is, en minder verspreid, bij de metingen uitgevoerd met driedimensionale 'speckle tracking' echocardiografie in vergelijking met metingen verricht met tweedimensionale 'speckle tracking' echocardiografie.[3] Dit zou wellicht kunnen betekenen dat driedimensionale 'speckle tracking' echocardiografie in de toekomst een aantrekkelijke nieuwe methode is voor de beoordeling van LV volume en en misschien ook voor de functie van de LV.

Deel II: Asymptomatische atherosclerose bij patiënten met symptomatisch perifeer vaatlijden.

Een systematische 'Medline search' is verricht in **Hoofdstuk 10**, gericht op studies gepubliceerd tussen 2000 en 2010 met als onderwerp: perioperatieve myocard schade gedetecteerd met troponine T of I, bij patiënten die een electief geplande perifere vaatoperatie ondergingen. De incidentie van perioperatieve myocard ischemie varieerde van 14-47% en de incidentie van perioperatieve myocard infarct (troponine T afgifte + angina pectoris en/of veranderingen op het electrocardiogram) varieerde van 1-26%. Hazard ratio's, die de prognostische waarde van troponine T of I ten opzichte van postoperatieve mortaliteit of van postoperatieve cardiale complicaties of mortaliteit weergeven, varieerden van 1.9 tot 9.0.

De prevalentie en prognostische implicaties van gegeneraliseerde atherosclerose, bij patiënten die een perifere vaatoperatie hebben ondergaan in het Erasmus Medisch Centrum gedurende 1990 en 2008, is beschreven in **Hoofdstuk 11**. Eén, twee en drie aangedane vaatbedden waren aanwezig in respectievelijk 1.369 (46%), 1.249 (43%) en 315 (11%) patiënten. Patiënten met twee of drie aangedane vaatbedden hadden een beduidend hoger risico op sterfte gedurende lange-termijn follow-up, vergeleken met patiënten met één aangedaan vaatbed.

In **Hoofdstuk 12** is het effect van een subklinisch toegenomen intimamedia dikte van de halsslagader (CCA-IMT) geëvalueerd bij patiënten die een vaatoperatie hebben ondergaan aan de abdominale aorta of de beenslagader. De optimale voorspellende waarde van de CCA-IMT ten opzichte van het risico op cardiovasculaire complicaties is berekend met behulp van 'receiver-operating characteristic curve' analyses, op 1.25 mm (sensitiviteit 70%, specificiteit 80%). Een belangrijk gegeven is dat een verhoogde CCA-IMT onafhankelijk geassocieerd was met (i) cardiovasculaire complicaties gedurende de eerste 30-dagen na de ingreep en (ii) cardiovasculaire mortaliteit gedurende lange-termijn follow-up. In **hoofdstuk 13** is de voorspellende waarde van een asymptomatisch verlaagde enkel-arm index (ABI) geevalueerd, in relatie tot het postoperatieve resultaat van patiënten die een vaatingreep aan de abdominale aorta of de halsslagader ondergingen. Een asymptomatische verlaagde ABI had een toegevoegde voorspellende waarde ten opzichte van het ontstaan van myocard schade gedurende de operatie en mortaliteit gedurende lange-termijn follow-up, als aanvulling op de voorspellende waarde van risico factoren gevat in conventionele cardiale risico modellen, zoals de 'Revised Cardiac Risk' index. De afzonderlijke en gecombineerde prognostische waarden van een asymptomatisch verlaagde ABI (<0.9) of een toename van CCA-IMT (>1.25 mm) is geëvalueerd in **Hoofdstuk 14**, bij een groep van patiënten die een perifere vaatingreep ondergingen ter herstel van een aneursyma van de abdominale aorta. Hoewel een asymptomatisch verlaagde ABI <0.9 en subklinisch toegenomen CCA-IMT >1.25 onafhankelijk van elkaar (i) het optreden van cardiale complicaties gedurende de eerste 30 dagen na de ingreep en (ii) de mortaliteit gedurende lange-termijn follow-up voorspellen, is een combinatie van deze twee markers geassocieerd met het hoogste risico op het voorkomen van de studie eindpunten.

Hoofdstuk 15 illustreert dat het metabool syndroom, gedefinieerd volgens het 'National Cholesterol Education Program's Adult Treatment Panel III report',[4] veel voorkomt in de vaatheelkundige patiënten populatie. Het metabool syndroom werd gediagnosticeerd bij 41% van de patiënten met stenoserend arterieel vaatlijden en bij 42% van de patiënten met aneurysmatisch arterieel vaatlijden. Verder was het metabool syndroom een onafhankelijke voorspeller van cardiovasculaire complicaties gedurende de lange-termijn follow-up, bij zowel patiënten met stenoserend, als patiënten met aneurysmatisch arterieel vaatlijden.

De relatie tussen (i) anemie voorafgaand aan de operatie en (ii) N-terminale pro-B-type natriuretisch peptide, en de invloed van deze variabelen op het voorspellen van postoperatieve cardiale complicaties bij vaatheelkundige patiënten, wordt geëvalueerd in **Hoofdstuk 16**. De optimale voorspellende waarde van de N-terminale pro-B-type natriuretisch peptide ten opzichte van het risico op cardiovasculaire complicaties is berekend met behulp van 'receiver-operating characteristic curve' analyses, op 350 pg/ml. Anemie werd gedefinieerd als serum hemoglobine <13 g/dL voor mannen en <12 g/dL voor vrouwen. Zowel de N-terminale pro-B-type natriuretisch peptide als anemie waren onafhankelijk geassocieerd met een verhoogd risico op postoperatieve cardiale complicaties. Echter, N-

terminale pro-B-type natriuretisch peptide had een matige voorspellende waarde bij anemische patiënten.

In **Hoofdstuk 17** wordt de diagnostische nauwkeurigheid van een nieuwe draagbare echo scanner (Aortascan BVI 9600), ontwikkeld voor de automatische detectie van aneurysma's van de abdominale aorta, besproken. Hiertoe werden 150 patiënten eerst gescand met conventionele echografie, die als de referentie techniek fungeerde. Een abdominale aorta met een diameter ≥30 mm was gedefinieerd als een aneurysma. De BVI 9600 Aortascan detecteerde de aorta diameter ≥30 mm met een sensitiviteit van 90%.

DEEL III: Preventie en behandeling

In **Hoofdstuk 18**, worden toonaangevende gerandomiseerde onderzoeken besproken die zich richten op het nut van preoperatieve bètablokker therapie of profylactische revascularisatie van de coronair vaten voorafgaan aan een perifere vaatingreep. In de afgelopen jaren is er uitgebreid gediscussieerd over het nut van bètablokker therapie bij perifere vaatoperaties. Belangrijke factoren die van invloed kunnen zijn op de effectiviteit van bètablokker therapie zijn het cardiale risicoprofiel van de patiënt en de variaties van behandelingsprotocollen in (i) start van bètablokker therapie, (ii) type bètablokker, (iii) startdosering, (iv) aanpassen van de dosering op geleide van het hart ritme en (v) de duur van de behandeling, zoals besproken in dit hoofdstuk. Profylactische revascularisatie van de coronair vaten, bij patiënten met ≥3 'Revised Cardiac Risk' risicofactoren, verschaft onvoldoende bescherming als aanvulling op de behandeling met een bètablokker. Uit retrospectieve data blijkt dat profylactische revascularisatie van de coronair vaten het meest effectief is bij patiënten met 1-2 'Revised Cardiac Risk' risicofactoren.

Het effect van profylactische revascularisatie van de coronair vaten, bij cardiale hoog-risico patiënten die een vaatingreep ondergaan, wordt geëvalueerd in **Hoofdstuk 19**. In deze studie zijn patiënten geincludeerd met ≥3 'Revised Cardiac Risk' risicofactoren + uitgebreide ischemie geïnduceerd gedurende stress echocardiografie. De patiënten werden gerandomiseerd in de volgende groepen: (i) de beste medische behandeling of (ii) preoperatieve coronaire revascularisatie + beste medische behandeling. Follow-up percentages van patiënten die niet overleden waren, geen myocardinfarct hadden gehad of een coronaire revascularisatie hadden ondergaan, waren vergelijkbaar in beide groepen, te weten 49% bij patiënten die de beste medische behandeling kregen en 42% bij patiënten die preoperatieve coronaire revascularisatie + beste medische behandeling kregen. Het verbeterde postoperatieve of lange-termijn resultaat werd vergeleken met de beste medische behandeling. Profylactische revascularisatie van de coronair vaten voorafgaand aan een perifere vaatingreep bij hoog-risico patiënten was niet geassocieerd met een verbeterd postoperatieve lange-termijn resultaat, in vergelijking met de beste medische behandeling.

Hoofdstuk 20 heeft tot doel te beoordelen wat de invloed is, op het ontstaan van perioperatieve cardiale complicaties, van (i) verschillende intervallen tussen het plaatsen van een stent (bare metal of drug-eluting strent) in één van de coronair vaten en het verrichten van niet cardiale chirurgie en (ii) het gebruik van gecombineerde aggregatie trombocyten remming. De studie toont aan dat een langer interval tussen stent plaatsing en niet cardiale chirurgie gerelateerd is aan een lagere hoeveelheid perioperatieve cardiale complicaties. Verder biedt voortzetting van gecombineerde aggregatie trombocyten remming geen volledige bescherming tegen perioperatieve cardiale complicaties. Op basis van deze resultaten, moet electieve niet cardiale chirurgie bij voorkeur 90 dagen worden uitgesteld na plaatsing van een drug-eluting stent en ≥1 jaar na plaatsing van een bare metal stent.

De studie beschreven in **Hoofdstuk 21** is verricht om te evalueren wat de invloed is van het moment van starten met bètablokker therapie 0 tot 1, >1 tot 4, of >4 weken voorafgaand aan een perifere vaatingreep op (i) het preoperatief hartritme en de plasma waarden van het hs-CRP en (ii) het postoperatieve resultaat. De resultaten van deze studies geven aan dat bètablokker therapie gestart >1 week vóór de operatie leidt tot een lager hartritme vóór, en een verbeterde cardiale uitkomst ná de vaatheelkundige ingreep, in vergelijking tot een behandeling gestart <1 week vóór de operatie. Er werd geen verlaging van median hs-CRP waarden waargenomen, ook niet bij patiënten die >1 week voor de vaatingreep behandeld werden met een bètablokker. De resultaten van deze studie onderstrepen het belang van adequate controle van de hart frequentie tussen de 60-70 slagen per minuut, zoals ook besproken wordt in **Hoofdstuk 22**.

REFERENTIES

1. Poldermans D, Bax JJ, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: the Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur Heart J.* 2009;30(22):2769-2812.

2. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J.* 2008;29(19):2388-2442.

3. Nesser HJ, Mor-Avi V, Gorissen W, et al. Quantification of left ventricular volumes using three-dimensional echocardiographic speckle tracking: comparison with MRI. *Eur Heart J.* 2009;30(13):1565-1573.

4. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002;106(25):3143-3421.

PUBLICATIONS

Manuscripts

- **Flu WJ**, van Kuijk JP, Winkel TA, Bax JJ, Poldermans D. Preoperative evaluation of patients with possible coronary artery disease. *Current Cardiology Reports. 2010, in press.*
- **Flu WJ**, van Kuijk JP, Bax JJ, Poldermans D. Perioperative β-blockers, is it still usefull? *Indian Heart J. 2010, in press.*
- **Flu WJ**, Schouten O, van Kuijk JP, Winkel TA, Bax, JJ, Poldermans D. Perioperative cardiac damage in vascular surgery patients. *Eur J Vasc Endovasc Surg. 2010, in press.*
- **Flu WJ**, van Kuijk JP, Hoeks SE, Kuiper R, Schouten O, Elhendy A, Verhagen HJ, Thomson IR, Bax JJ, Fleisher LA, Poldermans D. Prognostic implications of asymptomatic left ventricular dysfunction in patients undergoing vascular surgery. *Anesthesiology. 2010, in press.*
- Van Gestel YR, Goei D, Hoeks SE, Sin DD, **Flu WJ**, Stam H, Mertens FW, Bax JJ, van Domburg RT, Poldermans D. Predictive value of NT-proBNP in vascular surgery patients with COPD and normal left ventricular systolic function. *COPD. 2010; 7(1): 70-75.*
- Van Kuijk JP, **Flu WJ**, Poldermans D. Comparing endovascular and open repair of abdominal aortic aneurysm. *Jama. 2010; Feb 10l202(6): 513-514*
- Galal W, Hoeks SE, **Flu WJ**, van Kuijk JP, Goei D, Galema T, den Uil C, can Gestel YR, Bax JJ, Verhagen HJ, Poldermans D. Relation between preoperative and intraoperative new wall motion abnormalities in vascular surgery patients: A transesophageal echocatdiographic study. *Anesthesiology. 2010; Mar; 112(3): 557-566.*
- **Flu WJ**, van Kuijk JP, Galal W, Kuiper R, van de Ven LL, Verhagen HJ, Bax JJ, Poldermans Prevalence and Pharmacological treatment of Left ventricular Dysfunction in Patients undergoing Vascular Surgery, *Eur J Heart Fail. 2010; 12(3): 288-293.*
- Van Kuijk JP**, Flu WJ**, Chonchol M, Welten GM, Verhagen HJ, Bax JJ, Poldermans D. The prevalence and prognostic implications of polyvascular atherosclerotic disease in patients with chronic kidney disease. *Nephrol Dial Transplant. 2010; Jan 8.*
- Van Kuijk JP**, Flu WJ**, Chonchol M, Bax JJ, Verhagen HJ, Poldermans D. Metabolic syndrome is an independent predictor of cardiovascular events in high-risk patients with occlusive and aneurysmatic peripheral arterial disease. *Atherosclerosis. 2009; Dec 22.*
- Van Kuijk JP**, Flu WJ**, Welten GM, Hoeks SE, Chonchol M, Vidakovic R, Verhagen HJ, Bax JJ, Poldermans D. Long-term prognosis of patients with peripheral arterial disease with or without polyvascular atherosclerotic disease. *Eur Heart J. 2009; Dec 27.*
- **Flu WJ**, Van Gestel YR, van Kuijk JP, Hoeks SE, Kuiper R, Verhagen HJ, Bax JJ, Sin D, Poldermans D. Co-existence of COPD and Left ventricular Dysfunction in Vascular Surgery Patients, *Respir Med. 2009; Nov 24.*
- Van Kuijk JP, **Flu WJ**, Verhagen HJ, Bax JJ, Poldermans D. Remote ischemic preconditioning in vascular surgery patients: the additional value to medical treatment. *J Endovasc Ther. 2009; Dec 16(6): 690-693*

- Van Gestel YR, **Flu WJ**, van Kuijk JP, Hoeks SE, Bax JJ, Sin D, Poldermans D. Association of COPD with Carotid Wall Intima-Media Thickness in Vascular Surgery Patients, *Respir Med. 2009; Nov 24.*
- Goei D, **Flu WJ**, Hoeks SE, Galal W, Dunkelgrun M, Boersma E, Kuiper R, van Kuijk JP, Winkel TA, Schouten O, Bax JJ, Poldermans D. The Interrelationship Between Preoperative Anemia and N-terminal Pro-B-type Natriuretic Peptide: Effect on Predicting Postoperative Cardiac Outcome in Vascular Surgery Patients. *Anesth Analg. 2009; Nov 109: 1403-1408.*
- van Kuijk JP**, Flu WJ**, Schouten O, Hoeks SE, Schenkeveld L, de Jaegere JPT, Bax JJ, van Domburg RT, Serruys PW, Poldermans D. Timing of non-cardiac surgery after coronary stenting with bare-metal or drug-eluting stents, *Am J Cardiol. 2009; Nov 1;104(9): 1229-1234.*
- **Flu WJ**, van Kuijk JP, Voûte MT, Kuiper R, Verhagen HJ, Bax JJ, Poldermans D. Asymptomatic Low Ankle Brachial Index in Vascular Surgery Patients: A Predictor of Perioperative Myocardial Damage. *Eur J Vasc Endovasc Surg. 2010; Jan 39(1): 62-69.*
- Van Kuijk JP, **Flu WJ**, Witteveen OP, Voute M, Bax JJ, Poldermans D. The influence of statins on the expansion rate and rupture risk of abdominal aortic aneurysms. *J Cardiovasc Surg (Torino). 2009; Oct 50(5): 599-609.*
- van Kuijk JP, **Flu WJ**, Voûte MT, Poldermans D, Schouten O. Asymptomatic perioperative cardiac damage: long-term prognosis. *Future Cardiol. 2009 Sep;5(5):417-20.*
- **Flu WJ**, van Kuijk JP, Bax JJ, Gorcsan J 3rd, Poldermans D. Three-dimensional speckle tracking echocardiography: a novel approach in the assessment of left ventricular volume and function? *Eur Heart J. 2009; Aug 27.*
- **Flu WJ**, van Kuijk JP, Hoeks SE, Kuiper R, Schouten O, Goei D, Winkel T, van Gestel YR, Verhagen HJ, Bax JJ, Poldermans D. Intima media thickness of the common carotid artery in vascular surgery patients: a predictor of postoperative cardiovascular events. *Am Heart J. 2009; Aug 158(2): 202-208.*
- Hoeks SE, Scholte op Reimer WJM, van Gestel YRBM, Schouten O, Lenzen MJ, **Flu WJ**, van Kuijk JP, Latour C, Bax JJ, van Urk H, Poldermans D. Medication underuse during long-term follow-up in patients with peripheral arterial disease. *Circ Cardiovasc Qual Outcomes. 2009; 2: 338-343.*
- van Kuijk JP, Schouten O, **Flu WJ**, den Uil CA, Bax JJ, Poldermans D. Perioperative Blood Glucose Monitoring and Control in Major Vascular Surgery Patients. *Eur J Vasc Endovasc Surg. 2009; Jul 14.*
- **Flu WJ**, Poldermans D. Foreword**:** β-blockers in noncardiac surgery: do they really work? *Hot topics in Cardiology. 2009; issue 16.*
- Vidakovic R, Schouten O, Kuiper R, Hoeks SE, **Flu WJ**, van Kuijk JP, Goei D, Verhagen HJ, Neskovic AN, Poldermans D. The Prevalence of Polyvascular Disease in Patients Referred for Peripheral Arterial Disease. *Eur J Vasc Endovasc Surg. 2009; Jun 26.*
- **Flu WJ**, van Kuijk JP, Merks EJ, Kuiper R, Verhagen HJ, Bosch JG, Bom N, Bax JJ, Poldermans D. Screening for abdominal aortic aneurysms using a dedicated portable ultrasound system: early results. *Eur J Echocardiogr. 2009; Jul 10(5): 602-606.*

- van Kuijk JP, **Flu WJ**, Bax JJ, Poldermans D. Prevalence of (a)symptomatic peripheral arterial disease; the additional value of ankle-brachial index on cardiovascular risk stratification. *Eur J Vasc Endovasc Surg. 2009 Sep;38(3):312-3.*
- Hoeks S, **Flu WJ**, van Kuijk JP, Bax J, Poldermans D. Cardiovascular risk assessment of the diabetic patient undergoing major noncardiac surgery. *Best Pract Res Clin Endocrinol Metab. 2009; Jun 23(3): 361-673.*
- **Flu WJ**, van Kuijk JP, Winkel T, Hoeks S, Bax J, Poldermans D. Prevention of acute coronary events in noncardiac surgery: β-blocker therapy and coronary revascularization. *Expert Rev Cardiovasc Ther. 2009; May 7(5): 521-532.*
- van Kuijk JP, Dunkelgrun M, Schreiner F, **Flu WJ**, Galal W, van Domburg RT, Hoeks SE, van Gestel YR, Bax JJ, Poldermans D. Preoperative oral glucose tolerance testing in vascular surgery patients: long-term cardiovascular outcome. *Am Heart J. 2009; May 157(5): 919-25.*
- Schouten O, van Kuijk JP, **Flu WJ**, Winkel TA, Welten GM, Boersma E, Verhagen HJ, Bax JJ, Poldermans D; DECREASE Study Group. Long-term outcome of prophylactic coronary revascularization in cardiac high-risk patients undergoing major vascular surgery (from the randomized DECREASE-V Pilot Study). *Am J Cardiol. 2009; Apr 1 103(7): 897-901.*
- Goei D, Hoeks SE, Boersma E, Winkel TA, Dunkelgrun M, **Flu WJ**, Schouten O, Bax JJ, Poldermans D. Incremental value of high-sensitivity C-reactive protein and N-terminal pro-B-type natriuretic peptide for the prediction of postoperative cardiac events in noncardiac vascular surgery patients. *Coron Artery Dis. 2009; May 20(3) :219-224.*
- **Flu WJ**, Winkel TA, Bax JJ, Poldermans D. Bisoprolol in patients with chronic heart failure undergoing noncardiac surgery. *Aging Health. 2009; Feb 5(1): 19-27.*
- Van Kuijk JP, **Flu WJ**, Dunckelgrun M, Bax JJ, Poldermans D. Coronary artery disease in patients with abdominal aortic aneurysm: a review article. *J Cardiovasc Surg (Torino). 2009; Feb 50(1): 93-107.*
- **Flu WJ**, Hoeks SE, van Kuijk JP, Bax JJ, Poldermans D. Treatment recommendations to prevent myocardial ischemia and infarction in patients undergoing vascular surgery. *Curr Treat Options Cardiovasc Med. 2009; Feb 11(1): 33-44.*
- Dunkelgrun M, Welten GM, Goei D, Winkel TA, Schouten O, van Domburg RT, van Gestel YR, **Flu WJ**, Hoeks SE, Bax JJ, Poldermans D. Association between serum uric acid and perioperative and late cardiovascular outcome in patients with suspected or definite coronary artery disease undergoing elective vascular surgery. *Am J Cardiol. 2008; Oct 1 102(7): 797-801.*

Bookchapter

- Poldermans D, **Flu WJ**, Marwick T Echocardiography and detections of coronary artery disease. European Society of Cardiology Textbook of Cardiovascular Imaging, Chapter 3A. 2009.

PhD PORTFOLIO

Name PhD student: Willem-Jan Flu Erasmus MC Department: Anesthesiology Research School: COEUR		
1. PhD training		
	Year	**ECTS**
General courses		
- Cardiac CT and MRI, Albert Schweitzer hospital, Rotterdam	2009	0.3
- FlowCyte training program, Boston MA	2008	0.3
- Radiation course, Boston MA	2008	0.3
Specific courses (e.g. research school, medical training)		
- NIHES, Biostatistics for clinicians	2009	1.5
- COEUR, Neurovascular and peripheral vascular disease	2008	1.5
- COEUR, Vascular medicine	2008	1.5
Seminars and workshops		
- Cardiomyocyte transplantation, seminar, Leiden	2009	0.3
- Reveal training, Medtronic, Arnhem	2008	0.3
- Journal club, Rotterdam (weekly)	2008-10	1.2
- Research meeting, Rotterdam (weekly)	2008-10	1.2
- Vascular clinical meeting, Rotterdam (weekly)	2008-10	1.2
- Ultrasound clinical meeting, Rotterdam (weekly)	2008-10	0.6
Presentations		
- National conferences	2009-10	2
- International conferences	2008-10	3
(Inter)national conferences		
- European Society of Cardiology Congress, annual	2008-10	
- NVVC, voorjaarscongres, Arnhem	2010	
- NVVC, najaarscongres, Amsterdam	2009	
2. Teaching		
	Year	**ECTS**
Lecturing		
- Clinical applications of the Aortascan BVI 9600, Dusseldorf	2010	0.6
- Accuracy of the Aortascan BVI 9600, IJselstijn	2009	0.6
- Early results of the Aortascan BVI 9600, Rotterdam	2009	0.6
Supervising		
- MsC students	2008-10	1.8

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CURRICULUM VITAE

Willem-Jan Peter Flu is geboren op 11 augustus 1978 te Rotterdam. In 1997 slaagde hij voor het eindexamen Voorbereidend Wetenschappelijk Onderwijs aan het Rotterdams Montessori Lyceum, waarna hij aansluitend twee jaar Rechten studeerde aan de Universiteit Leiden. In 1999 werd hij ingeloot voor de studie Geneeskunde aan de Universiteit Leiden. Tijdens de studie heeft hij één jaar als onderzoeker gewerkt in het het Brigham and Women's Hospital, Harvard Medical School, Boston, Massachussets (begeleider: Dr. A Chandraker). In 2007 werd het artsexamen behaald. Vervolgens werkte hij als arts niet in opleiding tot specialist op de afdeling Interne Geneeskunde en de afdeling Cardiologie van het Rijnland ziekenhuis te Leiderdorp. Begin 2008 startte hij als arts-onderzoeker in het Erasmus Medisch Centrum te Rotterdam (promotor: Prof. dr. D Poldermans). Op 1 juli 2010 zal hij de opleiding tot cardioloog aanvangen in het Onze Lieve Vrouwe Gasthuis te Amsterdam (opleider: Dr. GA Somsen).

Willem-Jan Peter Flu was born on August 11th 1978 in Rotterdam, the Netherlands. He attended secondary school at the Rotterdam Montessori Lyceum, where he graduated in 1997. After studying Law for two years, he started Medical School in 1999 at Leiden University. During his studies, he worked one year as a reseach fellow at the Brigham and Women's Hospital, Harvard Medical School, Boston, Massachussets (supervisor: Dr. A Chandraker). In 2007 he obtained his medical degree. Next, he worked as a junior house officer at the department of Internal Medicine and the department of Cardiology of the Rijnland hospital in Leiderdorp. At the beginning of 2008, he started a PhD-project at the Erasmus Medical Center in Roterdam (supervisor: Prof. dr. D Poldermans). July the 1st 2010, he will start his training as a cardiologist at the Onze Lieve Vrouwe Gasthuis in Amsterdam (supervisor: Dr. GA Somsen).