

**Perioperative Cardiac Care;  
From Guidelines to Clinical Practice**

**Sanne Hoeks**

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# **Perioperative Cardiac Care; From Guidelines to Clinical Practice**

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# INTRO



**DUCTION**



Cardiovascular disease is the major cause of death and disability in the Western world. The main disease underlying cardiovascular disorders is atherosclerosis. Atherosclerosis is a systemic disease affecting numerous vascular beds, including the coronary and peripheral circulation i.e. cerebrovascular, aortic and lower limb arterial circulation. The global ageing phenomenon will further increase the burden of cardiovascular disease and also enforce a change in health care towards the elderly population. Peripheral arterial disease (PAD) is a common condition.<sup>1</sup> Importantly, only 1 out of 9 patients with PAD are symptomatic while vascular morbidity and mortality is estimated to be similar in patients with symptomatic or asymptomatic PAD.<sup>2</sup> This poses PAD to be a major health burden. Risk factors for atherosclerotic disease are common and polyvascular disease is highly prevalent in the PAD population. The prognosis of patients with PAD is predominantly determined by the presence and extent of the underlying ischemic heart disease (IHD).<sup>3-6</sup> The estimated cardiovascular risk in PAD is, moreover, as high as in IHD.<sup>3,4</sup> Mc Dermott and colleagues reported already in 1997 that PAD patients received less intensive drug treatment compared to IHD patients, irrespective of comparable risk.<sup>7</sup> Additionally, in a large risk factor matched population, patients with IHD received more cardiac medications, compared with PAD patients (beta-blockers 74% vs. 34%, aspirin 88% vs. 40%, nitrates 37% vs. 19%, statins 67% vs. 29% and ACE-inhibitors 57% vs. 31%, respectively).<sup>3</sup> The observed poor medical control of PAD patients may be an explanation for the worse outcome of PAD patients compared with IHD patients as observed by the study of Welten et al.<sup>3,6</sup> The REACH registry showed that cardiovascular events increased in a stepwise fashion with the number of symptomatic vascular beds.<sup>4</sup> The combined 1-year outcome of atherothrombotic events ranged from 17% in patients with PAD as a single affected vascular bed to 26% in patients with 3 diseased vascular beds. Patients with PAD undergoing vascular surgery are known to be at higher risk for both early and late cardiovascular events compared to patients with IHD.<sup>3,7</sup> Hertzner's landmark study in 1000 consecutive patients undergoing surgery for PAD who underwent preoperative cardiac catheterizations reported that only 8% had normal coronary arteries, and approximately one third had severe-correctable or severe-inoperable IHD.<sup>8</sup>

## PREOPERATIVE RISK ASSESMENT

Risk stratification is of utmost importance in current clinical practice to identify patients who are at risk of adverse outcome and consequently may benefit from a more aggressive treatment and intensified follow-up. At the other hand, patients at low risk probably need no further risk management. Prior to surgery, the perioperative cardiac risk is commonly assessed using the Lee Risk Index.<sup>8</sup> This index identifies six predictors of major cardiac complications: high-risk surgery, ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease,

insulin therapy for diabetes mellitus, and renal insufficiency. Based on the presence of none, 1, 2, or  $\geq 3$  predictors, the rate of major perioperative cardiac complications was estimated to be 0.4%, 0.9%, 7% and 11%, respectively. In the short term, identification of high-risk patients may direct decisions regarding (non)invasive testing, change of open to endovascular surgery, delay of surgery, and optimal perioperative medical management. In the long term, high risk patients may benefit from more intensified follow-up and aggressive treatment, including pharmacological, invasive and/or behavioural interventions. Although the predictive value of the Lee Risk Index for short term outcomes is well established<sup>9</sup>, studies on the prognostic ability of the Lee Risk Index for late mortality are scarce and for patient-centered outcomes even lacking.

The first part of this thesis covers current knowledge on preoperative cardiac risk assessment. **Chapters 1, 2 and 4** describe an overview of perioperative risk management and risk reduction. The value of the Lee Risk Index on long term mortality and health status is described in **chapter 3**.

## GUIDELINES

When considering a patient for vascular surgery, a careful preoperative clinical risk evaluation and subsequent risk-reduction strategies are essential to reduce postoperative cardiac complications. To assist physicians with decision making, clinical guidelines are developed. The aim of clinical guidelines is to improve patient care by providing recommendations about appropriate health-care in specific circumstances. Development of clinical guidelines is an important component in improving quality of care. The prerequisite for improved quality of care is that a guideline is valid, in other words, adherence to guideline will result in the expected health outcome and the expected costs. Potential benefits of clinical guidelines include reduced morbidity and mortality, improved efficiency and cost containment. Clinical guidelines are ideally based on the best evidence available, supplemented with clinical expertise and patient preferences. For some aspects of clinical care, there may be insufficient evidence available and in such cases, reliance is on expert opinion. The recommendations should ideally be accompanied by a statement of strength of the underlying evidence and expert judgment. Furthermore, design flaws of studies should be discussed as they contribute to bias or poor generalizability. Clinical guidelines provide easily accessible information regarding optimal care. Furthermore, prioritising of research activities can be made according to the gaps in current knowledge stated in the guidelines. Guidelines can also improve the consistency of care; studies across Europe show that the frequency of procedures that are performed varies dramatically between physicians, specialties and geographical regions. Importantly, guidelines are nowadays increasingly used by medical insurers and governmental agencies in rationing healthcare policy.

In 2009 the first European Society of Cardiology (ESC) guidelines on perioperative care were developed.<sup>9</sup> Before, the American College of Cardiology/American Heart Association (ACC/AHA guidelines) were the central guidelines for perioperative care. These ACC/AHA guidelines recommended an algorithm for a stepwise approach to preoperative cardiac assessment.<sup>10</sup> This decision-making process integrates clinical markers, early coronary evaluation, functional capacity and the type of surgery involved. Atherosclerotic risk factor control and optimal pharmacological treatment are key elements of perioperative and long-term management of patients with PAD. Adherence to evidence-based guidelines is a critical component to improve cardiovascular outcome in PAD patients.

The second part of this thesis includes the new ESC guidelines on perioperative care and related topics (**chapters 5-8**). Recent important studies on medical risk reduction strategies included in these guidelines are also discussed (**chapters 9 and 10**).

## **CLOSING THE GAP BETWEEN GUIDELINES AND CLINICAL PRACTICE**

Development of clinical guidelines is important for improving quality of care. Guideline development needs to be completed by evidence-based implementation which should ultimately lead to 'evidence-based clinical practice'. These efforts can be summarised as a cycle of quality improvement (Figure 1). The quality framework follows the Plan-Do-Study-Act (PDSA) cycle.<sup>11</sup> European, national and local education programmes have been developed to inform physicians about guidelines for patient management. Surveys and registries of clinical practice close the circle of quality improvement. The ESC initiated the Euro Heart Survey (EHS) programme in order to evaluate the application of recommended management of cardiovascular diseases in Europe. The programme included surveys and registries in major cardiovascular fields of interests including: Acute Coronary Syndromes, Diabetes, Heart Failure, Stable Angina, Adult Congenital Heart Diseases, Atrial Fibrillation and Percutaneous Coronary Interventions. Clinical data on over 100,000 patients have been collected in 35 countries. The aims of the survey programme were to a) evaluate to which extent clinical practice corresponds with existing guidelines, b) evaluate clinical applicability of guideline-based medicine in every day clinical practice, and c) to evaluate the outcome of different disease management strategies.

The Netherlands Heart Foundation (NHF) recognized the importance of the EHS programme, and supported this initiative through the NHF-Health Care programme (2000T101). In the Netherlands, a combined EHS and NHF-Health Care programme was conducted. Two extra topics were incorporated in the survey programme in the Netherlands; stroke and PAD. The last survey

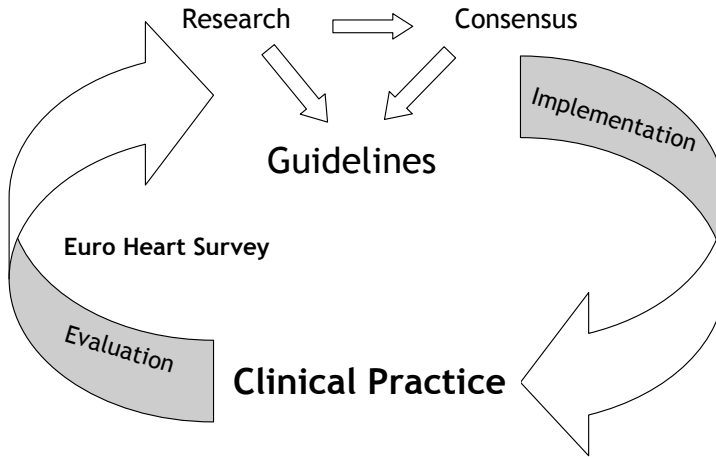


FIGURE 1 - Quality improvement cycle.

will be the main focus of this thesis. In 2005 the EHS survey on PAD was initiated in 11 hospitals in the Netherlands and includes 711 patients.

In part III we investigate the management of patients observed in clinical practice. **Chapter 11** describes the application of noninvasive testing. **Chapters 12 and 14** describe medication use in the perioperative period, whereas **chapter 13** covers medication use during long-term follow-up. **Chapter 15** investigates the the prevalence of smoking in patients undergoing vascular surgery.

## OUTCOME ASSESSMENT

In PAD, mortality is often due to the associated coronary and cerebrovascular disease rather than the PAD directly. As such, treatment of PAD is directed towards the goal of improving symptoms and its associated health status rather than survival only. In general, the principal aim of medical treatment is to relieve symptoms related to the specific disease and to improve the patient's health status and prognosis. The management of patients with PAD has changed in the last decade with the introduction of endovascular techniques and other treatment modalities.<sup>12</sup> Traditionally, treatment success is measured with clinical measures, such as the ankle-brachial index, patency rates, and survival. The question regarding the impact of the intervention on the patient's ability to function in daily life remains, however, when only relying upon these technical measures.<sup>12</sup> Since patients' main concerns are symptom relief and improvement in their daily functioning, treatment should also be assessed by its success in improving patients' health status. In order to quantify the benefits of different treatment strategies and their cost-effectiveness,<sup>13</sup> sensitive patient-centered

outcome measures are increasingly adopted in outcomes research with cardiovascular patients. Furthermore, clinical measures as the ankle-brachial index are known to correlate poorly with changes in health status scores<sup>14,15</sup>, which also supports the use of direct, patient-centered assessments of the effects of treatment on patients' health status. As such, health status is increasingly being assessed in clinical research studies comparing different treatment options.<sup>15,17</sup> Moreover, patient-based outcome measures can provide substantial insights into related clinical factors and processes of care that are useful in assessing healthcare quality. Traditional metrics for evaluating healthcare have been mortality and morbidity, but these measures often lack the sensitivity to differentiate providers and omit a major outcome from the perspective of patients.

In the last part we focus on outcome assessment. The validation of a new disease specific health status questionnaire: the Peripheral Artery Questionnaire is described in **chapters 16 and 17**. The value of self-perceived health status in predicting mortality is discussed in **chapter 18**. **Chapter 19** focuses on the variation in mortality between hospitals after peripheral vascular surgery.

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**Preoperative**

# PART I

## **Risk Assessment**



# CHAPTER

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## Preoperative risk assessment and risk reduction before surgery

# 1

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Don Poldermans

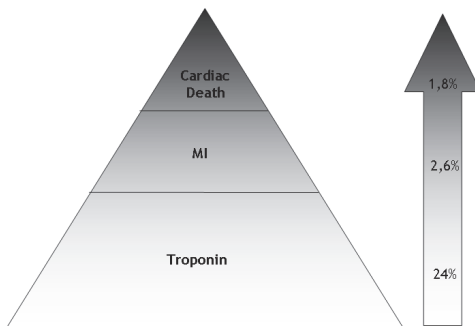
*J Am Coll Cardiol* 2008;51:1913-1924

## ABSTRACT

Perioperative myocardial infarctions are the predominant cause of morbidity and mortality in patients undergoing noncardiac surgery. The pathophysiology of perioperative myocardial infarction is complex. Prolonged myocardial ischemia due to the stress of surgery in the presence of a haemodynamically significant coronary lesion leading to subendocardial ischemia, and acute coronary artery occlusion after plaque rupture and thrombus formation contribute equally to these devastating events. Perioperative management aims at optimizing of the patients' condition by identification and modification of underlying cardiac risk factors and diseases. During recent decades there has been a shift from the assessment and treatment of the underlying culprit coronary lesion, toward a systemic medical therapy aiming at prevention of myocardial oxygen supply demand mismatch and coronary plaque stabilization. Beta-blockers, statins and aspirin are widely used in this setting. The role of prophylactic coronary revascularization has been restricted to the same indications as the nonoperative setting. Therefore preoperative cardiac testing is only recommended if test results will change perioperative management. In addition to the limited perioperative period, physicians should benefit from this opportunity to initiate lifestyle changes and medical therapy to lessen the impact of cardiac risk factors, as patients should live long enough after the operation to enjoy the benefits of surgery.

## INTRODUCTION

Patients undergoing major noncardiac surgery are at significant risk of cardiovascular morbidity and mortality. It is estimated that in Europe 40 million surgical procedures are performed annually, with a postoperative myocardial infarction (MI) rate of 1% (400.000), and a cardiovascular mortality rate of 0.3% (133.000). Although the perioperative event rate has declined over the past 30 years as a consequence of recent developments in anesthesiologic and surgical techniques (e.g. regional anesthesia and endovascular treatment modalities) perioperative cardiac complications remain a significant problem. A pooled analysis of several large studies found a 30-day incidence of cardiac events (perioperative myocardial infarction (PMI) or cardiac death) of 2.5% in unselected patients over the age of 40 years.<sup>1</sup> These complications were higher in vascular surgery patients who had an incidence of 6.2% for cardiac events.<sup>2</sup> The risk of perioperative cardiac complications is the summation of the individual patient's risk and cardiac stress related to the surgical procedure. In addition, the incidence is also related to the postoperative surveillance screening adopted, as the great majority of cardiac events are asymptomatic (Figure 1). Studies that routinely assessed postoperative cardiac isoenzymes (i.e. troponin T or I measurements) detected an incidence of PMI up to 25% in high-risk patients.<sup>3,4</sup>



**FIGURE 1 - Perioperative cardiac events.** The incidence of perioperative cardiac events in major noncardiac surgery. Data from Poldermans et al.<sup>19</sup> MI, myocardial infarction.

According to the World Health Organization, the global epidemic of cardiovascular disease will not only increase, but will also shift from developed to developing nations. It is further estimated that in the second half of the 21st century, more than 1 in 4 individuals will be 65 years of age or older. In the past, major surgery was rarely performed on patients in their '80s or '90s. Nowadays, many major surgical interventions are performed in this very elderly population. A recent study performed in 1,351 patients undergoing noncardiac surgery showed that the rate of cardiac events increased

with advanced age, independent of other clinical variables, in those patients with myocardial perfusion abnormalities during stress scintigraphy.<sup>5</sup> With the growing elderly population, an increased incidence of underlying cardiovascular disease and the availability of advanced surgical techniques, these noncardiac surgery patients continue to demand our attention.

## **PATHOPHYSIOLOGY OF PMI**

Although the pathophysiology of PMI 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 of acute perioperative coronary syndromes. This is similar to the nonoperative setting. The perioperative surgical stress response includes a catecholamine surge with associated haemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation and consequent hypercoagulability.<sup>6</sup> In patients with significant coronary artery disease (CAD), PMI may also be caused by a sustained myocardial supply/demand imbalance due to tachycardia and increased myocardial contractility.<sup>6</sup>

Episodes of perioperative ST-segment depression, indicating subendocardial myocardial ischemia, has been described in up to 41% of vascular surgery patients mostly occurring within the first 2 days after surgery.<sup>7</sup> The association of PMI with myocardial ischemia and non-transmural or circumferential subendocardial infarction supports this mechanism. Landesberg et al. demonstrated that 85% of postoperative cardiac complications were preceded by prolonged ST-segment depression.<sup>8</sup> Fleisher et al. found that 78% of patients with cardiac complications had at least 1 episode of prolonged myocardial ischemia (i.e. >30 min.) either before or at the same time of the cardiac event.<sup>9</sup> In the majority of cases, it presents without Q waves. The hypothesis that ST-segment depression can lead to PMI is further supported by increased troponin T levels during or shortly after prolonged ST-segment depression ischemia.<sup>10</sup>

ST-segment elevation-type ischemia is considered relative uncommon, confirmed by the incidence (12%) of intraoperative ST-segment elevation in a study by London et al.<sup>11</sup> Few data exist on this topic. As demonstrated in the autopsy study by Dawood et al., 55% of the fatal PMIs have direct evidence of plaque disruption defined as fissure or rupture of plaque and haemorrhage into the plaque cavity.<sup>12</sup> Similar autopsy results were found in the study of Cohen and Aretz; a plaque rupture was found in 46% of patient with postoperative myocardial infarction.<sup>13</sup> Time-to-death interval in patients with plaque rupture was significantly longer than in patients without plaque-rupture.

In a submitted study of Feringa et al., 401 vascular surgery patients were evaluated by continuous 12-lead electrocardiographic monitoring during surgery and studied for the presence



and location of ischemia. The relationship with the preoperative assessed culprit coronary artery lesion using noninvasive cardiac imaging was studied. In patients with perioperative ST-segment depression the location corresponded with the preoperatively assessed coronary lesion in 89% and only in 53% of those with ST-segment elevation ( $P < 0.001$ ). This study showed one of the limitations of preoperative cardiac risk assessment focusing on the identification of the culprit coronary artery lesion. Using cardiac testing, one can identify the patient at risk; however, the location of the PMI is difficult to foresee owing to the unpredictable progression of (asymptomatic) coronary artery lesions towards unstable plaques due to the stress of surgery.

## PERIOPERATIVE MANAGEMENT

### Risk stratification

The first step in preoperative care is an adequate identification of patients at risk for perioperative cardiac events. In the past decades, several risk indexes have been developed in this context to stratify surgical patients. Goldman et al.<sup>14</sup> in 1977 developed the first multifactorial risk index specifically for cardiac complications. The risk index was developed in a large surgical population and included 9 independent risk factors correlated with serious or fatal cardiac complications.<sup>14</sup> Subsequently, this index was modified by Detsky et al.<sup>15</sup> in 1986, who used a Bayesian approach using pre-test probabilities and presented the modified cardiac risk index in a simple nomogram. The Revised Cardiac Risk Index, developed in 1999 by Lee et al.<sup>16</sup>, is nowadays the most widely used model of risk assessment in noncardiac surgery. This index identifies 6 predictors of major cardiac complications: high-risk surgery, ischemic heart disease, congestive heart failure, cerebrovascular disease, insulin-dependent diabetes mellitus, and renal failure. Based on the presence of none, 1, 2, or 3 predictors, the rate of major cardiac complications in the validation cohort (n 1,422) was estimated to be 0.4%, 0.9%, 7%, and 11%, respectively. Recently, it was demonstrated in 108,593 patients undergoing all types of noncardiac surgery that this Revised Cardiac Risk Index was indeed predictive of cardiovascular mortality but could be substantially improved by adding age and a more detailed classification of type of surgical procedure (C-statistic improved from 0.63 to 0.85).<sup>17</sup>

### Noninvasive testing

Once the preoperative risk assessment indicates an increased cardiac peri- or postoperative risk, further cardiac testing is warranted. The predominant theme of testing is the impact of test results on perioperative management; if test results will not influence management, testing is not recommended.<sup>18</sup> According to the 2007 guidelines of the American College of Cardiology (ACC) and

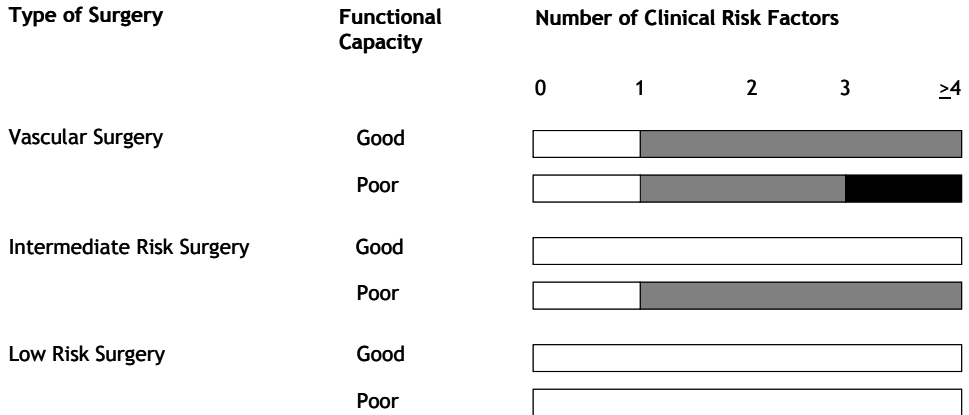
American Heart Association (AHA), patients with active cardiac conditions (i.e., unstable coronary syndromes, decompensated heart failure, significant arrhythmias, or severe valvular disease) have to be evaluated and treated before surgery.<sup>18</sup> Preoperative cardiac testing for elective surgery is reasonable for patients with 3 clinical risk factors and poor functional capacity who require vascular surgery (Class IIa) (Table 1, Figure 2). Preoperative testing may be considered in patients with at least 1 to 2 clinical risk factors and poor functional capacity who require intermediate-risk noncardiac surgery and in patients with at least 1 to 2 clinical risk factors and good functional capacity who are undergoing vascular surgery (Class IIb). Noninvasive testing is not recommended for patients without clinical risk factors undergoing intermediate- or low-risk noncardiac surgery (Class III).

Although preoperative testing may be considered for patients with 1 or 2 risk factors scheduled for vascular surgery, the results of the randomized, multicenter DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo)-II study showed differently. If patients received beta-blockers with tight heart rate control, the perioperative cardiac event rate was already so reduced that test results and subsequent alteration in perioperative management were redundant.<sup>19</sup> No differences in cardiac death and MI at 30 days were observed between 770 patients assigned to no testing versus cardiac stress testing (1.8% vs. 2.3%; odds ratio (OR) 0.78, 95% confidence interval (CI) 0.28 to 2.1). Importantly, preoperative testing delayed surgery for more than 3 weeks.

**TABLE 1 - ACC/AHA classification of recommendation.**

ACC/AHA classification of recommendations	
Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is beneficial, useful, and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III:	Conditions for which there is evidence and/or general agreement that the procedure/ treatment is not useful/effective, and in some cases may be harmful

AHA, American College of Cardiology; AHA, American Heart Association



**FIGURE 2 - Recommendations for noninvasive testing according to the ACC/AHA guidelines (2007).** White bars indicate no recommendations of noninvasive testing and that patients can go directly to surgery; grey bars indicate that patients for whom testing may be considered if it will change management (class IIb); and the black bars indicates a class IIa recommendation for noninvasive testing. ACC/AHA, American College of Cardiology/American Heart Association. Data from Fleisher et al.<sup>18</sup>

Several noninvasive and exercise stress tests are available for perioperative risk assessment. The most commonly used stress test for detecting myocardial ischemia is the treadmill or cycle ergometer test. These tests provide an estimate of the functional capacity and hemodynamic response and detect myocardial ischemia by ST-segment changes. The accuracy varies widely among studies.<sup>20</sup> However, an important limitation in patients undergoing noncardiac surgery is the frequently limited exercise capacity in the elderly and the presence of claudication, arthrosis, or chronic obstructive pulmonary disease. Consequently, nonphysiologic stress tests, such as dobutamine stress echocardiography or dipyridamol myocardial perfusion scintigraphy (MPS), are recommended in patients with limited exercise capacity.

During dobutamine stress echocardiography, incremental doses of dobutamine mimic physical exercise by increasing myocardial contractility and heart rate, leading to enhanced oxygen demand. In a region supplied by a hemodynamically significant coronary artery lesion, myocardial ischemia is induced, leading to contractile dysfunction that can be assessed by echocardiography as new wall motion abnormalities. Dobutamine stress echocardiography is an established test to predict perioperative events in patients undergoing surgery, with a high negative predictive value and a moderate positive predictive value.<sup>18,20-25</sup>

Myocardial perfusion scintigraphy is a widely used imaging technique for preoperative evaluation. This technique involves intravenous administration of a small quantity of a radioactive tracer such as a technetium-99m-labeled radiopharmaceutical. Images are obtained at rest and

during vasodilator stress. Detection of CAD is based on a difference in blood flow distribution during vasodilator stress, induced by insufficient coronary blood flow increment attributed to coronary stenosis. A positive MPS is associated with increased risk of peri- and postoperative cardiac complications. Studies indicate that MPS is highly sensitive for prediction of cardiac complications, but the specificity has been reported as less satisfactory.<sup>20,21,26,27</sup>

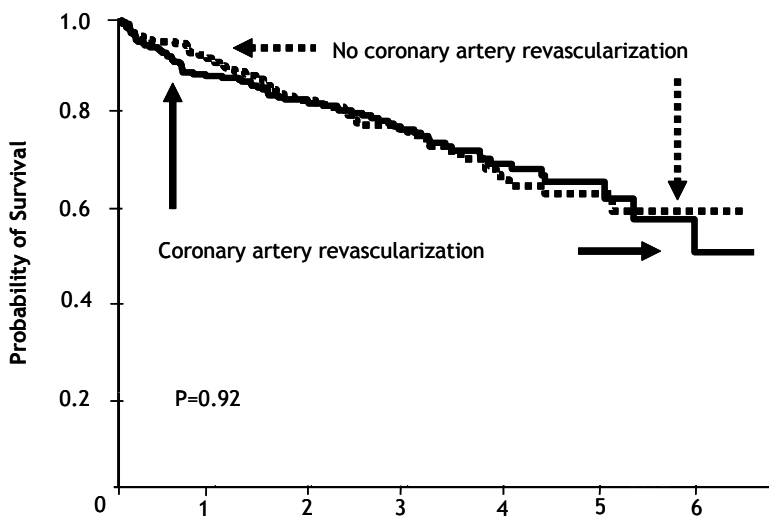
Although no head-to-head comparisons of large numbers of patients have been performed, 2 large meta-analyses have compared these techniques with respect to sensitivity and specificity. The studies by Kertai et al.<sup>20</sup> and Beattie et al.<sup>21</sup> concluded that stress echocardiography was slightly favorable to predict post-operative events owing to the better negative predictive characteristics. However, the literature gives no definite answer in selecting the most accurate test. The choice of the test should therefore be based on the center's experience and short-term availability as highlighted in the ACC/AHA guidelines.<sup>18</sup>

### **Prophylactic revascularization**

Prophylactic preoperative coronary revascularization of the culprit lesion may prevent perioperative complications in patients with significant CAD scheduled for surgery. However, the value of prophylactic revascularization is controversial.<sup>28-30</sup> Whereas former evidence was based on small observational studies and expert opinions, 2 recent randomized controlled trials have clarified this issue. The CARP (Coronary Artery Revascularization Prophylaxis) trial conducted by McFalls et al.<sup>31</sup> was the first randomized trial that investigated the benefit of coronary revascularization before elective major vascular surgery. In that study, 510 patients with significant artery stenosis were randomized to either revascularization or no revascularization before surgery. Within 30 days, no reduction in the number of MIs or deaths or in lengths of hospital stay was observed. Furthermore, as illustrated in Figure 3, long-term outcome in patients who underwent preoperative coronary revascularization was similar to patients who received optimized medical therapy (22% vs. 23% mortality; relative risk (RR) 0.98, 95% CI 0.70 to 1.37). Because the majority of patients in the CARP trial had only 1- or 2-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. In a recent study evaluating vascular surgery patients with predominantly 3-vessel disease, similar findings were obtained.<sup>32</sup> The incidence of the composite end point of all-cause mortality and MI at 30 days was 43% versus 33% (OR 1.4, 95% CI 0.7 to 2.8) and at 1 year was 49% versus 44% (OR 1.2, 95% CI 0.7 to 2.3). Both studies suggest that prophylactic coronary revascularization of cardiac-stable patients provides no benefit for immediate postoperative outcome, although the studies were not

significantly powered to detect differences in outcome. In accordance with this evidence, the new ACC/AHA guidelines indicate that routine prophylactic coronary revascularization is not recommended in patients with stable CAD before noncardiac surgery.<sup>18</sup>

Another important clinical situation is the management of patients with previous coronary stenting undergoing noncardiac surgery.<sup>33</sup> The risk of perioperative stent thrombosis in these patients is increased by the noncardiac surgical procedure, especially when surgery is performed early after stent implantation and particularly if dual antiplatelet therapy is discontinued. When possible, it is advised to delay surgery until after the time window that requires dual antiplatelet therapy. The new ACC/AHA guidelines recommend, based on expert opinion, 30 to 45 days for bare-metal stents and 1 year for drug-eluting stents.<sup>18</sup>



No. at Risk	Time from Randomization (Years)						
	0	1	2	3	4	5	6
Revascularization	226	175	113	65	18	7	
No revascularization	229	172	108	55	17	12	

**FIGURE 3 - Prophylactic coronary revascularization.** Results of the CARP (Coronary Artery Revascularization Prophylaxis) study: long-term survival among patients assigned to undergo coronary artery revascularization or no revascularization. Reprinted with permission from McFalls et al.<sup>31</sup>

### Perioperative Management – new insights

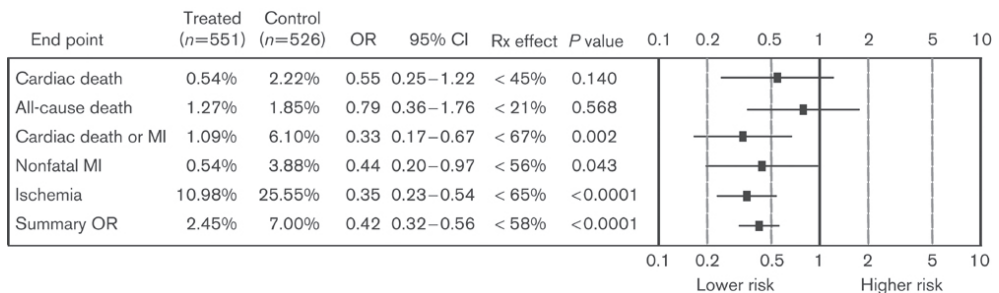
The beneficial effect of a preoperative localized treatment of a coronary stenosis is hampered because of the unpredictable progression of a nonsignificant coronary lesion toward plaque rupture, thrombus formation and subsequent coronary artery occlusion. Plaque instability is driven

by the stress of surgery. Systemic therapy with medical treatment aiming at plaque stabilisation therefore seems promising for perioperative but as well as for long-term risk reduction. Perioperative beta-blockers, statins and aspirin have all shown a significant benefit in decreasing cardiac mortality and morbidity.<sup>34-38</sup> These effects can be divided into acute and chronic effects.

### Beta-blocker therapy

Beta-adrenergic receptor antagonists (beta-blockers) are divided into beta<sub>1</sub>-selective and non-selective (beta<sub>1</sub>- and beta<sub>2</sub>-) adrenoreceptor blockers. Atenolol, metoprolol and bisoprolol, all beta<sub>1</sub>-selective blockers, are commonly used for perioperative care. The classic idea of the benefit of beta-blocking agents is its effect on restoring the oxygen supply/demand mismatch. However, the complexity of the interactions among the heart, the sympathetic nervous system and inflammation also contributes to the benefit of beta-blockade.<sup>39</sup> This latter effect is supposed to evolve only after some time.

Although nowadays widely prescribed, there is still considerable debate about the protective effect of beta-blockers, especially after the results of the POISE trial became available.<sup>40</sup> Some studies showed a clear evidence in favour of beta-blocker use in the perioperative period<sup>35,36</sup>, although other studies failed to demonstrate a cardioprotective effect.<sup>41-43</sup> A recent large meta-analysis by Schouten et al.<sup>44</sup> included 15 studies (1077 patients) showed a significant beneficial effect of beta-blockers in noncardiac surgery patients (Figure 4).



**FIGURE 4 - Perioperative beta-blocker therapy.** Comparison of patients treated with perioperative beta-blocker therapy versus no drug or placebo. CI, confidence interval; MI, myocardial infarction; OR, odds ratio; Rx, treatment. Reprinted, with permission, from Schouten et al.<sup>44</sup>

The recently presented POISE (Perioperative Ischemic Evaluation) study showed a benefit of high-dose metoprolol controlled-release therapy on the risk of MI but, importantly, at the costs of an increased risk of stroke and overall mortality.<sup>40,45</sup> Different explanations exist regarding the conflicting evidence for perioperative beta-blocker use. In particular, the initiation time and dose

of beta-blocker therapy, the type of beta-blocker, dose adjustments for heart rate control, and the patients' underlying cardiac risk are important factors that may relate to the effectiveness of therapy.

### **Initiation time**

It is unclear whether the effect on coronary plaque stabilization, in contrast to heart rate control, can be achieved instantly after beta-blocker start. The onset of beta-blocker therapy before surgery in studies evaluating the cardioprotective effect differs considerably, from months to just hours before operation. Mangano et al.<sup>35</sup> conducted the first randomized controlled trial investigating the effect of beta-blockers in patients undergoing noncardiac surgery. In that trial, 200 patients with known or suspected CAD were randomized for atenolol or placebo just before the induction of anesthesia. No difference in perioperative cardiac events was observed, although the incidence of electrocardiographically assessed ischemia was reduced. The MAVS (Metoprolol After Vascular Surgery) trial randomized 496 patients to metoprolol or placebo starting 2h before surgery until hospital discharge or a maximum of 5 days after surgery.<sup>43</sup> No significant differences in outcome were observed at 30 days after surgery or after 6 months. In the POBBLE (Perioperative Beta-Blockade) trial, 103 patients undergoing vascular surgery who were randomized to metoprolol or placebo, starting less than 24h before surgery until 7 days after, also showed no beneficial effect on 30-day cardiovascular outcome.<sup>41</sup> Within 30 days, cardiovascular events occurred in 32% and 34% patients in the metoprolol and placebo groups, respectively (adjusted RR 0.87, 95% CI 0.48 to 1.55). The DIPOM (Diabetic Postoperative Mortality and Morbidity) trial, which started therapy at the earliest in the evening before major noncardiac surgery, again showed no improved 30-day outcome.<sup>42</sup> The POISE trial randomized patients to receive either controlled-release metoprolol or placebo starting 2 to 4h before surgery and continued for 30 days. In contrast to these studies, the DECREASE-I trial started bisoprolol at an average of 37 (range 7 to 89) days before surgery in 112 high-risk patients. In this period, careful titration of bisoprolol therapy was performed. That study showed a 10-fold reduction in incidence of perioperative cardiac death and MI versus placebo (3.4% vs. 34%;  $P < 0.001$ ).<sup>37</sup>

The importance of the initiation time of beta-blocker therapy before surgery can be argued by the pathophysiology of PMI. The acute effects of beta-blockade include the reduction of myocardial oxygen demand by a decrease in heart rate, systolic pressure, and ventricular contractility. Otherwise, the suggested effect of beta-blockers on coronary plaque stabilization may be related to anti-inflammatory properties and possibly only be observed after prolonged use. Beta-blockade has been shown to decrease the level of

inflammatory cytokines in both the myocardium and the systemic circulation.<sup>46-48</sup> A study in patients with acute MI demonstrated that beta-blocker treatment reduced inflammatory responses only after 48h of treatment.<sup>49</sup>

Although the study of Mangano et al.<sup>35</sup> did not demonstrate a perioperative effect, atenolol use was associated with significantly lower mortality rates at 6 months after discharge (0% vs. 8%;  $P < 0.001$ ), over the first year (3% vs. 14%;  $P < 0.005$ ), and over 2 years (10% vs. 21%;  $P < 0.019$ ). Another randomized trial also showed benefit of beta-blocker use on the long term, even up to 30 months.<sup>37</sup> These findings support the hypothesis that not all effects of beta-blockers are achieved immediately after initiation of therapy. The long-term beneficial effects of beta-blockers were recently confirmed by a study which demonstrated a decreased progression of coronary atherosclerosis in patients receiving beta-blockers. Sipahi et al.<sup>50</sup> performed a pooled analysis of individual patient data from 4 intravascular ultrasonography trials to investigate the relationship between concomitant beta-blocker treatment and the progression of coronary atherosclerosis. The use of beta-blockers was significantly associated with a decrease of the atheroma volume at follow-up, whereas this was not changed in patients without beta-blockers. In addition, it seems to be crucial to continue beta-blockers in the perioperative period. It has been shown that perioperative withdrawal of beta-blocker therapy was associated with a 2.7-fold increased risk of 1-year mortality compared with patients not using beta-blockers.<sup>51</sup>

### **Type**

The predominant perioperative cardioprotective effect is regulated by beta<sub>1</sub>-adrenoreceptor blockade. The perioperative period is associated with high adrenaline and noradrenalin levels<sup>52,53</sup>, creating a potentially dangerous situation in the presence of vulnerable plaques. The danger has 2 aspects: a hemodynamic effect and a stimulation of the inflammatory process. The hemodynamic risk is associated with increased heart rates and blood pressure associated with high sympathetic nerve activity.<sup>7</sup> The beta-blocker benefit could thus clearly be operating via its ability to lower heart rate. Blood pressure and velocity of blood flow rise under the influence of high catecholamine activity, and so beta-blocker normalizes turbulent flow and vessel wall shear forces. However, blocking both beta<sub>1</sub>- and beta<sub>2</sub>-receptors in the presence of raised adrenaline levels during surgery will lead to uncontrolled alpha stimulation and a subsequent adverse rise in blood pressure.<sup>54</sup> Metoprolol and atenolol, which are only moderately beta<sub>1</sub>-selective, may increase myocardial oxygen demand and might therefore be less recommended than the highly beta<sub>1</sub>-selective bisoprolol. In the same vein, the inflammatory process is exacerbated by high noradrenalin levels<sup>55</sup>, undoubtedly acting through beta<sub>1</sub>-receptor overactivity, which increases inflammation, necrosis, apoptosis, and matrix metalloproteinase activity.<sup>56</sup> Interestingly beta<sub>2</sub>-receptor overactivity inhibits the inflammatory necrotic/apoptotic process<sup>57</sup>, thus making beta<sub>2</sub>-blockade

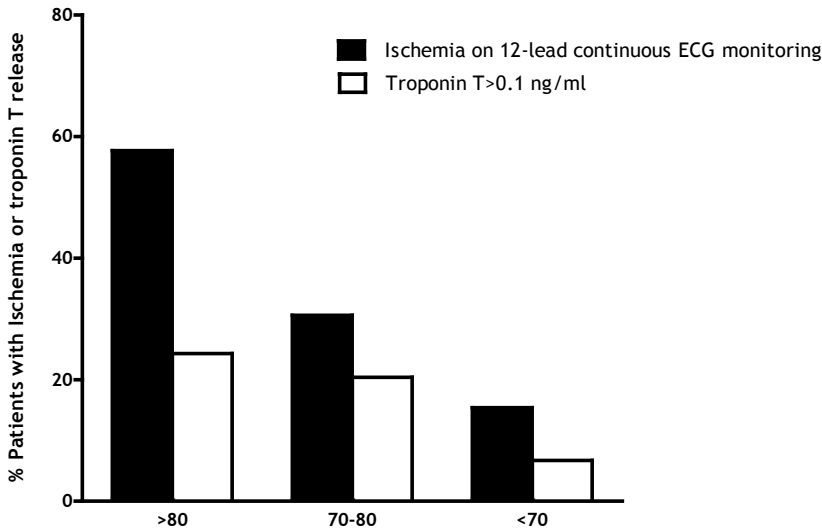


unwelcome. The different beta-blockers have various plasma half-lives and peak ratios. Bisoprolol and atenolol are long-acting agents with half-lives of 10 to 11h and 6 to 7h, respectively, whereas metoprolol has a short duration of action of about 3.5h. A study by Redelmeier et al.<sup>58</sup> in elderly patients undergoing elective surgery reported that long-acting beta-blockers are associated with higher cardioprotective benefits than short-acting beta-blockers in the perioperative period. In patients with CAD/unstable plaques, beta-blockers with short half-lives will increase the risk of a cardiovascular event on sudden withdrawal.<sup>51,59</sup> In the acute absence of beta<sub>2</sub>-blockade, the up-regulated beta<sub>1</sub>-receptors plus high catecholamine levels would be a dangerous mix. Therefore, long-acting beta-blockers, such as bisoprolol, will be safer than agents with short half-lives.<sup>21</sup>

### **Dosing and tight heart rate control**

In addition to the initiation time before surgery and type of beta-blocker, dose adjustment for heart rate control is important. Raby et al.<sup>60</sup> were the first to show positive results on strict heart rate control in 26 patients undergoing major noncardiac surgery. A recent study demonstrated in 272 patients that higher doses of beta-blockers and tight heart rate control were associated with reduced perioperative myocardial ischemia, troponin T release, and improved long-term outcome (Figure 5).<sup>61</sup> Accordingly, the new ACC/AHA guidelines on perioperative care strongly recommend achieving and maintaining a heart rate of 60 to 65 beats/min.<sup>18</sup> Tight heart rate control will increase the likelihood that a patient will receive the benefit of beta-blockade.

The POISE trial initiated randomized treatment of controlled-release metoprolol just before surgery, and the maximum recommended therapeutical dose of metoprolol (400 mg) was already achieved within the first day of surgery.<sup>45</sup> Medication was continued at 200 mg daily afterwards. This is in contrast to the DECREASE studies, where a low dose of bisoprolol at an average 12.5% of maximum recommended therapeutical dose was carefully up-titrated during a mean period of 30 days. The primary findings of the POISE trial were a reduction of perioperative MI by high-dose metoprolol controlled-release therapy, but an excess of overall mortality.<sup>40</sup> They observed an incidence of stroke of 1% in the group randomized to metoprolol compared with an incidence of 0.4% in the DECREASE studies. Several issues have to be clarified in the POISE study to interpret their findings properly. The increased incidence of ischemic stroke in the POISE study in combination with intraoperative bradycardia and hypotension suggests an overtreatment effect. The lesson from the POISE study might be that beta-blockers should be carefully titrated and that the stopping rule of a systolic blood pressure of 100 mm Hg for metoprolol controlled-release therapy might be hazardous in elderly patients with a history of stroke.



**FIGURE 5 - Heart rate control.** Mean heart rate in relation to myocardial ischaemia assessed by continuous electrocardiography and troponin T release. Data from Feringa et al.<sup>61</sup> ECG, electrocardiogram.

### **Cardiac risk**

Another important issue is the identification of surgical patients who may benefit from beta-blocker therapy. The evidence of the beneficial effect of beta-blockers is strongest in high-risk patients. Lindenauer et al.<sup>62</sup> performed a retrospective cohort study of 782,969 patients who underwent major noncardiac surgery to investigate the association of beta-blockers with perioperative outcome. They observed a relationship between cardiac risk and the effect of perioperative beta-blocker use. Beta-blocker use showed no benefit or possible harm in low-risk patients but had a significant beneficial effect in high-risk patients. Important to note is that in the MAVS trial, most patients were at low risk for complications, as almost 60% had a Revised Cardiac Risk Index score of only 1.<sup>43</sup> The negative DIPOM trial also included many low-risk patients.<sup>42</sup> Additionally, in contrast to the ACC/AHA guidelines<sup>18</sup>, in the Juul et al. study<sup>42</sup>, major noncardiac surgery was defined as surgery with an expected duration of 1h.

### **Guidelines**

Recently, the ACC and AHA introduced a guideline update on perioperative beta-blocker therapy.<sup>63</sup> These recommendations are summarized in Table 2. The class I recommendations of these guidelines are to continue beta-blocker therapy in patients already receiving beta-blockers and to start patients with a positive stress test on beta-blockers. Furthermore, beta-blocker therapy is probably recommended for patients undergoing vascular surgery in which preoperative

assessment identifies coronary heart disease or high cardiac risk as defined by the presence of multiple clinical risk factors (Class IIa). The same class of recommendation holds for patients in whom preoperative assessment identifies coronary heart disease or high cardiac risk and who are undergoing intermediate- or high-risk procedures. Class IIb recommendations include patients with intermediate cardiac risk who are undergoing intermediate- or high-risk procedures and patients with low cardiac risk who are scheduled for vascular surgery and are currently not on beta-blockers. Further large randomized trials are definitely needed to give more conclusive recommendations regarding beta-blocker therapy for patients undergoing noncardiac surgery in different risk groups. The ongoing DECREASE-IV study may give more insight into the optimal pharmaceutical prevention with beta-blockers and statins of perioperative cardiovascular complications.<sup>64</sup>

**TABLE 2 - Recommendations for perioperative beta-blocker therapy according to the ACC/AHA guidelines.**

<b>Surgery</b>	<b>No clinical risk factors</b>	<b>≥1 Clinical risk factors</b>	<b>CHD or high cardiac risk</b>	<b>Patients taking beta-blockers</b>
Vascular	Class IIb, B	Class IIa, B	Class I, B	Class I, B
Intermediate Risk	...	Class IIb, C	Class IIa, B	Class I, C
Low Risk	...	...	...	Class I, C

Adapted from Fleisher et al.<sup>17</sup>. Level of evidence according to the ACC/AHA; A = data derived from multiple, randomized, clinical trials; B, data derived from a single randomized trial or non-randomized studies and C = only consensus opinion of experts, case studies, or standard-of-care.

\*Applies to patients found to have coronary ischemia on preoperative testing. \*\*Applies to patients found to have coronary heart disease.

CHD, coronary heart disease; other abbreviations as in Table 1

## **Statins**

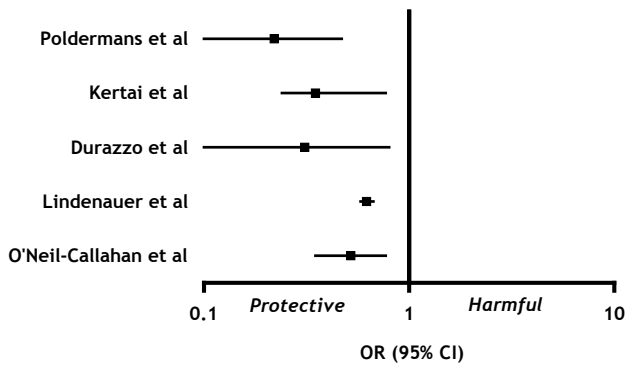
Statins are widely prescribed in patients with or at risk for CAD because of their well-established lipid-lowering capacity. Statins have other important beneficial effects on atherosclerotic vascular disease, which are known as its pleiotropic effects.<sup>65</sup> These effects include atherosclerotic plaque stabilization, oxidative stress reduction, and a decrease of vascular inflammation. In human carotid plaques, statins have been demonstrated to decrease lipids, lipid oxidation, inflammation, matrix metalloproteinase and cell death and to increase tissue inhibitors of metalloproteinase and collagen.<sup>65</sup> These properties of statins may stabilize coronary artery plaques, thereby preventing

plaque rupture and subsequent MI in the perioperative period.

Different large clinical trials in patients with CAD have shown a beneficial effect of statins. The 4S (Scandinavian Simvastatin Survival Study) demonstrated that simvastatin in CAD patients was safe and improved long-term outcome.<sup>67</sup> Importantly, that same research group showed that the beneficial effect of simvastatin is not restricted to coronary atherosclerosis, as statin use was also associated with a reduction of new or worsening intermittent claudication and other noncoronary ischemic symptoms and signs.<sup>68</sup> These positive observations of statin therapy are also observed during vascular surgery (Figure 6). A retrospective case-control study among 2,816 patients who underwent major noncardiac vascular surgery was the first study to show a benefit of statins in the perioperative period. That study demonstrated a 4-fold significant reduction in all-cause mortality (adjusted OR=0.22, 95%CI=0.10-0.47).<sup>36</sup> A year later, the first prospective, placebo-controlled, blinded, randomized clinical trial evaluating the effects of statin therapy on perioperative cardiovascular complications was reported by Durazzo et al.<sup>34</sup> They randomized 100 patients to either 20 mg atorvastatin or placebo for 45 days. The combined cardiovascular endpoint in the trial was defined as cardiac death, non fatal MI, stroke or unstable angina pectoris. After 6 months of follow-up, the incidence of cardiovascular events was more than 3-fold higher with placebo than with atorvastatin (26% vs. 8%;  $P=.031$ ).

Different retrospective trials also evaluated the effects of statin therapy on perioperative complications in patients undergoing noncardiac surgery.<sup>69-71</sup> Lindenauer et al.<sup>70</sup> performed a large retrospective cohort study of 780,591 patients undergoing major noncardiac surgery at 329 hospitals. After correction for numerous baseline differences, the 70,159 statin users had a 1.4-fold reduced risk of in-hospital mortality (adjusted OR=0.62, CI=0.58-0.67). The StaRRS (Statins for Risk Reduction in Surgery) study assessing the effect of statins on cardiac complications in patients undergoing noncardiac vascular surgery also supported the use of perioperative statin therapy.<sup>71</sup> In the retrospective study cohort of 1,163 patients, statin users had a significant lower perioperative complication rate than patients without statin therapy (adjusted OR=0.52, 95% CI=0.35-0.77). The protective effect of statin use was similar across the different risk group categories and persisted after adjusting for the propensity of statin use. Several systematic review articles demonstrated supportive evidence of statin therapy.<sup>72-74</sup>

In addition, the long-term benefit of statins was reported in patients undergoing successful abdominal aortic aneurysm surgery. Kertai et al.<sup>75</sup> followed 510 patients who survived aortic aneurysm surgery for a median of 4.7 years.



**FIGURE 6 - Perioperative statin therapy.** Results of the effect of statin therapy in different studies. CI, confidence interval; OR, odds ratio.

### ***Safety of perioperative statin use***

A major concern of statin therapy are the potential side effects, such as statin-induced myopathy and rhabdomyolysis. Perioperatively, patients might be unaware of these symptoms, owing to sedation, or they are erroneously associated with postoperative surgery complaints. In a retrospective study, Schouten et al.<sup>76</sup> studied 981 consecutive patients undergoing major vascular surgery without PMI to assess the potential risk of myopathy associated with statin therapy. Statin therapy was initiated before surgery in a total of 44 patients with elevated cholesterol levels and continued in 182 patients already taking statin therapy. Blood samples were taken and patients were monitored for muscle complaints at days 1, 3, and 7 after surgery and at discharge. Myopathy was defined as creatine kinase elevations with or without observed muscle complaints. After correcting for cardiac risk factors and clinical risk factors for myopathy, length of surgery remained the only factor independently associated with creatine kinase elevations. Rhabdomyolysis, defined as creatine kinase levels above 10 times the upper limit of normal, was not observed. Considering that the risk of perioperative cardiovascular complications is far greater than the risk of statin-induced myopathy and rhabdomyolysis, the potential benefits of perioperative statin use appear to outweigh the potential hazards. It has to be noticed that these observations need confirmation in large randomized trials.

### ***Dosage and timing***

The optimal dosing and timing of statins for the prevention of perioperative events has still to be elucidated. An important concern is the continuation of statins in the perioperative period. Unintended interruption in the immediate postoperative period is a well-known phenomenon because of the unavailability of an intravenous formula of statins. From patients with CAD, it is known that sudden withdrawal of statin therapy can be harmful.<sup>77,78</sup> Recently, it has been demonstrated in vascular surgery patients that statin discontinuation was associated with an

increased risk for postoperative troponin release (HR 4.6, 95%CI=2.2-9.6) and the combination of MI and cardiovascular death (HR 7.5, 95%CI=2.8-0.1).<sup>79</sup> Furthermore, they observed that the extended release of fluvastatin appeared to have beneficial effects over other statins when discontinued. This increased postoperative risk associated with the withdrawal of statins was also observed by Le Manach et al.<sup>80</sup> These findings indicate that statins with a prolonged half-life time or with an extended release formula should be preferred.

Following the available evidence of both beta-blockers and statins in the perioperative period, the question arises whether these medications should be used as a combination therapy. Some retrospective studies have already reported a beneficial effect of using both beta-blockers and statins on perioperative outcome.<sup>81</sup> The previously mentioned DECREASE-IV trial could give more insights in this topic as it aims to assess the clinical efficacy of beta-blocker, statin, and the combination therapy in patients undergoing major noncardiac surgery.<sup>64</sup>

### **Acetylsalicylic acid**

Acetylsalicylic acid (ASA) is one of the cornerstones in the primary and secondary prevention of cardiovascular diseases. Furthermore, the combination of ASA and clopidogrel is commonly used for the prevention of stent thrombosis. The evidence of ASA in the perioperative period in patients undergoing noncardiac surgery is less clear. In a randomized trial of patients undergoing carotid endarterectomy, ASA showed to be effective in preventing intraoperative and postoperative stroke but had no effect on death or MI.<sup>82</sup> In another trial comparing low-dose and high-dose ASA in carotid surgery, results indicated reduced mortality, MI and stroke in the low-dose group.<sup>83</sup> A meta-analysis of Robless et al.<sup>84</sup> in 2001 demonstrated a reduction of serious vascular events and vascular death in patients with peripheral vascular disease. This study included 10 trials of antiplatelet treatment in lower limb bypass surgery, of which 6 involved ASA treatment. However, the benefit of antiplatelet therapy did not reach statistical significance for the combined endpoint of vascular events (OR=0.76; 95% CI 0.54-1.05) in that vascular surgery population. Concerns of promoting perioperative hemorrhagic complications often withheld continuation of ASA in the perioperative period. No randomized controlled trials exist, however, on preoperative discontinuation of ASA. A meta-analysis of Burger et al.<sup>85</sup> concluded that ASA should be discontinued if low-dose ASA may cause bleeding risks with increased mortality or if sequels similar to the observed cardiovascular risks after ASA withdrawal. In 41 studies they observed that ASA increased the risk of bleeding complications by 1.5-fold but did not lead to higher severity levels of bleeding complications. A systematic review in subjects at risk for or with CAD demonstrated that ASA nonadherence/withdrawal was associated with 3-fold higher risk of major adverse cardiac events (OR=3.14 [1.75-5.61],  $P < .001$ ).<sup>86</sup>

## CONCLUSION

In the growing elderly population with an increased cardiovascular comorbidity, underlying ischemic heart disease in surgical patients is becoming a key problem. Myocardial infarctions are the major cause of perioperative morbidity and mortality. The pathophysiology of a PMI is related to the stress of surgery, inducing an oxygen supply/demand imbalance in the presence of a coronary artery stenosis or a sudden coronary plaque rupture with thrombosis and vessel occlusion. In the latter condition, inflammation plays a major role. To prevent these devastating conditions, multiple, systemic strategies are required. Beta-blockers correct the imbalance between myocardial oxygen supply and demand, and statins and aspirin will focus on plaque stabilization by a reduction of the inflammatory response. Moreover, current data clearly reveal a shift from preoperative coronary revascularization towards intensified medical treatment. Current recommendations of prophylactic coronary revascularization have been restricted to the same indications as the nonoperative setting. In cardiac stable patients noninvasive cardiac stress testing is therefore indicated only if it will change management. In high-risk patients, prophylactic coronary revascularization might be switched to later post-operative revascularization, preventing the delay of surgery. The optimal timing of beta-blocker therapy before surgery has not been resolved yet. Beta-blockers have both a hemodynamic and anti-inflammatory effect. To obtain maximum benefits of beta-blockade, therapy should be initiated at least some days before surgery in combination with dose adjustments for tight heart rate control. Furthermore, it is strongly advised to continue the beta-blocker therapy throughout the perioperative period. The pleiotropic effects of statins have also been shown beneficial in patient undergoing noncardiac surgery. The preoperative risk assessment is an ideal opportunity to initiate life-style changes and medical therapy to lessen the impact of cardiac risk factors to improve both perioperative and long-term outcome.

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# CHAPTER

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## Noncardiac surgery in cardiac patients



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# 2

## SUMMARY

The number of cardiac patients undergoing noncardiac surgery is steadily increasing. Some patients may be at substantial risk of perioperative morbidity and mortality. In this respect, vascular surgery is considered as high-risk surgery. Perioperative myocardial infarctions are the predominant cause of morbidity and mortality in patients undergoing noncardiac surgery. The pathophysiology of perioperative myocardial infarction is complex. Prolonged myocardial ischemia due to the stress of surgery, in the presence of a hemodynamically significant coronary lesion leading to subendocardial ischemia, and acute coronary artery occlusion after plaque rupture and thrombus formation, contribute equally to these devastating events. Preoperative management aims at optimizing of the patients' condition by identification and modification of underlying cardiac risk factors and diseases. Beta-blockers and statins are widely used in this setting. In contrast, the role of prophylactic coronary revascularization has been restricted to the same indications as the non-operative setting. This chapter will review the main aspects of perioperative care and management of cardiac patients undergoing noncardiac surgery in line with the recent European Society of Cardiology guidelines on perioperative care.

## INTRODUCTION

Patients undergoing noncardiac surgery are at increased risk of cardiovascular morbidity and mortality. Hertzner's landmark study in 1000 consecutive patients undergoing operations for peripheral arterial disease (PAD) who underwent preoperative cardiac catheterizations reported that only 8% of their patients (who were roughly divided into thirds—aortic, infrainguinal, and carotid disease) had normal coronary arteries, and approximately one-third had severe-correctable or severe-inoperable coronary artery disease (CAD).<sup>1</sup> More recent studies using functional tests for CAD, such as dobutamine stress echocardiography, confirmed these findings. In a study population of 1097 vascular surgical patients, the incidence of rest wall-motion abnormalities was nearly 50%, while one-fifth of patients had stress-induced myocardial ischemia.<sup>2</sup> Careful management of patients undergoing surgery is therefore mandatory in the perioperative setting. In general, the risk of perioperative complications depends on the condition of the patient prior to surgery, the prevalence of comorbidities, and the severity and duration of the surgical procedure. Cardiac complications are especially suspected in patients with documented or hidden CAD undergoing procedures that are associated with prolonged hemodynamic and cardiac stress.

Although the perioperative event rate has declined over the past decades as a result of achievements in anaesthesiologic and surgical techniques, perioperative complications remain a significant problem. Importantly, a large study showed that long-term prognosis of vascular surgery patients was significantly worse than for patients with CAD.<sup>3</sup> Estimations of cardiac outcome can be derived from the few large-scale clinical trials and registries that have been undertaken in patients undergoing noncardiac surgery. Lee et al. studied 4,315 patients undergoing elective major noncardiac procedures in a tertiary-care teaching hospital during 1989-1994.<sup>4</sup> Major cardiac complications, including cardiac death and myocardial infarction (MI), were observed in 2.1% of this patient cohort. In a cohort of 108,593 consecutive patients who underwent surgery during 1991-2000 in a university hospital in The Netherlands, perioperative mortality occurred in 1877 (1.7%) cases, of whom 543 (0.5%) were attributed to cardiovascular causes. The Dutch Echographic Cardiac Risk Evaluating Applying Stress Echo (DECREASE) -I, -II and -IV trials enrolled 3,893 surgical patients during 1996-2008, consisting of intermediate- and high-risk patients, and 136 (3.5%) had perioperative cardiac death or MI.<sup>5,7</sup> The recently published RCT PeriOperative ISchemic Evaluation trial (POISE) randomized 8,351 patients who underwent noncardiac surgery in the period 2002-2007 and perioperative mortality occurred in 226 patients (2.7%), of whom 133 (1.6%) had cardiovascular death, whereas nonfatal MI was observed in another 367 (4.4%) subjects.<sup>8</sup> Overall, major noncardiac surgery is associated with an incidence of cardiac death between 0.5% and 1.5%, and an incidence of major cardiac complications in the range of 2.0% to 3.5%.

The global ageing phenomenon will have a major impact on perioperative management in future years. Ageing of the world's population can be seen as an indicator of improving global health but also enforces a change in health care toward the elderly population. Furthermore, the burden of cardiovascular disease (CVD) will even further increase in the coming years. It is estimated from primary care data that in the 75–84 year age group 19% of males and 12% of women have some degree of CVD.<sup>9</sup> In contrast to the past, major surgical interventions are increasingly performed in the elderly. Demographics of patients undergoing surgery indeed show a trend toward an enlarged number of preoperative risk factors, including increasing age and more comorbidities.<sup>10</sup>

With the growing elderly population, increased incidence of CVD, and the availability of advanced surgical techniques, preoperative cardiac risk assessment and perioperative cardiac management continues to be a major challenge.

## **PATHOPHYSIOLOGY OF MYOCARDIAL INFARCTION**

Perioperative myocardial infarction (PMI) is one of the most important predictors of short- and long-term morbidity and mortality associated with noncardiac surgery. The highest incidence of PMI is within the first 3 days after surgery ( $\pm 5\%$ ).<sup>11–13</sup> The prevalence of acute coronary syndrome with symptomatic or asymptomatic perioperative myocardial ischemia assessed by serum troponin I or T in major vascular surgery patients is high, even 15% to 25%. Hence, the prevention of a PMI is the cornerstone for improvement in overall postoperative outcome. To achieve this, knowledge about the pathophysiology of a PMI is essential.

Unfortunately the exact underlying mechanism of a PMI is still not clear, but seems to be the same as in other settings. Coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion, is considered to be an important cause of acute perioperative coronary syndromes. This is similar to MIs occurring in the non-operative setting. Surgery itself is a significant stress factor leading to an increased risk of plaque rupture. The perioperative surgical stress response includes a catecholamine surge with associated hemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation, and consequent hypercoagulability.<sup>11</sup> Two retrospective studies investigated the coronary pathology of fatal PMI. As demonstrated in the autopsy study by Dawood and colleagues, 55% of the fatal perioperative MIs have direct evidence of plaque disruption defined as fissure or rupture of plaque and haemorrhage into the plaque cavity.<sup>14</sup> Similar autopsy results were found in the study of Cohen and Aretz; a plaque rupture was found in 46% of patients with postoperative MI.<sup>15</sup> Time-to-death interval in patients with plaque rupture was significantly longer than in patients without plaque-rupture.

In patients with significant CAD, PMI may also be caused by a sustained myocardial supply/demand imbalance due to tachycardia and increased myocardial contractility.<sup>11</sup> Episodes of perioperative ST-depression, indicating subendocardial myocardial ischemia, has been described in up to 41% of vascular surgery patients, mostly occurring within the first two days after operation.<sup>16</sup> The association of PMI with myocardial ischemia and non-transmural or circumferential subendocardial infarction supports this mechanism. Landesberg and colleagues demonstrated that 85% of postoperative cardiac complications were preceded by prolonged ST-segment depression.<sup>17</sup> Fleisher and colleagues found that 78% of patients with cardiac complications had at least one episode of prolonged myocardial ischemia (i.e. >30 minutes) either before or at the same time of the cardiac event.<sup>18</sup> In the majority of cases, it presents without Q waves. The hypothesis that ST-depression can lead to PMI is further supported by increased troponin T levels during or shortly after prolonged ST-depression ischemia.<sup>19</sup>

ST-elevation-type ischemia is considered relative uncommon, confirmed by the incidence (12%) of intraoperative ST-elevation in a study by London and colleagues.<sup>14</sup> Few data exist on this topic. Using cardiac testing, one can identify the patient at risk; however, the location of the PMI is difficult to foresee due to the unpredictable progression of (asymptomatic) coronary artery lesions towards unstable plaques during the stress of surgery.

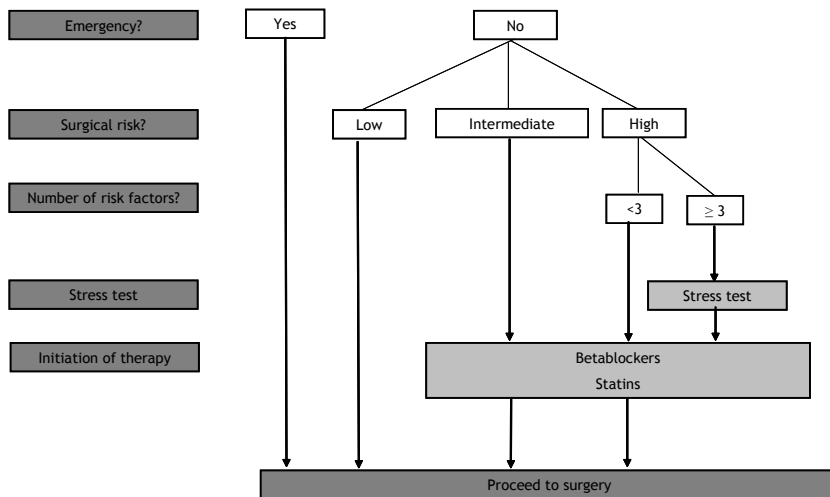


FIGURE 1 - Decision tree for perioperative care.

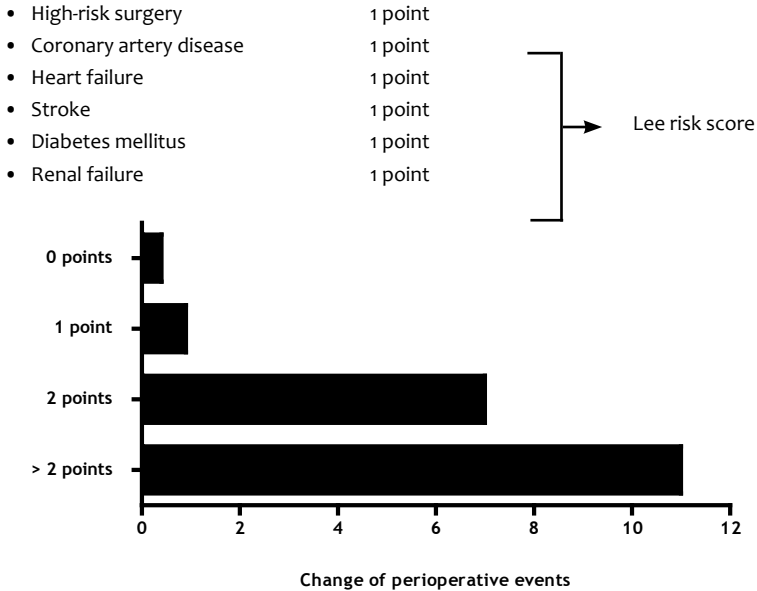
# RISK STRATIFICATION

The first question arising in perioperative care is which patients are at risk for perioperative cardiac events. This is an important issue as patients with a suspected low cardiac risk can be operated on safely without any delay while patients with an increased cardiac risk could benefit from preoperative risk reduction strategies (Figure 1). In this context, adequate risk stratification of patients undergoing noncardiac surgery is of utmost importance. Several risk indices have therefore been developed in the past decades for noncardiac surgery patients. Goldman and colleagues were in 1977 the first to develop a multifactorial risk index specifically for perioperative cardiac complications. This risk index was developed in a noncardiac surgical population and included 9 independent risk factors correlated with major cardiac complications.<sup>20</sup> This index was subsequently modified by Detsky and colleagues in 1986, who added the presence of angina and a remote history of MI to the original model.<sup>21</sup>

Nowadays, the Lee Index is considered by many clinicians and researchers to be the best currently available cardiac risk prediction model in noncardiac surgery.<sup>4</sup> This risk index was developed in 1999 on a cohort of 2893 consecutive patients who underwent a wide spectrum of procedures. The Lee Index consists of six independent predictors of major cardiac complications: high-risk surgery, ischemic heart disease, congestive heart failure, cerebrovascular disease, insulin-dependent diabetes mellitus, and renal failure (Figure 2). All factors contribute equally to the index with each factor assigned to 1 point. The incidence of major cardiac complications in the validation cohort (n=1422) was estimated at 0.4%, 0.9%, 7% and 11% in patients with an index of 0, 1, 2, or ≥3 points, respectively. Evidence exists in 108,593 patients undergoing all types of noncardiac surgery that this revised cardiac risk index was indeed predictive of cardiovascular mortality but could be substantially improved by adding age and an extensive description of the type of surgery (C-statistic improved from 0.63 to 0.85).<sup>22</sup> The Lee Index was also included in the algorithm of the 2007 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines on perioperative cardiovascular evaluation. Furthermore, it was recently shown that the preoperative Lee Index is not only an important prognostic factor for in-hospital outcome but also for late mortality and impaired health status in patients with PAD.

## Surgery

The extent of preoperative cardiac evaluation will also depend on the type and the urgency of surgery in question.<sup>22-24</sup> Every operation will elicit a stress response to injury. This response is initiated by tissue injury and mediated by neuro-endocrine factors inducing tachycardia and hypertension. Fluid shifts in the postoperative period add to the surgical stress. This stress will influence the balance between myocardial oxygen supply and demand. Surgery will also cause



**FIGURE 2 - Risk factors according to the Lee risk index.<sup>4</sup>**

alterations in the balance between prothrombotic and fibrinolytic factors resulting in hypercoagulability (elevation of fibrinogen and other coagulation factors, increased platelet aggregation and activation, reduced fibrinolysis). This is relative to the extent and duration of the intervention. Other factors that can influence cardiac stress are blood loss, perioperative fluid shifts and body core temperature. These may cause hemodynamic changes and/or cardiac depression and are related to an increased cardiac risk.

Firstly, the urgency of the surgery determines the weight of cardiac evaluation. In case of truly emergency and life-saving operations such as ruptured abdominal aortic aneurysm, or major trauma, cardiac evaluation will not change the course and result of the intervention. However, it can influence the management in the immediate postoperative period. With regard to cardiac risk, surgical interventions can be divided into a high-, intermediate- and low-risk group with an estimated event rate of <1%, 1-5% and >5%, respectively (Table 1).

**TABLE 1 - Cardiac risk from surgical interventions**

## Low risk: &lt;1%

Breast  
Dental  
Endocrine  
Eye  
Gynecology  
Reconstructive  
Orthopedic- minor  
Urologic- minor

## Intermediate: 1-5%

Abdomial  
Carotid  
Head- and neck surgery  
Neurological  
Orthopedic - major  
Pulmonary  
Renal transplant  
Urologic -major  
Peripheral angioplasty  
Endovascular aneurysm repair

## High risk: &gt;5%

Aortic and major vascular surgery  
Peripheral vascular surgery

In cases of non-emergent but urgent surgical conditions, such as bypass for acute limb ischemia or treatment of bowel obstruction, cardiac evaluation may influence the perioperative measures taken to reduce the cardiac risk but will not influence the decision to perform the intervention or allow for prophylactic coronary revascularization. When cardiac risk evaluation in patients scheduled for elective surgery demonstrates high cardiac risk, less invasive interventions such as peripheral angioplasty instead of infra-inguinal bypass can be considered. Moreover, it can be decided to delay or cancel the intended surgical intervention in case of high estimated risk.

Special attention is given to vascular procedures as they are categorized as high-risk procedures. Furthermore, although minimally invasive, the risk associated with peripheral angioplasties should not be neglected. Long-term survival does not seem to be influenced by the surgical technique that is used, but is determined by underlying cardiac disease.<sup>25</sup>



## Chronic Heart Failure

The prevalence of chronic heart failure (CHF) is high in the overall population and still increasing. Furthermore, it has been suggested that the prevalence of patients with symptomatic CHF is similar to the prevalence of patients with asymptomatic CHF, which may lead to an underestimation of the extent of heart failure in the general population.<sup>26</sup> Chronic heart failure can be considered as a large health problem with major clinical impact. The prognosis of patients with diagnosed CHF is poor. Half of the patients will die within 4 years and of patients diagnosed with severe heart failure >50% will die within 1 year.<sup>27</sup>

The effect of CHF on postoperative outcome was first described by Kazmers et al. who concluded that survival rates are reduced in patients with an impaired left ventricular (LV) ejection fraction being  $\leq 35\%$ .<sup>28</sup> Historically, heart failure is also part of many different cardiac risk stratification models.<sup>4,20-22,29</sup> Although previous studies emphasize ischemic heart disease as the most important risk factor for perioperative complications, heart failure has been suggested to be equally important.<sup>30</sup> Recently, Hammil et al. demonstrated that elderly patients with heart failure who undergo major noncardiac surgery have an increased risk of operative mortality and hospital readmission compared to CAD patients.<sup>31</sup> They noted that improvements in perioperative care are needed for this growing population of heart failure patients undergoing surgery. Coupled to the growing prevalence of CHF and the elderly population, is the increase in surgical procedures. Therefore, adequate treatment of CHF in the perioperative setting is of pivotal importance to reduce morbidity and mortality after noncardiac surgery. Perioperative management of these patients is aimed at optimizing hemodynamic status and providing intensive postoperative surveillance. In 2006, Feringa et al. concluded that the use of beta-blockers in patients with heart failure undergoing major vascular surgery was associated with a reduced incidence of in-hospital and long-term postoperative mortality.<sup>32</sup> Statins, angiotensin-converting enzyme (ACE)-inhibitors and aspirin may also be of benefit in patients with LV dysfunction because these patients frequently have CAD comorbidity.

Recent studies showed that an increased plasma level of N-terminal pro-B-type natriuretic peptide (NT-proBNP) or B-type natriuretic peptide (BNP) is associated with adverse postoperative outcome. NT-proBNP is increased in patients with LV dilatation caused by fluid overload (e.g., CHF and renal dysfunction), pressure overload (e.g., aortic valve stenosis) and myocardial ischemia, which might explain the excellent correlation with adverse postoperative outcome. Feringa et al. reported on the prognostic value of NT-proBNP in 170 patients scheduled for major vascular surgery. Patients with NT-proBNP levels  $>533$  pg/ml had an independent 17-fold increased risk for postoperative cardiac events, even after adjustment for preoperative dobutamine stress echocardiography results (Figure 3).<sup>33</sup> The general assessment of postoperative patients with decompensated heart failure should be focussed on evaluating asymptomatic and unstable

myocardial ischemia. The diagnosis of postoperative MI is often difficult to make since it often presents atypically and may have a different aetiology compared to non-postoperative MI. The evaluation of postoperative MI should include cardiac monitoring, electrocardiography, and serial cardiac enzyme measurements. Special attention should be given to perioperative volume infusion since excessive fluid administration is a common cause of decompensated heart failure. Once the aetiology of postoperative decompensated heart failure is diagnosed, treatment should be no different compared to the management of CHF during a general medical service admission.<sup>19</sup>

### Valvular Disease

Valvular heart disease (VHD) is a common finding in patients presenting for noncardiac surgery. These patients are known to be at increased risk for perioperative cardiovascular complications during noncardiac surgery.<sup>34</sup> Aortic stenosis is the most common VHD in Europe, particularly among the elderly.<sup>35</sup> Severe aortic stenosis (defined as aortic valve area  $<1 \text{ cm}^2$ ,  $<0.6 \text{ cm}^2/\text{m}^2$  body surface area) constitutes a well established risk factor for perioperative mortality and MI.<sup>36</sup> In symptomatic patients, aortic valve replacement should be considered before elective surgery. In patients who are not candidates for valve replacement due to either high risk associated with serious comorbidities or those who refuse, noncardiac surgery should be performed only if strictly needed. In these patients percutaneous balloon aortic valvuloplasty may be reasonable therapeutic option before surgery.<sup>34</sup>

Noncardiac surgery can be performed at relatively low risk in patients with nonsignificant mitral stenosis (valve area  $>1.5 \text{ cm}^2$ ) and in asymptomatic patients with significant mitral stenosis (valve area  $<1.5 \text{ cm}^2$ ) and systolic pulmonary artery pressure  $<50 \text{ mmHg}$ .

Nonsignificant aortic regurgitation and mitral regurgitation do not independently increase risk of cardiovascular complications during noncardiac surgery. Patients with severe mitral regurgitation and aortic regurgitation may benefit from optimization of pharmacological therapy to produce maximal hemodynamic stabilization before high-risk surgery.

### Renal

A decreased level of kidney function is an independent risk factor for adverse postoperative CVD outcomes including MI, stroke, and progression of heart failure. Traditionally, this function is assessed by serum creatinine concentration. For example, the serum creatinine cut-off value of  $>2.0 \text{ mg/dL}$  ( $177 \text{ mmol/L}$ ) is used in the Lee index.<sup>4</sup> However, creatinine clearance ( $\text{ml/minute}$ ) incorporating serum creatinine, age, and weight provides a more accurate assessment of renal function than serum creatinine alone. Most commonly used is the Cockcroft-Gault formula<sup>37</sup>:  $([140 - \text{age in years}] \times [\text{weight in kg}] \times 0.85 [\text{if female}]) / (72 \times \text{serum creatinine in mg/dl})$ . Kertai et al. evaluated 852 subjects undergoing major vascular surgery and demonstrated an increase in

mortality as serum creatinine was  $>2.0$  mg/dl, experiencing odds for perioperative mortality of 5.2 (95% confidence interval (CI) 2.9-10.8).<sup>38</sup> However, it might be argued that patients with less pronounced renal insufficiency also do worse compared to patients with normal serum creatinine values. Using creatinine clearance among the entire strata of renal function a 10 ml/min decrease in creatinine clearance was associated with a 40% increased risk of postoperative mortality (odds ratio (OR) 1.4; 95%CI 1.2-1.5; receiver operating characteristic (ROC) area: 0.70, 95%CI 0.63-0.76). ROC curve analysis showed that the cut-off value of 64 ml/min for creatinine clearance yielded the highest sensitivity/specificity to predict postoperative mortality.

In addition to the preoperative renal function, changes in kidney function in the postoperative period frequently occur and are predictive for adverse outcome. Ellenberger and colleagues reported an elevated mortality within 30 days after elective abdominal aortic surgery in patients with a serum creatinine  $>0.5$  mg/dl, within 3 days after surgery, compared with baseline value.<sup>39</sup> Furthermore, worsening of kidney function in the postoperative period has shown to be a prognostic factor for late outcome. In 1324 patients who underwent elective open abdominal aortic aneurysm surgery creatinine clearance was measured preoperatively and on days 1, 2, and 3 after surgery.<sup>40</sup> Patients were divided into 3 groups according to the change in renal function after surgery compared to baseline. Group 1 showed an improved or unchanged (change in creatinine clearance,  $\pm 10\%$  of function compared with baseline); group 2 showed a temporary worsening (worsening  $>10\%$  at day 1 or 2, then complete recovery within 10% of baseline at day 3); and group 3 experienced a persistent worsening ( $>10\%$  decrease compared with baseline). Mortality during 30 days after surgery was 1.3%, 5.0%, and 12.6% in groups 1 to 3, respectively. Adjusted for baseline characteristics and postoperative complications, 30-day mortality was the greatest in patients with persistent worsening of renal function (hazard function (HR) 7.3; 95%CI 2.7-19.8), followed by those with temporary worsening (HR 3.7; 95%CI 1.4-9.9). During  $6.0 \pm 3.4$  years of follow-up, 348 patients (36.5%) died. Risk of late mortality was 1.7 (95%CI 1.3-2.3) in the persistent-worsening group followed by those with temporary worsening (HR 1.5; 95%CI 1.2-1.4). This study showed that although renal function may recover completely after aortic surgery, temporary worsening of renal function was associated with an increased long-term mortality.

Identification of patients who might experience perioperative worsening of renal function is important in order to initiate supportive measures as maintenance of adequate intravascular volume for renal perfusion and vasopressor use. In a large retrospective study, risk factors for postoperative acute renal failure within the first 7 days after major noncardiac surgery among patients with previously normal renal function were evaluated. Thirty-day, 60-day, and 1-year all-cause mortality was also evaluated. A total of 65,043 cases between 2003-2006 were reviewed.<sup>41</sup> Of these, 15,102 patients met the inclusion criteria; 121 patients developed acute renal failure (0.8%), and 14 required renal replacement therapy (0.1%). Seven independent preoperative predictors

were identified ( $P < 0.05$ ): age, emergency surgery, liver disease, body mass index, high-risk surgery, peripheral arterial occlusive disease, and chronic obstructive pulmonary disease (COPD) necessitating chronic bronchodilator therapy.

### **Neurological**

Stroke is one of the leading causes of death in the Western world and an established risk factor in noncardiac surgery. The risk of clinically apparent perioperative brain injury varies widely among different types of surgery and depends on the type and complexity of the surgical procedure. Whereas patients undergoing general surgery appear to be at low risk (0.08-0.7%), those undergoing heart valve surgery and aortic arch repair have a high incidence of perioperative stroke (8-10%).<sup>42-44</sup> The increasing population of elderly patients undergoing surgery will draw even further attention to the risk of cerebrovascular diseases in this population. Importantly, the true incidence of cerebral complications is probably underestimated because of lack of major sensory-motor symptoms or the presence of only subtle neuropsychological deficits, which are more difficult to identify. Perioperative strokes are predominantly ischemic and embolic instead of related to hypoperfusion. Risk factors for perioperative (a)symptomatic transient or permanent cerebrovascular events (transient ischemic attack/stroke) are embolism or hemodynamic compromise in large (aorta, carotid, vertebral and main cerebral arteries intracranially) or small vessels (perforating and penetrating arterioles and capillaries). The diagnosis of significant carotid stenosis itself is a major indicator of the atherosclerotic burden associated with an increased stroke risk. Although fatal and nonfatal stroke can be reduced significantly in symptomatic patients with moderate/severe carotid stenosis associated with ipsilateral symptoms in particular if treated early, the benefit of this interventional/surgical treatment might be smaller in neurologically asymptomatic subjects. Preoperative risk evaluation should carefully identify patients and procedure-related factors associated with an increased risk of perioperative stroke to evaluate the individual risk:benefit ratio and optimize care, including appropriate risk modification and timing of surgery. A history of recent stroke or transient ischemic attack is a strong predictor for perioperative stroke. Therefore, physicians should inquire specifically about the history of cerebrovascular events and treat the patient accordingly.

### **Arrhythmias**

Cardiac arrhythmias are frequent perioperative cardiovascular abnormalities in patients undergoing both cardiac and noncardiac surgery. Their significance must be considered in association with many other factors, especially the presence and severity of underlying heart disease, since their presence alone is usually of little importance.

### Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease is associated with CVD, increasing the risk by 2 to 3-fold for cardiovascular mortality. For every 10% reduction in forced expiratory volume at 1s (FEV<sub>1</sub>) value, the risk of nonfatal coronary events increased with 20% and the risk of cardiovascular mortality with 28%.<sup>45</sup> Consequently, it might be suggested that the presence of COPD affects postoperative cardiac outcome in surgical patients. Although contradictory results have been reported on 30-day mortality in patients undergoing surgical repair of abdominal aortic aneurysm<sup>46-48</sup>, there is no consistent evidence indicating that COPD is associated with higher risk of perioperative cardiac complications and death in patients undergoing noncardiac vascular surgery. Preoperative identification of patients with COPD might encourage clinicians to start a more stringent pulmonary therapy and may reduce the perioperative cardiac morbidity and mortality. In contrast to the small postoperative cardiac risk, pulmonary complications frequently occur in surgical patients with COPD, especially after abdominal or thoracic surgery. Preoperative COPD management is therefore important in these surgical patients including optimization of pulmonary function to prevent deterioration during or after surgery. Bronchodilators and/or corticosteroids are essential in the preoperative pulmonary management of patients with COPD.

Although beta-blockers are often recommended in patients undergoing noncardiac surgery<sup>24</sup>, beta-blockers are frequently withheld from patients with concomitant COPD because of fear of bronchoconstriction from blockade of beta<sub>2</sub>-adrenoreceptors. Nevertheless, there is substantial evidence that cardioselective beta-blockers can be used in COPD patients without provoking bronchospasm and pulmonary deterioration.<sup>49,50</sup> In addition, (cardioselective) beta-blockers are associated with reduced 30-day (and long-term) mortality in COPD patients after vascular surgery.<sup>51</sup> However, even cardioselective beta-blocking agents have slight effects on the beta<sub>2</sub>-adrenoreceptors, and these medications still need to be used cautiously in patients with COPD. The drug should be initiated at a low dose and, if tolerated well, carefully increased to the target dose.

In addition to beta-blockers, statins are also associated with reduced 30-day mortality and long-term mortality in vascular surgery patients with concomitant COPD.<sup>52</sup> Besides of this, it is suggested that statins might have additional effects in patients with COPD because of the anti-inflammatory properties associated with a reduced number of hospitalizations<sup>53</sup>, exacerbations and intubations.<sup>54</sup> However, more research is needed before new therapeutic strategies can be made.

## NONINVASIVE TESTING

When the preoperative risk assessment identifies a patient with an increased cardiac risk, or if there is a suspicion of CAD upon examination, further cardiac testing is warranted in this patient.<sup>24</sup>

A Dutch survey showed poor agreement between ACC/AHA guideline recommendations and daily clinical practice.<sup>55</sup> Only 1 of every 5 patients underwent noninvasive testing when recommended. Furthermore, patients who had not undergone testing despite recommendations received as little cardiac management as the low-risk population. The goals of noninvasive risk stratification are:

1. to identify patients at extremely high risk in whom surgery should be cancelled, or another less hazardous procedure should be considered;
2. to identify those patients in whom the optimization of medical therapy or a coronary revascularization before surgery might reduce the risk of the surgical procedure;
3. to identify those patients in whom an invasive and intensive monitoring might reduce the risk of perioperative events;
4. to assess the long-term risk of a future cardiac event.

Several noninvasive and (non)exercise stress tests are available for perioperative risk assessment. The most commonly used stress test for detecting myocardial ischemia is treadmill or cycle ergometer test. These tests provide an estimate of the functional capacity, hemodynamic response, and detect myocardial ischemia by ST-segment changes. The accuracy varies widely among studies.<sup>56</sup> However, an important limitation in patients undergoing noncardiac surgery is the frequently limited exercise capacity in the elderly, the presence of claudication, arthrosis, or COPD. Consequently, non-physiological stress tests like dobutamine stress echocardiography (DSE) and dipyridamol myocardial perfusion scintigraphy (MPS) are recommended in patients with limited exercise capacity.

### Stress agents

Exercise stress testing is more physiologic compared to pharmacologic stress, however, in many situations not generally feasible. Pharmacologic stress testing is performed during the infusion of a catecholamine, dobutamine, for increased contractility or oxygen consumption or agents with vasodilatory properties such as adenosine and dipyridamole. Although vasodilators (i.e. dipyridamole or adenosine) may have advantages for assessment of myocardial perfusion, dobutamine is the preferred pharmacological stressor when the test is based on assessment of regional wall motion abnormalities.<sup>57</sup> Dobutamine is a synthetic catecholamine with predominantly  $\beta_1$ -receptor stimulating properties resulting in a strong positive inotropic and modest chronotropic effect on the heart. During the stress test, dobutamine is intravenously administered. During dobutamine infusion, contractility and heart rate increase, leading to increased myocardial

oxygen demand. Myocardial ischemia leading to systolic contractile dysfunction occurs in regions supplied by hemodynamically significant stenotic coronary arteries. Performing stress-rest tests requires careful patient monitoring, access to antidotes to stress agents and the presence of an experienced physician.

### **Stress echocardiography**

As most patients with peripheral vascular disease are not able to exercise maximally, stress echocardiography with pharmacological stressors like dobutamine is a good alternative. A graded dobutamine infusion starting at 5 mg/kg/min and increasing at 3-minute intervals to 10, 20, 30 and 40 mg/kg/min is the standard for dobutamine stress echocardiography.

Tissue harmonic imaging is advised for stress echocardiography. This special imaging setting reduces near-field artifact, improves resolution, enhances myocardial signals and is superior to fundamental imaging for endocardial border visualization. The improvement in endocardial visualization is further improved by the use of contrast agents for LV opacification. Contrast agents increase the number of interpretable LV wall segments. These recent developments have decreased interobserver variability and improved the sensitivity of stress echocardiography.<sup>58</sup>

Many reports have demonstrated that dobutamine stress echocardiography (DSE) predict perioperative events in patients undergoing vascular surgery.<sup>59-62</sup> The negative predictive value of dobutamine stress tests is high but the positive predictive value is much lower.

Kertai et al. reported a weighted sensitivity of 85% (95%CI 74%-97%) and a specificity of 70% (95%CI 62%-69%) for DSE in 850 patients from 8 studies.<sup>56</sup> A recent meta-analysis by Beattie et al. analyzed the predictive value of pharmacological stress testing compared to MPS.<sup>63</sup> 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 3.21-6.56).

### **Myocardial perfusion scintigraphy**

Since their introduction in the early 1970's, positron emission tomography (PET) and single photon emission computed tomography (SPECT) have been widely used as a diagnostic tool in the detection of CAD. Both PET and SPECT scanners globally assess LV function by detecting gamma radiation emitted by radiotracers, which are administered intravenously in a small quantity. In PET scanning, radiotracers with short half-lives are used; such as [15-O] water, [13-N] ammonia and [82-Rb] rubidium. With half-lives of 2 and 10 minutes respectively, an on-site cyclotron is needed for the clinical use of [15-O] water and [13-N] ammonia. [82-Rb] rubidium-82, with an half-life of 78 seconds can be readily produced with a 82-rubidium generator without the need of a cyclotron. In SPECT scanning [Tl-201] thallium-201 and technetium-99 labeled agents such as sestamibi (Cardiolite TM),

tetrofosmin (Myoview TM) and teboroxime (Cardiotec TM) are available. Due to difficulties in imaging, teboroxime (Cardiotec TM) is not used for clinical practice.

Nuclear imaging differs from other imaging techniques by focusing on physiologic processes in the LV myocardium instead of anatomy.<sup>64</sup> Myocardial uptake of radiotracers is the result of 1) blood flow dependent delivery of radiotracers to the cell surface and 2) subsequent extraction and retention of radiotracers into the cell, a process dependent on cell membrane integrity and viability.<sup>65</sup> The detection of CAD is based on a difference in blood-flow distribution through the LV myocardium. These perfusion abnormalities can be explained by insufficient coronary blood-flow based on coronary stenosis. To assess the extent of abnormal myocardial tissue a distinction should be made between non-viable myocardium (scar tissue) and viable myocardium, which is dysfunctional. Viable myocardium is still alive, therefore a potential target for revascularization treatment, and can be subdivided in stunning and hibernating myocardium. Myocardial stunning is a temporary post-ischemic myocardial dysfunction, characterized by a flow-contraction mismatch, which will persist for several hours to days following the ischemic event and restoration of flow.<sup>66,67</sup> Myocardial hibernation is a chronic process of diminished myocardial contractile function, caused by a persistent reduction in coronary blood-flow (flow-contraction mismatch) and can be considered as a protective mechanism of the heart to prevent irreversible damage of myocytes.<sup>66,68</sup>

To evaluate myocardial viability, a MPS is performed during rest, exercise or pharmacological induced stress. Pharmacological agents such as adenosine, dipyridamole and dobutamine are used to obtain maximal vasodilatation, needed to evaluate perfusion abnormalities during stress. To distinct viable and irreversible myocardial abnormalities, results derived from stress and rest MPS should be compared.<sup>69</sup> Different patterns of wall motion or perfusion responses can be assessed to a graded infusion of dobutamine, such as; 1) a normal wall motion or perfusion response, 2) a biphasic response, with initial improvement of wall motion or perfusion at low doses of dobutamine followed by worsening at higher infusion rates (ischemic viable myocardium) and 3) lack of initial improvement in wall motion or perfusion response (non-viable myocardium). A biphasic and ischemic response to dobutamine signifies viable myocardium with possible improvement of LV dysfunction after revascularization.<sup>70,71</sup> This might be an indication to delay surgery and perform a cardiac intervention first, based on the patient individual profile.

Perioperative myocardial infarction occurs in 2% to 15% of patients undergoing vascular surgery with great impact on postoperative cardiovascular outcome. Many patients undergoing vascular surgery are unable to exercise, therefore a non-exercising test, such as MPS, is mandatory. MPS has been widely used for the evaluation of patients undergoing vascular surgery and serves as a valuable diagnostic tool in preoperative risk stratification. The major goal of noninvasive risk stratification with MPS is to identify patients at high-risk for developing unrecognized MI or myocardial ischemia perioperatively.



Previous studies indicate that MPS is highly sensitive in predicting cardiac complications; however, the positive predictive value of MPS remains less satisfactory. A meta-analysis conducted by Kertai and colleagues reported a sensitivity of 83% (95%CI 77%-89%) and a much lower specificity of 47% (95%CI 41%-57%) for  $^{201}\text{Tl}$  MPS to predict perioperative cardiac events.<sup>56</sup> Although MPS demonstrated lower diagnostic accuracy compared to DSE they conclude MPS is a valuable test for cardiac risk assessment, especially in patients with contraindications to DSE. Using several specific analysis, Beattie et al. conclude that DSE has a superior negative predictive value in preoperative cardiac assessment compared to MPS.<sup>63</sup> This meta-analysis identified 75 studies of preoperative noninvasive testing, including 25 MPS and 50 DSE studies involving vascular surgery patients over a 20-year period. They demonstrated that the likelihood ratio (LR) of a postoperative cardiac event was higher for DSE (LR 4.09; 95%CI 3.21-6.56;  $P=0.001$ ) compared to MPS (LR 1.83; 1.59-2.1;  $P=0.001$ ). Prognostic variables which increase the positive predictive value of future cardiac events are:

- a large defect size (>20% of the LV)
- defects in >1 coronary vascular supply region (suggestive for multivessel CAD)
- large numbers of nonreversible defects (even in the supply region of a single coronary artery).<sup>72</sup>

Although MPS is a diagnostic tool with low specificity, the negative predictive value derived from a normal scan is high in predicting future MI and cardiac death. A meta-analysis by Shaw et al. identified the results of 10 articles describing the use of dipyridamole- $^{201}\text{Tl}$  in vascular surgery patients in a time period of 10 years. They conclude that cardiac death and nonfatal MI was correlated with the positive predictive value of a reversible  $^{201}\text{Tl}$  defect. Cardiac event rates were low in patients without a history of CAD compared with: 1) patients with CAD and a normal or fixed defect pattern and 2) patients with one or more  $^{201}\text{Tl}$  redistribution abnormalities (1% (n=176), 4.8% (n=83), and 18.6% (n=97),  $P=0.0001$ , respectively).<sup>62</sup> Boucher and colleagues 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.<sup>73</sup> Husmann et al. evaluated the diagnostic accuracy of PET ( $^{13}\text{N}$  ammonia-PET) and SPECT ( $^{201}\text{Tl}$ -SPECT and MIBI-SPECT) imaging using coronary angiography as the standard of reference. PET imaging showed a higher sensitivity for locating coronary artery stenosis compared to SPECT (95% and 77% respectively); however, no difference in specificity was found (84% in both groups). In detecting ischemia the specificity of PET was 91% compared to 74% for SPECT.<sup>74</sup>

Preoperative risk assessment with noninvasive stress tests, such as MPS and DSE, is indicated only in high-risk patients without unnecessary delay for vascular surgery. The use of dipyridamole, in both MPS and stress echocardiography, is contraindicated in patients: 1) receiving theophylline treatment; 2) with bronchospasms; 3) with unstable carotid disease; 4) with second and third

degree atrioventricular block; and 5) asthmatic patients. DSE is contraindicated in patients with severe hypertension and relative hypotension.<sup>75-76</sup> When to choose between MPS and DSE the following advantages are in favour of DSE: 1) higher specificity; 2) higher versatility; 3) greater convenience; and 4) lower costs. The advantages of stress perfusion imaging include: 1) higher sensitivity; 2) higher technical success rate; and 3) better accuracy when multiple resting left-wall abnormalities are present.<sup>76</sup> All these factors should be considered when deciding which noninvasive stress tests to use for preoperative risk stratification.

In the future, a combination of noninvasive coronary angiography and MPS could provide a new noninvasive strategy focusing on the physiologic processes in the LV myocardium as well as the anatomy.

### **Myocardial perfusion magnetic resonance imaging**

As already noted, the identification of viable myocardium in patients undergoing noncardiac surgery is of significant clinical relevance. Currently, stress echocardiography and MPS are the most established methods in the identification of viable myocardium. However, cardiac perfusion magnetic resonance imaging (cMRI) has also shown to assess the extent of injury after MI including the ability to discriminate viable from nonviable zones. cMRI protocols focus on wall motion analysis, wall thickness, tissue characteristics, and perfusion imaging.<sup>77</sup> Pharmacological protocols with stress perfusion MRI have been adapted from stress imaging with echocardiography, PET, or SPECT with the use of adenosine, dipyridamole, and dobutamine. During stress perfusion MRI the heart is analyzed after administration of gadolinium chelates, which serves as contrast. Gadolinium chelates are large molecules that rapidly diffuse from the intravascular space into the interstitium and remain in the extracellular space of the myocardium, provided that the tissue cell membranes are intact.<sup>78</sup> Gadolinium clearance from the normal myocardium is a process dependent by several factors such as 1) the wash out rate of gadolinium contrast from the myocardium 2) overall cardiac function 3) renal function and 4) the administered dose of gadolinium.<sup>79</sup> Ischemic areas show up as areas with delayed and diminished contrast enhancement<sup>80</sup>, although acutely stunned or chronic hibernating myocardium with a decreased function but intact cell membranes do not show delayed enhancement on MRI.<sup>79</sup>

Ishida et al. compared cMRI with SPECT in patients without MI and evaluated which diagnostic tool correlated most closely to results obtained with quantitative coronary angiography. They note an overall sensitivity of cMRI of 90% for depicting at least one coronary artery with significant stenosis compared to a sensitivity of SPECT ranging from 76%-86%. The specificity of cMRI for the identification of patients with significant coronary artery stenosis was 85%.<sup>81</sup> Gutberlet et al. compared dobutamine cMRI with [201]-TI SPECT for viability assessment both before and after coronary artery bypass grafting (CABG). cMRI performed best with a sensitivity of 99% and a

specificity of 94% for viability compared to SPECT which showed a high sensitivity of 86% and a low specificity of 68%.<sup>82</sup>

Nagel and colleagues compared cMRI with dobutamine stress MRI in patients referred for diagnostic coronary angiography and showed DSE provided superior sensitivity and specificity, of 89% vs. 74% and 86% vs 70% respectively, in detecting CAD.<sup>83</sup> As already noted, pharmacologic protocols with dobutamine stress MRI have been adapted from other imaging methods, therefore contraindications towards stress agents are identical. Tomlinson et al. propose a pragmatic approach in the decision which test to choose for additional diagnostic information in viability assessment. Recourse implications in terms of personnel and cost favour DSE. If resting echo shows adequate imaging quality and complete wall-motion scoring is possible, the proposed next step should be to perform DSE. Conversely, when image quality derived from resting echo is poor and complete wall-motion scoring is not possible, cMRI is the diagnostic tool of preference.<sup>84</sup>

Little is known about the use of stress cMRI to predict cardiac risk in patients undergoing noncardiac surgery. However, dobutamine stress cMRI has shown to be feasible in predicting myocardial recoverability in patients undergoing CABG.<sup>85</sup> Future studies will have to evaluate the role of stress cMRI in preoperative risk stratification in patients undergoing noncardiac surgery.

### **Myocardial stress computed tomography**

Myocardial perfusion imaging with pharmacologic stress computed tomography (CT) has been used to evaluate subendocardial ischemia in patients with CAD.<sup>86</sup> Disadvantages of cardiac CT imaging compared to other noninvasive imaging modalities are: 1) the use of an iodine contrast medium which may cause an adverse reaction and 2) X-ray exposure.<sup>87</sup> However, acceptability of metal devices such as an infusion pump, pacemaker and an intra aortic balloon pump is an advantage compared to myocardial perfusion MRI. Kurata and colleagues evaluated the use of contrast-enhanced multislice CT to detect myocardial ischemia as hypoperfusion areas using adenosine triphosphate as a coronary vasodilator. They conclude myocardial stress CT is a potential alternative to stress MPS; however they note that rest images were of higher quality and therefore more feasible for clinical use at present.<sup>86</sup> In animal models the use of myocardial perfusion CT during adenosine stress shows promising results. George et al. evaluated myocardial perfusion CT in a canine model of left anterior descending artery stenosis and conclude that differences in myocardial perfusion can be reliably assessed using this diagnostic tool. In conclusion, myocardial stress CT to assess myocardial perfusion at rest and stress is currently being explored and is not clinically established yet.

## INVASIVE TESTING

Coronary angiography is a well-established invasive diagnostic procedure for the evaluation of cardiac patients. However, in patients scheduled for noncardiac surgery there is paucity of information focusing on the efficacy of this procedure. Nevertheless, as already extensively discussed, the majority of the patients scheduled for noncardiac surgery presents with underlying ischemic heart disease. Invasive testing should only be performed if test results will alter preoperative or perioperative management. In patients with known CAD, indications for perioperative coronary angiography and revascularization should be similar to angiography indications for the nonoperative setting.<sup>88-91</sup>

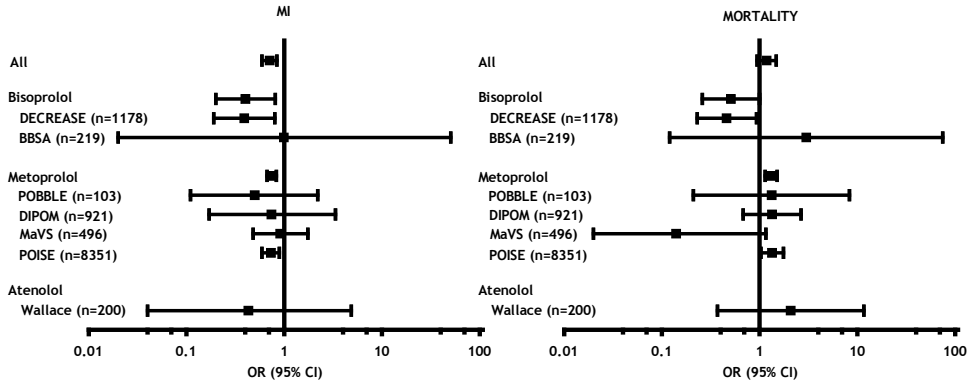
## MEDICAL THERAPY

Pharmacological risk reduction is one of the most important elements of perioperative management. Data from observational studies and registries, however, observe a poor compliance with guidelines in pharmacological treatment.<sup>92-94</sup> In particular, it has been shown that the prescription rate of beta-blockers is low in patients undergoing noncardiac surgery.

### **Beta-blockers**

Randomized controlled trials investigating the effect of beta-blockers in the perioperative period have shown divergent results (Figure 4). There are different explanations regarding this conflicting evidence for perioperative beta-blocker use. In particular, the initiation time and dose of beta-blocker therapy, dose adjustments for heart rate control, and the patients' underlying cardiac risk are important factors that may relate to the effectiveness of therapy.<sup>95</sup>

Evidence supporting the use of beta-blockers is based mainly on two small, prospectively randomized clinical trials and several observational studies. In the first study, Mangano et al. randomized 200 patients with either known or suspected CAD undergoing high-risk noncardiac surgery to receive atenolol (50 mg or 100 mg) or placebo just before the induction of anaesthesia.<sup>96</sup> Atenolol therapy was not associated with an improved in-hospital outcome



**FIGURE 4** The effect of beta-blockers on 30-day rates of non-fatal MI and all-cause mortality.

(cardiac death or MI); however, it was associated with a 50% reduction in electrocardiogram evidence of myocardial ischemia detected with continuous 3-lead Holter monitoring during the first 48 h after surgery. Furthermore, although the study of Mangano did not demonstrate a perioperative effect, 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%;  $P=0.019$ ).

The other trial, the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study)-I trial, randomized 112 vascular surgery patients with evidence of myocardial ischemia on preoperative DSE. The DECREASE-I trial started bisoprolol at an average of 37 (range 7-89) days before surgery and careful titration was performed. Poldermans et al. showed a 10-fold reduction in the incidence of perioperative cardiac death and MI with perioperative bisoprolol use compared with placebo (3.4% vs. 34%;  $P<0.001$ ).<sup>7</sup> The high incidence of perioperative cardiac events was explained by the selection of high-risk patients for study. From a population of 1351 patients, only 112 met entrance criteria of inducible myocardial ischemia.

Several trials also showed evidence not supporting the use of perioperative beta-blockade. The MAVS (Metoprolol After Vascular Surgery) trial randomized 496 patients to metoprolol or placebo starting 2 hours before surgery until hospital discharge or a maximum of 5 days after surgery.<sup>97</sup> The combined endpoint of death, MI, heart failure, arrhythmias or stroke at 30 days did not differ between the metoprolol and the placebo groups (10% and 12% respectively,  $P=0.057$ ). In the POBBLE (PeriOperative Beta-BLockadE) trial, only low-risk patients (history of ischemic heart disease was an exclusion) scheduled for vascular surgery were studied.<sup>98</sup> In total 103 patients were randomized to receive either metoprolol 25 mg or 50 mg, or placebo, starting the day before until 7 days after surgery. There was no difference in the incidence of perioperative cardiovascular events between the placebo and metoprolol groups (34% vs. 32%; relative risk 0.87, 95%CI 0.48-

1.55). The duration of hospitalization though was shorter for those patients receiving metoprolol versus placebo (10 days vs. 12 days). The DIPOM (Diabetic Postoperative Mortality and Morbidity) trial also showed no differences in 30-day morbidity and mortality (21% vs. 20%;  $P=0.66$ ). In this study 921 diabetic patients were randomized to 100 mg metoprolol or placebo started the evening before major noncardiac surgery.<sup>99</sup>

Recently the results of the large randomized POISE trial were published. A total of 8351 patients were randomized to controlled-release oral metoprolol succinate, or placebo. Patients >45 years were included if they had known CVD, at least 3 out of 7 clinical risk factors, or would undergo major vascular surgery. The POISE trial initiated randomized treatment of controlled-release metoprolol just before surgery, and the maximum recommended therapeutical dose (400 mg) could already be achieved within the first day of surgery (Figure 5). The primary endpoint of cardiac death, MI, or cardiac arrest was reduced in the metoprolol group, compared to placebo (5.8% vs. 6.9%, HR 0.83, 95%CI 0.70-0.99,  $P=0.04$ ). However, the 30% decrease of non-fatal MI (3.6 vs. 5.1%,  $P=0.0008$ ) was accompanied by a 33% increase in total mortality (3.1% vs. 2.3%,  $P=0.03$ ) and a twofold increase risk in stroke (1.0 vs. 0.5%,  $P=0.0005$ ).

Stroke was associated with perioperative bradycardia, hypotension, and bleeding in patients randomized to metoprolol with a diseased cerebrovascular tree. 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 metoprolol without dose titration.

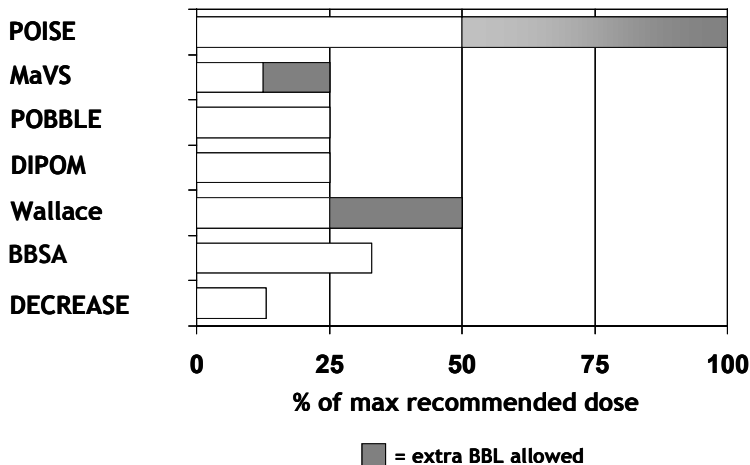


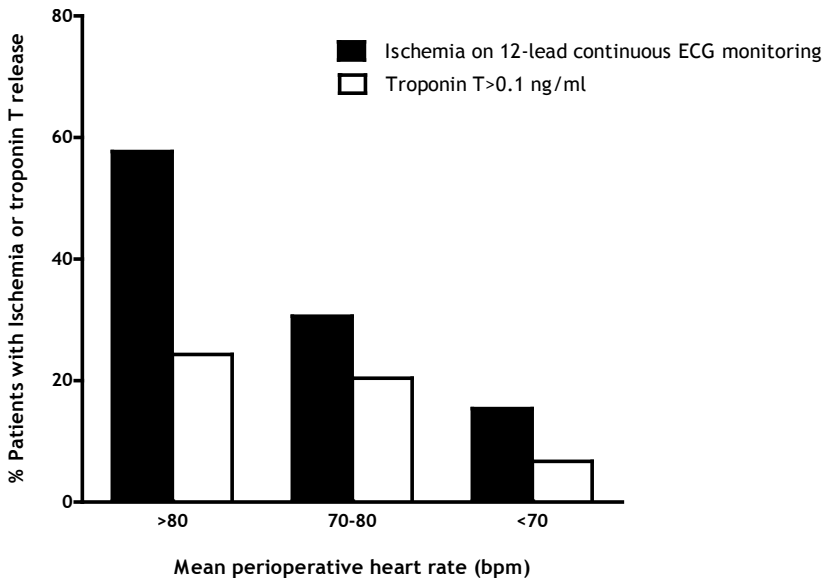
FIGURE 5 - Beta-blocker trials and dosage used.

Importantly, the earlier mentioned randomized trials assessing the effect of beta-blocker use in the perioperative period differ in the population of surgical patients at risk. The MAVS trial and DIPOM trial both included many patients at low risk for complications. In the MAVS trial almost 60% had a Lee Risk Index of only 1. This in contrast to the DECREASE study which randomized vascular surgery patients with a positive dobutamine echocardiography. In a large retrospective cohort study of 782,969 patients undergoing major noncardiac surgery a relationship between the effect of beta-blocker use and the patient risk profile was observed.<sup>100</sup> Beta-blocker use was associated with a significant beneficial effect in high-risk patients but showed no effect or possible harm in low-risk patients.

Other explanations regarding the divergent results of the perioperative beta-blocker studies are related to the beta-blocker treatment protocol. First, the use of a fixed versus individualized dose titrated to the patients heart rate is of significant importance. In a study of 150 patients, Raby et al. assessed the heart rate threshold for myocardial ischemia before surgery using Holter monitoring.<sup>101</sup> Patients with myocardial ischemia (n=26) were then randomized to receive a) IV esmolol titrated to aiming at tight heart rate 20% less than the ischemic threshold but >60 bpm or placebo. Of the 15 patients receiving esmolol, 9 had mean heart rates below the ischemic threshold and none experienced postoperative ischemia. Four of 11 patients receiving placebo had a mean heart rate below the ischemic threshold, and 3 of the 4 had no postoperative ischemia. Together, of the 13 patients with heart rates below the ischemic threshold, 1 (7.7%) had postoperative electrocardiogram myocardial ischemia versus 12 of 13 (92%) patients with heart rates exceeding the ischemic threshold. Feringa et al. found similar results in a study of 272 patients receiving beta-blocker therapy and undergoing vascular surgery.<sup>102</sup> In that study it was shown that higher doses of beta-blockers and lower heart rate were associated with reduced Holter monitoring-detected perioperative myocardial ischemia (HR 2.49; 95%CI 1.79-3.48) and troponin T release (HR 1.53; 95%CI 1.16-2.03) (Figure 6).

These data suggest that monitoring of the heart rate and consequent beta-blocker dose adjustment is of critical importance for the likelihood that a patient will receive benefit of beta-blockade. Another important explanation is the variation in the starting time and duration of therapy. In contrast to the instant effect on heart rate control, the effect of beta-blockers on plaque stabilization may be achieved only after prolonged treatment. This can be argued by the pathophysiology of PMI. The DECREASE-I trial showed the largest effect of perioperative beta-blocker treatment.<sup>7</sup> In this trial the mean time between initiation and surgery was 37 days. In contrast, the DIPOM, POBBLE and POISE trials started beta-blocker therapy only the day before surgery. As mentioned earlier, in the Mangano et al. study the benefits of atenolol were observed in the months after surgery.<sup>96</sup> These supposed long-term beneficial effects of beta-blockers were recently confirmed by a pooled analysis of 4 intravascular ultrasonography trials showing a decreased progression of coronary atherosclerosis.<sup>103</sup>

Further, withdrawal of beta-blocker therapy shortly before surgery, or in the immediate postoperative period, might contribute to adverse myocardial effects resulting from a “rebound” effect resulting in increased arterial blood pressure, HR, and plasma noradrenalin concentrations.<sup>104</sup> Redelmeier and colleagues have recently shown that the long-acting agent atenolol was superior to the short-acting drug, metoprolol, when given perioperatively, probably as the result of acute withdrawal effects from missed doses of short-acting beta-blockers.<sup>105</sup> On the other hand, care should be taken not to overtreat the patient. In the POISE study, metoprolol succinate, a long-acting  $\beta$ -blocker, the starting dose was 100 mg, 2-4 hours prior to surgery, again 100 mg 0-6 hours after surgery, and a dose of 200 mg 12 hours after the first postoperative dose. Thereafter the daily maintenance dose was started at 200 mg. Medication was withheld if blood pressure dipped below 100 mmHg or heart rate was <50 bpm. So, on the first day of surgery metoprolol succinate could have been administered at a dose up to 400 mg on the day of surgery, 100% of the maximum daily therapeutic dose (MDTD). In the nonsurgical setting, much lower starting doses are recommended, for instance in patients with NYHA Class II heart failure 12.5-25 mg daily is started for two weeks and for hypertension the initial dose is 25-100 mg, usually increased at weekly intervals.



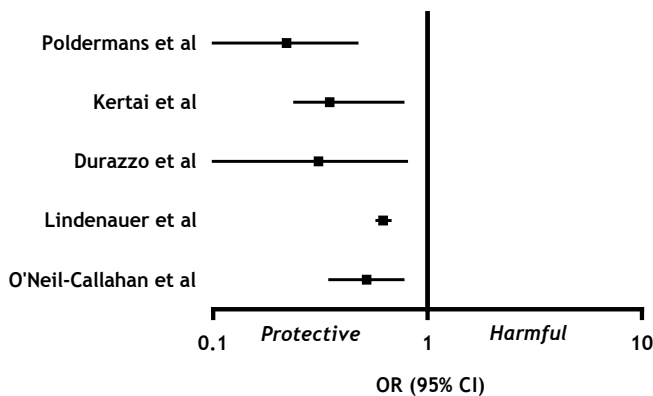
**FIGURE 6 - Mean heart rate in relation to myocardial ischemia assessed by continuous electrocardiography and Troponin T release.** Based on data from Feringa et al.<sup>102</sup>



## Statins

Statins are widely prescribed in patients with or at risk for CAD because of their effectiveness in lowering serum cholesterol concentrations through 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibition. Reduction of low-density lipoprotein cholesterol is one of the primary objectives of CVD prevention. Beyond the lipid-lowering effect of statins alone, evidence suggests that the more immediate benefits are related to the so-called pleiotropic effects of statins. These pleiotropic effects are thought to include improved endothelial function, enhanced stability of atherosclerotic plaques, decreased oxidative stress, and decreased vascular inflammation.<sup>106</sup> These effects of statins may consequently prevent plaque rupture and subsequent MI in the proinflammatory and prothrombotic environment of the perioperative period.

Two randomized controlled clinical trials have been performed to date evaluating the effect of statins in patients undergoing noncardiac surgery, i.e. vascular surgery. Durazzo et al. performed the first prospective randomized controlled trial in a small population carried out at a single center.<sup>107</sup> One-hundred patients scheduled for vascular surgery were randomized to either 20 mg atorvastatin or placebo. Patients received treatment for 45 days and at least 2 weeks before surgery. On average statins were prescribed around one month before surgery. The outcome of this trial was the combined endpoint of cardiac death, nonfatal MI, stroke, or unstable angina pectoris. After 6 months cardiovascular events had occurred in 26% of the placebo group but only in 8% of the statin group ( $P=0.03$ ). Though not powered to assess 30-day postoperative outcome, there was a clear trend for the beneficial effect of statins (OR 0.23, 95%CI 0.09-1.30). Lindenauer performed a large retrospective cohort study of 780,591 patients undergoing major noncardiac surgery at 329 hospitals (Figure 7).<sup>108</sup> The authors concluded that the 70,159 statin users had a 1.4-fold reduced risk of in-hospital mortality (adjusted OR=0.62, CI=0.58-0.67).



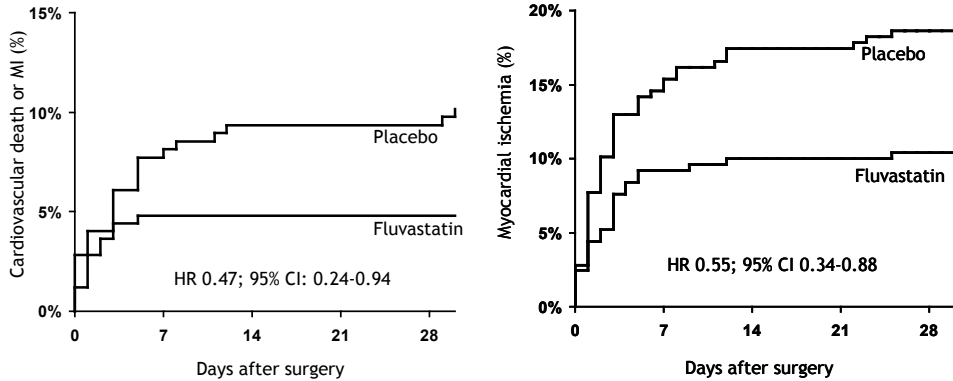
**FIGURE 7 - Perioperative statin therapy.** Results of the effect of perioperative statin therapy in different studies.

The meta-analysis by Hindler and colleagues including the randomized trial of Durazzo et al. and 6 other observational studies (n=5,373) demonstrated in the vascular surgery subgroup that preoperative statin therapy reduced the risk of short-term mortality significantly by 59% (1.7% vs. 6.1%,  $P < 0.001$ ).<sup>109</sup> Although this confirmed the observed beneficial effect of perioperative statin therapy in large systematic reviews<sup>109,110</sup>, the authors concluded that evidence was insufficient to recommend routine statin treatment. The recently reported DECREASE III study is the first adequately powered randomized controlled trial, which could address the role of statins in the perioperative period. This trial randomized 497 vascular surgery patients to either fluvastatin-extended release 80 mg once daily or placebo.<sup>111</sup> The incidence of the MI in fluvastatin and placebo allocated groups respectively was 10.8% vs. 19.0% (OR 0.55; 95%CI 0.34-0.88) (Figure 8). The incidence of the secondary, composite endpoint of cardiac death or myocardial ischemia was 4.8% vs. 10.2% (OR 0.47; 95%CI 0.24-0.94). With respect to intermediate-risk surgical patients, the DECREASE IV trial assessed the effectiveness and safety of beta-blockers, statins and their combination, on the incidence of perioperative cardiac death and MI. Patients randomized to fluvastatin experienced a lower incidence of the primary endpoint than those randomized to fluvastatin-control therapy (3.2% vs. 4.9% events; HR 0.65; 95%CI 0.35-1.10), but statistical significance was not reached ( $P=0.17$ ). This study was, however, limited by its lack of power.

An important issue in the perioperative setting is the use of concomitant medical treatment. The risk of myopathy might increase with concomitant drugs that are myotoxic or increase serum statin levels. Besides concomitant medication use, numerous other factors like renal impairment in the perioperative setting might increase the risk of statin-induced myopathy. Importantly, the recent DECREASE III study also did not observe myopathy or rhabdomyolysis within 30 days after surgery (Table 2).<sup>111</sup> Considering that the risk of cardiovascular complications is far greater than the risk of statin-induced myopathy and rhabdomyolysis in the perioperative period, the potential benefits of perioperative statin use seem to outweigh the potential hazards.

Another important concern is the continuation of statins in patients undergoing noncardiac surgery. Because of the unavailability of an intravenous formula of statins and the not readily appreciated pleiotropic effects of statins, statin withdrawal is a well-known phenomenon in the immediate postoperative period. From patients with CAD it is known that sudden withdrawal of statin therapy can be harmful.<sup>112,113</sup> Recently, it has been demonstrated in vascular surgery patients that statin discontinuation was associated with an increased risk for postoperative troponin release (HR 4.6, 95%CI=2.2-9.6) and the combination of MI and cardiovascular death (HR 7.5, 95%CI=2.8-0.1).<sup>114</sup> This increased postoperative risk associated with the withdrawal of statins was also observed by Le Manach and colleagues.<sup>13</sup> However, in 1 out of 4 patients included in the DECREASE III trial statins had to be interrupted for a median of 2 days after surgery, but this did not result in a significant increase in adverse outcome (adjusted OR 1.1, 95%CI=0.48-2.52).<sup>111</sup> These

findings suggest that statins with a prolonged half-life time or with an extended-release formula should be preferred and that statins should be restarted after surgery as soon as possible.



**FIGURE 8 - Results of the DECREASE III study. Kaplan-Meier curves of the cumulative probability of cardiovascular death or MI (left panel) and perioperative myocardial ischemia (right panel).<sup>111</sup>**

**TABLE 2 - Safety measures of statin use (DECREASE III study)<sup>34</sup>**

	Placebo (N=247)	Fluvastatin (N=250)	P-value
Discontinuation: no. (%)	18 (7.3)	16 (6.4)	0.73
CK >10x ULN: no. (%)	8 (3.2)	10 (4.0)	0.81
CK (U/L): median	113	141	0.24
ALAT >3x ULN: no. (%)	13 (5.3)	8 (3.2)	0.27
ALAT (U/L): median	23	24	0.43
Myopathy: no. (%)	-	-	
Rhabdomyolysis: no. (%)	-	-	

ALAT, alanine aminotransferas; CK, creatinine kinase; no., number of patients; ULN, upper limit of normal.

### Antiplatelet therapy

Acetylsalicylic acid (ASA) is one of the cornerstones in the primary and secondary prevention of CVDs. Furthermore, dual antiplatelet therapy, the combination of ASA and clopidogrel, has proven to be effective for the prevention of stent thrombosis. The evidence of ASA in the perioperative period in patients undergoing noncardiac surgery is less clear. Trials of patients undergoing carotid surgery showed some evidence in favour of ASA, although the evidence was inconclusive for all endpoints.<sup>115,116</sup> The meta-analysis of Robless et al. in 2001 demonstrated a reduction of serious vascular events and vascular death in patients with peripheral vascular disease.<sup>117</sup> This study included 10 trials of antiplatelet treatment in lower limb bypass surgery of which 6 involved ASA

treatment. However, the benefit of antiplatelet therapy did not reach statistical significance for the combined endpoint of vascular events (OR=0.76; 95%CI 0.54-1.05) in this vascular surgery population.

An important issue is how to manage patients with antiplatelet therapy in the perioperative period. Concerns of promoting perioperative haemorrhagic complications often withheld continuation of ASA in the perioperative period. In their extensive review on the impact of antiplatelet therapy on perioperative bleeding complications, Harder et al. concluded that monotherapy with aspirin or clopidogrel alone usually does not have to be discontinued in the perioperative period.<sup>118</sup> This conclusion was confirmed in the meta-analysis of Burger and colleagues.<sup>119</sup> In 41 studies, including a total of 49,590 patients undergoing a variety of noncardiac surgical procedures (14,981 on perioperative aspirin and 34,609 not on aspirin) they found that aspirin continuation led to a 1.5 times increased risk of bleeding complication, but not to a higher level of the severity of bleeding complications. They concluded that based on their meta-analysis aspirin should only be discontinued perioperatively if bleeding risks with increased mortality or sequels are comparable to the observed cardiovascular risks after aspirin withdrawal.

## REVASCULARIZATION

### Prophylactic coronary revascularization

Preoperative cardiac risk evaluation by means of risk factor assessment and noninvasive testing may often identify patients at increased cardiac risk. Importantly, the number of patients with CAD undergoing noncardiac surgery steadily increases. These patients may either have documented symptomatic involvement or be fully asymptomatic. Furthermore, they may present with a life-threatening condition requiring immediate noncardiac surgery or have a need for an elective intervention in which case a full cardiac work-up can be planned if indicated. Faced with a medical emergency, there is no other choice than to proceed with surgery and to postpone cardiac evaluation until afterwards. If not, the need for diagnostic evaluation and subsequent revascularization will have to be questioned, in particular in those patients requiring surgery within weeks or a few months. After the presence of severe CAD is confirmed by angiography, coronary revascularization via percutaneous coronary intervention (PCI) or CABG can be considered as prophylactic therapy in these patients prior to noncardiac surgery.

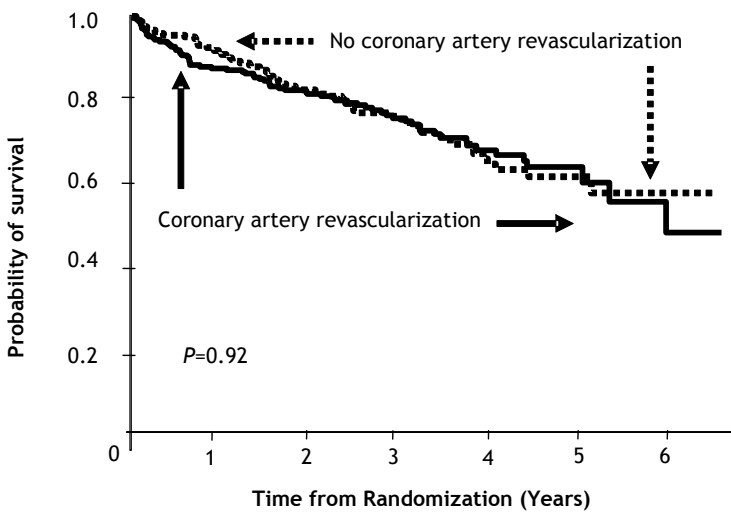
The main goal of preoperative coronary revascularization is the prevention of the occurrence of PMI in patients with significant CAD scheduled for noncardiac surgery. The cumulative risk of prophylactic coronary revascularization and noncardiac surgery needs to be weighted against the risk of the surgical procedure performed without preoperative interventions.

In recent years 2 conducted randomized controlled trials have shed some light on the controversial role of prophylactic revascularization prior to noncardiac surgery. Former evidence was based on small-scale observational studies and expert opinions.<sup>120-122</sup> The Coronary Artery Revascularization Prophylaxis (CARP) trial conducted by McFalls and colleagues was the first randomized trial that investigated the benefit of coronary revascularization before elective major vascular surgery.<sup>123</sup> Of 5,859 screened patients at 18 Veterans Affairs US hospitals, 510 patients with significant artery stenosis were randomized to either revascularization or no revascularization before surgery. The main finding of this study 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 to patients who received optimized medical therapy (22% vs. 23%, relative risk=0.98; 95%CI=0.70-1.37). The corresponding Kaplan-Meier curve is shown in Figure 9. Although the study was not powered to test the short-term benefit of prophylactic revascularization, no reduction in the number of MIs, deaths or length of hospital stay was observed within 30 days after vascular surgery. The results of this trial suggest that prophylactic revascularization might not provide additional benefit in reducing the incidence of perioperative and long-term cardiac morbidity and mortality in cardiac stable, elective vascular surgery patients. The generalizability of this trial to patients with multivessel disease has, however, been questioned because the majority of the patients in the CARP trial had only 1- or 2-vessel disease. To address this issue, the CARP investigators recently studied the long-term outcome of all screened patients (randomized + registry) who underwent coronary angiography before vascular surgery from the original population.<sup>124</sup> Of the total 1,048 patients who underwent a preoperative coronary angiography before their vascular operation, multivessel CAD without previous CABG was present in 382 (36.5%). In line with the results of the randomized CARP results, no long-term survival benefit was observed in patients with 2- and 3-vessel disease. In contrast, in the cohort of 48 patients (4.6%) with left main coronary artery stenosis, patients who had undergone preoperative revascularization did seem to have an improved 2.5 year survival (84% vs. 52%) (Figure 10).

In a recent study evaluating vascular surgery patients with predominantly 3-vessel disease similar findings were obtained.<sup>125</sup> Cardiac-stable, elective vascular surgery patients were screened for risk factors, and those with three or more clinical risk factors (age>70 years, MI, angina pectoris, congestive heart failure, diabetes mellitus, renal failure, and cerebrovascular events) underwent cardiac stress testing. All patients with extensive stress-induced ischemia were randomly assigned for additional revascularization. All patients received optimized medical therapy including beta-blockers aiming at a heart rate of 60-65 bpm and continued antiplatelet therapy. Of 430 high-risk patients, 101 (23%) showed extensive ischemia and were randomly assigned to revascularization (N=49) or no-revascularization (N=52). Coronary angiography showed 2-vessel disease in 12 (24%), 3-vessel disease in 33 (67%), and left main in 4 (8%). This study population reflects the patients at

highest cardiac risk in the perioperative period. Revascularization did not improve perioperative outcome, the incidence of cardiac death and MI was 43 vs. 33%, OR 1.4, 95%CI 0.7-2.8 (P=0.30). Also no benefit during 1-year follow-up was observed after coronary revascularization, 49 vs. 44%, OR 1.2, 95%CI 0.7-2.3 (P=0.48) (Figure 11).

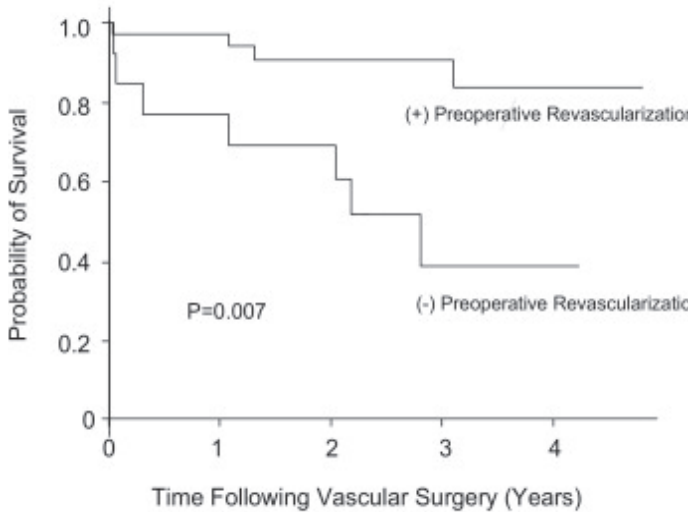
To summarize, both randomized trials hint that prophylactic coronary revascularization of cardiac stable patients provides no benefit for postoperative outcome. Although limited by the small patient number and its observational nature, the CARP trial indicates that prophylactic coronary revascularization seems to be only beneficial in patients with left main coronary artery stenosis. No trials exist investigating the role of prophylactic revascularization in patients with unstable angina pectoris requiring noncardiac surgery. If noncardiac surgery can be postponed safely, diagnosis and treatment for these patients should be in line with the recent guidelines on unstable angina management.<sup>89</sup>



**No. at Risk**

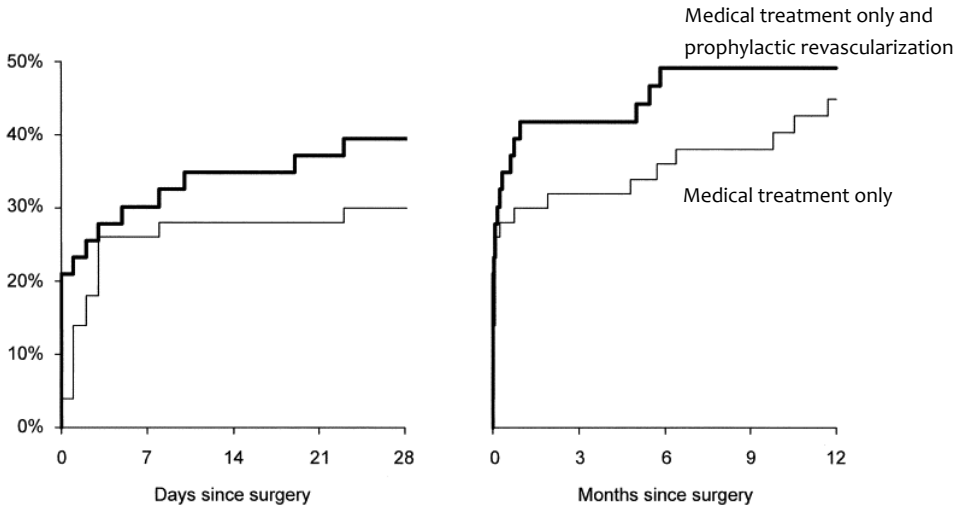
Revascularization	226	175	113	65	18	7
No revascularization	229	172	108	55	17	12

**FIGURE 9 - Results of the CARP study: long-term survival among patients assigned to undergo coronary-artery revascularization or no revascularization.<sup>123</sup>**



**FIGURE 10 - Kaplan-Meier survival curve according to preoperative coronary artery revascularization for patients with unprotected left main coronary artery stenoses.**

The reasoning behind the apparent lack of benefit of prophylactic revascularization is not fully understood. It could likely be related to the fact that patients with stress-induced ischemia not only suffer from a blood flow-limiting coronary lesion but also from (multiple) non-significant lesions which are vulnerable to rupture due to the stress of surgery. The perioperative stress response, which includes a cytokine response, catecholamine surge with associated hemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation and, consequent hypercoagulability triggers coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion. Importantly, as discussed earlier, autopsy reports have shown that half of the cases of PMI have coronary plaque rupture as the underlying pathophysiologic mechanism. This also explains the lack of specificity of stress echocardiography or nuclear imaging techniques in predicting infarct-related coronary artery lesions.<sup>126,127</sup> Surgical or percutaneous treatment of the culprit coronary lesion(s) apparently provides insufficient extra protection on top of medical treatment for rupture of these unstable lesions.



**FIGURE 11 - Results of the DECREASE V trial.** Kaplan-Meier cumulative probability of all-cause death or MI during 1-year follow-up according to the allocated strategy in patients with three or more risk factors with extensive stress-induced ischemia.

### Previous coronary revascularization

Another important clinical situation is the management of patients with previous coronary stenting undergoing noncardiac surgery.<sup>128</sup> The risk of perioperative stent thrombosis in these patients is increased by the noncardiac surgical procedure, especially when surgery is performed early after stent implantation and particularly if dual antiplatelet therapy is discontinued. When possible, delaying surgery is advised until after the time window that requires dual antiplatelet therapy.

In the early days of angioplasty, it seemed that conventional percutaneous transluminal coronary angioplasty (PTCA) did not worsen outcomes after surgery even if performed as early as 11 days after PTCA.<sup>129</sup> However, the introduction of stenting accompanied with frequent occurrence of acute stent thrombosis directed physicians to postpone elective surgery up to 3 months after bare metal stent placement.<sup>130</sup> Thrombosis of a stent is associated with major morbidity and mortality. Dual antiplatelet therapy during the period of stent endothelialization effectively reduces the risk of stent thrombosis to <1% and is therefore recommended. An important issue is the timing of the noncardiac surgical procedure after PCI. A recent large study of 899 patients demonstrated a clear association between the duration of time between PCI and noncardiac surgery and ischemic cardiac events.<sup>131</sup> The incidence of major cardiovascular events was lowest (2.8%) if noncardiac surgery was performed at least 90 days after PCI with bare metal stent. Bleeding events were not associated with duration of time between PCI and noncardiac surgery.



In 2002, drug-eluting stents were introduced in Europe to further reduce in-stent restenosis. The use of these stents has grown exponentially over the last few years. However, their major drawback is the need for prolonged dual antiplatelet therapy by aspirin and clopidogrel from 3 up to 12 months. It is now generally accepted that after drug-eluting stent placement, elective surgery should not take place before 12 months.<sup>132</sup>

## CONCLUSION

Patients undergoing noncardiac surgery have an increased risk of cardiovascular perioperative morbidity and mortality. Preoperative management aims at optimizing of the patient's condition by identification and modification of underlying cardiac risk factors and diseases. Systemic medical therapy with beta-blockers and statins is currently one of the cornerstones of individualized perioperative management.

## PERSONAL PERSPECTIVE

Preoperative cardiac risk evaluation currently aims at stratifying patients into 3 main categories; patients at low risk in whom additional testing and medical therapy is redundant, and can be send for surgery safely without delay; patients in whom the risk of surgery clearly outweighs the potential benefit of the procedure; and patients in whom medical therapy and/or coronary revascularization reduces the potential risk significantly and can be send for surgery afterwards. Commonly, in the latter group noninvasive cardiac testing is performed after an initial screening with common clinical cardiac risk markers and biomarkers such as high-sensitive C-reactive protein or NT-proBNP. Medical therapy has been shown to improve postoperative outcome in patients with CAD and heart failure, similar to the nonsurgical setting. The question to be answered will be: is therapy safe to be initiated prior to surgery? Statin therapy seems to fulfil this criterion. It is safe and effective. However, a potential problem is the lack of intravenous formula. This might induce effects of statin withdrawal in those patients who cannot take oral medication after surgery. Long-acting statins or the development of statins for rectal administration might be alternatives. Beta-blockers are still controversial. Although proven to be effective in the nonsurgical setting in patients with heart failure and CAD, safety issues such as hypotension and bradycardia leading to stroke are a potential problem. The use of low-dose regimens with careful up-titration and intraoperative use of ultra-short acting beta-blockers are currently recommended. Additional randomized clinical trials including sufficient number of patients are warranted to proof safety and efficacy of these treatment regimens.

The more widespread use of perioperative cardioprotective medication will reduce the indication for additional preoperative noninvasive cardiac testing, as outcome is improved and coronary revascularization as a consequence of test results is unlikely to improve postoperative outcome further. For instance in patients in whom the risk can be reduced <2%, coronary revascularization with its procedure-related morbidity and mortality, is unlikely to be of additional benefit. Moreover, the introduction of coronary stents, in patients treated with a PCI necessitates use of antiplatelet therapy early after stent placement with the risk of perioperative surgical bleeding, while early interruption might lead to in-stent thrombosis.

Most of medical therapies and interventions have focussed on restoration of the oxygen demand/supply mismatch in patients with CAD. However, coronary plaque instability due to the stress of surgery has become an important topic. Currently, nonspecific anti-inflammatory medication such as aspirin and statins are considered. However, potentially interesting is the use of selective immunomodulation in patients at risk. The lessons we have learned from differences in outcome of perioperative beta blocker trials highlight the importance of careful evaluation and understanding of the complex changes that occur during surgery with respect to hemodynamic changes by endogenous catecholamine surge and anaesthetic therapies. Although, there seems to be a trend towards less noninvasive testing it should be considered that testing also serves additional purposes such as patient counselling about postoperative outcome, choice of anesthesia technique, and the consideration of alternative surgical procedures in high-risk patients.

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# CHAPTER

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## Preoperative cardiac risk index predicts long-term mortality and health status

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## ABSTRACT

**Objectives:** Peripheral arterial disease patients undergoing vascular surgery are known to be at risk for the occurrence of (late) cardiovascular events. Prior to surgery, the perioperative cardiac risk is commonly assessed using the Lee Risk Index score, a combination of six cardiac risk factors. This study assessed the predictive value of the Lee Risk Index for late mortality and long-term health status in patients after vascular surgery.

**Methods:** Between May and December 2004, data on 711 consecutive peripheral arterial disease patients undergoing vascular surgery were collected from 11 hospitals in The Netherlands. Prior to surgery, the Lee Risk Index was assessed in all patients. At 3-year follow-up, 149 patients died (21%) and the disease-specific Peripheral Artery Questionnaire (PAQ) was completed in 84% (n=465) of the survivors. Impaired health status according to the PAQ was defined by the lowest tertile of the PAQ summary score. Multivariable regression analyses were performed to investigate the prognostic ability of the Lee Index for mortality and impaired health status at 3-year follow-up.

**Results:** The Lee Risk Index showed to be an independent prognostic factor for both late mortality (1 risk factor HR=2.1, 95%CI 1.2-3.6; 2 risk factors HR=2.4, 95%CI 1.4-4.0 and  $\geq 3$  risk factors HR=3.2, 95%CI: 1.7-6.2) and impaired health status at 3-year follow-up (1 risk factor OR=2.0, 95%CI: 1.1-3.5; 2 risk factors OR=2.9, 95%CI: 1.6-5.2 and  $\geq 3$  risk factors OR=3.2, 95%CI 1.3-7.5). The predominant contributing factors associated with late mortality were cerebrovascular disease, insulin-dependent diabetes, and renal insufficiency. For impaired health status, ischemic heart disease, heart failure, cerebrovascular disease, insulin-dependent diabetes and renal insufficiency were the prognostic factors.

**Conclusions:** The preoperative Lee Risk Index is not only an important prognostic factor for in-hospital outcome but also for late mortality and impaired health status in patients with peripheral arterial disease.



## INTRODUCTION

Peripheral arterial disease patients undergoing vascular surgery are known to be at high risk for the occurrence of perioperative and late cardiovascular events.<sup>1</sup> Therefore, risk stratification is of utmost importance in current clinical practice to identify patients who are at risk of adverse outcome and consequently may benefit from a more aggressive treatment and intensified follow-up. Prior to surgery, the perioperative cardiac risk is commonly assessed using the Lee Risk Index.<sup>2</sup> This index identifies six predictors of major cardiac complications: high-risk surgery, ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, insulin therapy for diabetes mellitus, and renal insufficiency. Based on the presence of none, 1, 2, or  $\geq 3$  predictors, the rate of major perioperative cardiac complications was estimated to be 0.4%, 0.9%, 7% and 11%, respectively. Although the predictive value of the Lee Risk Index for short term outcomes is well established<sup>3</sup>, studies on the prognostic ability of the Lee Risk Index for late mortality are scarce.<sup>6,7</sup>

Health status is increasingly being assessed as an outcome parameter, especially in chronic diseases such as peripheral arterial disease, in which the goal of treatment is not only to prolong life but also to relieve symptoms and improve function.<sup>8-11</sup> Furthermore, from a methodological perspective these measures are also important because the discriminative power of mortality as an outcome measure is, as a result of improved treatment, poor. In this regard, the disease-specific Peripheral Artery Questionnaire (PAQ) proved to be a reliable and valid instrument for the assessment of health status in peripheral arterial disease patients.<sup>12-14</sup> In contrast to late morbidity and mortality, evidence of a predictive value of the Lee Risk Index for health status is totally lacking.

This study assessed the predictive value of the Lee Risk Index for late mortality and long-term health status in patients after vascular surgery. We hypothesized that the prognostic value of this preoperative risk index could be extended to late outcome.

## METHODS

### Study population

Between May and December 2004, a survey of clinical practice was conducted in 11 hospitals in The Netherlands.<sup>15</sup> This survey was an integral part of the infrastructure of the survey program supported by The Netherlands Heart Foundation in the context of the Euro Heart Survey Programme. All patients who were admitted to the vascular surgery department of the participating hospitals were screened. Patients undergoing peripheral vascular repair were eligible for participation in the survey. All consecutive patients included in this survey were seen at the participating vascular

surgery departments and were undergoing noncardiac vascular repair (endovascular or open procedures). Endovascular procedures included aortic endograft procedures and peripheral angioplasties with and without stenting. Open procedures included: elective abdominal aortic surgery, carotid endarterectomy, or infrainguinal arterial reconstruction. Patients below the age of 18 years and patients undergoing thoracic or brain surgery were excluded. The total study population consisted of 711 consecutively enrolled patients. Trained research assistants obtained data on patient characteristics, cardioprotective treatment and the surgical procedure from the patients' hospital charts. More details on the study population and methods of data collection can be found in an earlier publication on this survey.<sup>15</sup> After three years follow-up, information on survival status was obtained through the civil registries.

### **Lee Risk Index**

We determined the cardiac risk score for each patient in our dataset, according to the Lee-index<sup>2</sup>, and one point was assigned to each of the following characteristics: open vascular surgery, history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, insulin therapy for diabetes and renal insufficiency. The Lee Risk Index is validated in different studies and is a well-established risk stratification tool in noncardiac surgery.<sup>2,5</sup>

### **Health Status**

Health status was measured at three years of follow-up by the translated Dutch version of the PAQ, a disease-specific instrument for assessing health status in patients with peripheral arterial disease.<sup>14,16</sup> The instrument consists of 20 items with one item identifying the most symptomatic leg and the other items being answered along variable Likert response scales with equidistant gradations of response. Previous validation of the Dutch PAQ revealed three domains: physical limitation, perceived disability, and treatment satisfaction.<sup>12</sup> Internal reliability of the three domains quantified by Cronbach's  $\alpha$  was reported high for the Dutch PAQ (mean  $\alpha = 0.94$ ).<sup>12</sup> A summary score can be obtained by combining the physical limitation and perceived disability subscale scores. Given that the response categories are different across items, standardized scoring algorithms are applied to obtain scale scores ranging from 0 to 100, with high scores indicating good health status. Impaired health status according to the PAQ was defined by the lowest tertile of the PAQ summary score. Others have also advocated dichotomization of health status measures to facilitate interpretability in clinical practice.<sup>17</sup> Previous studies also showed that the PAQ had a good test-retest reliability and sensitivity to change.<sup>13,14</sup> In addition, we have previously demonstrated good clinical validity of the PAQ as the instrument discriminated well between patients with or without symptomatic peripheral arterial disease and its severity and was sensitive to the presence of risk factors relevant for peripheral arterial disease.<sup>12</sup>

## Endpoints

The endpoints of this study were all-cause mortality and impaired health status at 3-year follow-up. In The Netherlands survival status is systematically registered at the civil registries. Impaired health status according to the PAQ was defined by the lowest tertile of the PAQ summary score.

## Statistical Analyses

Differences between baseline characteristics and outcome were described as numbers and percentages and compared with chi-square tests. The continuous variable age was reported as mean with standard deviation and compared with a t-test. The method of Kaplan-Meier was used to describe the cumulative incidence of death over time. A log-rank test was applied to study differences in survival between Lee Risk Index categories. The relation between Lee Risk Index and mortality was further evaluated by multivariable Cox' proportional hazard regression analysis, with adjustment for potential confounders (age, gender, obesity, smoking, hypertension, cardiac arrhythmias, valvular heart disease and chronic obstructive pulmonary disease (COPD)). Multivariable logistic regression analysis was applied to assess the association between the Lee Risk Index and health status after three years of follow-up. Adjustments were performed for confounders and duration of follow-up. For all tests, a *P*-value <0.05 (two-sided) was considered significant. All statistical analyses were performed using SPSS 15.0 statistical software.

## RESULTS

Patient status was able to be determined in 701 (99%) of the original 711 patients revealing that 149 (21%) of the original cohort had died in the three year period since the original survey. All 552 surviving patients were contacted to complete the PAQ questionnaire, 454 (82%) of whom provided complete responses to obtain PAQ summary scores. The median follow up time of these patients was 3.1 years (interquartile range 3.07-3.19). The mean PAQ summary score was 62.0±28.2. Impaired health status was defined as the lowest tertile of the PAQ summary score, which equalled a score below 46.5 points.

Baseline characteristics of the patients according to late mortality and long term health status are presented in Table 1. Both late mortality and impaired health status were proportionally related to the number of risk factors according to the Lee Risk Index (Figure 1). Cumulative survival curves of the different risk groups are presented in Figure 2. The log rank test assessing differences in survival showed a *P*-value of <.001. Moreover, the Lee Risk Index proved to be an independent prognostic factor for late mortality (1 risk factor HR=2.1, 95%CI: 1.2-3.6; 2 risk factors HR=2.4, 95%CI 1.4-4.1 and ≥3 risk factors HR=3.3, 95%CI 1.7-6.3) and impaired health status at 3-year follow-up (1

risk factor OR=2.0, 95%CI 1.1-3.5; 2 risk factors OR=2.9; 95%CI: 1.6-5.2 and  $\geq 3$  risk factors OR= 3.2; 95%CI: 1.3-7.5) (Figure 3).

TABLE 1 - Baseline characteristics according to late mortality and long term impaired health status

	3-year Mortality*			3-year Health Status**		
	Alive	Death	P-value	Good	Impaired	P-value
N	552	149		304	150	
<b>Demographics</b>						
Age yrs± SD	65.1±10.0	73.9±8.9	<.001	63.9±9.6	67.3±10.0	<.001
Male gender %	69.0	72.5	.41	70.7	66.0	.31
<b>Risk factors (Lee)</b>						
Ischemic heart disease %	34.2	37.6	.45	30.6	46.7	.001
Heart failure %	3.4	12.1	<.001	2.0	6.7	.01
Cerebrovascular disease %	15.0	25.5	.003	12.8	20.0	.05
Insulin dependent diabetes %	7.4	14.1	.01	5.9	12.0	.02
Renal insufficiency%	4.9	16.1	<.001	3.3	9.3	.01
Surgical procedure %			.01			.81
Open	43.3	55.0		42.8	42.0	
Carotid endarterectomy	4.7	1.3		5.3	4.0	
Endovascular	52.0	43.6		52.0	54.0	
<b>Other risk factors</b>						
Obesity %	11.6	7.4	.14	8.6	20.0	<.001
Current smoker %	38.2	27.5	.02	33.9	38.0	.39
Hypertension %	38.8	35.6	.48	37.8	38.7	.86
Valvular heart disease %	5.4	12.1	.004	4.6	6.0	.52
COPD# %	11.6	24.2	<.001	7.9	15.3	.01
Cardiac arrhythmias %	8.0	21.5	<.001	6.9	5.3	.52
<b>Medical treatment</b>						
Beta-blockers %	50.2	40.3	.032	50.7	45.3	.286
Statins %	60.0	43.0	<.001	61.8	61.3	.916
Antiplatelet therapy %	83.2	71.1	.001	83.9	82.7	.743

\*Survival status of the original 711 patients was known in 701 patients (99%) after three years of follow-up

\*\*Impaired health status according to the PAQ was defined by the lowest tertile of the PAQ summary score. A PAQ summary score was available in 454 surviving patients.

#COPD, Chronic Obstructive Pulmonary Disease

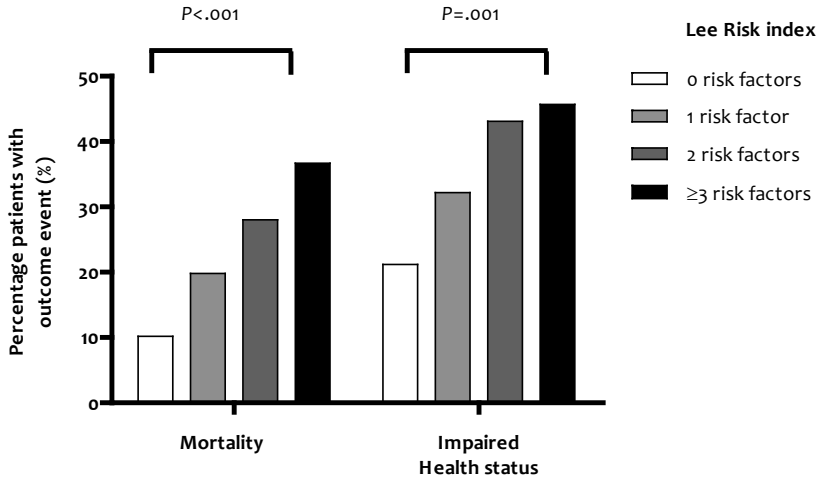


FIGURE 1 - Percentage patients with outcome event according to the Lee Risk Index.

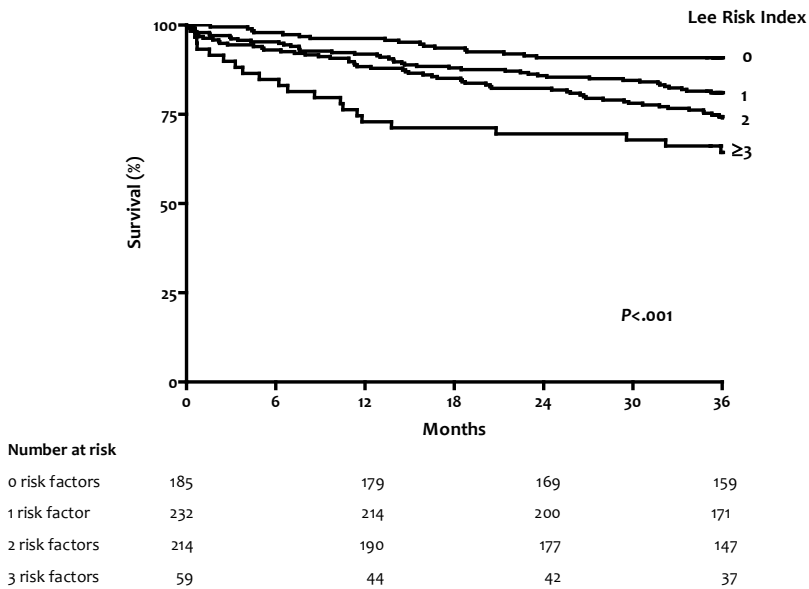


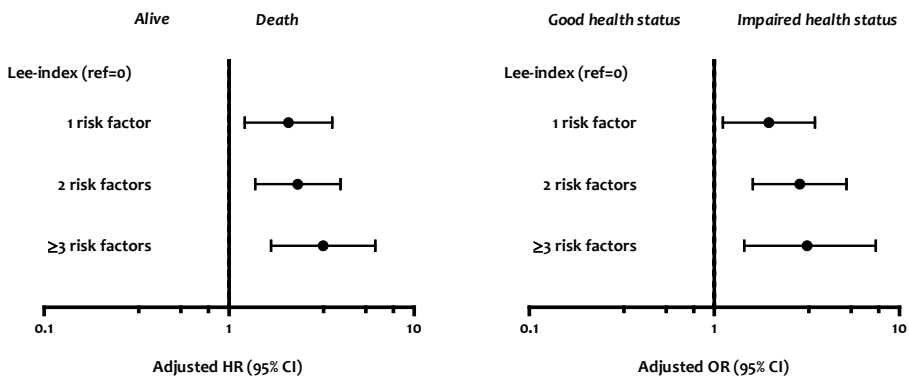
FIGURE 2 - Cumulative survival curve according to the Lee Risk Index.

For late mortality, cerebrovascular disease, insulin-dependent diabetes and renal insufficiency were the independent prognostic factors contributing to the Lee Risk Index (Table 2). Furthermore, age (HR=1.1, 95%CI 1.06-1.11) and COPD (HR=1.8, 95%CI 1.2-2.6) were independent predictors for long term mortality. The factors of the Lee Risk Index significantly associated with long term impaired health status were ischemic heart disease, heart failure, cerebrovascular disease, insulin-dependent diabetes and renal insufficiency. Other independent prognostic factors were age (OR=1.04, 95%CI 1.02-1.06), obesity (OR=3.0, 95%CI 1.6-5.7) and smoking (OR=1.8, 95%CI 1.1-2.9).

**TABLE 2** - Risk factors independently contributing to the Lee Risk Index within predicting 3-year outcome

	3-year Mortality		3-year Health Status	
	HR	95% CI	OR	95% CI
Ischemic heart disease	0.81	0.56-1.14	2.03	1.28-3.21
Heart failure	1.74	0.98-3.07	3.93	1.20-12.85
Cerebrovascular disease	1.88	1.28-2.76	1.98	1.06-3.69
Insulin dependent diabetes	2.23	1.39-3.58	2.22	1.05-4.70
Renal insufficiency	1.92	1.23-2.99	2.55	1.02-6.38
Surgical procedure				
Open	0.39	0.09-1.64	0.43	0.14-1.36
Carotid endarterectomy	1.66	1.18-2.33	0.82	0.51-1.30
Endovascular	1		1	

HR, hazard ratio; OR, odds ratio



**FIGURE 3** - Multivariable analysis to assess relation between Lee Risk Index and 3-year outcome.

## DISCUSSION

The main finding of our study is that the prognostic value of the Lee Cardiac Risk extends from major complications in the perioperative period to long term mortality and health status.

The Lee Risk Index was introduced to assess perioperative risk.<sup>2</sup> In general, risk stratification tools are designed to identify patients in clinical practice who are at relatively high risk for adverse outcomes. In the short term, identification of high risk patients may direct decisions regarding (non)invasive testing, change of open to endovascular surgery, delay of surgery, and optimal perioperative medical management. In this manner, the Lee Risk Index is also incorporated in the 2007 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on perioperative care to guide clinical decision making.<sup>5</sup> In the long term, high risk patients may benefit from more intensified follow-up and aggressive treatment, including pharmacological, invasive and/or behavioral interventions. Patients undergoing noncardiac vascular surgery frequently have underlying coronary heart disease and furthermore, have often other comorbid diseases. These facts pose the peripheral arterial disease population at a very high risk, which is also demonstrated by a study of Welten and colleagues concluding that the long-term prognosis of peripheral arterial disease patients undergoing vascular surgery is significantly worse compared with coronary artery disease patients.<sup>18</sup> The undertreatment of peripheral arterial disease patients in this study<sup>18</sup> and previously reported by others<sup>19,20</sup> may be one of the explanations of this worse long-term outcome. These results underscore the importance of effective risk stratification patients to improve long term patient outcome.

In our large consecutive cohort of peripheral arterial disease patients undergoing vascular surgery, the Lee Risk Index shows to have a good predictive value for late mortality. This finding confirms earlier research reporting on the prognostic ability of this risk index for late outcome.<sup>6,7</sup> Although not their primary research question, the Lee Risk Index was predictive of mortality in a comparable linear fashion as we observed.

In peripheral arterial disease, mortality is often due to the associated coronary and cerebrovascular disease rather than the peripheral arterial disease directly. As such, treatment of peripheral arterial disease is directed towards the goal of improving symptoms and its associated health status rather than survival only. In order to quantify the benefits of different treatment strategies and their cost-effectiveness<sup>11</sup>, sensitive patient-centered outcome measures are increasingly adopted in outcomes research with cardiovascular patients. In this study, health status measurements were performed at three years of follow-up in vascular surgery patients. Our results demonstrate that the Lee Risk Index proves to be also a valid method for identifying patients at high risk for impaired long-term health status.

Comorbid diseases are an important aspect of quality of life in peripheral arterial disease patients. Previous studies demonstrated that ischemic heart disease, cerebrovascular disease and obesity negatively impact patients' health status.<sup>21,22</sup> In our study heart failure contributed greatly to the perceived health status after long-term follow-up. Also the other comorbid conditions contributing to the Lee Risk Index, i.e. ischemic heart disease, cerebrovascular disease, insulin-dependent diabetes and renal insufficiency, were independently associated with an impaired health status. From literature, there is wide acceptance that heart failure is associated with an impaired quality of life.<sup>23</sup> One contributing factor is the common presence of depressive symptoms in patients with chronic heart failure which is known to have a great impact on patient's baseline health status and health status over time.<sup>24</sup> Available studies report also a high prevalence of depressive symptoms in peripheral arterial disease patients.<sup>25,26</sup> Importantly, depressive patients with comorbid conditions show 3-fold higher risk for medical noncompliance compared with non-depressed patients.<sup>27</sup> In addition, baseline perceived health status has shown to predict prognosis in patients with cardiovascular disease.<sup>15,28-30</sup> In cardiac disease and stroke, health professionals are familiar with a tradition of multidisciplinary disease management programs, which have proven to be effective in improving clinical outcomes and health status.<sup>31-33</sup> A comparable approach is needed in patients with peripheral arterial disease as atherosclerosis is a systemic disease affecting numerous vascular beds and these patients have consequently multiple comorbidities. A well-coordinated multidisciplinary program addressing clinical risk factors may enhance both survival and health status in patients with peripheral arterial disease.

Our study revealed that, although age is not included in the Lee Risk Index, increasing age is an important predictive factor for both long-term mortality as well as health status. These results are in line with earlier research showing the additional value of age in risk stratification in vascular surgery.<sup>37</sup> The global ageing phenomenon will further increase the burden of cardiovascular disease and also enforces a change in health care towards the elderly population. Major surgical interventions are for example now increasingly performed in the elderly.<sup>34</sup> Importantly, available data from surveys in vascular surgery<sup>35</sup> and cardiology<sup>36-38</sup> show, however, that evidence-based therapies are still less frequently being used in the elderly population. In other words, there is much room for improvement to effectively guide disease management in these high risk populations.

This study has some potential limitations. Firstly, patients who did not complete the PAQ had to be excluded from the analysis. However, a comparison between responders and nonresponders revealed no major differences in clinical risk profile. Secondly, health status was assessed only once and no baseline health status measurements were available. Strengths of this study are, however, the relatively large number of patients consecutively enrolled from different hospitals across The Netherlands. Furthermore, the 82% response rate of complete responses of the questionnaires can be seen as very good.



In conclusion, this study adds that the preoperative Lee Risk Index is not only an important prognostic factor for in-hospital outcome but also for late mortality and impaired health status in peripheral arterial disease patients. The Lee Risk Index might be an important tool for risk stratification providing evidence based treatment in patients undergoing noncardiac vascular surgery. Together with effective disease management programs specific for this relatively high risk population, better long term clinical outcome and patient-centered outcome may be achieved in the coming years.

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# CHAPTER

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## Preoperative cardiac testing before major vascular surgery

# 4

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## INTRODUCTION

Patients undergoing noncardiac vascular surgery are at significant risk of perioperative cardiac complications.<sup>1,2</sup> Though recent developments in anesthesiological and surgical techniques, e.g. loco-regional anesthesia and endovascular treatment modalities, have improved postoperative cardiac outcome considerably, perioperative cardiac complications remain a significant problem.

Myocardial infarction (MI) accounts for 10% to 40% of perioperative fatalities, and is considered to be the major determinant of postoperative mortality in noncardiac vascular surgery.<sup>3,5</sup> This increased risk of perioperative cardiac complications is a function of both the patient population at risk and the surgical procedure. Importantly, noncardiac vascular surgery patients frequently have underlying symptomatic or asymptomatic coronary artery disease (CAD). A landmark study by Hertzner et al. showed that 61% of 1000 patients undergoing noncardiac vascular surgery had at least one significant coronary artery stenosis ( $\geq 50\%$ ).<sup>6</sup>

Patients for vascular surgery should have an extensive preoperative workup for perioperative cardiovascular risk. The primary goal of treatment is to reduce cardiovascular complications around the vascular surgical procedure. Evidently, the long-term cardiovascular event risk will also decrease.<sup>7</sup>

This review will describe the current status of preoperative workup for patients undergoing noncardiac vascular surgery, including noninvasive cardiac testing for myocardial ischemia, a major determinant of perioperative outcome.

## PERIOPERATIVE MYOCARDIAL INFARCTION

Myocardial infarction is known to be the major cause of morbidity and mortality in noncardiac vascular surgery patients. The highest incidence of perioperative MI (PMI) is within the first 3 days after surgery ( $\pm 5\%$ ).<sup>2</sup> The prevalence of acute coronary syndrome with symptomatic or asymptomatic perioperative myocardial ischemia assessed by serum troponin I or T in major vascular surgery patients is even 15% to 25%.<sup>8,9</sup>

The pathophysiology of PMI is not entirely clear compared to MIs occurring in the nonoperative setting. Coronary plaque rupture leading to occlusive coronary thrombosis is suggested as an important causal mechanism, like in MIs occurring in the nonoperative setting. Surgery itself is a significant stress factor leading to an increased incidence of plaque rupture. Factors provoking physiologic stress during surgery include anesthetic agents, response to surgically induced hypotension, anemia, and postoperative pain. Two retrospective studies investigated the coronary pathology of fatal PMI. Dawood et al.<sup>10</sup> performed histopathologic analyses of coronary arteries

in 42 patients with a fatal PMI within the first 30 days after surgery. Evidence of plaque rupture was found in only 55% of the patients. In more than half of the patients, the investigators were unsuccessful at predicting the site of infarction based on the severity of the underlying coronary artery stenosis. These findings were confirmed by Cohen and Aretz, who analyzed the coronary pathology of 26 patients with PMI.<sup>11</sup> In only 12 of these patients (46%) plaque rupture was identified as the causative mechanism of PMI.

Perioperative MI may also be caused by a sustained myocardial oxygen supply/demand imbalance due to prolonged hemodynamic stress. Surgery-related factors such as increased heart rate, elevated blood pressure, pain, and the use of sympathomimetic drugs may further increase myocardial oxygen demand. In addition, surgery may cause a decrease in oxygen supply as the result of hypotension, vasospasm, anemia, and hypoxia.

Plaque rupture and sustained myocardial oxygen supply/demand imbalance probably contribute equally to the occurrence of PMI. As already noted, the location of a plaque rupture is impossible to predict with commonly used techniques. However, the extent of significant coronary atherosclerosis can be defined with cardiac stress testing. These two pathophysiological mechanisms imply that multiple strategies are required to reduce perioperative cardiac risk. In this respect, beta-blockers were suggested to prevent MI by reducing the mechanical and hemodynamic stress on vulnerable plaques, and by preventing prolonged, stress-induced ischemia.<sup>12</sup>

## CARDIAC RISK STRATIFICATION

Adequate preoperative cardiac risk assessment is essential for identifying high-risk patients for perioperative cardiac events. Several risk indices were developed to stratify vascular surgical patients, based on clinical cardiac risk factors. The cardiac risk index of Goldman et al.<sup>13</sup> in 1977 was the first multifactorial model specifically for perioperative cardiac complications to be widely used. This risk index was developed in a noncardiac surgical population. The authors identified nine independent risk factors correlated with postoperative serious or fatal cardiac complications: (1) preoperative third heart sound or jugular venous distention; (2) MI in the preceding 6 months; (3) >5 premature ventricular contractions per minute documented at any time before operation; (4) rhythms other than sinus rhythm or the presence of premature atrial contractions on preoperative electrocardiogram (ECG); (5) age >70 years; (6) an intraperitoneal, intrathoracic, or aortic operation; (7) emergency operation; (8) important valvular aortic stenosis; and (9) poor general medical condition. This index was modified by Detsky et al. in 1986<sup>14</sup>, who added the presence of angina and a remote history of MI to the original model of Goldman et al.<sup>13</sup> They used a Bayesian approach involving pretest probabilities, and presented the modified cardiac risk index in a simple normogram.

The Glasgow aneurysm score, described in 1994, was one of the first cardiac risk scores only intended for vascular surgical procedures.<sup>15</sup> In a retrospective study of 500 randomly chosen patients scheduled for open abdominal aortic aneurysm repair, potential preoperative risk factors were related to postoperative in-hospital mortality. One year later, the Leiden Risk Model for perioperative mortality in patients with an abdominal aortic aneurysm was developed by Steyerberg et al.<sup>16</sup> This clinical prediction rule was based on several risk factors obtained from the literature, and validated in a cohort of 246 patients undergoing open abdominal aortic aneurysm repair.

In 1996, L'Italien et al. developed and validated a Bayesian model for preoperative cardiac risk assessment in a total of 1081 consecutive patients undergoing elective major vascular surgery.<sup>17</sup> This study had a combined endpoint of nonfatal MI or cardiac death. Using 567 patients as a derivation cohort, the following risk factors were identified as predictors of adverse postoperative outcome: myocardial infarction, congestive heart failure, angina pectoris, prior coronary revascularization, diabetes mellitus, and age >70 years. Importantly, the validation cohort (514 patients) exhibited a prognostic accuracy of 74%. Patients classified as low-risk, intermediate-risk, and high-risk had cardiac event rates of 3%, 8%, and 18%, respectively.

In 1999, Lee et al.<sup>18</sup> developed the largest and currently most widely used model of risk assessment, the Revised Cardiac Risk Index. This index identifies six predictors of major cardiac complications: (1) high-risk type of surgery, (2) history of ischemic heart disease, (3) history of congestive heart failure, (4) history of cerebrovascular disease, (5) preoperative treatment with insulin, and (6) preoperative serum creatinine >2.0 mg/dL. Based on the presence of none, 1, 2, or  $\geq 3$  predictors, the rate of major cardiac complications in the validation cohort ( $n = 1422$ ) was estimated to be 0.4%, 0.9%, 7%, and 11%, respectively.

The Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo (DECREASE) I Trial identified comparable independent clinical risk factors associated with major vascular surgery: a history of myocardial infarction, angina, congestive heart failure, diabetes, renal dysfunction, cerebrovascular events, and age >70 years.<sup>19</sup> Recently, Kertai et al. developed a Bayesian model for the prediction of all-cause perioperative mortality in 1537 patients undergoing all types of open vascular surgery.<sup>20</sup> Risk factors associated with postoperative all-cause death included ischemic heart disease, congestive heart failure, cerebrovascular events, hypertension, renal dysfunction, chronic pulmonary disease, and type of vascular surgery, i.e. ruptured aneurysm abdominal aorta (AAA), elective AAA, lower extremity, and carotid vascular surgery. The final logistic regression model with nine independent predictors (including beta-blocker and statin use) of perioperative mortality was used to create a variable-weight index, the customized probability index, where scores were assigned based on parameter estimates of individual predictors. The sum of scores of surgical risk (0-46 points), medical history (0-67 points), and cardioprotective medication (statins -10 points and beta-blockers -15 points) was calculated for an overall cardiac risk.

# NONINVASIVE TESTING

Once the assessment of risk factors indicates an increased cardiac perioperative risk, or if there is a suspicion of CAD upon examination, further cardiac testing is warranted. According to the current guidelines of the American College of Cardiology/American Heart Association<sup>21</sup>, preoperative cardiac exercise or pharmacologic stress testing is recommended for (1) patients with an intermediate pretest probability of CAD, (2) patients undergoing initial evaluation for suspected or proven CAD, (3) subjects with a significant change in clinical status, (4) demonstration of proof of myocardial ischemia before coronary revascularization, (5) evaluation of adequacy of medical treatment, and (6) prognostic assessment after an acute coronary syndrome.

One of the main issues in preoperative cardiac risk assessment is to identify those patients who should undergo additional stress testing before surgery. The randomized, multicenter DECREASE II Study assessed the value of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight heart-rate control.<sup>22</sup> In total, 1476 vascular surgical patients were divided into three risk groups based on the risk score of Boersma et al.<sup>19</sup> All 770 intermediate-risk patients were randomly assigned to preoperative cardiac stress testing or no testing. Importantly, all patients in the DECREASE II Study received beta-blocker therapy, irrespective of stress test results, aiming at tight heart-rate control, i.e. a heart rate of 60 to 65 beats per minute. This study demonstrated no differences in cardiac death and MI at 30 days between patients assigned to no testing versus cardiac stress testing (1.8% versus 2.3%; odds ratio [OR]=0.78, 95% confidence interval [CI] 0.28 to 2.1). Also, 2-year outcomes were comparable in intermediate-risk patients with and without testing, i.e. 4.3% versus 3.1%, respectively. These results indicate that intermediate-risk patients undergoing major vascular surgery are at a relatively low perioperative risk and do not benefit from preoperative cardiac testing when receiving beta-blocker therapy with tight heart-rate control.

For those patients who require cardiac testing, several noninvasive and physiological (and nonphysiological) stress tests are available for the evaluation of perioperative risk. Nonphysiological stress tests are especially recommended to detect preoperative myocardial ischemia in asymptomatic vascular surgery patients.

## Rest Electrocardiography

Different studies associated abnormal ECG findings with perioperative cardiac complications.<sup>13,14,23</sup> In a large prospective study by Lee et al.<sup>18</sup> involving 4315 patients undergoing major noncardiac surgery, a history of ischemic heart disease was one of the six independent predictors of major cardiac complications. Pathological Q-waves, as an electrocardiographic sign of MI in the past, were found in 17% of patients, with a 2.4-fold increased risk of perioperative events. A recent

retrospective study confirmed the prognostic value of routine preoperative electrocardiography in 22,457 noncardiac operations.<sup>24</sup> Patients with abnormal ECG findings had a higher incidence of 30-day cardiovascular death compared with patients with a normal ECG (1.8% versus 0.3%; adjusted OR=3.4, 95%CI 2.4-4.5). In addition, it was demonstrated that a preoperative ECG is also predictive for long-term outcome, independent of clinical findings and perioperative ischemia, in CAD patients undergoing major noncardiac surgery.<sup>25</sup>

### **ST-segment Holter**

The use of ambulant 24-hour ST-segment registration for evaluation of perioperative cardiac risk was first described by Raby et al.<sup>26</sup> They reported a sensitivity of 75% and a specificity of 83% for the prediction of a combined endpoint of cardiac death and nonfatal MI. A large meta-analysis showed lower values, comprising eight studies with a total of 893 patients, with a weighted sensitivity of 52% (95%CI, 21% to 84%) and a specificity of 70% (95% CI, 57% to 83%).<sup>27</sup> The advantages of ST-segment Holter include its low cost and wide availability.

### **Exercise Electrocardiogram**

The most commonly used physiologic stress test for detecting myocardial ischemia uses a treadmill or cycle ergometer. Among its advantages, this test provides an estimate of functional capacity, and hemodynamic response, and detects myocardial ischemia through ST-segment changes. The accuracy of an exercise ECG varies widely among studies. A meta-analysis by Kertai et al.<sup>27</sup> for the detection of myocardial ischemia with treadmill testing in vascular surgery patients showed a rather low sensitivity (74%; 95%CI 60% to 88%) and specificity (69%; 95%CI 60% to 78%), comparable to daily clinical practice. However, important limitations in patients with peripheral vascular disease involve their frequently limited exercise capacity. Furthermore, preexisting ST-segment deviations, especially in the precordial leads V<sub>5</sub> and V<sub>6</sub> at the rest ECG, make a reliable ST-segment analysis more difficult.<sup>28</sup>

### **Stress Echocardiography**

Because most patients with peripheral vascular disease are unable to exercise maximally, stress echocardiography with pharmacologic stressors (such as dobutamine) is a good alternative. Although vasodilators (e.g., dipyridamole or adenosine) may have advantages for the assessment of myocardial perfusion, dobutamine is the preferred pharmacological stressor when the test is based on an assessment of regional wall-motion abnormalities.<sup>29</sup> Dobutamine is a synthetic catecholamine with predominantly beta<sub>1</sub>-receptor-stimulating properties, resulting in a strong positive inotropic effect and modest chronotropic effect on the heart. During the stress test, dobutamine is intravenously administered. A graded dobutamine infusion starting at 5 µg/

kg/min, and increasing at 3-minute intervals to 10, 20, 30, and 40  $\mu\text{g}/\text{kg}/\text{min}$ , is the standard for dobutamine stress echocardiography (DSE). During dobutamine infusion, contractility and heart rate increase, leading to increased myocardial oxygen demand. Myocardial ischemia leading to systolic contractile dysfunction, detectable by echocardiography, occurs in regions supplied by hemodynamically significant stenotic coronary arteries.

Tissue harmonic imaging is advised for stress echocardiography. This special imaging setting reduces near-field artifacts, improves resolution, enhances myocardial signals, and is superior to fundamental imaging for endocardial border visualization. The improvement in endocardial visualization is further enhanced by the use of contrast agents for left-ventricular (LV) opacification. Contrast agents increase the number of interpretable LV wall segments. These recent developments exhibit decreased interobserver variability, and have improved the sensitivity of stress echocardiography.<sup>30</sup>

Many reports demonstrated that DSE predicts perioperative events in patients undergoing vascular surgery.<sup>31-34</sup> The negative predictive value of dobutamine stress tests is high, although the positive predictive value is much lower.

Kertai et al. reported a weighted sensitivity of 85% (95%CI 74% to 97%) and a specificity of 70% (95%CI 62% to 69%) for DSE in 850 patients from eight studies.<sup>27</sup> A recent meta-analysis by Beattie et al. analyzed the predictive value of pharmacological stress testing compared with myocardial perfusion scintigraphy.<sup>35</sup> This report included 25 studies (3373 patients) of mainly dobutamine as well as dipyridamole stress echocardiography. The likelihood ratio of a perioperative event with a positive stress echocardiography was 4.09 (95%CI 3.21 to 6.56).

### **Myocardial Perfusion Scintigraphy**

Myocardial perfusion scintigraphy (MPS) is a widely used technique in the preoperative risk assessment of patients undergoing vascular surgery. The technique involves intravenous administration of a small quantity of a radioactive tracer. The detection of CAD is based on a difference in blood-flow distribution through the LV myocardium. These differences in perfusion can be explained by insufficient coronary blood flow based on coronary stenosis. Nowadays, technetium-99m-labeled radiopharmaceutical is the most widely used tracer. Myocardial perfusion scintigraphy is used in combination with exercise or pharmacologic stress testing to diagnose the presence of CAD. If there is a decrease or loss in regional perfusion after maximal vasodilatation with, for example, adenosine, as seen in hemodynamically significant CAD or in transmural MI, a reduced radiopharmaceutical signal is observed. Stress and rest MPS are compared for reversible abnormalities. A positive MPS is associated with an increased risk of perioperative and postoperative cardiac complications.

This method of noninvasive testing has been extensively studied, and was included in several meta-analyses.<sup>27,35-37</sup> Boucher et al. were among the first to report on using MPS for preoperative cardiac risk assessment.<sup>36</sup> They performed preoperative dipyridamole-thallium imaging in 48 patients scheduled for peripheral vascular surgery. Half of the patients with thallium redistribution had cardiac events, whereas no events occurred in the 32 patients with a normal scan or with nonreversible defects only ( $P < 0.001$ ).

Studies indicate that MPS is highly sensitive for the prediction of cardiac complications, but its specificity was reported as less satisfactory. A meta-analysis by Etchells et al.<sup>37</sup> investigated the prognostic value of semiquantitative dipyridamole MPS for perioperative cardiac risk in patients undergoing noncardiac vascular surgery. They included nine studies, involving a total of 1179 vascular surgery patients, with a 7% cardiac complication rate. One of the most important findings in this study was that reversible ischemia in <20% of the myocardial segments did not change the likelihood of perioperative complications. Patients with more extensive reversible defects were at increased risk: 20 to 29% reversibility (likelihood ratio [LR] 1.6; 95%CI 1.0 to 2.6), 30 to 39% reversibility (LR 2.9; 95%CI 1.6 to 5.1), 40 to 49% reversibility (LR 1.6; 95%CI 1.0 to 2.6), 40% to 49% reversibility (LR 2.9; 95%CI 1.4 to 6.2) and  $\geq 50\%$  or more reversibility (LR 11; 95%CI 5.8 to 20). These reversible defects in >20% of myocardial segments were only seen in 23% of all patients.

Another meta-analysis which assessed the prognostic value of six diagnostic tests reported a sensitivity of 83% (95%CI, 77% to 89%) and a much lower specificity of 47% (95% CI, 41% to 57%) for MPS.<sup>27</sup> More recently, Beattie et al.<sup>35</sup> performed a meta-analytic comparison, including in total 39 thallium-imaging studies involving vascular surgery patients were included, and resulted in a summary likelihood ratio of 1.83 (95% CI, 1.57 to 2.13).

### **Which Test to Choose?**

There is no large direct comparison of these techniques in perioperative risk assessment in the same patient population. However, several meta-analyses compared different techniques with respect to sensitivity and specificity. An early comparison of dipyridamole perfusion imaging and DSE was performed by Shaw et al.<sup>34</sup> The recent meta-analysis by Kertai et al. compared six different diagnostic tests for diagnostic accuracy to predict perioperative cardiac risk in patients undergoing major vascular surgery.<sup>27</sup> Eventually, 58 studies met the inclusion criteria, with a total of 8119 patients. A positive trend in favor of DSE for better diagnosis compared with other tests was indicated. However, this was only statistically significant compared with MPS. Beattie et al. conducted a meta-analysis of 68 studies comparing thallium MPS with stress echocardiography in 10,049 noncardiac surgery patients.<sup>35</sup> The authors concluded that stress echocardiography was preferable for predicting postoperative events because of its better negative predictive characteristics.

Nevertheless, because the tests have comparable accuracy, there is no definite answer to the question of which test to choose. The choice of test should be based on the center's experience and short-term availability. Accurate assessment of the ischemic burden is important in predicting perioperative and postoperative risk.

## PERIOPERATIVE MANAGEMENT

In general, two strategies have been used in an attempt to reduce the incidence of PMIs and other cardiac complications: preoperative coronary revascularization, and prophylactic pharmacological treatment. In recent years, more attention has been focused on the role of pharmacological treatment, whereas controversy continues over the appropriate management of patients diagnosed preoperatively with significant coronary artery disease. With respect to prophylactic coronary revascularization, American College of Cardiology/American Heart Association guidelines recommend revascularization only for subgroups of high-risk patients with unstable cardiac symptoms or with likely long-term benefits of coronary artery revascularization.<sup>21</sup> However, these current guideline recommendations are based on studies not designed to answer the research question of prophylactic revascularization.<sup>38,39</sup> Recently, the randomized Coronary Artery Revascularization Prophylaxis (CARP) Trial demonstrated that there is no reduction in the number of perioperative or postoperative MIs, deaths, lengths of hospital stay, or improved long-term outcomes in patients who undergo preoperative coronary revascularization compared with patients who receive optimized medical therapy.<sup>40</sup> Yet it must be noted that the majority of patients in the CARP Trial had only one-vessel or two-vessel disease, with preserved LV function. Optimal preoperative medical treatment, especially with tight heart rate control, is essential for decreasing perioperative risk. The aim of the recent randomized pilot study DECREASE V was to assess the feasibility of prophylactic coronary revascularization in patients with preoperative, extensive, stress-induced ischemia.<sup>41</sup> Patients with  $\geq 3$  risk factors, and who had extensive stress-induced ischemia using DSE, were randomly assigned to prophylactic revascularization or pharmaceutical treatment. Revascularization did not improve 30-day or 1-year outcomes. The incidence of the composite endpoint of all-cause 30-day mortality and MI for patients with preoperative revascularization or medical treatment was 43% versus 33%, respectively (OR=1.4, 95%CI, 0.7 to 2.8) and at 1 year, 49% versus 44% (OR=1.2, 95%CI, 0.7 to 2.3).

These findings of both CARP and DECREASE V support the current guidelines of the American College of Cardiology and American Heart Association for perioperative management in high-risk patients, to reserve revascularization only for cardiac unstable patients. In high-risk patients scheduled for major noncardiac vascular surgery, prophylactic revascularization might be switched to postoperative revascularization, preventing the delay of surgery.



It must be noted that preoperative revascularization can even be harmful for the patient because of periprocedural complications during revascularization and postponement of the noncardiac procedure. Importantly, the cumulative risk of prophylactic coronary revascularization and noncardiac surgery needs to be weighed against the risk of noncardiac surgery alone and the immediate benefits of prophylactic coronary revascularization.

Besides coronary revascularization, an extensive preoperative cardiac evaluation with noninvasive cardiac testing might improve outcomes by inducing optimal medical management in the perioperative periods. Perioperative beta-blockers and statins have, in this respect, shown a significant benefit in decreasing perioperative cardiac mortality and morbidity.<sup>42-46</sup> Because of the increasing evidence of the beneficial effects of beta-blockers in the perioperative period, the guidelines on perioperative beta-blocker therapy were recently updated.<sup>47</sup>

## CONCLUSIONS

Preoperative risk assessment with a noninvasive stress test (MPS or DSE) is necessary only in high-risk patients without unnecessary delay for vascular surgery. High-risk patients can easily be selected through the risk score index. Prophylactic revascularization should only be performed in those with unstable coronary artery disease. The optimal perioperative medical treatment, especially tight heart-rate control, is essential for decreasing perioperative and postoperative cardiac risk.

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# **PART II**

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# CHAPTER

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## **Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in noncardiac 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).**

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# 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)

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## List of acronyms and abbreviations

AAA	abdominal aortic aneurysm
ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
AHA	American Heart Association
AR	aortic regurgitation
ARB	angiotensin receptor blocker
AS	aortic stenosis

AF	atrial fibrillation
BBSA	β-blocker in spinal anaesthesia
BNP	brain natriuretic peptide
CABG	coronary artery bypass grafting
CARP	coronary artery revascularization prophylaxis
CASS	coronary artery surgery study
CI	confidence interval
COX-2	cyclooxygenase-2
COPD	chronic obstructive pulmonary disease
CPET	cardiopulmonary exercise testing
CPG	Committee for Practice Guidelines
CRP	C-reactive protein
CT	computed tomography
cTnI	cardiac troponin I
cTnT	cardiac troponin T
CVD	cardiovascular disease
DECREASE	Dutch Echocardiographic Cardiac Risk Evaluating Applying Stress Echo
DES	drug-eluting stent
DIPOM	Diabetes Postoperative Mortality and Morbidity
DSE	dobutamine stress echocardiography
ECG	electrocardiography
ESC	European Society of Cardiology
FEV <sub>1</sub>	forced expiratory volume in 1 s
FRISC	fast revascularization in instability in coronary disease
HR	hazard ratio
ICU	intensive care unit
IHD	ischaemic heart disease
INR	international normalized ratio
LMWH	low molecular weight heparin
LQTS	long QT syndrome
LR	likelihood ratio
LV	left ventricular
MaVS	metoprolol after surgery
MET	metabolic equivalent
MI	myocardial infarction
MR	mitral regurgitation
MRI	magnetic resonance imaging
MS	mitral stenosis
NICE-SUGAR	normoglycaemia in intensive care evaluation and survival using glucose algorithm regulation
NSTEMI	non-ST-segment elevation myocardial infarction
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OPUS	orbofiban in patients with unstable coronary syndromes
OR	odds ratio
PaCO <sub>2</sub>	mixed expired volume of alveolar and dead space gas

PAH	pulmonary arterial hypertension
PETCO <sub>2</sub>	end-tidal expiratory CO <sub>2</sub> pressure
PCI	percutaneous coronary intervention
PDA	personal digital assistant
POISE	PeriOperative ISchaemic Evaluation trial
QUO-VADIS	QUinapril On Vascular ACE and Determinants of ISchemia
ROC	receiver operating characteristic
SD	standard deviation
SMVT	sustained monomorphic ventricular tachycardia
SPECT	single photon emission computed tomography
SPVT	sustained polymorphic ventricular tachycardia
STEMI	ST-segment elevation myocardial infarction
SVT	supraventricular tachycardia
SYNTAX	synergy between percutaneous coronary intervention with taxus and cardiac surgery
TACTICS	treat angina with aggrastat and determine cost of therapy with an invasive or conservative strategy
TIA	transient ischaemic attack
TIMI	thrombolysis in myocardial infarction
TOE	transoesophageal echocardiography
UFH	unfractionated heparin
VCO <sub>2</sub>	carbon dioxide production
VE	minute ventilation
VHD	valvular heart disease
VKA	vitamin K antagonist
VO <sub>2</sub>	oxygen consumption
VPB	ventricular premature beat
VT	ventricular tachycardia

## Preamble

Guidelines and Expert Consensus Documents aim to present management and recommendations based on the relevant evidence on a particular subject in order to help physicians to select the best possible management strategies for the individual patient suffering from a specific condition, taking into account not only the impact on outcome, but also the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines are no substitutes for textbooks. The legal implications of medical guidelines have been discussed previously.<sup>1</sup>

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by the European Society of Cardiology (ESC) and also by other organizations or related societies. Because of the impact on clinical practice, quality criteria for development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC guidelines and Expert Consensus Documents can be found on the ESC website in the guidelines section ([www.escardio.org](http://www.escardio.org)).

In brief, experts in the field are selected and undertake a comprehensive review of the published evidence for management and/or prevention of a given condition. A critical evaluation of diagnostic and therapeutic procedures is performed, including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger societies are included, where data exist. The level of

evidence and the strength of recommendation of particular treatment options are weighted and graded according to pre-defined scales, as outlined in *Tables 1 and 2*.

The experts of the writing panels have provided disclosure statements of all relationships they may have which might be perceived as real or potential sources of conflicts of interest. These disclosure forms are kept on file at the European Heart House, headquarters of the ESC. Any changes in conflict of interest that arise during the writing period must be notified to the ESC. The Task Force report is entirely supported financially by the ESC without any involvement of industry.

The ESC Committee for Practice Guidelines (CPG) supervises and coordinates the preparation of new Guidelines and Expert Consensus Documents produced by Task Forces, expert groups, or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines and Expert Consensus Documents or statements. Once the document has been finalized and approved by all the experts involved in the Task Force, it is submitted to outside specialists for review. The document is revised, and finally approved by the CPG and subsequently published.

After publication, dissemination of the message is of paramount importance. Pocketsize versions and personal digital assistant (PDA)-downloadable versions are useful at the point of care. Some surveys have shown that the intended end-users are sometimes not aware of the existence of guidelines, or simply do not translate them into practice, so this is why implementation programmes for new guidelines form an important component of the dissemination of knowledge. Meetings are organized by the ESC, and are directed towards its member National Societies and key opinion leaders in Europe. Implementation meetings can also be undertaken at national levels, once the guidelines have been endorsed by the ESC member societies, and translated into the national language. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.<sup>2</sup>

Thus, the task of writing Guidelines or Expert Consensus Documents covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. The development of clinical guidelines and implementation into clinical practice can then only be completed if surveys and registries are performed to verify its use in real-life daily practices. Such surveys and registries also make it possible to evaluate the impact of implementation of the guidelines on patient outcomes. Guidelines and recommendations should help physicians and other healthcare providers to make decisions in their daily practice. However, the physician in charge of his/her care must make the ultimate judgement regarding the care of an individual patient.

## Introduction

### Magnitude of the problem

The present guidelines focus on the cardiological management of patients undergoing non-cardiac surgery, i.e. patients where heart

**Table 1** Classes of recommendations

Classes of Recommendations	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

**Table 2** Level of evidence

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

disease is a potential source of complications during surgery. The risk of perioperative complications depends on the condition of the patient prior to surgery, the prevalence of co-morbidities, and the magnitude and duration of the surgical procedure.<sup>3</sup> More specifically, cardiac complications can arise in patients with documented or asymptomatic ischaemic heart disease (IHD), left ventricular (LV) dysfunction, and valvular heart disease (VHD) who undergo procedures that are associated with prolonged haemodynamic and cardiac stress. In the case of perioperative myocardial ischaemia, two mechanisms are important: (i) chronic mismatch in the supply-to-demand ratio of blood flow response to metabolic demand, which clinically resembles stable IHD due to a flow limiting stenosis in coronary conduit arteries; and (ii) coronary plaque rupture due to vascular inflammatory processes presenting as acute coronary syndromes (ACSs). Hence, although LV dysfunction may occur for various reasons in younger age groups, perioperative cardiac mortality and morbidity are predominantly an issue in the adult population undergoing major non-cardiac surgery.

The magnitude of the problem in Europe can best be understood in terms of (i) the size of the adult non-cardiac surgical cohort; and (ii) the average risk of cardiac complications within this cohort. Unfortunately, at a European level, no systematic data are available on the annual number and type of operations, nor on patient outcome. Information is collected at the national level in several countries, but data definitions, amount of data, and data quality vary greatly. In The Netherlands, with a population of 16 million, throughout 1991–2005, 250 000 major surgical procedures were conducted on average annually in patients above the age of 20 years, implying an annual rate of 1.5%.<sup>4</sup> When applied to Europe, with an overall population of 490 million, this figure translates into a crude estimate of 7 million major procedures annually in patients who present with cardiac risk.

Data on cardiac outcome can be derived from the few large-scale clinical trials and registries that have been undertaken in patients undergoing non-cardiac surgery. Lee *et al.* studied 4315 patients undergoing elective major non-cardiac procedures in a tertiary care teaching hospital throughout 1989–1994.<sup>5</sup> They

observed that 92 (2.1%) patients suffered major cardiac complications, including cardiac death and myocardial infarction (MI). In a cohort of 108 593 consecutive patients who underwent surgery throughout 1991–2000 in a university hospital in The Netherlands, perioperative mortality occurred in 1877 (1.7%) patients, with a cardiovascular cause being identified in 543 cases (0.5%).<sup>6</sup> The Dutch Echocardiographic Cardiac Risk Evaluating Applying Stress Echo (DECREASE) -I, -II and -IV trials enrolled 3893 surgical patients throughout 1996–2008, and these comprised intermediate- and high-risk patients of whom 136 (3.5%) suffered perioperative cardiac death or MI.<sup>7–9</sup> A final piece of evidence with respect to patient outcome is derived from the Perioperative Ischaemic Evaluation (POISE) trial, which was conducted throughout 2002–2007, and enrolled 8351 patients undergoing non-cardiac surgery.<sup>10</sup> Perioperative mortality occurred in 226 patients (2.7%), of whom 133 (1.6%) suffered cardiovascular death, whereas non-fatal MI was observed in another 367 (4.4%) subjects. Differences in incidences between the studies are mainly explained by patient selection and endpoint MI definitions—major non-cardiac surgery is associated with an incidence of cardiac death of between 0.5 and 1.5%, and of major cardiac complications of between 2.0 and 3.5%. When applied to the population in the European Union member states these figures translate into 150 000–250 000 life-threatening cardiac complications due to non-cardiac surgical procedures annually.

### Impact of the ageing population

Within the next 20 years, the acceleration in ageing of the population will have a major impact on perioperative patient management. It is estimated that elderly people require surgery four times more often than the rest of the population.<sup>11</sup> Although exact data regarding the number of patients undergoing surgery in Europe are lacking, it is estimated that this number will increase by 25% by 2020, and for the same time period the elderly population will increase by >50%. The total number of surgical procedures will increase even faster because of the rising frequency of interventions with age.<sup>12</sup> Results of the US National Hospital Discharge Survey show that, in general, the number of surgical procedures will increase in almost all age groups, but that the largest increase will occur in the middle aged and elderly (Table 3).

Demographics of patients undergoing surgery show a trend towards an increasing number of elderly patients and co-morbidities.<sup>13</sup> Although mortality from cardiac disease is decreasing in the general population, the prevalence of IHD, heart failure, and cardiovascular risk factors, especially diabetes, is increasing. Among the significant co-morbidities in elderly patients presenting for general surgery, cardiovascular disease (CVD) is the most prevalent. It is estimated from primary care data that in the 75–84 year age group 19% of men and 12% of women have some degree of CVD.<sup>14</sup> Age *per se*, however, seems to be responsible for only a small increase in the risk of complications; greater risks are associated with urgency and significant cardiac, pulmonary, and renal disease. The number of affected individuals is likely to be higher in countries with high CVD mortality, particularly in Central and Eastern Europe. These conditions should, therefore, have a greater impact on the evaluation of patient risk than age alone.

**Table 3** Change in numbers of discharges for surgical procedures by age for the time periods 1994/95 and 2004/05 as reported from the 2005 US National Hospital Discharge Survey (non-federal short-stay hospitals)<sup>15</sup>

Age (years)	Number of procedures (in thousands)		% change
	1994/95	2004/05	
18–44	7311	7326	+2.1
45–64	4111	5210	+26.7
65–74	3069	3036	–1.1
75 and over	3479	4317	+24.1
18 and over	17 969	19 889	+10.7

### Purpose

Currently there are no official ESC guidelines on pre-operative risk assessment and perioperative cardiac management. The objective is to endorse a standardized and evidence-based approach to perioperative cardiac management. The guidelines recommend a practical, stepwise evaluation of the patient, which integrates clinical risk factors and test results with the estimated stress of the planned surgical procedure. This results in an individualized cardiac risk assessment, with the opportunity to initiate medical therapy, coronary interventions, and specific surgical and anaesthetic techniques in order to optimize the patient's perioperative condition. Compared with the non-surgical setting, data from randomized clinical trials, which are the ideal evidence base for the guidelines, are sparse. Therefore, when no trials are available on a specific cardiac management regimen in the surgical setting, data from the non-surgical setting are used, and similar recommendations made, but with different levels of evidence. Emphasis is placed on the restricted use of prophylactic coronary revascularization, as this is rarely indicated simply to ensure the patient survives surgery. Pre-operative evaluation requires an integrated multidisciplinary approach from anaesthesiologists, cardiologists, internists, pulmonologists, geriatricians, and surgeons. Anaesthesiologists, who are experts on the specific demands of the proposed surgical procedure, usually coordinate the process.

Guidelines have the potential to improve post-operative outcome. However, as shown in an observational study of 711 vascular surgery patients from The Netherlands, adherence to guidelines is poor.<sup>16–18</sup> Although 185 of a total of 711 patients (26%) fulfilled the ACC/AHA guideline criteria for pre-operative non-invasive cardiac testing, clinicians had performed testing in only 38 of those cases (21%).<sup>16</sup> The guideline-recommended medical therapy for the perioperative period, namely the combination of aspirin and statins in all patients and  $\beta$ -blockers in patients with ischaemic heart disease, was followed in only 41% of cases.<sup>18</sup> Significantly, the use of evidence-based medication during the perioperative period was associated with a reduction in 3-year mortality after adjustment for clinical characteristics [hazard ratio (HR), 0.65; 95% confidence interval (CI), 0.45–0.94]. These data

highlight the existence of a clear opportunity for improving the quality of care in this high-risk group of patients.

In addition to promoting an improvement in immediate perioperative care, guidelines should provide long-term advice, as patients should live long enough to enjoy the benefits of surgery. Following the development and introduction of perioperative cardiac guidelines, their effect on outcome should be monitored. The objective evaluation of changes in outcome will be an essential part of future perioperative guideline developments.

## Pre-operative evaluation

### Surgical risk for cardiac events

Cardiac complications after non-cardiac surgery depend not only on specific risk factors but also on the type of surgery and the circumstances under which it takes place.<sup>19</sup> Surgical factors that influence cardiac risk are related to the urgency, magnitude, type, and duration of the procedure, as well as the change in body core temperature, blood loss, and fluid shifts.<sup>12</sup>

Every operation elicits a stress response. This response is initiated by tissue injury and mediated by neuroendocrine factors, and may induce tachycardia and hypertension. Fluid shifts in the perioperative period add to the surgical stress. This stress increases myocardial oxygen demand. Surgery also causes alterations in the balance between prothrombotic and fibrinolytic factors, resulting in hypercoagulability and possible coronary thrombosis (elevation of fibrinogen and other coagulation factors, increased platelet activation and aggregation, and reduced fibrinolysis). The extent of such changes is proportionate to the extent and duration of the intervention. All these factors may cause myocardial ischaemia and heart failure. Certainly in patients at elevated risk, attention to these factors should be given and lead, if indicated, to adaptations in the surgical plan.

Although patient-specific factors are more important than surgery-specific factors in predicting the cardiac risk for non-cardiac surgical procedures, the type of surgery cannot be ignored when evaluating a particular patient undergoing an intervention.<sup>6,20</sup> With regard to cardiac risk, surgical interventions can be divided into low-risk, intermediate-risk, and high-risk groups with estimated 30-day cardiac event rates (cardiac death and MI) of <1, 1–5, and >5%, respectively (Table 4). Although only a rough estimation, this risk stratification provides a good indication of the need for cardiac evaluation, drug treatment, and assessment of risk for cardiac events.

The high-risk group consists of major vascular interventions. In the intermediate-risk category the risk also depends on the magnitude, duration, location, blood loss, and fluid shifts related to the specific procedure. In the low-risk category the cardiac risk is negligible unless strong patient-specific risk factors are present.

The need for, and value of, pre-operative cardiac evaluation will also depend on the urgency of surgery. In the case of emergency surgical procedures, such as those for ruptured abdominal aortic aneurysm (AAA), major trauma, or for perforated viscus, cardiac evaluation will not change the course and result of the intervention but may influence the management in the immediate post-operative period. In non-emergent but urgent untreated surgical conditions such as bypass for acute limb ischaemia or treatment of bowel obstruction, the morbidity and mortality of the untreated underlying condition will outweigh the potential cardiac risk related to the intervention. In these cases, cardiological evaluation may influence the perioperative measures taken to reduce the cardiac risk, but will not influence the decision to perform the intervention. In some cases, the cardiac risk can also influence the type of operation and guide the choice to less invasive interventions, such as peripheral arterial angioplasty instead of infrainguinal bypass, or extra-anatomic reconstruction instead of aortic procedure, even when these may yield less favourable

**Table 4** Surgical risk<sup>a</sup> estimate (modified from Boersma et al.<sup>6</sup>)

Low-risk <1%	Intermediate-risk 1–5%	High-risk >5%
<ul style="list-style-type: none"> <li>▪ Breast</li> <li>▪ Dental</li> <li>▪ Endocrine</li> <li>▪ Eye</li> <li>▪ Gynaecology</li> <li>▪ Reconstructive</li> <li>▪ Orthopaedic—minor (knee surgery)</li> <li>▪ Urologic—minor</li> </ul>	<ul style="list-style-type: none"> <li>▪ Abdominal</li> <li>▪ Carotid</li> <li>▪ Peripheral arterial angioplasty</li> <li>▪ Endovascular aneurysm repair</li> <li>▪ Head and neck surgery</li> <li>▪ Neurological/orthopaedic—major (hip and spine surgery)</li> <li>▪ Pulmonary renal/liver transplant</li> <li>▪ Urologic—major</li> </ul>	<ul style="list-style-type: none"> <li>▪ Aortic and major vascular surgery</li> <li>▪ Peripheral vascular surgery</li> </ul>

<sup>a</sup>Risk of MI and cardiac death within 30 days after surgery.

**Table 5 Lee index and Erasmus model: clinical risk factors used for pre-operative cardiac risk stratification<sup>5,6</sup>**

Clinical characteristics	Lee index	Erasmus model
IHD (angina pectoris and/or MI)	x	x
Surgical risk	High-risk surgery	High, intermediate-high, intermediate-low, low risk
Heart failure	x	x
Stroke/transient ischaemic attack	x	x
Diabetes mellitus requiring insulin therapy	x	x
Renal dysfunction/haemodialysis	x	x
Age		x

IHD = ischaemic heart disease; MI = myocardial infarction.

results in the long term. Lastly, in some situations, the cardiac evaluation, in as far as it can reliably predict perioperative cardiac complications and estimate late survival, should be taken into consideration even when deciding whether to perform an intervention or not. This is the case in certain prophylactic interventions such as the treatment of small AAAs or asymptomatic carotid stenosis where the life expectancy of the patient and the risk of the operation are important factors in evaluating the potential benefit of the surgical intervention.

Vascular interventions are of specific interest, not only because they carry the highest risk of cardiac complications, explained by the high probability that the atherosclerotic process also affects the coronary arteries, but also because of the many studies that have shown that this risk can be influenced by adequate perioperative measures in these patients. Open aortic and infra-inguinal procedures have both to be considered as high-risk procedures.<sup>6</sup> Although a less extensive intervention, infra-inguinal revascularization entails a cardiac risk similar to or even higher than aortic procedures. This can be explained by the higher incidence of diabetes, renal dysfunction, IHD, and advanced age in this patient group. This also explains why the risk related to peripheral artery angioplasties, which are minimally invasive procedures, is not negligible. Several randomized trials, as well as community-based studies, have shown that the cardiac risk is substantially lower after endovascular aortic aneurysm repair compared with open repair.<sup>21</sup> This can be related to the lesser tissue damage and the avoidance of aortic cross-clamping and post-operative ileus. However, long-term survival does not seem to be influenced by the surgical technique that is used, but is determined by the underlying cardiac disease.<sup>22</sup> Carotid endarterectomy is considered to be an intermediate-risk procedure. Nevertheless, elevated cardiac risk and late survival should be taken into account in the decision-making process and can influence the choice between endarterectomy or stenting.

Laparoscopic procedures have the advantage of causing less tissue trauma and intestinal paralysis compared with open procedures, resulting in less incisional pain and diminished post-operative fluid shifts related to bowel paralysis.<sup>23</sup> On the other hand, the pneumoperitoneum used in these procedures results in elevated intra-abdominal pressure and a reduction in venous return. It will result in a decrease in cardiac output and an increase in systemic vascular resistance. Therefore, cardiac risk in patients with heart failure is not diminished in patients undergoing

laparoscopy compared with open surgery, and both should be evaluated in the same way. This is especially true in patients undergoing interventions for morbid obesity.<sup>24,25</sup>

**Recommendation/statement on surgical risk estimate**

Recommendation/statement	Class <sup>a</sup>	Level <sup>b</sup>
Laparoscopic procedures demonstrate a cardiac stress similar to open procedures and it is recommended that patients be screened prior to intervention accordingly	I	A

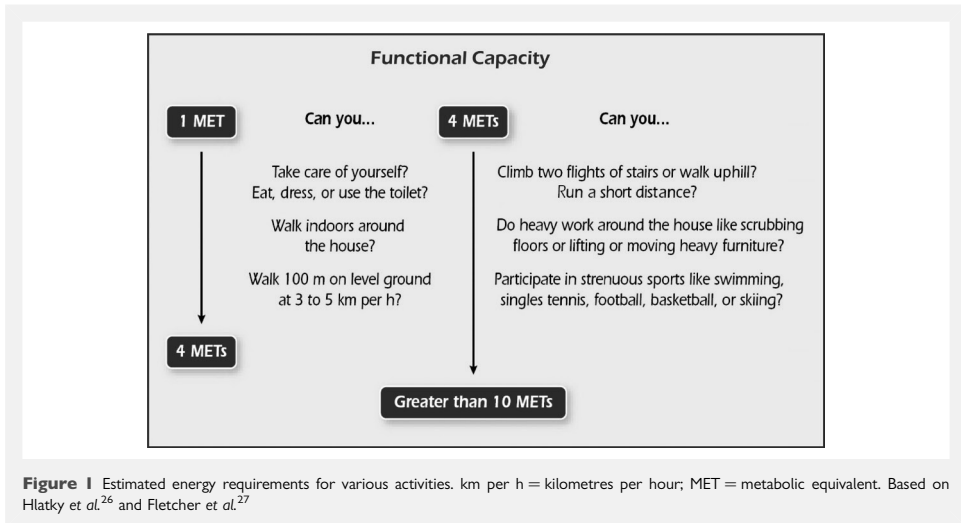
<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.

**Functional capacity**

Determination of functional capacity is considered to be a pivotal step in pre-operative cardiac risk assessment. Functional capacity is measured in metabolic equivalents (METs). One MET equals the basal metabolic rate. Exercise testing provides an objective assessment of functional capacity. Without testing, functional capacity can be estimated by the ability to perform the activities of daily living. Given that 1 MET represents metabolic demand at rest, climbing two flights of stairs demands 4 METs, and strenuous sports such as swimming >10 METs (Figure 1).

The inability to climb two flights of stairs or run a short distance (<4 METs) indicates poor functional capacity and is associated with an increased incidence of post-operative cardiac events. After thoracic surgery, a poor functional capacity has been associated with an increased mortality (relative risk 18.7, 95% CI 5.9–59). However, in comparison with thoracic surgery, a poor functional status was not associated with an increased mortality after other non-cardiac surgery (relative risk 0.47, 95% CI 0.09–2.5).<sup>28</sup> This may reflect the importance of pulmonary function, strongly related to functional capacity, as a major predictor of survival after thoracic surgery. These findings were confirmed in a study of 5939 patients scheduled for non-cardiac surgery in which the prognostic importance of pre-operative functional capacity was measured in METs.<sup>29</sup> Using receiver operating characteristic (ROC) curve analysis, the association of functional capacity with post-operative cardiac events or death showed an area under





the ROC curve of just 0.664, compared with 0.814 for age. Considering the relatively weak association between functional capacity and post-operative cardiac outcome, what importance should we attach to functional capacity assessment in the pre-operative evaluation of the risk of non-cardiac surgery? When functional capacity is high, the prognosis is excellent, even in the presence of stable IHD or risk factors.<sup>30</sup> In this case, perioperative management will rarely be changed as a result of further cardiac testing and the planned surgical procedure can proceed. Using functional capacity evaluation prior to surgery, the ability to climb two flights of stairs or run for a short distance indicated a good functional capacity. On the other hand, when functional capacity is poor or unknown, the presence and number of risk factors in relation to the risk of surgery will determine pre-operative risk stratification and perioperative management.

### Risk indices

Effective strategies aimed at reducing the risk of perioperative cardiac complications should involve cardiac evaluation using medical history prior to the surgical procedure, for two main reasons. First, patients with an anticipated low cardiac risk—after thorough evaluation—can be operated on safely without further delay. It is unlikely that risk reduction strategies can reduce the perioperative risk further. Secondly, risk reduction by pharmacological treatment is most cost-effective in patients with a suspected increased cardiac risk. Additional non-invasive cardiac imaging techniques are tools to identify patients at higher risk. However, imaging techniques should be reserved for those patients in whom test results would influence and change management. Obviously, the intensity of the pre-operative cardiac evaluation must be tailored to the patient's clinical condition and the urgency of the circumstances requiring surgery. When emergency surgery is needed,

the evaluation must necessarily be limited. However, most clinical circumstances allow the application of a more extensive, systematic approach, with cardiac risk evaluation that is initially based on clinical characteristics and type of surgery, and then extended—if indicated—to resting electrocardiography (ECG), laboratory measurements, and non-invasive (stress) testing.

During the last 30 years, several risk indices have been developed, based on multivariable analyses of observational data, which represent the relationship between clinical characteristics and perioperative cardiac mortality and morbidity. The indices that were developed by Goldman (1977), Detsky (1986), and Lee (1999) became well known.<sup>5,31,32</sup> The Lee index, which is in fact a modification of the original Goldman index, is considered by many clinicians and researchers to be the best currently available cardiac risk prediction index in non-cardiac surgery. It was developed using prospectively collected data on 2893 unselected patients (and validated in another 1422 patients) who underwent a wide spectrum of procedures. They were followed systematically throughout the post-operative phase for a range of clinically relevant cardiac outcomes. The Lee index contains five independent clinical determinants of major perioperative cardiac events: a history of IHD, a history of cerebrovascular disease, heart failure, insulin-dependent diabetes mellitus, and impaired renal function. High-risk type of surgery is the sixth factor that is included in the index. All factors contribute equally to the index (with 1 point each), and the incidence of major cardiac complications is estimated at 0.4, 0.9, 7, and 11% in patients with an index of 0, 1, 2, and  $\geq 3$  points, respectively. The area under the ROC curve in the validation data set was 0.81, indicating that the index has a high capability for discriminating between patients with and without a major cardiac event.

However, the patients studied by Lee *et al.* cannot be considered to be an average, unselected non-cardiac surgical cohort. Patients

undergoing thoracic (12%), vascular (21%), and orthopaedic surgery (35%) were over-represented. Furthermore, despite its respectable size, the study was too underpowered to reveal a broad range of cardiac outcome determinants, as only 56 cardiac events were observed in the derivation cohort. Several external validation studies have suggested that the Lee index is probably suboptimal for identifying patients with multiple risk factors.<sup>6</sup> In fact, the type of surgery was only classified as two subtypes: first, high-risk, including intraperitoneal, intrathoracic, and suprainguinal vascular procedures; and, secondly, all remaining non-laparoscopic procedures, mainly including orthopaedic, abdominal, and other vascular procedures. Evidence exists that a more subtle classification, such as the Erasmus model, results in better risk discrimination.<sup>6</sup> In this model, an extensive description of the type of surgery and age increased the prognostic value of the model for perioperative cardiac events (area under the ROC curve for the prediction of cardiovascular mortality increased from 0.63 to 0.85).

#### Recommendations/statements on cardiac risk stratification

Recommendations/statements	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended clinical risk indices be used for post-operative risk stratification	I	B
It is recommended that the Lee index model applying six different variables for perioperative cardiac risk be used	I	A

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## Biomarkers

A biological marker—biomarker—is a characteristic that can be objectively measured and evaluated and which is an indicator of abnormal biological and pathogenic processes or responses to therapeutic interventions. In the perioperative setting, biomarkers can be divided into markers focusing on myocardial ischaemia and damage, inflammation, and LV function.

Cardiac troponins T and I (cTnT and cTnI) are the preferred markers for the diagnosis of MI because they demonstrate sensitivity and tissue specificity superior to other available biomarkers.<sup>33,34</sup> The prognostic information is independent of, and complementary to, other important cardiac indicators of risk such as ST deviation and LV function. The prognostic significance of even small elevations in troponins has been independently confirmed in community-based studies and in clinical trials (TACTICS-TIMI 18, FRISC II, OPUS-TIMI),<sup>35,36</sup> not only in high-risk, but also in intermediate-risk groups. cTnI and cTnT seem to be of similar value for risk assessment in ACS in the presence and absence of renal failure.<sup>33</sup> The prognosis for all-cause death in patients with end-stage renal disease and with even minor elevations in cTnT is 2–5 times worse than for those with undetectable values. Existing evidence suggests that even small increases in cTnT in the perioperative period reflect clinically relevant myocardial injury with worsened cardiac prognosis and outcome.<sup>37</sup> The development of new biomarkers, including

high-sensitivity troponins, will further enhance the assessment of myocardial damage. It should be noted that troponin elevation may be observed in many other conditions. The diagnosis of non-ST-segment elevation myocardial infarction (NSTEMI) should never be made solely on the basis of biomarkers.

Inflammatory markers might identify pre-operatively those patients with an increased risk of unstable coronary plaque. C-reactive protein (CRP) is an acute-phase reactant produced in the liver. CRP is also expressed in smooth muscle cells within diseased atherosclerotic arteries and has been implicated in many aspects of atherogenesis and plaque vulnerability, including expression of adhesion molecules, induction of nitric oxide, altered complement function, and inhibition of intrinsic fibrinolysis.<sup>38</sup> However, in the surgical setting, no data are currently available using CRP as a marker for the initiation of risk reduction strategies.

Brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are produced in cardiac myocytes in response to increases in myocardial wall stress. This may occur at any stage of heart failure, independently of the presence or absence of myocardial ischaemia. Plasma BNP and NT-proBNP have emerged as important prognostic indicators in patients with heart failure, ACS, and stable IHD in non-surgical settings.<sup>39–41</sup> Pre-operative BNP and NT-proBNP levels have additional prognostic value for long-term mortality and for cardiac events after major non-cardiac vascular surgery.<sup>42–46</sup>

Data on pre-operative biomarker use from prospective controlled trials are sparse. Based on the present data, routine assessment of serum biomarkers for patients undergoing non-cardiac surgery cannot be proposed for routine use as an index of cell damage.

#### Recommendations/statements on biomarkers

Recommendations/statements	Class <sup>a</sup>	Level <sup>b</sup>
NT-proBNP and BNP measurements should be considered for obtaining independent prognostic information for perioperative and late cardiac events in high-risk patients.	IIa	B
Routine biomarker sampling to prevent cardiac events is not recommended	III	C

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

BNP = brain natriuretic peptide; NT-proBNP = N-terminal pro-brain natriuretic peptide.

## Non-invasive testing

Pre-operative non-invasive testing aims at providing information on three cardiac risk markers: LV dysfunction, myocardial ischaemia, and heart valve abnormalities, all major determinants of adverse post-operative outcome. LV function is assessed at rest, and various imaging modalities are available. For myocardial ischaemia detection, exercise ECG and non-invasive imaging techniques may be used. The overall theme is that the diagnostic algorithm for risk stratification of myocardial ischaemia and LV function should be similar to that proposed for patients in the non-surgical setting with known or suspected IHD.<sup>47</sup> Non-invasive testing should not

only be considered for coronary artery revascularization but also for patient counselling, change of perioperative management in relation to type of surgery, anaesthetic technique, and long-term prognosis. Echocardiography is preferred for evaluation of valve disease (see section on specific diseases, subheading valvular heart disease).

## Non-invasive testing of cardiac disease

### Electrocardiography

The 12-lead ECG is commonly performed as part of pre-operative cardiovascular risk assessment in patients undergoing non-cardiac surgery. In IHD patients, the pre-operative electrocardiogram contains important prognostic information and is predictive of long-term outcome independent of clinical findings and perioperative ischaemia.<sup>48</sup> However, the electrocardiogram may be normal or non-specific in a patient with either ischaemia or infarction. The routine use of ECG prior to all types of surgery is a subject of increasing debate. A retrospective study investigated 23 036 patients scheduled for 28 457 surgical procedures; patients with abnormal ECG findings had a greater incidence of cardiovascular death than those with normal ECG results (1.8% vs. 0.3%). In patients who underwent low-risk or low- to intermediate-risk surgery, the absolute difference in the incidence of cardiovascular death between those with and without ECG abnormalities was only 0.5%.<sup>49</sup>

### Recommendations on ECG

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Pre-operative ECG is recommended for patients who have risk factor(s) and are scheduled for intermediate- or high-risk surgery	I	B
Pre-operative ECG should be considered for patients who have risk factor(s) and are scheduled for low-risk surgery	IIa	B
Pre-operative ECG may be considered for patients who have no risk factor and are scheduled for intermediate-risk surgery	IIb	B
Pre-operative ECG is not recommended for patients who have no risk factor and are scheduled for low-risk surgery	III	B

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

ECG = electrocardiography.

## Assessment of left ventricular function

Resting LV function can be evaluated before non-cardiac surgery by radionuclide ventriculography, gated single photon emission computed tomography (SPECT) imaging, echocardiography, magnetic resonance imaging (MRI), or multislice computed tomography (CT), with similar accuracy.<sup>50</sup> Routine echocardiography is not recommended for the pre-operative evaluation of LV function, but may be performed in asymptomatic patients undergoing high-risk surgery. A meta-analysis of the available data demonstrated that an LV ejection fraction of <35% had a sensitivity of 50% and a specificity of 91% for prediction of perioperative non-fatal

MI or cardiac death.<sup>51</sup> The limited predictive value of LV function assessment for perioperative outcome may be related to the failure to detect severe underlying IHD. Recommendations for the pre-operative evaluation of (asymptomatic) patients with cardiac murmurs are discussed in the section on VHD.

### Recommendations on resting echocardiography

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Rest echocardiography for LV assessment should be considered in patients undergoing high-risk surgery	IIa	C
Rest echocardiography for LV assessment in asymptomatic patients is not recommended	III	B

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

LV = left ventricular.

## Non-invasive testing of ischaemic heart disease

Physiological exercise using a treadmill or bicycle ergometer is the preferred method for detection of ischaemia. Physiological exercise provides an estimate of functional capacity, provides blood pressure and heart rate response, and detects myocardial ischaemia through ST-segment changes. The accuracy of exercise ECG varies significantly among studies. Meta-analysis of the reported studies using treadmill testing in vascular surgery patients showed a rather low sensitivity (74%, 95% CI 60–88%) and specificity (69%, 95% CI 60–78%), comparable with daily clinical practice.<sup>51</sup> The positive predictive value was as low as 10%, but the negative predictive value was very high (98%). However, risk stratification with exercise is not suitable for patients with limited exercise capacity due to their inability to reach an ischaemic threshold. Furthermore, pre-existing ST-segment abnormalities, especially in the pre-cordial leads V<sub>5</sub> and V<sub>6</sub> at rest, hamper reliable ST-segment analysis. A gradient of severity in the test result relates to the perioperative outcome: the onset of a myocardial ischaemic response at low exercise workloads is associated with a significantly increased risk of perioperative and long-term cardiac events. In contrast, the onset of myocardial ischaemia at high workloads is associated with significantly less risk.<sup>50</sup> Pharmacological stress testing with either nuclear perfusion imaging or echocardiography is more suitable in patients with limited physical capabilities.

The role of myocardial perfusion imaging for pre-operative risk stratification is well established. In patients with limited exercise capacity, pharmacological stress (dipyridamole, adenosine, or dobutamine) is an alternative stressor. Images reflect myocardial blood distribution at the time of injection. Studies are performed both during stress and at rest to determine the presence of reversible defects, reflecting jeopardized ischaemic myocardium, or fixed defects, reflecting scar or non-viable tissue.

The prognostic value of the extent of ischaemic myocardium, using semi-quantitative dipyridamole myocardial perfusion imaging, has been investigated in a meta-analysis of studies in vascular surgery patients.<sup>52</sup> Study endpoints were perioperative

cardiac death and MI. The authors included nine studies, totalling 1179 vascular surgery patients, with a 7% 30-day event rate. In this analysis, reversible ischaemia in <20% of the LV myocardium did not change the likelihood of perioperative cardiac events, compared with those without ischaemia. Patients with more extensive reversible defects were at increased risk: 20–29% reversibility [likelihood ratio (LR) 1.6, 95% CI 1.0–2.6], 30–39% reversibility (LR 2.9, 95% CI 1.6–5.1), 40–49% reversibility (LR 2.9, 95% CI 1.4–6.2), and ≥50% reversibility (LR 11, 95% CI 5.8–20).

A second meta-analysis, that assessed the prognostic value of six diagnostic tests, reported a sensitivity of 83% (95% CI 77–92%) with a much lower specificity of 47% (95% CI, 41–57%) for myocardial perfusion imaging.<sup>51–53</sup> The positive and negative predictive values were 11 and 97%, respectively.

A third meta-analysis pooled the results of 10 studies evaluating dipyridamole thallium-201 imaging in vascular surgery candidates over a 9-year period (1985–1994).<sup>53</sup> The 30-day cardiac death or non-fatal MI rates were 1% in patients with normal test results, 7% in patients with fixed defects, and 9% in patients with reversible defects on thallium-201 imaging. Moreover, three out of the 10 studies analysed used semi-quantitative scoring, demonstrating a higher incidence of cardiac events in patients with two or more reversible defects.

Overall, the positive predictive value of reversible defects for perioperative death or MI has decreased over recent years. This is probably related to changes in perioperative management and surgical procedures, resulting in a reduced cardiac event rate in patients with myocardial ischaemia as detected by pre-operative cardiac stress tests. However, because of the high sensitivity of nuclear imaging studies for detecting IHD, patients with a normal scan have an excellent prognosis. Myocardial perfusion imaging using dobutamine stress has a good safety profile. Hypotension, a systolic blood pressure decrease of ≥40 mmHg, occurred in 3.4%, and serious cardiac arrhythmias in 3.8% of cases, in a consecutive series of 1076 patients. All arrhythmias terminated either spontaneously or after metoprolol administration.<sup>54</sup>

Stress echocardiography using exercise or pharmacological (dobutamine, dipyridamole) stress has been widely used for pre-operative cardiac risk evaluation. The test combines information on LV function at rest, heart valve abnormalities, and the presence and extent of stress-inducible ischaemia.<sup>55</sup> In one study, 530 patients were enrolled to evaluate the incremental value of dobutamine stress echocardiography (DSE) for the assessment of cardiac risk before non-vascular surgery.<sup>56</sup> Multivariable predictors of post-operative events in patients with ischaemia were found to be a history of heart failure [odds ratio (OR) 4.7, 95% CI 1.6–14.0] and ischaemic threshold <60% of age-predicted maximal heart rate (OR 7.0, 95% CI 2.8–17.6). DSE identified 60% of patients as low risk (no ischaemia), 32% as intermediate risk (ischaemic threshold ≥60%), and 8% as high risk (ischaemic threshold <60%); post-operative event rates were 0, 9, and 43%, respectively. A recent meta-analysis showed that the sensitivity and specificity of DSE for perioperative cardiac death and MI are high (85 and 70%, respectively).<sup>51</sup> DSE can be performed safely with reasonable patient tolerance [incidence of cardiac arrhythmias and hypotension (defined as a

systolic blood pressure decrease of ≥40 mmHg)]. DSE has some limitations, e.g. it should not be used in patients with severe arrhythmias, significant hypertension, large thrombus-laden aortic aneurysms, or hypotension.

In general, stress echocardiography has a high negative predictive value (between 90 and 100%): a negative test is associated with a very low incidence of cardiac events and indicates a safe surgical procedure. However, the positive predictive value is relatively low (between 25 and 45%); this means that the post-surgical probability of a cardiac event is low, despite wall motion abnormality detection during stress echocardiography.

In a meta-analysis of 15 studies comparing dipyridamole thallium-201 imaging and DSE for risk stratification before vascular surgery, it was demonstrated that the prognostic value of stress imaging abnormalities for perioperative ischaemic events is comparable when using available techniques, but that the accuracy varies with IHD prevalence.<sup>53</sup> In patients with a low incidence of IHD, the diagnostic accuracy is reduced compared with those with a high incidence of IHD.

MRI can also be used for detection of ischaemia; both perfusion and wall motion can be detected during stress and at rest.<sup>57</sup> Ischaemia, more than IHD, is associated with adverse post-operative cardiac events. Therefore, functional testing is preferred to the detection of anatomical stenosis. The accuracy for assessment of ischaemia is high, with a sensitivity of 83% (95% CI 79–88%) and specificity of 86% (95% CI 81–91%) when wall motion is used (14 studies, 754 patients). When perfusion is added on top of wall motion abnormalities (24 studies, 1516 patients), sensitivity in the assessment of ischaemia increases to 91% (95% CI 88–94%); however, specificity decreases to 81% (95% CI 77–85%). MRI with dobutamine stress was used in 102 patients undergoing major non-cardiac surgery.<sup>58</sup> New wall motion abnormalities were used as a marker of ischaemia. Applying multivariable analysis, myocardial ischaemia was the strongest predictor of perioperative cardiac events (death, MI, and heart failure). MRI enabled non-invasive angiography and meta-analysis of existing data to be undertaken, using IHD detected by coronary angiography as a reference, and demonstrated sensitivity and specificity of 75% (95% CI 68–80%) and 85% (95% CI 78–90%), respectively, on a vessel basis (16 studies, 2041 vessels); on a patient basis (13 studies, 607 subjects), sensitivity and specificity were 88% (95% CI 82–92%) and 56% (95% CI 53–68%) respectively.<sup>59</sup> Currently no data are available in the setting of pre-operative risk stratification.

CT can be used to detect coronary calcium, which reflects coronary atherosclerosis. In addition, both electron beam and multi-slice CT have been used for non-invasive angiography, and a meta-analysis of existing data, using IHD detected by coronary angiography as a reference, demonstrated a sensitivity and a specificity of 82% (95% CI 80–85%) and 91% (95% CI 90–92%), respectively, on a vessel basis (eight studies, 2726 vessels); on a patient basis (21 studies, 1570 patients), sensitivity and specificity were 96% (95% CI 94–98%) and 74% (95% CI 65–84%), respectively.<sup>60</sup> Data in the setting of pre-operative risk stratification are not yet available. A word of caution should be given with respect to the risk of radiation.<sup>61</sup> In patients undergoing heart valve surgery, CT angiography has been used to exclude

concomitant IHD, thereby avoiding the need for invasive coronary angiography.<sup>62</sup> This approach may also be of use for pre-operative risk stratification; however, currently no data are available in the setting of pre-operative risk stratification.

How can these data be put into a practical algorithm? Testing should only be performed if it changes perioperative management. Patients with extensive stress-induced ischaemia represent a high-risk population in whom standard medical therapy appears to be insufficient to prevent perioperative cardiac events.<sup>63</sup> Pre-operative testing may be considered in high-risk surgery patients with fewer than three clinical risk factors. However, in these patients, the beneficial effect of cardioprotective therapy appears to be sufficient to preclude pre-operative stress testing. The results of the randomized, multicentre DECREASE-II study showed that the perioperative cardiac event rate of vascular surgery patients on  $\beta$ -blocker therapy was already so reduced that test results and subsequent alteration in perioperative management were redundant.<sup>8</sup> No differences in cardiac death and MI at 30 days were observed between 770 patients assigned to no cardiac stress testing vs. testing (1.8 vs. 2.3%; OR 0.78; 95% CI 0.28–2.1). Importantly, pre-operative testing delayed surgery for >3 weeks. Likewise, similar recommendations are given for intermediate-risk surgery patients, although no data from randomized trials are available. Considering the low event rate of patients scheduled for low-risk surgery, it is unlikely that test results in cardiac-stable patients will alter perioperative management.

#### Recommendations on stress testing prior to surgery

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Stress testing is recommended in high-risk surgery patients with $\geq 3$ clinical factors <sup>c</sup>	I	C
Stress testing may be considered in high-risk surgery patients with $\leq 2$ clinical factors	IIb	B
Stress testing may be considered in intermediate-risk surgery	IIb	C
Stress testing is not recommended in low-risk surgery	III	C

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Clinical risk factors are presented in Table 13.

## Integrated assessment of cardiopulmonary function

Cardiopulmonary exercise testing (CPET) provides a global assessment of the integrated response to exercise involving the pulmonary, cardiovascular, and skeletal muscle systems. CPET is a programmed exercise test on either a cycle ergometer or a treadmill during which inspired and expired gases are measured through a facemask or a mouthpiece. This test provides information on oxygen uptake and utilization.<sup>64</sup> The most commonly used data from this test are  $O_2$  consumption at peak exercise ( $VO_{2peak}$ ) and at anaerobic threshold ( $VO_{2AT}$ ), defined as the point when metabolic demands exceed oxygen delivery, and

anaerobic metabolism begins to occur. The thresholds for classifying patients as low risk are usually taken as  $VO_{2peak} > 15$  mL/kg/min and  $VO_{2AT} > 11$  mL/kg/min. These thresholds roughly equate to 4 METs.<sup>65</sup> CPET before lung resection may help in stratifying the surgical risk and optimizing perioperative care. In a cohort of 204 consecutive patients who had undergone pulmonary lobectomy or pneumonectomy, a  $VO_2$  peak  $< 20$  mL/kg/min was a predictor of pulmonary complications, cardiac complications, and mortality; a  $VO_{2peak} < 12$  mL/kg/min was associated with a 13-fold higher rate of mortality.<sup>66</sup> In a study of 187 elderly patients  $VO_{2AT}$  was measured before major abdominal surgery.<sup>67</sup> The overall mortality was 5.9%. Patients who had a  $VO_{2AT} < 11$  mL/kg/min ( $n = 55$ ) had a mortality of 18% compared with those who had a  $VO_{2AT} > 11$  mL/kg/min ( $n = 132$ ) whose mortality was 0.8% (risk ratio 24, 95% CI 3.1–183). In patients who exhibited signs of myocardial ischaemia during testing, the mortality was 42% for patients whose  $VO_{2AT}$  was  $< 11$  mL/kg/min and only 4% for those whose  $VO_{2AT}$  was  $> 11$  mL/kg/min ( $P < 0.001$ ). CPET also carries accurate prognostic information in the setting of heart failure patients: an abnormally high relationship between minute ventilation (VE) and carbon dioxide production ( $VCO_2$ ), expressed as the  $VE/VCO_2$  slope measured between the onset of loaded exercise and the end of the isocapnic buffering period, identified by the rise in the  $VE/VCO_2$  slope and the reduction of end-tidal expiratory  $CO_2$  pressure (PET $CO_2$ ) (or mixed expired value of alveolar and dead space gas, Pa $CO_2$ ), is associated with a poor outcome, as is an oscillatory pattern of ventilation during exercise, defined as cyclic fluctuations in minute ventilation at rest that persist during effort.<sup>68</sup> There are potential discrepancies between a CPET and functional assessment using METs that preclude a widespread use of CPET. Non-cardiac and non-respiratory factors such as skeletal muscle function and physical training can underestimate aerobic metabolic activity. A further consideration must be the availability of CPET testing, which at present is not available in all centres. The role of CPET in pre-operative risk assessment has not been established and CPET should not be considered to be a substitute for stress testing in routine practice.

## Angiography

Coronary angiography is a well-established invasive diagnostic procedure but is rarely indicated to assess the risk of non-cardiac surgery. There is a lack of information derived from randomized clinical trials on its usefulness in patients scheduled for non-cardiac surgery. Moreover, adopting an invasive coronary angiography assessment may cause an unnecessary and unpredictable delay in an already planned surgical intervention. Nevertheless, IHD may be present in a significant number of patients in whom non-cardiac surgery is indicated. In patients with known IHD, indications for pre-operative coronary angiography and revascularization are similar to angiography indications in the non-surgical setting.<sup>47,69–71</sup> The control of ischaemia before surgery, either medically or with intervention, is recommended whenever non-cardiac surgery procedures can be delayed.

### Recommendations on pre-operative coronary angiography

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Pre-operative angiography is recommended in patients with acute STEMI	I	A
Pre-operative angiography is recommended in patients with NSTEMI and unstable angina	I	A
Pre-operative angiography is recommended in patients with angina not controlled with adequate medical therapy	I	A
Pre-operative angiography may be considered in cardiac-stable patients undergoing high-risk surgery	IIb	B
Pre-operative angiography may be considered in cardiac-stable patients undergoing intermediate-risk surgery	IIb	C
Pre-operative angiography is not recommended in cardiac-stable patients undergoing low-risk surgery	III	C

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction.

## Risk reduction strategies

### Pharmacological

The occurrence of MI during the intra- or early post-operative period is frequently preceded by prolonged or recurrent myocardial ischaemia. The stress of surgery and anaesthesia may trigger ischaemia through an imbalance between myocardial oxygen demand and supply. Besides specific risk reduction strategies adapted to patient characteristics and the type of surgery, pre-operative evaluation is an opportunity to check and optimize the control of all cardiovascular risk factors.

### β-Blockers

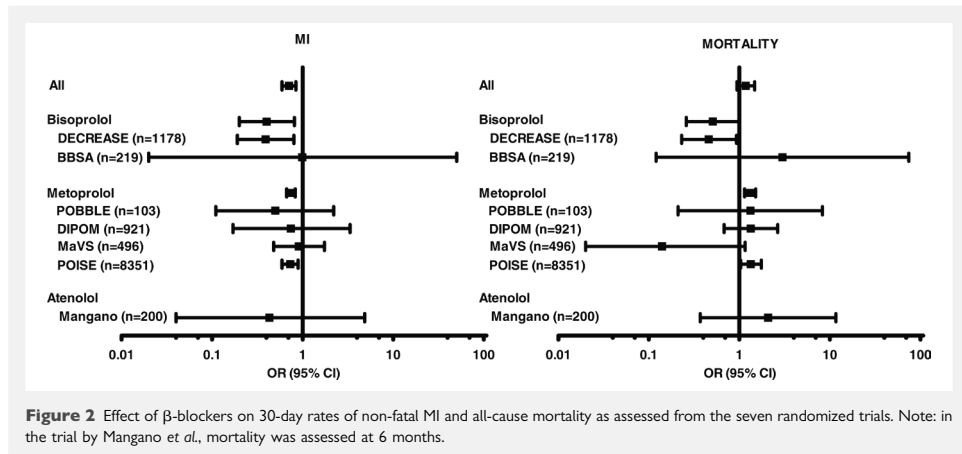
During the perioperative period, there is a catecholamine surge, resulting in an increased heart rate and myocardial contractility and subsequent increased myocardial oxygen consumption. The main rationale for perioperative β-blocker use is to decrease myocardial oxygen consumption by reducing heart rate, resulting in a lengthening of the diastolic filling period, and decreased myocardial contractility.<sup>72</sup> Additional cardioprotective factors are redistribution of coronary blood flow to the subendocardium, plaque stabilization, and an increase in the threshold for ventricular fibrillation.<sup>72</sup> Randomized studies have shown that β-blockers and other drugs that lower the heart rate can reduce perioperative myocardial ischaemia as assessed by continuous ST-segment monitoring.<sup>73</sup> However, whether this translates into a clinical benefit can be established only through trials analysing the incidence of cardiovascular events. Seven multicentre randomized trials evaluating the effect of perioperative β-blockade on clinical endpoints have been published in peer-reviewed journals (Table 6 and Figure 2).<sup>9,10,74–78</sup>

**Table 6 Summary of randomized controlled trials evaluating the effect of perioperative β-blockade on post-operative mortality and non-fatal MI**

Study	n	Vascular surgery (%)	β-Blocker Type	Onset (before surgery)	Duration (days after surgery)	Dose titration	Patient selection according to cardiac risk		30-day mortality (%)		30-day rate of non-fatal MI (%)	
							β-Blocker	Control	β-Blocker	Control	β-Blocker	Control
Mangano <i>et al.</i> <sup>76</sup>	200	40	Atenolol	30 min	7	No	IHD or ≥ 2 risk factors	5/99 (5.1 <sup>a</sup> )	12/101 (11.9 <sup>a</sup> )	—	—	
DECREASE <sup>9</sup>	112	100	Bisoprolol	7 days	30	Yes	Positive DSE	2/59 (3.4)	9/53 (17.0)	0/59 (0)	9/53 (17.0)	
POBBLE <sup>74</sup>	103	100	Metoprolol tartrate	<24 h	7	No	No	3/55 (5.4)	1/48 (2.1)	3/55 (5.5)	5/48 (10.4)	
MaVS <sup>77</sup>	496	100	Metoprolol succinate	2 h	5	No	no	0/246 (0)	4/250 (1.6)	19/246 (7.7)	21/250 (8.4)	
DIPOM <sup>75</sup>	921	7	Metoprolol succinate	12 h	8	No	diabetes	74/462 (16.0)	72/459 (15.7)	3/462 (0.6)	4/459 (0.9)	
BBSA <sup>78</sup>	219	5	Bisoprolol	>3 h	10	Yes	IHD or ≥ 2 risk factors	1/110 (0.9)	0/109 (0)	0/110 (0)	0/109 (0)	
POISE <sup>10</sup>	8351	41	Metoprolol succinate	2–4 h	30	No	IHD or atherosclerosis or major vascular surgery or ≥ 3 risk factors	129/4174 (3.1)	97/4177 (2.3)	152/4174 (3.6)	215/4177 (5.1)	

<sup>a</sup>At 6 months.

DSE = dobutamine stress echocardiography; IHD = ischaemic heart disease; MI = myocardial infarction.



Three trials targeted patients at high risk for perioperative complications because of the type of surgery, the presence of IHD, or risk factors for perioperative cardiac complications.<sup>9,76,78</sup> Three other trials did not require the presence of clinical risk factors, except for diabetes in one case.<sup>74,75,77</sup> The POISE trial included patients with a wide spectrum of risk of perioperative cardiac complications.<sup>10</sup>

The first trial randomized 200 patients with at least two risk factors for IHD or with known IHD, who were scheduled for non-cardiac surgery under general anaesthesia, including 40% major vascular surgery procedures.<sup>76</sup> Atenolol was associated with a significant decrease in overall mortality and an increase in event-free survival at 6 months, and this benefit was sustained for up to 2 years. The Dutch Echographic Cardiac Risk Evaluating Applying Stress Echo (DECREASE) trial selected 112 out of 1453 vascular surgery patients who combined at least one clinical risk factor and positive DSE, excluding patients with extensive wall motion abnormalities.<sup>9</sup> Patients were randomized to standard care or bisoprolol, which was started at least 1 week before surgery and titrated according to heart rate. There was an 89% reduction in cardiac mortality and/or MI in the bisoprolol group (3.4% vs. 34%,  $P < 0.001$ ), which was sustained for up to 3 years.

The PeriOperative Beta-Blockade (POBBLE) trial included 103 low-risk patients undergoing elective infrarenal vascular surgery, randomized to metoprolol tartrate or placebo.<sup>74</sup> The incidence of death, MI, or stroke at 30 days did not differ between the metoprolol and placebo groups (13 and 15%, respectively,  $P = 0.78$ ). Patients were at low cardiac risk and those with a history of MI within the previous 2 years were excluded. In the Metoprolol after Vascular Surgery (MaVS) trial, 497 patients undergoing abdominal or infringuinal vascular surgery were randomized to metoprolol succinate or placebo.<sup>77</sup> The combined endpoint of death, MI, heart failure, arrhythmias, or stroke at 30 days did not differ between the metoprolol and placebo groups (10.2 and 12%, respectively,  $P = 0.57$ ). The Lee index was  $\leq 2$  in 90% of patients and  $\leq 1$  in 60%.

The Diabetes Postoperative Mortality and Morbidity (DIPOM) trial selected 921 patients with diabetes, age  $> 39$  years, and a duration of surgery of  $> 1$  h (39% low-risk surgery).<sup>75</sup> Patients were randomized to receive metoprolol succinate or placebo. The combined endpoint of death, MI, unstable angina, or heart failure at 30 days did not differ between the metoprolol and placebo groups (6 and 5%, respectively,  $P = 0.66$ ). However, only 54% of the patients had a history of IHD, or an additional cardiac risk factor, and underwent high- or intermediate-risk surgery.

In the POISE trial, 8351 patients were randomized to metoprolol succinate or placebo.<sup>10</sup> Patients were aged  $\geq 45$  years and were included if they had known CVD, at least three out of seven clinical risk factors, or were scheduled for major vascular surgery. Treatment consisted of metoprolol succinate, 100 mg 2–4 h prior to surgery, 100 mg during the first 6 h after surgery, but withheld if systolic blood pressure dipped below 100 mmHg. Maintenance therapy was started 12 h later, bringing the total dose of metoprolol succinate in the first 24 h to 400 mg, at least in a number of patients. There was a 17% decrease in the composite endpoint, defined as death, MI, or non-fatal cardiac arrest at 30 days (5.8% vs. 6.9%,  $P = 0.04$ ). However, the 30% decrease in non-fatal MI (3.6% vs. 5.1%,  $P < 0.001$ ) was partially offset by a 33% increase in total mortality (3.1% vs. 2.3%,  $P = 0.03$ ) and a 2-fold increase in stroke (1.0% vs. 0.5%,  $P = 0.005$ ). Hypotension was more frequent in patients receiving metoprolol (15.0% vs. 9.7%,  $P < 0.0001$ ). *Post hoc* analysis showed that hypotension had the largest population-attributable risk for death and stroke.

Seven meta-analyses have pooled 5, 11, 6, 15, 8, 22 and 33 randomized published trials on perioperative  $\beta$ -blockers, totalling respectively 586, 866, 632, 1077, 2437, 2057, and 12 306 patients.<sup>79–85</sup> Five meta-analyses gave consistent results showing a significant reduction in perioperative myocardial ischaemia and MI in patients receiving  $\beta$ -blockers.<sup>79–83</sup> These meta-analyses gave consistent results showing a significant reduction in perioperative myocardial ischaemia, MI, and cardiac mortality in patients





comparison of in-hospital mortality between 119 632 patients receiving  $\beta$ -blockers and 216 220 propensity-matched patients without  $\beta$ -blockers showed no difference overall (2.3% vs. 2.4%, respectively,  $P = 0.68$ ). However, there were marked differences according to patient risk profile.  $\beta$ -Blocker use was associated with a significant decrease in mortality when the Lee index was  $\geq 3$ . No significant difference was observed for a Lee index of 1 or 2. Mortality was increased in the lowest risk group (Lee index of 0).

Randomized trials selecting high-risk patients, cohort studies, and meta-analyses provide consistent evidence supporting a decrease in cardiac mortality and MI by  $\beta$ -blockers in patients with clinical risk factors undergoing high-risk (mainly vascular) surgery. Perioperative  $\beta$ -blockade is also cost-effective in these patients. However, patients with extensive ischaemia as demonstrated by stress testing are at particularly high risk of perioperative cardiac complications, despite perioperative  $\beta$ -blockers.

Conversely, randomized trials including low-risk patients and cohort studies suggest that perioperative  $\beta$ -blockade does not decrease the risk of cardiac complications in patients without clinical risk factors. The possibility of a harmful effect on mortality has been suggested by a retrospective cohort<sup>87</sup> and the POISE trial.<sup>10</sup> Bradycardia and hypotension may be harmful in patients with atherosclerosis, and possibly favour stroke.

This does not justify exposing low-risk patients to potential side effects in the absence of proven benefit. The issue remains debatable in intermediate-risk patients, i.e. those with one or two clinical risk factors. Results of the DECREASE IV trial suggest that  $\beta$ -blockers should also be used in patients undergoing intermediate-risk surgery.<sup>88</sup> Patients randomized to bisoprolol ( $n = 533$ ) had a lower incidence of the primary efficacy endpoint than those randomized to bisoprolol-control therapy (2.1% vs. 6.0% events, HR 0.34, 95% CI 0.17–0.67). An increased mortality following pre-operative  $\beta$ -blocker withdrawal has been reported in observational studies.<sup>89,90</sup>  $\beta$ -Blockers should be continued when prescribed for IHD or arrhythmias. When  $\beta$ -blockers are prescribed for hypertension, the absence of evidence in favour of a perioperative cardioprotective effect with other antihypertensive drugs does not support a change of therapy.  $\beta$ -Blockers should not be withdrawn in patients treated for stable heart failure due to LV systolic dysfunction. In decompensated heart failure,  $\beta$ -blocker therapy may need to be reduced, or temporarily omitted.<sup>91</sup> If possible, non-cardiac surgery should be deferred so that it can be performed under optimal medical therapy in a stable condition. Contra-indications to  $\beta$ -blockers (asthma, severe conduction disorders, symptomatic bradycardia, and symptomatic hypotension) should be respected.  $\beta$ -Blockers are not contra-indicated in patients with intermittent claudication, as in randomized trials, worsening of symptoms has not been shown to occur more frequently.<sup>92</sup> Furthermore, a recent study showed that cardioselective  $\beta$ -blockers were associated with reduced mortality in patients with chronic obstructive pulmonary disease (COPD) undergoing vascular surgery.<sup>93</sup> In the absence of contra-indications,  $\beta$ -blocker dose should be titrated to achieve a heart rate between 60 and 70 beats/min.  $\beta_1$ -Selective blockers without intrinsic sympathomimetic activity are favoured.

### Recommendations on $\beta$ -blockers<sup>a</sup>

Recommendations	Class <sup>b</sup>	Level <sup>c</sup>
$\beta$ -Blockers are recommended in patients who have known IHD or myocardial ischaemia according to pre-operative stress testing <sup>a</sup>	I	B
$\beta$ -Blockers are recommended in patients scheduled for high-risk surgery <sup>a</sup>	I	B
Continuation of $\beta$ -blockers is recommended in patients previously treated with $\beta$ -blockers because of IHD, arrhythmias, or hypertension	I	C
$\beta$ -Blockers should be considered for patients scheduled for intermediate-risk surgery <sup>a</sup>	Ila	B
Continuation in patients previously treated with $\beta$ -blockers because of chronic heart failure with systolic dysfunction should be considered	Ila	C
$\beta$ -Blockers may be considered in patients scheduled for low-risk surgery with risk factor(s)	Ilb	B
Perioperative high-dose $\beta$ -blockers without titration are not recommended	III	A
$\beta$ -Blockers are not recommended in patients scheduled for low-risk surgery without risk factors	III	B

<sup>a</sup>Treatment should be initiated optimally between 30 days and at least 1 week before surgery. Target: heart rate 60–70 beats/min, systolic blood pressure  $> 100$  mmHg.

<sup>b</sup>Class of recommendation.

<sup>c</sup>Level of evidence.

IHD = ischaemic heart disease.

Treatment onset and the choice of the optimal dose of  $\beta$ -blockers are closely linked. Perioperative myocardial ischaemia and troponin release are reduced, and long-term outcome is improved, in patients who have a lower heart rate.<sup>94</sup> On the other hand, bradycardia and hypotension should be avoided. This highlights the importance of preventing overtreatment with fixed high initial doses. The dose of  $\beta$ -blockers should be titrated, which requires that treatment be initiated optimally between 30 days and at least 1 week before surgery. It is recommended that treatment start with a daily dose of 2.5 mg of bisoprolol or 50 mg of metoprolol succinate which should then be adjusted before surgery to achieve a resting heart rate of between 60 and 70 beats/min with systolic blood pressure  $> 100$  mmHg. The goal for heart rate is the same during the whole perioperative period, using i.v. administration when oral administration is not possible. Post-operative tachycardia should result in the first instance in the treatment of the underlying cause, for example hypovolaemia, pain, blood loss, or infection, rather than the  $\beta$ -blocker dose simply being increased.

The optimal duration of perioperative  $\beta$ -blocker therapy cannot be derived from randomized trials. The occurrence of delayed cardiac events is an incentive to continue  $\beta$ -blocker therapy for at least several months. Long-term  $\beta$ -blocker therapy should be used in patients who had a positive pre-operative stress test. Current concepts of cardioprotection have led to recommendations to use selective  $\beta_1$ -blockers without intrinsic sympathomimetic activity and with a long half-life, e.g. bisoprolol.

## Statins

3-Hydroxy-3-methylglutaryl co-enzyme A reductase inhibitors (statins) are widely prescribed in patients with or at risk of IHD because of their lipid-lowering effect. Patients with non-coronary atherosclerosis (carotid, peripheral, aortic, renal) should receive statin therapy for secondary prevention, independently of non-cardiac surgery.<sup>96</sup> Statins also induce coronary plaque stabilization by decreasing lipid oxidation, inflammation, matrix metalloproteinase, and cell death, and by increasing tissue inhibitor of metalloproteinase and collagen. These so-called non-lipid or pleiotropic effects may prevent plaque rupture and subsequent MI in the perioperative period.<sup>97</sup>

Multiple large clinical trials and observational studies have demonstrated a beneficial effect of perioperative statin use.<sup>98,99</sup> In the first prospective, randomized controlled trial, 100 patients scheduled for vascular surgery were allocated to 20 mg of atorvastatin or placebo once a day for 45 days, irrespective of their serum cholesterol concentration.<sup>100</sup> Vascular surgery was performed on average 31 days after randomization, and patients were followed-up over 6 months. During these 6 months of follow-up, atorvastatin significantly reduced the incidence of cardiac events (8% vs. 26%,  $P = 0.03$ ). A meta-analysis of 223 010 patients from 12 retrospective and three prospective trials showed that statins reduced mortality significantly by 44% in non-cardiac surgery and by 59% in vascular surgery.<sup>98</sup> The most recent randomized controlled trial was the DECREASE III study. A total of 497 vascular surgery patients were allocated to either fluvastatin (extended release 80 mg once daily) or placebo, starting 37 days prior to surgery. The incidence of myocardial ischaemia in patients allocated to fluvastatin or placebo was 10.8% vs. 19.0%, respectively (OR 0.55, 95% CI 0.34–0.88). The incidence of cardiac death or MI in the two study groups was 4.8% vs. 10.2%, respectively (OR 0.47, 95% CI 0.24–0.94).<sup>101</sup>

A concern related to the use of perioperative statin therapy has been the risk of statin-induced myopathy and rhabdomyolysis. Perioperatively, factors increasing the risk of statin-induced myopathy are numerous, e.g. the impairment of renal function after major surgery, and multiple drug use during anaesthesia. Furthermore, the use of analgesic drugs and post-operative pain may mask signs of myopathy. Failure to detect statin-induced myopathy may then lead to the statin being continued and the subsequent development of rhabdomyolysis and acute renal failure. However, no studies have been published that support this concern, except for some case reports. In a retrospective study of 981 consecutive patients undergoing vascular surgery, no cases of rhabdomyolysis, significantly higher creatine kinase level, or increased incidence of myopathy were observed in statin users.<sup>102</sup>

Recently it has been suggested that discontinuation of statins may cause a rebound effect and be disadvantageous.<sup>99,103</sup> A potential limitation of perioperative statin use is the lack of an i.v. formulation.

Therefore, statins with a long half-life or extended release formulations such as rosuvastatin, atorvastatin, and fluvastatin extended release are recommended, to bridge the period immediately after surgery when oral intake is not feasible.

### Recommendations on statins

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended that statins be started in high-risk surgery patients, optimally between 30 days and at least 1 week before surgery	I	B
It is recommended that statins be continued perioperatively	I	C

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## Nitrates

Nitroglycerin is well known to reverse myocardial ischaemia. One small but controlled study has demonstrated decreased perioperative myocardial ischaemia in patients with stable angina given i.v. nitroglycerin during non-cardiac surgery.<sup>104</sup> However, no effect was observed on the incidence of MI or cardiac death. These observations were confirmed in a similar study, showing no effect on either myocardial ischaemia, MI, or cardiac death.<sup>105</sup> Furthermore, perioperative use of nitroglycerin may pose a significant haemodynamic risk to the patients. Decreased preload may lead to tachycardia, and hypotension.

### Recommendations on nitrates

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Perioperative nitroglycerin use for the prevention of adverse ischaemic events may be considered	IIb	B

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## Angiotensin-converting enzyme inhibitors

Independently of the blood pressure-lowering effect, angiotensin-converting enzyme (ACE) inhibitors preserve organ function. This effect is related to improvement of endothelial function, anti-inflammatory properties, and a direct interference with atherogenesis.<sup>106</sup> The inhibition of ACE may prevent events related to myocardial ischaemia and LV dysfunction. Therefore, it seems reasonable to suggest that perioperative treatment with ACE inhibitors may have beneficial effects on post-operative outcome.

The QUO VADIS study compared the effect of the ACE inhibitors quinapril with that of placebo in patients undergoing cardiac surgery. Quinapril treatment was started 4 weeks before elective surgery and was continued up to 1 year after surgery.<sup>107</sup> This trial demonstrated that post-operative cardiovascular events were significantly reduced (HR 0.23, 95% CI 0.06–0.87) in patients treated with quinapril. The beneficial effect in the QUO VADIS study, however, could be the result of the post-operative treatment. A recent review provided conflicting data concerning ACE inhibitors after cardiac surgery.<sup>108</sup>

Additionally, perioperative use of ACE inhibitors carries a risk of severe hypotension under anaesthesia, in particular following induction and concomitant  $\beta$ -blocker use. Hypotension is less frequent when ACE inhibitors are discontinued the day before surgery. Although this remains debated, ACE inhibitor withdrawal may be considered 24 h before surgery when they are prescribed for hypertension. They should be resumed after surgery as soon as volume is stable. The risk of hypotension is at least as high with angiotensin receptor blockers (ARBs) as with ACE inhibitors, and the response to vasopressors may be impaired. In patients with LV systolic dysfunction who are in a stable clinical condition, it seems reasonable to continue ACE inhibitors during the perioperative period under close monitoring. When LV dysfunction is discovered during pre-operative evaluation in untreated patients in stable condition, surgery should be postponed, if possible, to introduce ACE inhibitors and  $\beta$ -blockers as recommended by the ESC Guidelines on heart failure.<sup>91</sup>

#### Recommendations on ACE inhibitor use

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended that ACE inhibitors be continued during non-cardiac surgery in stable patients with LV systolic dysfunction.	I	C
ACE inhibitors are recommended in cardiac-stable patients with LV systolic dysfunction scheduled for high-risk surgery	I	C
ACE inhibitors should be considered in cardiac-stable patients with LV systolic dysfunction scheduled for low-/intermediate-risk surgery	IIa	C
Transient discontinuation of ACE inhibitors before non-cardiac surgery in hypertensive patients should be considered.	IIa	C

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

ACE = angiotensin-converting enzyme; LV = left ventricular.

## Calcium channel blockers

The effect of calcium channel blockers on the balance between myocardial oxygen supply and demand makes them theoretically suitable for risk reduction strategies. It is necessary to distinguish between dihydropyridines that do not act directly on heart rate and diltiazem or verapamil that lower the heart rate.

The relevance of randomized trials assessing the perioperative effect of calcium channel blockers is limited by their small size, the lack of risk stratification, and the absence of the systematic reporting of cardiac death and MI. A meta-analysis pooled 11 randomized trials totalling 1007 patients. All patients underwent non-cardiac surgery under calcium channel blockers (diltiazem in seven trials, verapamil in two, and nifedipine in one, and one other trial incorporated three arms: control, diltiazem, and nifedipine).<sup>109</sup> There was a significant reduction in the number of episodes of myocardial ischaemia and supraventricular tachycardia (SVT) in the pooled analyses on calcium channel blockers. However, the decrease in mortality and MI reached statistical

significance only when both endpoints were combined in a composite endpoint of death and/or MI (relative risk 0.35, 95% CI 0.08–0.83,  $P=0.02$ ). Subgroup analyses favoured diltiazem. Another study in 1000 patients having acute or elective aortic aneurysm surgery showed that dihydropyridine calcium channel blocker use was independently associated with an increased incidence of perioperative mortality.<sup>110</sup> The use of short-acting dihydropyridines, in particular nifedipine capsules, should be avoided.

Thus, although heart rate-reducing calcium channel blockers are not indicated in patients with heart failure and systolic dysfunction, in patients who have contra-indications to  $\beta$ -blockers the continuation or the introduction of heart rate-reducing calcium channel blockers may be considered.

#### Recommendations on calcium channel blockers

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended that calcium channel blockers be continued during non-cardiac surgery in patients with Prinzmetal angina pectoris	I	C
Heart rate-reducing calcium channel blockers, in particular diltiazem, may be considered before non-cardiac surgery in patients who have contra-indications to $\beta$ -blockers	IIb	C
Routine use of calcium channel blockers to reduce the risk of perioperative cardiovascular complications is not recommended	III	C

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## Ivabradine

Ivabradine is a specific inhibitor of the pacemaker in the sino-atrial node and reduces heart rate independently of sympathetic activation. It does not affect blood pressure or myocardial contractility. In a randomized trial of 111 vascular surgery patients, both ivabradine and metoprolol succinate reduced the incidence of ischaemia and MI significantly when compared with placebo. These preliminary findings need to be confirmed by future studies; ivabradine might be considered for patients with strict contra-indications to  $\beta$ -blockers.<sup>111</sup>

## $\alpha_2$ Receptor agonists

$\alpha_2$  Receptor agonists reduce post-ganglionic noradrenaline output and therefore might reduce the catecholamine surge during surgery. The European Mivazerol trial randomized 1897 patients with IHD who underwent intermediate- or high-risk non-cardiac surgery.<sup>112</sup> Mivazerol did not decrease the incidence of death or MI in the whole population. However, there was a reduction of post-operative death or MI observed in a subpopulation of 904 vascular surgery patients. A more recent study including 190 patients with clinical risk factors or IHD showed a decrease in 30-day and 2-year mortality after perioperative use of clonidine.<sup>113</sup> However, there was no decrease in MI. A meta-analysis pooled 23 randomized trials, which included cardiac surgery in 10, vascular surgery in eight, and non-vascular surgery in three cases.<sup>114</sup>

Perioperative use of  $\alpha_2$  receptor agonists was associated with a decrease in mortality and MI only in the subgroup having vascular surgery, while there was no benefit in non-vascular surgery.

#### Recommendations on $\alpha_2$ receptor agonists

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
$\alpha_2$ Receptor agonists may be considered to reduce the risk of perioperative cardiovascular complications in vascular surgery patients	IIb	B

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## Diuretics

Diuretics are a frequent pharmacological treatment in patients with hypertension or heart failure as underlying diseases. In hypertension, diuretics are usually used at low dose with relatively moderate blood pressure-lowering effect. In general, diuretics for hypertension can be discontinued on the day of surgery, and resumed orally when possible. If blood pressure reduction is required before oral therapy can be continued, other antihypertensive agents given i.v. may be preferred. In heart failure, diuretics are often used at high dose. Dosage increase should be considered if signs of fluid retention are present. Dosage reduction should be considered if there is risk of hypovolaemia, hypotension, and electrolyte disturbances. In general, diuretic treatment, if necessary to control heart failure, should be continued up to the day of surgery, and resumed orally when possible. In the perioperative period, volume status in patients with heart failure should be carefully monitored and loop diuretics may be given i.v. to control volume overload.

In any patient given diuretics, the possibility of electrolyte disturbance should be considered, as diuretics increase renal excretion of K and Mg. Hypokalaemia is reported to occur in up to 34% of patients undergoing surgery (mostly non-cardiac).<sup>115</sup> Hypokalaemia is well known to increase significantly the risk of ventricular tachycardia (VT) and ventricular fibrillation in cardiac disease.<sup>116</sup> In a study of 688 patients with cardiac disease undergoing non-cardiac surgery, hypokalaemia was independently associated with perioperative mortality.<sup>117</sup> On the other hand, in a study of 150 patients undergoing non-cardiac surgery, no increase in intraoperative arrhythmias was observed with hypokalaemia.<sup>115</sup> However, this latter study was relatively small and most patients had no evidence of cardiac disease. Significantly, the use of K- and Mg-sparing diuretics, i.e. aldosterone antagonists (spironolactone and eplerenone), is now well known to reduce mortality in severe heart failure.<sup>118</sup> In general, K and Mg homeostasis should be evaluated pre-operatively. Special attention should be given to patients on diuretics and patients prone to develop arrhythmia. Any electrolyte disturbance—especially hypokalaemia and hypomagnesaemia—should be corrected in due time before surgery. Dietary advice to increase intake of K and Mg should be given; depleting drugs should, if possible, be reduced; sparing diuretics may be added or preferred; and supplementation may be given. Acute pre-operative repletion in asymptomatic patients

may be associated with more risks than benefits. Thus, minor, asymptomatic electrolyte disturbances should not delay acute surgery.

#### Recommendations on diuretics

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended that electrolyte disturbances be corrected before surgery	I	B
It is recommended that hypertensive patients discontinue low-dose diuretics on the day of surgery and resume orally when possible	I	C
It is recommended that diuretics be continued in heart failure patients up to the day of surgery, resumed intravenously perioperatively, and continued orally when possible	I	C

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## Aspirin

Though aspirin is widely used in patients with IHD and especially after coronary stent placement, the evidence of aspirin in the perioperative period setting is limited. In a randomized trial of 232 patients undergoing carotid endarterectomy, aspirin was shown to be effective in preventing intraoperative and postoperative stroke, though no effect on death or MI was noted.<sup>119</sup> A meta-analysis in 2001 demonstrated a reduction in serious vascular events and vascular death in vascular surgery patients.<sup>120</sup> This study included 10 trials of antiplatelet treatment in lower limb bypass surgery of which six involved aspirin treatment. However, the benefit of antiplatelet therapy did not reach statistical significance for the combined endpoint of vascular events (OR = 0.8, 95% CI 0.5–1.1) in this vascular surgery population.

Concerns of promoting perioperative haemorrhagic complications often led to the discontinuation of aspirin in the perioperative period. A large meta-analysis, including 41 studies in 49 590 patients, which compared perioperative withdrawal vs. bleeding risks of aspirin, concluded that the risk of bleeding complications was increased by 1.5 but that aspirin did not lead to higher severity levels of bleeding complications.<sup>121</sup> A systematic review in subjects at risk of or with IHD demonstrated that aspirin non-adherence/withdrawal was associated with a 3-fold higher risk of major adverse cardiac events (OR = 3.14, 95% CI 1.8–5.6).<sup>122</sup> Aspirin should only be discontinued if the bleeding risk outweighs the potential cardiac benefit. Prior to minor surgical or endoscopic procedures, a careful consideration should be given to the question of withdrawing antithrombotic medications. In principle and based on individualized 'risk to benefit' assessments, there is often no need for stopping the antiplatelet treatment prior to the aforementioned procedures in patients who are taking antiplatelet medications. For patients receiving antiplatelet therapy, i.e. aspirin, clopidogrel, or both, with excessive or life-threatening perioperative bleeding, transfusion of platelets or administration of other prohaemostatic agents is recommended.

**Recommendations on aspirin**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Continuation of aspirin in patients previously treated with aspirin should be considered in the perioperative period	Ila	B
Discontinuation of aspirin therapy in patients previously treated with aspirin should be considered only in those in whom haemostasis is difficult to control during surgery	Ila	B

<sup>a</sup>Class of recommendation.<sup>b</sup>Level of evidence.**Anticoagulant therapy**

Anticoagulant therapy is associated with increased bleeding during non-cardiac surgery. In some patients, this risk will be outweighed by the benefit of anticoagulant therapy, and drug therapy should be maintained or modified, whereas in other patients with low risk of thrombosis, therapy should be stopped in order to minimize bleeding complications.

Patients treated with oral anticoagulant therapy with vitamin K antagonists (VKAs) have an increased risk of periprocedural and

post-procedural bleeding. If the international normalized ratio (INR) is <1.5, surgery can be performed safely (Table 8). However, in patients with a high risk of thromboembolism, discontinuation of VKAs is hazardous and these patients will need bridging therapy with unfractionated heparin (UFH) or therapeutic-dose low molecular weight heparin (LMWH) i.v. or s.c.<sup>123–125</sup> A high thromboembolic risk is present among other conditions, in patients with atrial fibrillation (AF), mechanical prosthetic heart valves, biological prosthetic heart valves or mitral valvular repair within the last 3 months, or recent venous thromboembolism (<3 months) plus thrombophilia. Bridging therapy is now most often performed with therapeutic-dose s.c. LMWH. VKAs are stopped 5 days (i.e. five doses of VKA) prior to surgery; LMWH or UFH are started 1 day after acenocoumarol interruption, and 2 days after warfarin interruption. In high thromboembolic risk patients, 70 U/kg of antifactor Xa twice daily are recommended and prophylactic once-daily doses in low-risk patients (Table 9).<sup>126</sup> The last dose of LMWH should be administered at least 12 h before the procedure. In patients with mechanical prosthetic heart valves, the evidence for i.v. UFH is more solid. Thus, in some centres these patients are hospitalized and treated with i.v. UFHs up until 4 h prior to surgery, and treatment with UFH is resumed after surgery until the INR is in the therapeutic range.<sup>124</sup> On the day of the procedure, the INR is checked.

**Table 8 Bridging therapy of VKA with UFH or LMWH in high- and low-risk patients/procedures<sup>125</sup>**

<b>Low thromboembolic risk/low bleeding risk</b>
<ul style="list-style-type: none"> <li>Continue anticoagulant therapy with INR in therapeutic range.</li> </ul>
<b>Low thromboembolic risk/high bleeding risk</b>
<ul style="list-style-type: none"> <li>Discontinue anticoagulant therapy 5 days before the procedure.</li> <li>Start LMWH prophylaxis once daily or UFH i.v. 1 day after acenocoumarol interruption, and 2 days after warfarin interruption. Administer the last dose of LMWH at least 12 h before the procedure or give UFH i.v. up to 4 h prior to surgery.</li> <li>Resume LMWH or UFH at the pre-procedural dose 1–2 days (at least 12 h) after the procedure according to haemostatic status. Resume anticoagulant therapy 1 to 2 days after surgery at the pre-procedural dose + 50% boost dose for two consecutive days according to the haemostatic status.</li> <li>LMWH or UFH is continued until the INR has returned to therapeutic levels.</li> </ul>
<b>High thromboembolic risk</b>
<ul style="list-style-type: none"> <li>Discontinue anticoagulant therapy 5 days before the procedure.</li> <li>Start therapeutic LMWH twice daily or UFH i.v. 1 day after acenocoumarol interruption, and 2 days after warfarin interruption. Administer the last dose of LMWH at least 12 h before the procedure or give UFH i.v. up to 4 h prior to surgery.</li> <li>Resume LMWH or UFH at the pre-procedural dose 1–2 days (at least 12 h) after the procedure according to haemostatic status. Resume anticoagulant therapy 1–2 days after surgery at the pre-procedural dose + 50% boost dose for two consecutive days according to haemostatic status.</li> <li>LMWH or UFH is continued until the INR has returned to therapeutic levels.</li> </ul>

INR = international normalized ratio; LMWH = low molecular weight heparin; UFH = unfractionated heparin.

**Table 9 Anticoagulation protocols applied according to patient thromboembolic risk<sup>126</sup>**

Weight, kg	Patients at high thromboembolic risk		Patients at low thromboembolic risk	
	Nadroparin (twice daily, s.c.) (IU)	Enoxaparin (twice daily, s.c.) (IU)	Nadroparin (once daily, s.c.) (IU)	Enoxaparin (once daily, s.c.) (IU)
<50	2850	2000	2850	4000
50–69	3800	4000	3800	4000
70–89	5700	6000	5700	4000
90–110	7600	8000	5700	4000
>110	9500	10 000	5700	4000

IU = international units; LMWH = low molecular weight heparin; SC = subcutaneous.

Consideration should be given to postponing the procedure if the INR is >1.5. LMWH or UFH is resumed at the pre-procedural dose 1–2 days after surgery, depending on the haemostatic status, but at least 12 h after the procedure. Oral anticoagulants should be resumed on day 1 or 2 after surgery depending on haemostasis sufficiency (if the patient can take oral therapy) at the pre-operative maintenance dose plus a boost dose of 50% for two consecutive days; the maintenance dose should be administered thereafter. LMWH or UFH should be continued until the INR returns to therapeutic levels.

Furthermore, the type of surgical procedure should be taken into consideration, as the bleeding risk varies considerably and affects the ability to ensure haemostatic control. Procedures with a high risk of serious bleeding complications are those where compression cannot be performed. In these cases, discontinuation of oral anticoagulants and bridging therapy with LMWH are warranted. In patients undergoing surgery with a low risk of serious bleeding, such as cataract surgery, no changes in oral anticoagulation therapy are needed.

In patients who are receiving VKAs and require reversal of the anticoagulant effect for an urgent surgical procedure, low-dose (2.5–5.0 mg) i.v. or oral vitamin K is recommended. For more immediate reversal of the anticoagulant effect of VKAs, treatment with fresh-frozen plasma or another prothrombin concentrate in addition to low-dose i.v. or oral vitamin K is recommended. In patients receiving UFH and requiring reversal of the anticoagulant effect for an urgent surgical procedure, cessation of therapy is enough. When given as an infusion, the anticoagulant effect of UFH reaches steady state within 4–6 h. So on cessation of an infusion, coagulation should be mostly normal after 4 h. When UFH is given s.c., the anticoagulant effect is more prolonged. For immediate reversal, the antidote is protamine sulfate. However, protamine sulfate can potentially provoke anaphylactic reactions with cardiovascular collapse, especially if infused too quickly. The dose of protamine sulfate can be calculated by the assessment of the amount of heparin received in the previous 2 h. The dose of protamine sulfate for reversal for a heparin infusion then is

1 mg per 100 U of heparin sodium. If the heparin infusion was stopped for >30 min but <2 h, then use half the dose of protamine sulfate; if the heparin infusion was stopped for >2 h but <4 h, then use a quarter of the dose. The maximum dose of protamine sulfate is 50 mg. In patients who are receiving LMWH the anticoagulant effect may be reversed within 8 h of the last dose because of the short half-life. If immediate reversal is required, i.v. protamine sulfate can be used, but anti-Xa activity is never completely neutralized (maximum of 60–75%).

A summary of the recommended way to minimize bleeding and thromboembolic events during surgery is given in Table 8.

## Revascularization

The main objective of prophylactic myocardial revascularization is the prevention of potentially lethal perioperative MI. While revascularization may be particularly effective in treating high-grade stenoses, it cannot prevent rupture of vulnerable plaques during the stress of surgery. The latter mechanism has been advocated in at least half of fatal cases of perioperative MI and may explain the lack of specificity of stress imaging techniques in predicting infarct-related coronary artery lesions.<sup>37,127</sup>

Patients who are clinically stable in the years after coronary artery bypass grafting (CABG) have a diminished risk of cardiac complications after subsequent non-cardiac surgery. Data from the CASS registry indicate that this is particularly the case in patients with triple vessel disease and/or depressed LV function but also in the case of high-risk surgery.<sup>128</sup> Therefore, patients who had CABG within the previous 5 years can be sent for surgery, if their clinical condition has remained unchanged since their last examination.

Patients with previous percutaneous revascularization may be at higher risk of cardiac events during or after subsequent non-cardiac surgery, particularly in cases of unplanned or urgent surgery after coronary stenting. After the introduction of angioplasty, it seemed that conventional percutaneous coronary intervention (PCI) did not worsen outcomes after surgery, even if

performed as early as 11 days after PCI.<sup>129</sup> The advent of stenting in the mid 1990s dramatically changed the scenario. Indeed, extremely high mortality rates (up to 20%) were reported in relation to acute stent thrombosis at the time of surgery if performed within weeks after coronary stenting with discontinuation of antiplatelet therapy.<sup>130,131</sup> Therefore, it is preferred that elective surgery be postponed for a minimum period of 6 weeks and optimally up to 3 months after bare metal stent implantation and that dual antiplatelet therapy be continued. When surgery was performed within this period, discontinuation of dual antiplatelet therapy was associated with an increased incidence of stent thrombosis.<sup>130,131</sup> After 3 months, patients can be sent for non-cardiac surgery, with continuation of at least aspirin therapy.<sup>132</sup> (Figure 3).

In 2002, DESs were introduced in Europe and became widely accepted as an efficient tool to reduce in-stent restenosis further. However, their major drawback is the need for prolonged dual antiplatelet therapy by aspirin and clopidogrel for at least 12 months. When surgery was performed within this period, discontinuation of dual antiplatelet therapy was associated with an increased incidence of stent thrombosis. It is now generally accepted that after DES implantation, elective surgery should not take place until after at least 12 months of continuous dual antiplatelet therapy<sup>133</sup> (Figure 3). After 12 months, patients can be sent for non-cardiac surgery, with continuation of at least aspirin therapy. The need for surgery in relation to its timing and the specific pathology (e.g. malignant tumour, vascular aneurysm repair) should be balanced against the excessive risk of stent thrombosis during the first year following DES implantation and a careful 'case-by-case' consideration is advisable. Discussion between the surgeon, the anaesthesiologist, and the treating cardiologist about this matter is recommended in order to achieve a reasonable expert consensus.

In patients who require temporary interruption of aspirin- or clopidogrel-containing drugs before surgery or a procedure it is

recommended that this treatment be stopped at least 5 days and, preferably as much as 10 days, prior to the procedure. Therapy can be resumed after ~24 h (or the next morning) after surgery when there is adequate haemostasis. In patients in need of an urgent surgical or other invasive procedure, with potential excessive or life-threatening perioperative bleeding, transfusion of platelets or administration of other prohaemostatic agents is recommended.<sup>134</sup>

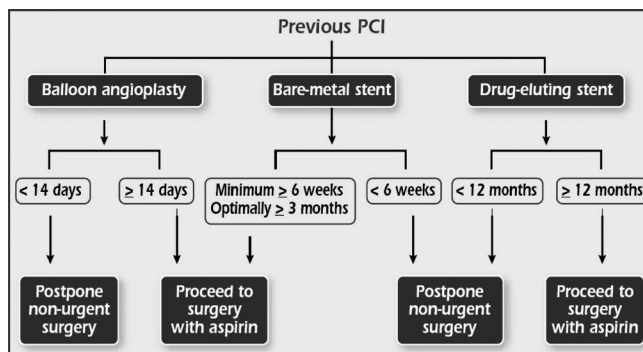
#### Recommendations on timing of non-cardiac surgery in cardiac-stable/asymptomatic patients with prior revascularization

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended that patients with previous CABG in the last 5 years be sent for non-cardiac surgery without further delay	I	C
It is recommended that non-cardiac surgery be performed in patients with recent bare metal stent implantation after a minimum 6 weeks and optimally 3 months following the intervention	I	B
It is recommended that non-cardiac surgery be performed in patients with recent drug-eluting stent implantation no sooner than 12 months following the intervention	I	B
Consideration should be given to postponing non-cardiac surgery in patients with recent balloon angioplasty until at least 2 weeks following the intervention	IIa	B

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

CABG = coronary artery bypass grafting.



**Figure 3** Recommendations for timing of non-cardiac surgery after PCI.<sup>133</sup> PCI = percutaneous coronary intervention.

## Prophylactic revascularization in patients with stable ischaemic heart disease

Only two randomized studies have addressed the role of prophylactic revascularization prior to non-cardiac surgery in stable patients scheduled for vascular surgery. The Coronary Artery Revascularization Prophylaxis (CARP) trial was the first to compare optimal medical therapy with revascularization (by CABG or PCI) in patients with stable IHD prior to major vascular surgery.<sup>135</sup> Of 5859 patients screened at 18 US Veterans Affairs hospitals, 510 patients were randomized to one or other of the treatment options. Patients were included on the basis of a combination of cardiovascular risk factors and the detection of ischaemia on non-invasive testing as assessed by the consultant cardiologist. There was no difference in the primary endpoint of long-term mortality at 2.7 years after randomization: 22% (revascularization) vs. 23% (no-intervention) ( $P = 0.92$ ). Furthermore, there was no difference in perioperative MI: 12% vs. 14%, respectively ( $P = 0.37$ ). The second trial, DECREASE-V, was a pilot study and applied a different, more precise screening methodology and a more contemporary perioperative medical management.<sup>136</sup> A total of 1880 patients scheduled for surgery were screened for the presence of the following risk factors: age >70 years, angina pectoris, prior MI, compensated or a history of congestive heart failure, drug therapy for diabetes mellitus, renal dysfunction, and prior stroke or transient ischaemic attack (TIA). In the presence of  $\geq 3$  risk factors, DSE or nuclear stress testing was performed and in the presence of extensive ischaemia (>5/16 segments or >3/6 walls), patients were randomized to either revascularization or no revascularization. Importantly,  $\beta$ -blocker therapy was initiated and aspirin was continued during surgery in all patients. Three-vessel or left main disease was present in 75% of cases. Also 43% of patients had a depressed ejection fraction of  $\leq 35\%$ . PCI was performed in 65% of patients ( $n = 32$ , of whom 30 had DESs). There was no difference in the composite primary endpoint (all-cause mortality and non-fatal MI at 30 days): 43% for revascularization vs. 33% for no revascularization ( $P = 0.30$ ).

CARP was the first trial to indicate that prophylactic revascularization prior to vascular surgery does not improve clinical outcomes in stable patients. Nevertheless, inclusion in the trial was based on subjective indicators and the study population was a relatively low risk group. DECREASE-V included high risk patients with extensive stress-induced ischaemia, as assessed by non-invasive stress testing. Despite the relatively small study cohort, DECREASE-V extends the conclusions of CARP to a higher risk population, with a majority of patients having three-vessel disease and a substantial proportion having asymptomatic LV dysfunction.

Successful achievement of a vascular procedure without prophylactic revascularization in a stable coronary patient does not imply that this patient would not need any revascularization afterwards. The limited data from DECREASE-V indicate a potential late catch-up phenomenon in the medically treated group.<sup>136</sup> Despite the lack of more scientific data, myocardial revascularization may therefore be recommended in patients prior to foreseen non-cardiac surgery without complications and who present with or have persistent signs of extensive ischaemia, according to the ESC Guidelines for non-surgical settings.

Both CARP and DECREASE-V have been conducted in the setting of vascular surgery, a type of surgery presenting particular risk to the patient with coronary heart disease. Despite this limitation, the conclusions of these trials can probably be extrapolated to other types of surgery.

### Recommendation for prophylactic revascularization in stable/asymptomatic patients

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
Late revascularization after successful non-cardiac surgery should be considered in accordance with ESC Guidelines on stable angina pectoris	IIa	C
Prophylactic myocardial revascularization prior to high-risk surgery may be considered in patients with proven IHD	IIb	B
Prophylactic myocardial revascularization prior to intermediate-risk surgery in patients with proven IHD is not recommended	III	B
Prophylactic myocardial revascularization prior to low-risk surgery patients with proven IHD is not recommended	III	C

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

IHD = ischaemic heart disease.

## Type of prophylactic revascularization in patients with stable ischaemic heart disease

Occasionally, patients with stable IHD may require elective surgery, meaning that surgery may be postponed for several months or even up to  $\geq 1$  year. There are no solid data to guide a revascularization strategy in this case, and recommendations can therefore only be based on experts' recommendations. Yet, these patients may to some extent be compared with patients who had previous revascularization. It seems therefore reasonable to propose a cardiovascular work-up according to the ESC Guidelines on stable angina pectoris.<sup>47</sup> CABG should be performed to improve prognosis and relieve symptoms in patients with significant left main disease or its equivalent, for significant three-vessel disease, in particular in the case of depressed LV function, as stated in these guidelines. PCI should be performed to improve symptoms in stable symptomatic patients with single or multivessel disease in whom intervention is technically suitable and in whom the procedural risk does not outweigh the potential benefit.<sup>70</sup>

The choice between PCI and CABG, often a matter of debate, will depend on several factors. Recently, the 1 year results of the SYNTAX trial, in which 1800 patients with three-vessel or left main IHD were randomized to undergo CABG or PCI, have been published.<sup>137</sup> They indicate that CABG remains the treatment of choice in these patients but that PCI is a valuable alternative. As mentioned before, current guidelines on the management of stable angina indicate a role for both treatments. Nevertheless, if PCI is performed prior to non-cardiac surgery the use of bare metal stents, in order not to delay surgery unnecessarily, is recommended.



### Recommendation on type of prophylactic revascularization in stable patients

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended that PCI or CABG be performed according to the applicable guidelines for management in stable angina pectoris	I	A

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

### Revascularization in patients with unstable ischaemic heart disease

No trial has investigated the role of prophylactic revascularization in patients with unstable angina pectoris requiring non-cardiac surgery. Unstable angina pectoris, in particular non-ST-segment elevation ACS, is considered to be a high-risk clinical entity and requires prompt diagnosis, risk stratification, and revascularization. Therefore, as long as the clinical condition for non-cardiac surgery is not life threatening, priority should be given to the diagnosis and proper treatment of unstable angina. In this case, the recent ESC Guidelines on the management of non-ST-segment elevation ACS apply.<sup>69</sup> The cornerstone of treatment includes antiplatelet and anticoagulant therapy,  $\beta$ -blocking agents, and prompt revascularization. Careful attention should be paid to avoiding overt anticoagulation and/or antithrombotic management of unstable coronary patients with concomitant surgical conditions, due to the risk of increased bleeding tendency secondary to the background surgical disease (malignancy, etc.). Except for the previously mentioned well-recognized indications for emergency CABG, most patients undergo PCI. In the exceptional situation of unstable angina and the need for subsequent non-cardiac surgery, preference should again be given to bare metal stents, in order not to delay surgery beyond 3 months.

### Recommendations on prophylactic myocardial revascularization in patients with unstable IHD

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
If non-cardiac surgery can be postponed safely, it is recommended that patients be diagnosed and treated in line with the guidelines on unstable angina management	I	A
In the unlikely combination of a life-threatening clinical condition requiring urgent non-cardiac surgery and ACS, it is recommended that surgery be given priority	I	C
However, on follow-up, aggressive medical treatment and myocardial revascularization according to the guidelines on unstable angina pectoris management is recommended	I	B
If PCI is indicated, the use of bare metal stents or even balloon angioplasty is recommended	I	C

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

ACS = acute coronary syndrome; IHD = ischaemic heart disease; PCI = percutaneous coronary intervention.

## Specific diseases

So far, the guidelines have discussed cardiac risk markers and risk reduction strategies. However, patients presenting with specific diseases prior to surgery benefit from an integrated evaluation and management of their disease in the perioperative period. In the following sections the most common cardiovascular diseases are discussed.

### Chronic heart failure

The prevalence of chronic heart failure in the adult population in the UK has been estimated to be 1.8%, and this increases with age. In patients >75 years the prevalence is as high as 8.0%.

The predictive value of heart failure for perioperative cardiac events is well recognized and is an important factor of clinical risk indices, such as Goldman's or Detsky's risk score.<sup>31,32</sup> A study evaluating LV function prior to vascular surgery in 1988 found an LV ejection fraction of  $\leq 35\%$  to be an optimal predictor of post-operative cardiac events.<sup>138</sup> In 2008, another study confirmed these findings and concluded that elderly patients with chronic heart failure scheduled for vascular surgery have higher risks of operative mortality and hospital readmission than other patients (including those with IHD) admitted for the same procedure.<sup>139</sup> The prognostic pre-operative value of heart failure with preserved LV ejection fraction is ill defined. Long-term outcome is similar to that of patients with reduced LV ejection fraction.<sup>140</sup> These patients could present an increased cardiovascular risk when undergoing surgery. In the absence of evidence-based studies, the committee recommends similar perioperative management in patients with preserved LV ejection fraction as in patients with a reduced ejection fraction.

The ability to assess myocardial viability during stress testing has allowed further risk stratification of cases with LV dysfunction. As shown in a study of 295 patients with a LV ejection fraction <35% scheduled for vascular surgery, post-operative cardiac events were related to the presence of stress-induced ischaemia and scar tissue.<sup>141</sup> However, there was an inverse relationship to the presence and extent of dysfunctional but viable segments, showing an improved function without signs of ischaemia during inotropic stimulation. Using multivariable analysis, the number of ischaemic segments was associated with perioperative cardiac events (OR per segment 1.6, 95% CI 1.05–1.8), whereas the number of segments with sustained improvement was associated with improved outcome (OR per segment 0.2, 95% CI 0.04–0.7). The stratification using stress testing enables the physician to identify a subgroup of patients with sustained improvement who have a relatively benign post-operative outcome, unlike patients with a predominantly ischaemic response.

Current ESC Guidelines recommend the use of ACE inhibitors (or ARBs in patients intolerant of ACE inhibitors) and  $\beta$ -blockers as primary treatment in chronic heart failure patients, to improve morbidity and mortality.<sup>91</sup> Unless contra-indicated or not tolerated, they should be given in optimal doses in all patients with symptomatic heart failure and an LV ejection fraction  $\leq 40\%$ . Either an ARB or an aldosterone antagonist may subsequently be added, depending on clinical condition and patient characteristics. In all patients with an LV ejection fraction  $\leq 35\%$  who remain severely symptomatic [New York Heart Association (NYHA) functional class III or IV], the addition of a low dose of aldosterone antagonist should be considered (in the absence of hyperkalaemia and significant renal

dysfunction). As an alternative option, addition of an ARB is recommended in heart failure patients with an LV ejection fraction  $\leq 40\%$  who remain symptomatic despite optimal treatment with an ACE inhibitor and  $\beta$ -blocker, unless also taking an aldosterone antagonist. Diuretics are recommended in heart failure patients with signs or symptoms of congestion.

It has been concluded that the perioperative use of ACE inhibitors,  $\beta$ -blockers, statins, and aspirin is independently associated with a reduced incidence of in-hospital mortality in patients with LV dysfunction who are undergoing major non-cardiac vascular surgery.<sup>142</sup> Thus, it is recommended that life-saving therapies in stable heart failure patients be continued up until the surgery and that they be reinstated post-operatively, as soon as clinical conditions are satisfactory.

The diagnosis of post-operative heart failure is often difficult to make since it often presents atypically and may have a different aetiology compared with the non-surgical setting. The evaluation should include physical examination, ECG, serial biomarker measurements, X-ray, and echocardiography. Special attention should be given to the patient's volume status since high-volume infusion is often needed in the intra- and immediate post-operative setting. In the period after surgery, fluids given during the operation may be mobilized to cause hypervolaemia and even heart failure, if not adequately handled. Fluid overloading may cause decompensation of chronic heart failure or development of *de novo* acute heart failure. Heart failure may develop perioperatively either immediately after surgery (due to prolonged procedure, myocardial ischaemia, rapid fluid shift) or some days later (due to third-space fluid re-absorption). According to the recent ESC Guidelines on heart failure, an attempt should be made to optimize pharmacological therapy before surgery. This may be of particular importance for  $\beta$ -blockers, which are recommended in the perioperative period in all high-risk patients. To avoid uncontrolled hypotension, routine use of i.v.  $\beta$ -blockers is not recommended. Importantly, if a heart failure patient is not receiving a  $\beta$ -blocker, such therapy should be initiated early enough before elective surgery to ensure optimal dose uptitration.

Once the aetiology of post-operative heart failure is diagnosed, treatment is similar to the non-surgical setting. Patients with heart failure have a significantly higher risk of hospital readmission after surgical procedures. This confirms the need for careful discharge planning and close follow-up, optimally using a multidisciplinary approach.

### Arterial hypertension

In general, the presence of arterial hypertension is not considered to be an independent risk factor for cardiovascular complications in non-cardiac surgery. Pre-operative evaluation allows the identification of patients with hypertension, enables a search for target organ damage and evidence of associated cardiovascular pathology to be undertaken, and allows initiation of appropriate therapy. This is particularly important for those with concomitant risk factors.

There is no clear evidence favouring one mode of antihypertensive therapy over another in patients undergoing non-cardiac surgery. Patients with arterial hypertension should be managed according to existing ESC Guidelines.<sup>143</sup> However, in hypertensive patients with concomitant IHD who are at high risk of cardiovascular complications, perioperative administration of  $\beta$ -blockers is recommended. In patients with hypertension, antihypertensive therapy should be continued up to the morning of surgery and

restarted promptly in the post-operative period.<sup>144</sup> In patients with grade 1 or 2 hypertension,<sup>143</sup> there is no evidence that delay in surgery in order to optimize therapy is beneficial. In these cases, antihypertensive medications should be continued during the perioperative period. In patients with grade 3 hypertension (systolic blood pressure  $\geq 180$  mmHg and/or diastolic blood pressure  $\geq 110$  mmHg), the potential benefits of delaying surgery to optimize the pharmacological therapy should be weighed against the risk of delaying the surgical procedure.<sup>20,144</sup>

### Valvular heart disease

Patients with VHD are at higher risk of perioperative cardiovascular complications during non-cardiac surgery.<sup>124</sup> Echocardiography should be performed in patients with known or suspected VHD, to assess its severity and consequences. On the basis of existing data, the following recommendations are particularly applicable in these patients.<sup>20,124</sup>

#### Recommendation on VHD

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
In the presence of severe VHD it is recommended that a clinical and echocardiographic evaluation be performed and, if needed, treatment before non-cardiac surgery	I	C

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

VHD = valvular heart disease.

### Aortic stenosis

Aortic stenosis (AS) is the most common VHD in Europe, particularly among the elderly.<sup>145</sup> Severe AS (defined as aortic valve area  $< 1$  cm<sup>2</sup>,  $< 0.6$  cm<sup>2</sup>/m<sup>2</sup> body surface area) constitutes a well established risk factor for perioperative mortality and MI.<sup>146</sup> In the case of urgent non-cardiac surgery in patients with severe AS, such procedures should be performed under haemodynamic monitoring.<sup>124</sup> In the case of elective non-cardiac surgery, the presence of symptoms is a key for decision making.

In symptomatic patients, aortic valve replacement should be considered before elective surgery. In patients who are not candidates for valve replacement either due to high risks associated with serious co-morbidities or those who refuse, non-cardiac surgery should be performed only if is essential. In these patients, balloon aortic valvuloplasty or transcatheter valve implantation may be a reasonable therapeutic option before surgery.<sup>124,147</sup>

In asymptomatic patients, non-cardiac surgery of low to intermediate risk can be safely performed. If high-risk surgery is planned, further clinical assessment is necessary for aortic valve replacement. In those at high risk for aortic valve replacement, elective surgery under strict haemodynamic monitoring should be performed only if strictly needed. In the remaining patients, aortic valve replacement should be considered as the initial procedure.<sup>124</sup>

### Mitral stenosis

Non-cardiac surgery can be performed at relatively low risk in patients with non-significant mitral stenosis (MS) (valve area  $> 1.5$  cm<sup>2</sup>) and in

asymptomatic patients with significant MS (valve area  $<1.5\text{ cm}^2$ ) and systolic pulmonary artery pressure  $<50\text{ mmHg}$ . Pre-operative surgical correction of MS in these patients is not indicated. It needs to be remembered that control of heart rate is essential to avoid tachycardia, which may cause pulmonary oedema. Strict control of fluid overload is also important. Also development of AF may cause serious clinical deterioration.<sup>20,124</sup> With the high risk of embolism, anticoagulation control is important. In asymptomatic patients with significant MS and systolic pulmonary artery pressure  $>50\text{ mmHg}$  and in symptomatic patients, the risk related to the non-cardiac procedure is significantly higher, and these patients may benefit from percutaneous mitral commissurotomy (or open surgical repair) particularly before high-risk surgery.<sup>20,124</sup>

### Aortic regurgitation and mitral regurgitation

Non-significant aortic regurgitation (AR) and mitral regurgitation (MR) do not independently increase the risk of cardiovascular complications during non-cardiac surgery. In asymptomatic patients with severe AR and MR (detailed classification presented in the ESC Guidelines<sup>124</sup>) and preserved LV function, non-cardiac surgery can be performed without additional risk. Symptomatic patients and those who are asymptomatic with severely impaired LV ejection fraction ( $<30\%$ ) are at high risk of cardiovascular complications, and non-cardiac surgery should be performed only if necessary.<sup>124</sup> Patients with severe MR and AR may benefit from optimization of pharmacological therapy to produce maximal haemodynamic stabilization before high-risk surgery.

### Patients with prosthetic valve(s)

Patients who have undergone surgical correction of VHD and have a prosthetic valve can undergo non-cardiac surgery without additional risk, when there is no evidence of valve or ventricular dysfunction. In these patients, endocarditis prophylaxis is recommended and a modification of the anticoagulation regimen needs to be considered in the perioperative period, with oral anticoagulants being temporarily replaced by i.v. UFH, s.c. UFH, or s.c. LMWH at therapeutic doses.

### Prophylaxis of infective endocarditis

In patients with VHD and those with prosthetic valves who are undergoing non-cardiac surgery at risk of bacteraemia, antibiotic prophylaxis against infective endocarditis should be initiated. This issue is discussed in detail in the ESC and AHA guidelines.<sup>148,149</sup>

### Arrhythmias

The occurrence of perioperative arrhythmias has been reported in 70% of patients subjected to general anaesthesia for various surgical procedures.<sup>150,151</sup> The incidence has been reported to vary from 16 to 62% with intermittent ECG monitoring<sup>152</sup> and 89% with continuous Holter monitoring.<sup>153</sup>

### Ventricular arrhythmias

Almost half of all high-risk patients undergoing non-cardiac surgery have frequent ventricular premature beats (VPBs) or non-sustained VT. There is no evidence that VPBs or non-sustained VTs alone are

associated with a worse prognosis. ACC/AHA/ESC Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death recommend approaches based on large clinical trials.<sup>154</sup> Regardless of the cause, sustained monomorphic ventricular tachycardia (SMVT) with serious haemodynamic compromise must be treated promptly with electric cardioversion.<sup>154</sup> I.v. amiodarone can be used for initial treatment of patients with stable SMVT.<sup>154</sup> It is also reasonable in patients with SMVT that is haemodynamically unstable, refractory to conversion with countershock, or recurrent despite other agents. In sustained polymorphic ventricular tachycardia (SPVT), if haemodynamic compromise is present, immediate electrical cardioversion should be performed.  $\beta$ -Blockers are useful for patients with recurrent SPVT, especially if ischaemia is suspected or cannot be excluded. Amiodarone is reasonable for patients with recurrent SPVT in the absence of long QT syndrome (LQTS).<sup>154</sup> Torsades de Pointes rarely occurs, and withdrawal of any offending drugs and correction of electrolyte abnormalities are recommended. Management with magnesium sulfate is reasonable for patients with Torsades de Pointes and LQTS.  $\beta$ -Blockade combined with pacing is suggested in patients who have Torsades de Pointes and sinus bradycardia. Isoproterenol is recommended in patients with recurrent pause-dependent Torsades de Pointes who do not have congenital LQTS.<sup>154</sup> In the event of perioperative pulseless VT or ventricular fibrillation, immediate defibrillation is required.

### Supraventricular arrhythmias

A greater number of patients undergoing non-cardiac surgery may suffer from SVT and AF compared with ventricular arrhythmias.<sup>153–158</sup> Sympathetic activity is the primary autonomic mechanism responsible for the trigger of AF.<sup>159</sup> Vagal manoeuvres may terminate SVT in some cases and these arrhythmias respond well to treatment with adenosine. When SVT is refractory to adenosine, effective therapy for termination of the arrhythmia includes a short-acting  $\beta$ -blocking agent or a non-dihydropyridine calcium channel blocker (diltiazem and verapamil) or amiodarone i.v.<sup>160–162</sup> Verapamil should be used with care because of its negative inotropic effect. The use of calcium channel blockers is not recommended in pre-excited SVT/AF. For perioperative AF, the goal of management is ventricular rate control.<sup>163</sup>  $\beta$ -Blockers and non-dihydropyridine calcium channel blockers (diltiazem and verapamil) are the drugs of choice for the rate control in AF. Digoxin may be used as a first-line drug only in patients with chronic heart failure, since it is not effective in high adrenergic states such as surgery.  $\beta$ -Blockers have been shown to accelerate the conversion of AF to sinus rhythm after non-cardiac surgery.<sup>164</sup> In several studies, the pre-operative administration of  $\beta$ -blockers was associated with better control of arrhythmias.<sup>165,166</sup>

### Bradyarrhythmias

Severe perioperative bradyarrhythmias requiring treatment have been reported in 0.4% of 17 021 patients, 6.4% of whom were American Association of Anaesthesiologists physical status 3 or 4.<sup>151</sup> These patients were monitored with routine intraoperative and early post-operative ECG monitoring. In general, perioperative bradyarrhythmias respond well to short-term pharmacological therapy, non-invasive transoesophageal atrial pacing in

anaesthetized individuals, or non-invasive transcutaneous pacing in awake or anaesthetized patients.<sup>160</sup> Temporary cardiac pacing is rarely required, even in the presence of pre-operative asymptomatic bifascicular block or left bundle branch block.<sup>167</sup> The indications for temporary pacemakers during the perioperative period are generally the same as those for permanent pacemakers.<sup>168</sup> Asymptomatic bifascicular block, with or without first degree atrio-ventricular block, is not an indication for temporary endocardial pacing.<sup>169,170</sup>

### Pacemaker/implantable cardioverter defibrillator

The use of unipolar electrocautery represents a significant risk to pacemaker-dependent patients. The electrical stimulus from electrocautery may inhibit demand pacemakers or may reprogramme the pacemaker. However, these problems can be avoided by positioning the ground plate for the electrical circuit, such that the electrical current travels away from the generator. Keeping the electrocautery device away from the pacemaker, giving only brief, bursts and using the lowest possible amplitude may decrease the interference. In many studies, the authors recommended setting the pacemaker in an asynchronous or non-sensing mode in patients who are pacemaker dependent and whose underlying rhythm is unreliable, and interrogating the device after surgery to ensure appropriate programming and sensing pacing thresholds.<sup>171–174</sup> Interference with implantable cardioverter defibrillator function can also occur during non-cardiac surgery as a result of electrical current generated by electrocautery.<sup>175,176</sup> The implantable cardioverter defibrillator should be turned off during surgery and switched on in the recovery phase before discharge to the ward. In addition, it is recommended that written instructions regarding the responsibility for surveillance and restarting of the implantable cardioverter defibrillator should be available.

#### Recommendations on ventricular arrhythmias

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Anti-arrhythmic drugs are recommended for patients with recurrent sustained VT	I	B
Continuation of amiodarone and β-blockers before surgery is recommended	I	C
It is recommended that wide QRS tachycardia be considered to be VT if the diagnosis is unclear	I	C
Prompt electrical cardioversion in patients with sustained VT with haemodynamic compromise is recommended	I	C
Anti-arrhythmic drugs for initial treatment of patients with stable sustained monomorphic VT should be considered	IIa	B
Anti-arrhythmic drugs for patients with non-sustained VT are not recommended	III	B
Anti-arrhythmic drugs for patients with VPBs are not recommended	III	A

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

VPB = ventricular premature beat; VT = ventricular tachycardia.

#### Recommendations on supraventricular arrhythmias

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Ventricular rate control is recommended in patients with AF without haemodynamic instability	I	A
Continuation of oral anti-arrhythmic drugs before surgery is recommended	I	C
Electrical cardioversion when haemodynamic instability occurs is recommended	I	C
Vagal manoeuvres and anti-arrhythmic therapy for termination of SVT in haemodynamic stable patients is recommended	I	C

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

AF = atrial fibrillation; SVT = supraventricular tachycardia.

#### Recommendations on implantable devices

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Interrogation of implantable devices pre-operatively and post-operatively is recommended	I	C
It is recommended that the hospital management state who is responsible for programming the devices before and after surgery	I	C

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

### Renal disease

Reduced kidney function is an independent risk factor for adverse post-operative cardiovascular outcomes including MI, stroke, and progression of heart failure. In most risk indices, renal function is taken into account. Traditionally, this function is assessed by serum creatinine concentration. For example, the serum creatinine cut-off value of >2.0 mg/dL (177 μmol/L) is used in the Lee index.<sup>5</sup> However, estimated creatinine clearance (mL/min) incorporating serum creatinine, age, and weight provides a more accurate assessment of renal function than serum creatinine alone. Most commonly used is the Cockcroft–Gault formula  $\{[(140 - \text{age in years}) \times (\text{weight in kg})] / [72 \times \text{serum creatinine in mg/dL}]\} \times (0.85 \text{ for females})$ .<sup>177</sup> An evaluation of 852 subjects undergoing major vascular surgery demonstrated an increase in mortality when serum creatinine was >2.0 mg/dL with an OR for perioperative mortality of 5.2, 95% CI 2.9–10.8.<sup>178</sup> However, it might be argued that patients with less pronounced renal insufficiency also do worse compared with patients with normal serum creatinine values. A 10 mL/min decrease in creatinine clearance was associated with a 40% increased risk of post-operative mortality (OR 1.4, 95% CI 1.2–1.5; ROC area: 0.70, 95% CI 0.63–0.76). ROC curve analysis showed that the cut-off value of 64 mL/min for creatinine clearance yielded the highest sensitivity/specificity to predict post-operative mortality.<sup>178</sup>

In addition to the pre-operative renal function, worsening of function after surgery is a prognostic factor for adverse late outcome. In 1324 patients who underwent elective open AAA surgery, creatinine clearance was measured pre-operatively and on days 1, 2, and 3 after surgery.<sup>179</sup> Patients were divided into three groups according to the change in renal function after surgery compared with baseline. Group 1 showed an improved or no change (change in creatinine clearance,  $\pm 10\%$  of function compared with baseline); group 2 showed a temporary worsening (worsening  $>10\%$  at day 1 or 2, then complete recovery within 10% of baseline at day 3); and group 3 experienced a persistent worsening ( $>10\%$  decrease compared with baseline). Mortality during 30 days after surgery was 1.3, 5.0, and 12.6% in groups 1, 2, and 3, respectively. Adjusted for baseline characteristics and post-operative complications, 30-day mortality was highest in patients with persistent worsening of renal function (HR 7.3, 95% CI 2.7–19.8), followed by those with temporary worsening (HR 3.7, 95% CI 1.4–9.9). During  $6.0 \pm 3.4$  years of follow-up, 348 patients (36.5%) died. The risk of late mortality was 1.7 (95% CI 1.3–2.3) in the persistent worsening group followed by those with temporary worsening (HR 1.5, 95% CI 1.2–1.4). This study showed that, although renal function may recover completely after aortic surgery, temporary worsening of renal function was associated with an increased long-term mortality.<sup>179</sup>

Identification of patients who might experience perioperative worsening of renal function is important in order to initiate supportive measures such as maintenance of adequate intravascular volume for renal perfusion and vasopressor use. In a large retrospective study, risk factors for post-operative acute renal failure within the first 7 days after major non-cardiac surgery among patients with previously normal renal function were evaluated.<sup>180</sup> Thirty-day, 60-day, and 1-year all-cause mortality was also assessed. A total of 65 043 cases throughout 2003 and 2006 were reviewed. Of these, 15 102 patients met the inclusion criteria; 121 patients developed acute renal failure (0.8%), and 14 required renal replacement therapy (0.1%). Seven independent pre-operative predictors were identified ( $P < 0.05$ ): age, emergency surgery, liver disease, high body mass index, high-risk surgery, peripheral arterial occlusive disease, and COPD necessitating chronic bronchodilator therapy.

Contrast-induced nephropathy, caused by renal hypoperfusion and direct tubular toxicity, occurs in up to 15% of patients with chronic renal dysfunction undergoing radiographic procedures.<sup>181</sup> Between 0.5 and 12% of these patients require haemodialysis and prolonged hospitalization. A considerable number of patients experience worsening of renal function, possibly progressing to end-stage renal failure. The cornerstone of prevention consists of periprocedural hydration and antioxidant drugs. Recently, three randomized studies have compared the effects of sodium bicarbonate vs. isotonic saline in humans, resulting in an impressive reduction in contrast nephropathy in the sodium bicarbonate group, with an incidence  $<2\%$ .<sup>182</sup> These results were recently evaluated in an adequately powered randomized trial comparing the efficacy of hydration with sodium bicarbonate vs. isotonic saline in addition to oral *N*-acetylcysteine for prophylaxis of contrast-induced nephropathy in a population of patients with chronic kidney dysfunction undergoing planned coronary angiography or intervention. A total of 502 patients

with an estimated creatinine clearance  $<60$  mL/min were randomized to receive infusion of either saline (0.9% NaCl) or sodium bicarbonate before and after administration of contrast medium on top of *N*-acetylcysteine orally (600 mg b.i.d.).<sup>183</sup> Treatment with isotonic saline consisted of 1 mL/kg/h 0.9% sodium chloride for 12 h before and after the procedure, and treatment with sodium bicarbonate (154 mEq/L in dextrose and water) consisted of 3 mL/kg for 1 h before the contrast medium, followed by an infusion of 1 mL/kg/h for 6 h after the procedure. Contrast-induced nephropathy was defined as an absolute increase in serum creatinine  $\geq 0.5$  mg/dL measured within 5 days after contrast exposure. No difference was observed between the two study groups; contrast-induced nephropathy occurred in 54 patients (10.8%); 25 (10%) were treated with sodium bicarbonate and 29 (11.5%) with saline ( $P = 0.60$ ). Thus, hydration with sodium bicarbonate plus oral *N*-acetylcysteine before contrast medium exposure was no more effective than hydration with isotonic sodium chloride plus oral *N*-acetylcysteine for prophylaxis of contrast-induced nephropathy in patients with moderate renal dysfunction. The discrepancies among randomized studies might be explained by differences in the concomitant use of *N*-acetylcysteine, use of contrast medium, or baseline renal dysfunction among randomized patients. Sodium bicarbonate requires only 1 h of pre-treatment and may represent an option in patients scheduled for urgent agent injection or for outpatient procedures.

#### Recommendation/statement for renal function

Recommendation/statement	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended that pre-operative renal function be considered as an independent cardiac risk factor for perioperative and long-term prognosis	I	B
For patients at risk of developing contrast-induced nephropathy (CIN), hydration with isotonic sodium chloride (with or without oral <i>N</i> -acetylcysteine) for prophylaxis of CIN is recommended prior to cardiac imaging procedures that are involved with administration of contrast medium injection (e.g. coronary and/or peripheral angiography)	I	B

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## Cerebrovascular disease

Cerebrovascular disease is the third leading cause of death in Western countries, with  $\sim 500$  TIAs and 2400 new strokes per million inhabitants. One-third of new stroke patients die within 1 year, and  $<50\%$  make a full recovery and regain independence. An increasing number of elderly patients are referred for non-cardiac surgery, including those with concomitant vascular diseases affecting the cerebral circulation. Risk factors for perioperative symptomatic or asymptomatic transient or permanent cerebrovascular events (TIA/stroke) are embolism or haemodynamic compromise in large (aorta, carotid, vertebral, and main cerebral arteries intracranially) or small vessels (perforating

and penetrating arterioles and capillaries). Although fatal and non-fatal stroke can be reduced significantly in symptomatic patients with moderate/severe carotid stenosis associated with ipsilateral symptoms, in particular if treated early (2–4 weeks, but at least within 3–6 months after the onset of symptoms), the benefit of this interventional/surgical treatment is smaller in neurologically asymptomatic subjects. Thus medical measures to prevent stroke are of utmost general importance and include a multifaceted strategy aimed at control of hypertension, hyperlipidaemia, diabetes, etc. The usefulness of specific antiplatelet agents or anticoagulants has been demonstrated in many randomized controlled trials for primary and secondary prevention, and may even be increased in elderly subjects undergoing non-cardiac surgery and anaesthesia.<sup>184</sup>

Apart from stroke and TIA, transient or permanent changes in mental status characterized by disturbances of attention, orientation, memory dysfunction, illusions, hallucinations, aphasia, etc. (the key diagnostic features of delirium) may occur, including anxiety and depression, which are often under-recognized or misdiagnosed. They may be due to perioperative medication, surgery itself, intraoperative hypo- or hypertension, and cerebral micro-embolism causing multiple small vessel occlusion and ischaemia, evidenced by transcranial Doppler and MRI diffusion-weighted imaging. In cardiac surgery, mental changes are common and may be associated with transient and occasionally even permanent cognitive dysfunction (25–30%). It is very likely that they also occur in the elderly high-risk patient undergoing non-cardiac surgery.

Current concepts of perioperative stroke are summarized in three major reviews<sup>185–187</sup> which compare the incidence of stroke for various surgical procedures (0.08–0.07% in general surgery, 1–5% in peripheral and carotid surgery, and 2–10% in cardiac surgery). Contrary to common belief, most strokes are not related to hypoperfusion, but occur mainly in the presence of an intact cerebral autoregulation.<sup>187</sup> Ischaemic and embolic mechanisms are far more common than haemodynamic compromise. Delayed stroke is mainly attributed to various sources of cardiac embolism, followed by hypercoagulability and increased risk of thrombotic events. Many strokes remain undiagnosed because of a lack of major sensory–motor symptoms or the presence of only subtle neuropsychological deficits, which are more difficult to identify. Several patient- and procedure-related factors are associated with an increased risk of perioperative stroke—they should be investigated carefully to evaluate the individual risk/benefit ratio and optimize care, including appropriate risk modification and timing of surgery. A history of recent stroke or TIA is the strongest predictor for perioperative stroke and should be identified after evaluating the history and the neurological status of each patient. In such cases, and if in doubt, additional brain and vascular images are recommended. In patients with both carotid and cardiac disease, death rates from cardiac causes exceed the risk of stroke; a review of the literature from 1970 to 2000 showed that patients with significant asymptomatic carotid stenosis are at high risk for fatal and non-fatal cardiac events (8%/year), but not for stroke (1–2%/year).<sup>96</sup> However, the overall perioperative stroke risk tends to be overstated. There is no evidence-based recommendation to treat

carotid stenosis prior to non-cardiac surgery, but there are exceptional cases prior to cardiac surgery.

Discontinuation of warfarin or antiplatelet agents in anticipation of surgery exposes patients to an increased risk of perioperative stroke. A review of perioperative outcome in patients requiring warfarin showed 0.6% thromboembolic events in those who continued therapy vs. 7.0% in patients who received i.v. heparin as bridging therapy.<sup>188</sup> Whether this is due to insufficient control or dosage of heparin administration is uncertain. In knee or hip replacement, continued use of moderate dose warfarin therapy during the perioperative period was safe and effective and was similar to patients undergoing dental procedures, cataract surgery, and diagnostic endoscopy without interrupting their antiplatelet agents or oral anticoagulants regimen. Lengthy operations are associated with higher risks for perioperative stroke; the choice of surgical technique is also important and the types of anaesthesia and anaesthetic agents require additional consideration. Optimal selection of individually guided best levels of blood pressure during surgery and thereafter, as well as management of the patient's body temperature and control of blood glucose, are suggested to reduce rates of incidental stroke and death. Pre-, intra-, and post-operative use of antiplatelet agents is useful. Whether or not so-called neuroprotective agents are needed is a matter of controversy.

#### Recommendations on stroke/transient ischaemic attack (TIA)

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
If carotid stenosis is >70%, additional therapy such as antiplatelet therapy and/or surgery is recommended	I	A
Routine pre-operative screening for symptomatic or asymptomatic carotid stenosis may be considered	IIb	C

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## Pulmonary disease

The co-existence of pulmonary disease in patients having non-cardiac surgery may increase the risk of operation. Such diseases include acute respiratory infections, COPD, asthma, cystic fibrosis, interstitial lung disease, and other conditions causing impairment of respiratory function. Pre-existing pulmonary disease has a significant impact on perioperative risk, but the most common effect is to increase the risk of post-operative pulmonary complications. These complications are mainly a consequence of the development of atelectasis during general anaesthesia. Post-operative shallow breathing, reduced lung expansion, and other factors may cause the lung collapse to persist and promote respiratory infection. These complications occur especially after abdominal or thoracic surgery, and the risk seems to be increased in smokers. Specific perioperative management is required to reduce the risks of pulmonary complications. There are some

respiratory conditions which are associated with cardiovascular abnormalities and which may require special cardiac risk assessment and management in addition to dealing with pulmonary complications per se. Two such conditions are COPD and pulmonary arterial hypertension (PAH).

COPD, defined as airways obstruction which is not completely reversible, is well recognized as a major cause of morbidity and mortality. The prevalence of COPD in adults in Europe has been found to vary between ~5 and 10%, with rates tending to be higher in males than females. Thus, up to one in 10 patients having non-cardiac surgery may have COPD.

Cor pulmonale with right heart failure is a direct complication of severe COPD. However, COPD is also associated with an increased risk of coronary heart disease. In a systematic review of 12 population cohort studies, those with a reduced forced expiratory volume in 1 s (FEV<sub>1</sub>) had a 75% increased risk of cardiovascular mortality compared with those with a normal FEV<sub>1</sub>.<sup>189</sup> Reduced expiratory flow has also been associated with a higher incidence of non-fatal coronary heart disease and stroke, carotid stenosis, low ankle-brachial index, and cerebral white matter lesions. These associations occur in both men and women and, despite a strong relationship of smoking with both COPD and CVD, are independent of traditional cardiovascular risk factors. For every 10% decrease in FEV<sub>1</sub>, cardiovascular mortality increases by ~30% and non-fatal coronary events by ~20%.

In patients undergoing aortic aneurysm repair, conflicting results have been found with short-term mortality (often due to cardiac complications). For example, COPD has been associated with operative death, but not 30-day mortality. In vascular surgery patients as a whole, COPD has not been associated with increased 30-day mortality. Thus, despite an association with CVD, there is no convincing evidence that COPD is related to a higher risk of perioperative cardiac complications.

PAH may be idiopathic, due to congenital heart disease, familial, or associated with specific conditions such as collagen vascular disease. It must be distinguished from other causes of PAH due to COPD, thromboembolism, and congenital disease. The diagnosis is based on a mean arterial pulmonary pressure of >25 mmHg at rest and a pulmonary wedge pressure of ≤15 mmHg. In surveys in Europe, the prevalence has varied between about 15 and 50 cases per million adults. Half the cases were idiopathic. The prevalence is thus low and consequently the condition is uncommon in surgical practice.

PAH increases surgical complications, especially right ventricular failure, myocardial ischaemia, and post-operative hypoxia. In patients having cardiopulmonary bypass surgery, a mean pre-operative arterial pressure >30 mmHg is an independent predictor of mortality. In a study of patients with pulmonary hypertension undergoing non-cardiac surgery, of whom over half had PAH, outcome predictors included NYHA functional class ≥II, intermediate- to high-risk surgery, right ventricular function, and duration of anaesthesia.<sup>190</sup> There is a need for further research on factors predicting poor outcomes. However, the study above did confirm that such patients are at high risk, the perioperative cardiopulmonary complication rate being 38% and mortality 7%.

Pre-existing COPD is often considered in terms of the risk of post-operative pulmonary complications. For perioperative cardiac risk, the lack of convincing evidence that COPD increases risk may have arisen because in COPD patients extra care was taken with cardiac management, thus negating any association. Nevertheless, COPD has not been included in pre-operative cardiac risk indices, such as Goldman, Detsky, and Lee and, indeed, no improvement was found in the prognostic value of the Lee index in vascular surgery patients when COPD was included.<sup>191</sup> For PAH, on the other hand, the condition is so uncommon that its inclusion in an integrated risk model has not been considered.

In patients with pulmonary disease having non-cardiac surgery, the treatment goals pre-operatively are to optimize pulmonary function and minimize respiratory complications. For COPD, treatment goals would include eliminating active infection with antibiotics; minimizing wheeze associated with any reversible disease using inhaled bronchodilators or steroids; reducing right and LV failure with diuretics; ensuring adequate oxygenation; and, finally, encouraging smoking cessation prior to surgery. In relation to perioperative cardiac management, patients with COPD should be managed in the same way as those without COPD and, in particular, there are no special contra-indications to the use of cardioselective β-blockers or statins in COPD patients.<sup>93,192</sup>

PAH is incurable and the treatment goal is to reduce symptoms, and improve exercise capacity and right ventricular function. Anaesthesia and surgery may be complicated by acute right heart failure due to increase of pulmonary vascular resistance related to the impairment of lung ventilation, typical of the operative and post-operative state of thoracic and abdominal surgery. Specific drug therapy for PAH includes calcium channel blockers (only for the few patients who are responders to the acute vasoreactivity test), prostanoids, endothelin receptor antagonists, and phosphodiesterase type-5 inhibitors.<sup>143,193</sup> Ideally, patients with PAH should have an optimized treatment regimen before any surgical intervention. It is recommended also that PAH-specific drug therapy is not withheld for >12 h due to the perioperative fasting state. In case of progression of right heart failure in the post-operative period, it is recommended that the diuretic dose be optimized and, if necessary, that inotropic support with dobutamine be initiated. The role of starting new specific PAH drug therapy in the perioperative period has not been established. In the case of severe right heart failure, not responsive to supportive therapy, the administration of temporary inhaled nitric oxide or i.v. epoprostenol with the guidance of a physician experienced in the treatment of PAH may be indicated. In this case, a period of progressive weaning from these medications may be required.

Patients with COPD and PAH have a relatively high frequency of heart failure and coronary heart disease. There is no consistent evidence indicating that COPD patients are at higher risk of perioperative cardiac complications and death, so that they can be managed in the same way as patients without COPD. On the other hand, PAH increases perioperative risk, and requires pre-operative assessment and, if severe, perioperative treatment.

**Recommendations on pulmonary diseases**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended that patients with pulmonary arterial hypertension have an optimized treatment regimen before any surgical intervention	I	C
In case of progression of right heart failure in the post-operative period of patients with pulmonary arterial hypertension, it is recommended the diuretic dose be optimized and if necessary that inotropic support with dobutamine be initiated	I	C
In the case of severe right heart failure not responsive to supportive therapy the temporary administration of inhaled nitric oxide or i.v. epoprostenol may be considered with the guidance of a physician experienced in the treatment of pulmonary arterial hypertension	IIb	C
Special perioperative cardiac risk management for patients with COPD is not recommended	III	C

<sup>a</sup>Class of recommendation.<sup>b</sup>Level of evidence.

COPD = chronic obstructive pulmonary disease.

## Perioperative monitoring

### Electrocardiography

Although even a single post-operative ECG demonstrating ischaemia in the recovery room is predictive of a major cardiac complication later during the hospital stay, ECG monitoring alone is not adequate to detect ischaemia in real time in the intensive care unit (ICU) and intraoperative settings.<sup>194–196</sup> Specifically, conventional visual ECG monitoring for the detection of transient ST-segment changes is inaccurate.<sup>196</sup> Although lead V<sub>5</sub> has been known as the best choice for the detection of intraoperative ischaemia for many years,<sup>197,198</sup> one study found that lead V<sub>4</sub> was more sensitive and appropriate than lead V<sub>5</sub> for detecting prolonged post-operative ischaemia and infarction.<sup>199</sup> Leads are not specific for ischaemic events, and, furthermore, ischaemic events are dynamic and may not always appear in the same lead. If a single lead is used for monitoring, there is an increased risk of missing ischaemic events. With the use of selected lead combinations, more ischaemic events can be precisely diagnosed in the intraoperative setting. In one study, although the best sensitivity was obtained with lead V<sub>5</sub> (75%), followed by lead V<sub>4</sub> (61%), combining leads V<sub>4</sub> and V<sub>5</sub> increased the sensitivity to 90%.<sup>198</sup> In the same study, when three leads (II, V<sub>4</sub>, and V<sub>5</sub>) were used simultaneously, the sensitivity increased to 96%.<sup>198</sup> Similarly, in another study in which two or more pre-cordial leads were used, the sensitivity of ECG monitoring was >95% for detection of perioperative ischaemia and infarction.<sup>199</sup> It was also shown that ECG monitoring with fewer leads (as few as three leads) had lower sensitivity than monitoring with 12 leads, and there was a statistically significant association, independent of perioperative troponin values,

between perioperative ischaemia on a 12-lead ECG and long-term mortality.<sup>200–202</sup> Thus, 12-lead ECG monitoring is recommended especially with high-risk patients.

ST-segment monitoring has been shown to be limited in patients who have intraventricular conduction defects (e.g. left bundle branch block) and ventricular paced rhythms.<sup>203</sup> The secondary ST–T changes, which were present in these patients, were due to abnormal depolarization, which also distorted the repolarization process. The distorted ST-segments can limit the sensitivity of the ST-segment monitoring system.<sup>203</sup> Because detection of ST-segment changes of the electrocardiogram by visual inspection is poor, computerized analysis has become standard in modern monitors. Continuous automated ST trending monitors are included in most new operating room ECG monitors to facilitate ischaemia detection. Such devices increase the sensitivity of ECG ischaemia detection.<sup>196</sup> In one study, Holter recordings were used as the reference standard for detection of intraoperative ischaemia, and the ST trending monitors were found to have overall sensitivity and specificity of 74 and 73%, respectively. Several conditions contributed to the inaccuracy of ST trend monitoring, and additional modification of their performance was necessary to achieve better agreement with the Holter analysis.<sup>196</sup>

In a series of studies during the past decade, the presence of ECG changes during monitoring in high-risk cohorts has been linked to a higher incidence of perioperative MI and cardiac events. In addition, the duration of ST-segment changes positively correlates with the incidence of perioperative MI.<sup>204</sup> Therefore, when ST-segment changes occur, the clinician should assume that myocardial ischaemia is present.<sup>205</sup> However, it is not clear if ECG monitoring is sufficiently sensitive to identify patients at low risk.<sup>206,207</sup> In addition, the usefulness of this test in the general population is limited because many studies have excluded patients with ECG findings that preclude accurate evaluation of ischaemia.

**Recommendations on 12-lead ECG monitoring**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
12-lead ECG monitoring is recommended for all patients undergoing surgery	I	C
Selected lead combinations for better ischaemia detection in operation room should be considered	IIa	B

<sup>a</sup>Class of recommendation.<sup>b</sup>Level of evidence.

ECG = electrocardiography.

### Transoesophageal echocardiography

Transoesophageal echocardiography (TOE) has frequently been used as a monitoring tool during cardiac surgery since the mid 1980s. However, few evidence-based data support TOE use in non-cardiac surgery. TOE has several advantages over alternative monitoring methods, such as the use of a pulmonary artery catheter. It is rapidly available, relatively non-invasive, and provides more versatile and comprehensive information. However, although TOE is in general a safe procedure, serious adverse events can



occur. The complication rates relate to the experience of the operator and the presence of severe oesophageal or gastric diseases. Specific training of users is mandatory to avoid inaccurate interpretation.

Myocardial ischaemia can be identified by abnormalities in regional wall motion and thickening. The concordance between intraoperative TOE and ECG is rather weak.<sup>208</sup> Both ST-segment changes and regional wall motion abnormalities can be present in the absence of acute ischaemia. Wall motion abnormalities may be difficult to interpret in the presence of left bundle branch block, ventricular pacing, AF, or right ventricular overload. The resolution of ischaemia is not necessarily detectable if ischaemia is followed by myocardial stunning. Episodes of new or worsened wall motion abnormalities have been shown to be relatively infrequent (20%) in high-risk patients undergoing non-cardiac surgery.<sup>208</sup> They were more common in patients submitted to aortic vascular surgery. Episodes were poorly correlated with post-operative cardiac complications.<sup>208</sup>

When compared with pre-operative clinical data and intraoperative monitoring using 2-lead ECG, routine monitoring for myocardial ischaemia with TOE or 12-lead ECG during non-cardiac surgery has little incremental clinical value in identifying patients at high risk of perioperative ischaemic outcomes.<sup>209</sup>

**Recommendations on intraoperative and/or perioperative transoesophageal echocardiography for detection of myocardial ischaemia**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
The use of TOE should be considered in patients who develop ST-segment changes on intraoperative or perioperative ECG monitoring	IIa	C
The use of TOE may be considered in patients at high risk of developing myocardial ischaemia who undergo major non-cardiac surgery	IIb	C

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

ECG = electrocardiography; TOE = transoesophageal echocardiography.

TOE is recommended if acute and severe haemodynamic instability or life-threatening abnormalities develop during or after surgery.<sup>210</sup> The main advantage of TOE over pulmonary artery catheterization is the more comprehensive evaluation of cardiac structure and function. Information is quickly available on regional or global, right and/or LV dysfunction, the presence of tamponade or cardiac thrombi, and preload estimation through the measurement of end-diastolic volume. Numerous indices of ventricular and atrial function have been proposed. However, most parameters are load dependent.

The role of TOE for haemodynamic monitoring in patients at risk is more controversial. Automated analysis systems exist but are not yet sufficiently validated. There is no evidence that haemodynamic monitoring by TOE accurately stratifies risk or predicts outcome.

TOE can be useful in the operating room in patients with severe valvular lesions. The loading conditions during general anaesthesia

differ from those present in the pre-operative evaluation. Functional and ischaemic mitral regurgitation are usually reduced during general anaesthesia. Organic mitral regurgitation can, conversely, increase. In the setting of severe mitral regurgitation, the LV ejection fraction overestimates LV function, and other parameters may be more accurate, such as myocardial velocities or deformation obtained by tissue Doppler imaging or 2D speckle tracking, an angle-independent method. These are promising techniques, but more validation is needed before they can be used routinely in this setting. In patients with severe aortic stenosis, appropriate preload is important during surgery. Monitoring of LV end-diastolic volume may be more accurate than that of pulmonary capillary pressure. An appropriate heart rate is crucial in patients with mitral stenosis and aortic regurgitation: a long diastolic period in the former and shorter duration of diastole in the latter. When inappropriate control of heart rate occurs, the consequences should be assessed: changes in transmitral mean gradient and pulmonary arterial pressures in mitral stenosis and changes in LV volumes and indices of LV function in aortic regurgitation.

**Recommendations on intraoperative and/or perioperative transoesophageal echocardiography in patients with or at risk of haemodynamic instability**

Recommendations on intraoperative and/or perioperative TOE in patients with or at risk of haemodynamic instability	Class <sup>a</sup>	Level <sup>b</sup>
TOE is recommended when acute sustained severe haemodynamic disturbances develop during surgery or in the perioperative period	I	C
TOE monitoring may be considered in patients at increased risk of significant haemodynamic disturbances during and after major non-cardiac surgery	IIb	C
TOE monitoring may be considered in patients who present severe valvular lesions during major non-cardiac surgical procedures accompanied by significant haemodynamic stresses	IIb	C

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

TOE = transoesophageal echocardiography.

**Right heart catheterization**

Most post-operative ischaemic episodes are silent and not accompanied by changes in pulmonary capillary wedge pressure. Right heart catheterization is not recommended for monitoring patients with intraoperative ischaemia. Indeed, both a large observational study and a randomized multicentre clinical trial did not show a benefit associated with the use of right heart catheterization after major non-cardiac surgery.<sup>211,212</sup> A case-control analysis was carried out on a subset of patients from the observational study who underwent pulmonary artery catheter placement and who were matched with a similar number of patients who did not undergo right heart catheterization. Patients, who were adjusted for surgical procedure and propensity of catheterization,

demonstrated a higher incidence of post-operative heart failure and non-cardiac events in the group submitted to catheterization.<sup>211</sup>

In the randomized study, no difference in mortality and hospital duration was found, but patients submitted to right heart catheterization had a higher incidence of pulmonary embolism.<sup>212</sup>

### Disturbed glucose metabolism

Diabetes mellitus is an important risk factor for perioperative cardiac complications and death. This condition promotes atherosclerosis, endothelial dysfunction, and activation of platelets and proinflammatory cytokines. Surgical stress is associated with haemodynamic stress and vasospasm and further enhances the prothrombotic state, while inhibiting fibrinolysis. This may lead to instability of pre-existing coronary plaques, thrombus formation, vessel occlusion, and MI. Also, hyperglycaemia in the absence of established diabetes plays an important role, emphasizing the need for pre-operative management of hyperglycaemia where possible. This is illustrated by studies on patients with pre-diabetes glucose levels who undergo non-cardiac vascular or non-vascular surgery, showing ~2- to 4-fold increases in risk of myocardial ischaemia, troponin release, 30-day and long-term cardiac events, and risk of death or cardiovascular mortality in particular.<sup>213,214</sup> Importantly, impaired glucose tolerance is often identified only after glucose loading. Critical illness is another condition characterized by disturbed glucose homeostasis ('stress diabetes' or 'diabetes of injury'), which develops independent of previously diagnosed diabetes and has repeatedly been identified as an important risk factor for morbidity and/or mortality.

Data from the International Diabetes Foundation reveal a high and increasing prevalence of diabetes in Europe, rising from 7.8% in 2003 to 8.4% in 2007, with an estimated prevalence of at least 9.1% by 2025.<sup>215</sup> More than 30% of the cases were previously undiagnosed, pointing to underestimation of the problem. With ~48 million people affected, diabetes has become one of the main causes of morbidity and mortality in Europe. According to the World Health Organization, ~50% of these patients die of CVDs. It has been well established that surgery in patients with diabetes is associated with longer hospital stay, higher healthcare resource utilization, and greater perioperative mortality. More recently, the emphasis has shifted from diabetes to hyperglycaemia on its own. New-onset hyperglycaemia, as compared with hyperglycaemia in known diabetics, may hold a much higher risk of adverse outcome.<sup>216</sup>

Evidence for strict blood glucose control for patients without known diabetes undergoing non-cardiac surgery is largely derived from studies in critically ill patients.<sup>217</sup> In 2001 the landmark Leuven prospective randomized controlled study demonstrated major clinical benefits for surgical ICU patients whose blood glucose levels were maintained normal (5.0–5.6 mmol/L; 90–100 mg/dL) with intensive insulin therapy, compared with patients who received conventional glucose management and developed hyperglycaemia (8.3–8.9 mmol/L; 150–160 mg/dL).<sup>218</sup> These benefits included lower ICU and in-hospital mortality and prevention of several critical illness-associated complications (critical illness polyneuropathy, severe infections, acute renal failure, and prolonged dependency on mechanical ventilation and intensive care). Also, long-term outcome improved, as shown for the

cardiac surgery subgroup. Five years later the Leuven group reported findings from the medical ICU, showing prevention of morbidity, but no mortality benefit from intensive glucose control, except in a subgroup requiring critical care for  $\geq 3$  days.<sup>219</sup> Based on these two trials recommendations were made aiming at tight glucose control. Several observational implementation studies on tight glucose management or small, randomized studies in selected ICU patient groups supported the clinical benefits of the Leuven studies.<sup>217</sup> Pooled analysis of the Leuven studies revealed reduced mortality and morbidity for all major clinical diagnostic subgroups, including cardiovascular, respiratory, gastrointestinal/hepatic disease or surgery, active malignancy, and sepsis upon ICU admission. Patients with known diabetes tended to experience less morbidity but a survival benefit appeared absent. All studies described above started glucose control after ICU admission. Timing of initiating insulin therapy is controversial, but a recent medical ICU study showed better outcome when initiated within the first 48 h than after 48 h. Tight intraoperative glucose control may provide additional benefit but appears a challenge and, so far, studies have mainly been set up for cardiac surgery. Moderate intraoperative glycaemic control during CABG (not continued in the ICU) resulted in decreased need for pacing, lower incidence of AF and infections, shortening of the ICU and hospital stay, and decreased recurrent ischaemic events in the long-run. In contrast, implementation of glycaemic control during cardiac surgery, superimposed upon post-operative ICU glycaemic control, did not further reduce perioperative mortality or morbidity.<sup>220</sup> In an observational study, stricter glucose control during liver transplantation was associated with a lower infection rate and 1-year mortality than poor glycaemic control.<sup>221</sup>

Studies in the field of critical care have demonstrated the detrimental effect of hyperglycaemia, due to an adverse effect on renal and hepatic function, endothelial function, and immune response, particularly in patients without underlying diabetes. In the Leuven studies, risk of death and degree of hyperglycaemia were positively correlated. Unequivocal demonstration that glycaemic control rather than direct insulin effects mediated the survival and most morbidity benefits of insulin therapy was provided in a rabbit model of critical illness.<sup>222</sup> Several risk factors for cardiac events after non-cardiac surgery are attenuated with strict blood glucose control in the ICU, including endothelial injury/dysfunction, CRP, and asymmetric dimethylarginine, apart from effects on mitochondrial damage, serum lipid profile, and the cortisol response. No effects, or only marginal ones, were seen on cytokines, coagulation, and fibrinolysis.

Recently, the favourable outcomes of the Leuven findings using tight glucose control were questioned. The NICE-SUGAR study investigators randomized >6000 patients (63% medical ICU and 37% surgical ICU) to either tight glucose control (target glucose level, 4.5–6.0 mmol/L; 81–108 mg/dL) or conventional glucose control (target glucose level, 8.0–10.0 mmol/L; 144–180 mg/dL).<sup>223</sup> Patients were randomized to treatment within 24 h after admission using i.v. insulin infusions for glucose control. The primary endpoint, death by 90 days after randomization, was increased with intensive glucose control (27.5%) as compared with 24.9% with conventional control. There was no morbidity difference between the two study groups, and hence the excess

mortality remains unexplained. As could be expected, hypoglycaemia (<40 mg/dL) occurred in more patients in the intensive-control group than in the conventional-control group (6.8% vs. 0.5%,  $P < 0.001$ ). The strength of the NICE-SUGAR trial was its large and multicentre design using a computer-guided insulin infusion protocol. However, this protocol used an if-then algorithm based upon inaccurate and non-standardized stand-alone glucometers for blood glucose measurements. In addition, NICE-SUGAR had an open-label design, a small imbalance between the groups with respect to corticosteroid therapy, and 10% of patients randomized to intensive glucose control discontinued the study prematurely. The differences in outcome between the two studies should be explained.

- (i) The Leuven trials were performed in a single centre with standardized care which included early parenteral nutrition supplementing enteral feeding, whereas in the NICE-SUGAR trial enteral nutrition predominated, resulting in hypocaloric feeding in particular during the first week after admission to ICU.
- (ii) The target for initiating insulin in the standard treatment group was different, with insulin being advocated in the Leuven study only when blood glucose exceeded the renal threshold of >215 mg/dL, an approach that considers hyperglycaemia as a possible beneficial adaptation, whereas in NICE-SUGAR a target of 144–180 mg/dL was used in the standard group, which resulted in 70% of the patients receiving insulin and reaching an average blood glucose level of 8.0 mmol/L (144 mg/dL).
- (iii) Also in the intervention group of NICE-SUGAR, the compliance to therapy was much lower than in the Leuven studies, which resulted in an average glucose level of 6.6 mmol/L (118 mg/dL) and a very large overlap with the glucose levels in the control group.
- (iv) The use of inaccurate glucometers in NICE-SUGAR may have misguided the insulin therapy and may have overlooked hypokalaemia, a possible cause of excess cardiovascular mortality, which is prevented with the use of blood gas analysers for glucose measurement.
- (v) The nurse experience with the intervention in NICE-SUGAR was much less than in the Leuven studies, in view of the limited number of patients recruited per centre (<15% of all patients screened in the participating ICUs) as compared with 70–95% in the Leuven studies.

The results of the NICE-SUGAR trial may suggest that intensive glucose control could harm patients admitted to the ICU, in terms of death, when glucose levels are below the range of 7.8–10.0 mmol/L (140–180 mg/dL). In contrast, evidence derived from previous studies suggests the clinical benefit of maintenance of normoglycaemia (4.4–6.1 mmol/L; 80–110 mg/dL) as compared with tolerating hyperglycaemia up to 11.9 mmol/L (215 mg/dL) for adult critically ill patients (Table 10).

Until further data become available clarifying the reasons for the different outcomes between the studies, it is recommended that the management of blood glucose in the ICU be optimized, avoiding the extremes of hyperglycaemia and also hypoglycaemia. The available data indicate that this therapy should be started immediately after ICU admission. It may be advisable to target a level of

**Table 10 Clinical benefits of intensive insulin therapy in critically ill patients with a non-cardiac diagnosis upon ICU admission<sup>218,219</sup>**

	ICU stay $\geq 3$ days		P-value
	CIT (n = 643)	IIT (n = 648)	
ICU mortality	27.4%	22.7%	0.05
In-hospital mortality	38.7%	32.1%	0.01
Renal replacement therapy	11.2%	7.3%	0.02
Critical illness polyneuropathy <sup>a</sup>	51.3%	34.4%	<0.01
Bacteraemia	13.5%	10.6%	0.11
Mechanical ventilation (days) <sup>b</sup>	8 (4–17)	7 (3–13)	0.01
ICU stay (days) <sup>b</sup>	9 (4–18)	8 (4–15)	0.05

<sup>a</sup>Percentage of those screened of screened.

<sup>b</sup>Median (interquartile range).

CIT = conventional insulin therapy; ICU = intensive care unit; IIT = intensive insulin therapy.

~8.0 mmol/L (144 mg/dL) for settings and patient populations that are comparable with those studied in NICE-SUGAR.

#### Recommendations on blood glucose control

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Post-operative prevention of hyperglycaemia [targeting levels at least below 10.0 mmol/L (180 mg/dL)] with intensive insulin therapy is recommended in adults after high-risk or complicated major surgery requiring admission to ICU	I	B
Intraoperative prevention of hyperglycaemia with insulin may be considered	IIb	C
Post-operative prevention of hyperglycaemia with insulin after uncomplicated elective surgery may be considered	IIb	C

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

ICU = intensive care unit.

## Anaesthesia

An optimal perioperative course stems from a close cooperation between cardiologists, surgeons, pulmonologists, and anaesthesiologists. Pre-operative risk assessment and pre-operative optimization of cardiac disease should be performed jointly.

There is a paucity of strong evidence-based data supporting the choice of a particular perioperative approach and thus several options are available. Sufficiently powered randomized trials addressing the potential relationship between patient outcome and perioperative management are still lacking for cardiac patients undergoing non-cardiac surgery.

## Intraoperative anaesthetic management

The choice of the anaesthetic agent has been considered to be of little importance with regard to patients' outcome provided the vital functions are adequately supported. There is conflicting evidence from cardiac surgery over whether a specific method is advantageous in cardiac disease, but there is no evidence of superiority of any specific anaesthetic agent in non-cardiac surgery.<sup>224,225</sup>

Most anaesthetic techniques reduce sympathetic tone, leading to vasodilatation and reduction in systemic blood pressure. Thus, anaesthesiological management must ensure the proper maintenance of organ perfusion pressure.

## Neuraxial techniques

Spinal and epidural anaesthesia also induce sympathetic blockade. Depending on the height of the block, it induces peripheral vasodilation with fall in blood pressure. When reaching the thoracic dermatome level 4, a reduction in cardiac sympathetic drive with subsequent reduction in myocardial contractility, heart rate, and change in cardiac loading conditions will appear. The speed and strength of sympathetic blockade will depend on dosage and drugs as well as the patient's condition. There is conflicting evidence on the effect of neuraxial blocks on patient outcome after non-cardiac surgery. One meta-analysis reported significantly improved survival and reduced incidence of post-operative thromboembolic, cardiac and pulmonary complications with neuraxial blockade compared with general anaesthesia.<sup>226</sup> A major criticism of this study has been the inclusion of older studies, which may have made the results invalid for current practice. A recent analysis of a large cohort of patients (10 564 patients without and 2253 patients with epidural) undergoing colon resection confirmed the improved survival with epidural analgesia at 7 and 30 days after surgery, but it was not possible to identify the cause of death.<sup>227</sup> Also cardiac morbidity was not different between the two groups.

Randomized studies and a meta-analysis of several randomized clinical trials in non-cardiac surgery patients, comparing outcome with regional and general anaesthetic techniques have shown little consistent evidence of improved outcome and reduced post-operative morbidity and mortality.<sup>228–230</sup> It has been estimated that the number of patients needed for a randomized clinical trial to determine whether epidural anaesthesia and analgesia would affect mortality in patients undergoing high-risk vascular surgery would be ~24 000, while enrolment of 1.2 million would be needed in a low-risk procedure.<sup>227</sup> Thus, present studies are underpowered for a valid analysis of risk of death for procedures with low surgical risk. No study has clearly demonstrated a difference in outcome with different monitoring techniques, fluid management, or transfusion strategies. Most studies have used different pre-determined therapeutic goals, often requiring inotropic support, a factor that may have been of importance for the results.<sup>212</sup> The importance of skilled anaesthesiological management in keeping adequate circulation is often underlined.<sup>231</sup>

## Post-operative pain management

Post-operative pain is a major concern, reported in 5–10% of the patients. It may increase sympathetic drive and delay recovery.<sup>232,233</sup> The evidence that pain causes organ complications

after surgery is less clear. Neuroaxial analgesia with local anaesthetics/opioids and/or  $\alpha_2$ -agonists, i.v. opioids alone or in combination with non-steroid anti-inflammatory drugs seems to be the most effective. The benefit of invasive analgesic techniques should be weighed against potential dangers. This is of special importance when considering the use of neuraxial blockade in patients under chronic antithrombotic therapy due to increased potential of a neuraxial haematoma. It is beyond the scope of these guidelines to give recommendations for the use of neuraxial blocks in patients with coagulation disturbances.

Patient-controlled analgesia is an alternative for post-operative pain relief. Recent meta-analyses of controlled randomized trials show that patient-controlled analgesia has some advantage with regard to patient satisfaction over nurse-controlled or on-demand analgesia.<sup>234</sup> No difference with regard to morbidity or final outcome was demonstrated. Patient-controlled analgesia is an adequate alternative in patients and situations not suited for regional anaesthesia. Routines for follow-up and documentation of effects should be in place.<sup>232,235–237</sup> Non-steroid anti-inflammatory drugs and the cyclooxygenase-2 (COX-2) inhibitors have the potential for promoting heart and renal failure as well as thromboembolic events and should be avoided in patients with myocardial ischaemia. The COX-2 inhibitors cause less gastrointestinal ulceration and bronchospasm. The final role for these drugs in the treatment of post-operative pain in cardiac patients undergoing non-cardiac surgery has not been defined. The drugs should be avoided in patients with renal and heart failure, elderly patients, patients on diuretics, as well as patients with unstable haemodynamics.<sup>238</sup>

### Recommendations on anaesthesia

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Consideration should be given to performing thoracic epidural anaesthesia in high-risk surgery for patients with cardiac disease	IIa	A
Use of non-steroidal anti-inflammatory drugs and COX-2 inhibitors for post-operative pain control is not recommended in patients with renal and heart failure, myocardial ischaemia, elderly patients, as well as in patients taking diuretics or having unstable haemodynamics	III	B

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

COX-2 = cyclooxygenase-2.

## Putting the puzzle together

Figure 4 presents in algorithmic form an evidence-based stepwise approach for determining which patient benefits from cardiac testing, coronary artery revascularization, and cardiovascular therapy prior to surgery. For each step the committee has included the level of the recommendations and the strength of evidence in the accompanying Table 11.

Step 1. The urgency of the surgical procedure should be assessed. In urgent cases, patient- or surgical-specific factors dictate the

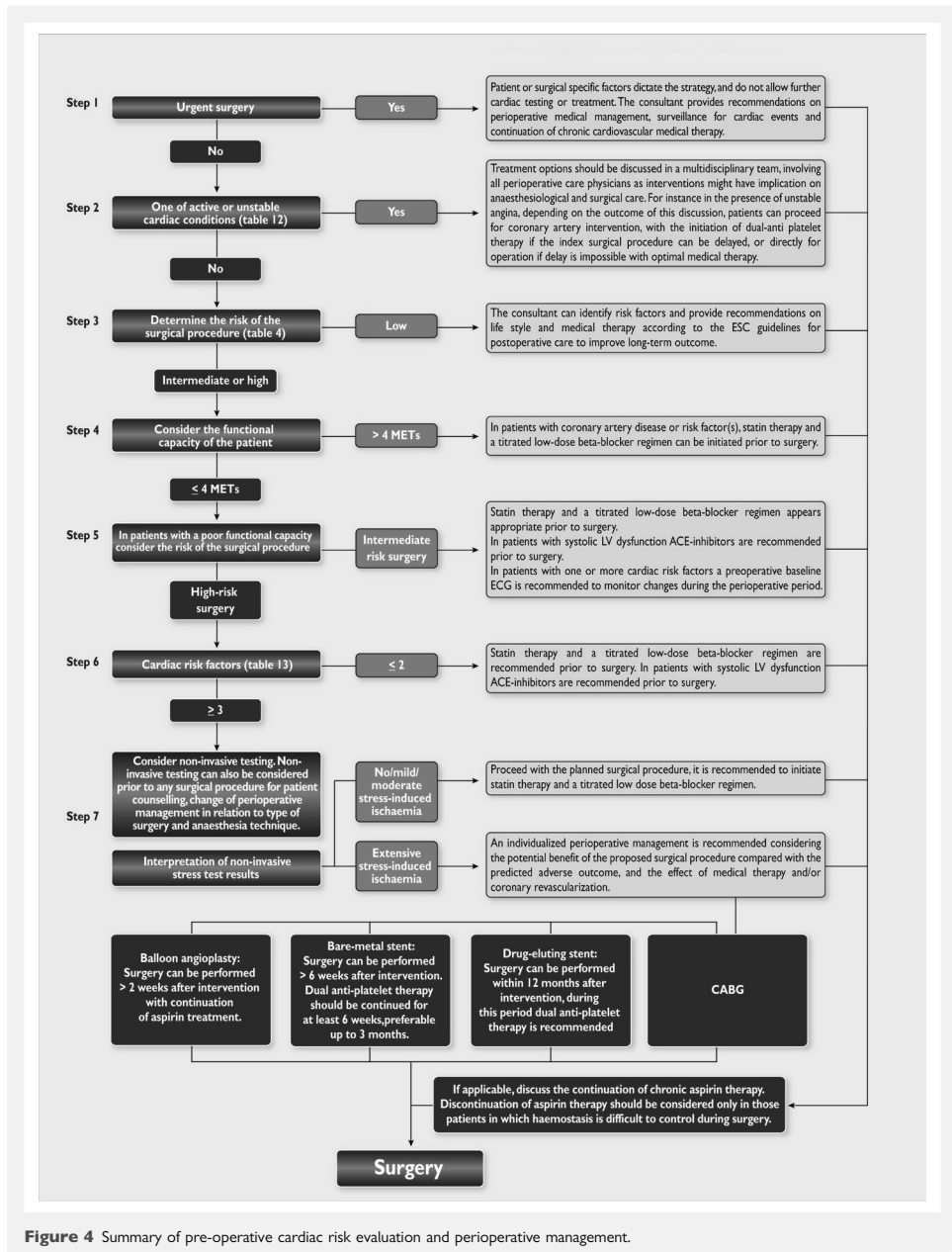


Figure 4 Summary of pre-operative cardiac risk evaluation and perioperative management.

**Table 11 Summary of pre-operative cardiac risk evaluation and perioperative management**

Step	Urgency	Cardiac condition	Type of surgery <sup>a</sup>	Functional capacity	Number of clinical risk factors <sup>b</sup>	LV echo	ECG	Stress Testing <sup>e</sup>	β-Blockers <sup>d</sup>	ACE-inhibitors <sup>d/e</sup>	Aspirin <sup>d</sup>	Statins <sup>d</sup>	Coronary Revascularisation <sup>f</sup>
1	Urgent surgery					III C	Ia C	III C	I C	I C	I C	I C	III C
2	Elective surgery	Unstable				I C	I C	III C					I C
3	Elective surgery	Stable	Low risk (< 1%)		None	III B	III B	III C	III B	Ia C	Ib C	Ia B	III C
					≥ 1	III B	Ia B	III C	Ib B (titration) III A (no titration)	Ia C	Ib C	Ia B	III C
4				Excellent or good		III B	Ia B	III C	Ib B (titration) III A (no titration)	Ia C	Ib C	Ia B	III C
5	Elective surgery		Intermediate risk (1 - 5%)	Moderate or poor	None	III B	Ib B	Ib C	Ia B (titration) III A (no titration)	I C	Ib C	Ia B	III B
					≥ 1	III B	I B	Ib C	Ia B (titration) III A (no titration)	I C	Ib C	Ia B	III B
6	Elective surgery		High risk (> 5%)	Moderate or poor	≤ 2	Ia C	I B	Ib B	I B (titration) III A (no titration)	I C	Ib C	I B	Ib B
					≥ 3	Ia C	I B	I C	I B (titration) III A (no titration)	I C	Ib C	I B	Ib B

<sup>a</sup>Type of surgery (Table 4): risk of MI and cardiac death within 30 days after surgery.  
<sup>b</sup>Risk factors (Table 13): angina pectoris, MI, heart failure, stroke/transient ischaemic attack, renal dysfunction (creatinine >170 μmol/L or 2 mg/dL or a creatine clearance of <60 mL/min), diabetes mellitus.  
<sup>c</sup>Non-invasive testing not only for revascularization but also for patient counselling, change of perioperative management in relation to type of surgery, and anaesthesia technique.  
<sup>d</sup>Initiation of medical therapy, but in case of emergency surgery continuation of current medical therapy. Aspirin should be continued after stent replacement.  
<sup>e</sup>In the presence of LV dysfunction (ejection fraction >40%).  
<sup>f</sup>Class I recommendations for revascularization are consistent with the 2004 ACC/AHA guidelines: 1 = stable angina and significant left main disease; 2 = stable angina and three-vessel disease, especially when LV ejection fraction is <50%; 3 = stable angina and two-vessel disease with significant proximal left anterior descending coronary artery stenosis and either LV ejection fraction <50% or demonstrable ischaemia on non-invasive testing; 4 = high-risk unstable angina or non-STEMI; 5 = acute STEMI.

strategy, and do not allow further cardiac testing or treatment. In these cases, the consultant provides recommendations on perioperative medical management, surveillance for cardiac events, and continuation of chronic cardiovascular medical therapy.

Step 2. If the patients is unstable, as presented in Table 12, this condition should be clarified and treated appropriately prior to surgery. Examples are unstable coronary syndromes, decompensated heart failure, severe arrhythmias, or symptomatic valvular disease. This usually leads to cancellation or delay of the surgical procedure. For instance, patients with unstable angina pectoris should be referred for coronary angiography to assess the therapeutic options. Treatment options should be discussed in a multidisciplinary team, involving all perioperative care physicians, because interventions might have implications

**Table 12 Unstable cardiac conditions**

Unstable angina pectoris Acute heart failure Significant cardiac arrhythmias Symptomatic valvular heart disease Recent MI <sup>a</sup> and residual myocardial ischemia
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<sup>a</sup>An MI within 30 days, according to the universal definition of MI.<sup>24</sup>

for anaesthesiological and surgical care. For example, the initiation of dual antiplatelet therapy after coronary artery stent placement might complicate loco-regional anaesthesia or

specific surgical procedures. Depending on the outcome of this discussion, patients can proceed for coronary artery intervention, namely CABG, balloon angioplasty, or stent placement with the initiation of dual antiplatelet therapy if the index surgical procedure can be delayed, or directly for operation if delay is incompatible with optimal medical therapy.

Step 3. Determine the risk of the surgical procedure (Table 4). If the estimated 30-day cardiac risk of the procedure in cardiac-stable patients is low, <1%, it is unlikely that test results will change management and it would be appropriate to proceed with the planned surgical procedure. The consultant can identify risk factors and provide recommendations on lifestyle and medical therapy according to the ESC Guidelines for post-operative care to improve long-term outcome.

Step 4. Consider the functional capacity of the patient. If an asymptomatic or cardiac-stable patient has moderate or good functional capacity, >4 METs, perioperative management is unlikely to be changed on the basis of test results irrespective of the planned surgical procedure. Even in the presence of clinical risk factors, it is appropriate to refer the patient for surgery. In patients with IHD or risk factor(s), statin therapy and a titrated low-dose  $\beta$ -blocker regimen can be initiated prior to surgery, as outlined in Table 11.

Step 5. It is recommended that chronic aspirin therapy be continued. Discontinuation of aspirin therapy should be considered only in those patients in which haemostasis is difficult to control during surgery.

Step 6. In patients with a moderate or poor functional capacity, consider the risk of the surgical procedure, as outlined in Table 4. Patients scheduled for intermediate-risk surgery can proceed for surgery; statin therapy and a titrated low-dose  $\beta$ -blocker regimen appears appropriate prior to surgery. In patients with systolic LV dysfunction, evidenced by LV ejection fraction <40%, ACE inhibitors (or ARBs in patients intolerant of ACE inhibitors) are recommended before surgery. In patients with one or more clinical risk factors, a pre-operative baseline ECG is recommended to monitor changes during the perioperative period. In patients scheduled for high-risk surgery, as described in Table 4, clinical risk factors (Table 13) are noted. In patients with up to two clinical risk factors, statin therapy and a titrated low-dose  $\beta$ -blocker regimen are recommended prior to surgery. In patients with systolic LV dysfunction, evidenced by LV ejection fraction <40%, ACE inhibitors (or ARBs in patients intolerant of ACE inhibitors) are recommended before surgery.

**Table 13 Clinical risk factors**

Angina pectoris
Prior MI <sup>a</sup>
Heart failure
Stroke/transient ischaemic attack
Renal dysfunction (serum creatinine >170 $\mu$ mol/L or 2 mg/dL or a creatinine clearance of <60 mL/min)
Diabetes mellitus requiring insulin therapy

<sup>a</sup>According to the universal definition of MI.<sup>34</sup>

Consider non-invasive testing in patients with  $\geq 3$  clinical risk factors (Table 13). Non-invasive testing can also be considered prior to any surgical procedure for patient counselling, or change of perioperative management in relation to type of surgery and anaesthesia technique.

Step 7. Interpretation of non-invasive stress test results. Patients without stress-induced ischaemia, or mild to moderate ischaemia suggestive of one- or two-vessel disease, can proceed with the planned surgical procedure. It is recommended that statin therapy and a titrated low-dose  $\beta$ -blocker regimen be initiated. In patients with extensive stress-induced ischaemia, as assessed by non-invasive testing, individualized perioperative management is recommended, taking into consideration the potential benefit of the proposed surgical procedure compared with the predicted adverse outcome. Also, the effect of medical therapy and/or coronary revascularization must be assessed, not only for immediate post-operative outcome, but also for long-term follow-up. In patients referred for percutaneous coronary artery intervention, the initiation and duration of antiplatelet therapy will interfere with the planned surgical procedure. In patients referred for angioplasty, non-cardiac surgery can be performed within 2 weeks after intervention with continuation of aspirin treatment. In patients with bare metal stent placement, non-cardiac surgery can be performed after 6 weeks to 3 months following intervention. Dual antiplatelet therapy should be continued for at least 6 weeks, preferably for up to 3 months. After this period, at least aspirin therapy should be continued. In patients with recent DES placement, non-cardiac surgery can be performed after 12 months following intervention, before which time dual antiplatelet therapy is recommended. After this period, at least aspirin therapy should be continued.



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CME questions for this article are available at: European Heart Journal [http://cme.oxfordjournals.org/cgi/hierarchy/oupcme\\_node:ehj](http://cme.oxfordjournals.org/cgi/hierarchy/oupcme_node:ehj) and European Society of Cardiology <http://www.escardio.org/guidelines>.

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# CHAPTER

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## **Perioperative guidelines on beta-blocker use on both sides of the Atlantic: are there any differences?**

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*Submitted*





## INTRODUCTION

Patients undergoing noncardiac surgery are at risk of cardiovascular morbidity and mortality. Although the perioperative event rate has declined over the past decades as a result of achievements in anaesthesiological and surgical techniques, perioperative cardiovascular complications remain a significant problem. Careful management of patients undergoing surgery is therefore mandatory in the perioperative setting. In general, the risk of perioperative complications depends on the condition of the patient prior to surgery, the prevalence of co-morbidities, and the severity, type and duration of the surgical procedure. Especially patients with documented or hidden coronary artery disease (CAD) undergoing procedures that are associated with prolonged hemodynamic and cardiac stress are prone to cardiac complications.

Perioperative myocardial infarction (PMI) is one of the most important predictors of short- and long term morbidity and mortality associated with noncardiac surgery. The highest incidence of PMI is within the first 3 days after surgery ( $\pm 5\%$ ).<sup>1,3</sup> Unfortunately the exact underlying mechanism of a PMI is still not clear, but seems to be the same as in other settings. Coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion, is considered to be an important cause of acute perioperative coronary syndromes. Surgery itself is a significant stress factor leading to an increased risk of plaque rupture. Two retrospective studies investigated the coronary pathology of fatal PMI and found that half of perioperative MIs are related to plaque rupture.<sup>4,5</sup> It is thought that the other half of PMIs are related to a sustained myocardial supply/demand imbalance due to tachycardia and increased myocardial contractility in patients with significant CAD.<sup>1</sup>

The classic idea of the benefit of beta-blocking agents in the perioperative period is its effect on restoring the oxygen supply/demand mismatch. Additional cardioprotective effects are redistribution of coronary blood flow to the subendocardium, plaque stabilization, and an increase in the threshold for ventricular fibrillation.<sup>6</sup> Beta-adrenergic receptor antagonists (beta-blockers) are divided into beta<sub>1</sub>-selective and non-selective (beta<sub>1</sub> and beta<sub>2</sub>) adrenoceptors-blockers. Atenolol, metoprolol and bisoprolol, all beta<sub>1</sub>-selective blockers, are commonly used for perioperative care.

## GUIDELINES ON PERIOPERATIVE CARE

The first-ever European Society of Cardiology (ESC) guidelines on the management of cardiac risk in noncardiac surgery were recently published.<sup>7</sup> In line, the American College of Cardiology (ACC) and the American Heart Association (AHA) have released their focused update on the

perioperative use of beta blockers for noncardiac surgery.<sup>8</sup> The specific issue of whether to use beta-blockers perioperatively in patients undergoing non-cardiac surgery has been controversial in the past few years. Previous guidelines outlined a paucity of evidence-based indications regarding heart rate control using beta-blockers. Recent trials have added important information. Therefore, this review compares the recent update of ACC/AHA guidelines and ESC guidelines regarding beta-blocker use. In general, both guidelines provide comparable evidence with only small difference in classes of recommendations (Table 1).

**TABLE 1 - Recommendations for perioperative beta-blocker therapy**

Indication	ACC/AHA 2006	ACC/ AHA 2009	ESC 2009
Continuation in patients previously treated with beta-blockers			
because of Class I guideline indications	IC	IC	IC
because of CHF with systolic dysfunction			IIaC
Patients who have absolute contraindications to beta-blockade	IIIC	IIIC	IIIC
Perioperative high-dose beta-blockers without titration		IIIB	IIIA
Patients undergoing vascular surgery			
With CAD or myocardial ischaemia on preoperative testing	IIaB	IIaB	IB
With >1 clinical risk factors	IIaB	IIaC	IB
With single clinical risk factors without CAD	IIbC	IIbC	IB
With no clinical risk factors who are not currently taking beta-blockers	IIbB	IIbB	IB
Patients undergoing intermediate risk surgery			
With >1 clinical risk factors	IIaC	IIaC	IIaB
With single clinical risk factors without CAD	IIbC	IIbC	IIaB
Patients undergoing low risk surgery			
With ≥ 1 risk factor			IIbB
With no risk factors			IIIB

CHF, chronic heart failure; CAD, coronary artery disease

### Classifications of recommendations

The level of evidence and strength of recommendation are weighted and graded according to predefined scales. The ESC and ACC/AHA guidelines use the same levels of recommendations, although the ACC/AHA guidelines have a more extensive description of the different levels. A summary of the recommendations is given in Table 2.

TABLE 2 - Summary of classification of recommendations and level of evidence.				
	Class I	Class IIa	Class IIb	Class III
	Benefit >>> Risk	Benefit >> Risk	Benefit ≥ Risk	Risk ≥ Benefit
<b>Level A</b>	Multiple RCTs or meta-analyses.	Multiple RCTs or meta-analyses.	Multiple RCTs or meta-analyses.	Multiple RCTs or meta-analyses.
	Benefit >>> Risk	Benefit >> Risk	Benefit ≥ Risk	Risk ≥ Benefit
<b>Level B</b>	Single RCT or large non-randomized studies.	Single RCT or large non-randomized studies.	Single RCT or large non-randomized studies.	Single RCT or large non-randomized studies.
	Benefit >>> Risk	Benefit >> Risk	Benefit ≥ Risk	Risk ≥ Benefit
<b>Level C</b>	Expert opinion and/or small studies, retrospective studies, registries.	Expert opinion and/or small studies, retrospective studies, registries.	Expert opinion and/or small studies, retrospective studies, registries.	Expert opinion and/or small studies, retrospective studies, registries.

RCT, randomized clinical trial

### Risk stratification

Risk stratification prior to surgery is an essential guide for beta-blocker therapy in both guidelines. Both the surgical risk as the assessment of clinical risk factors for perioperative cardiovascular complications are important in this respect. Table 3 and 4 give a comparison of the definitions of risks used in the two guidelines and show no major differences.

TABLE 2 - Clinical risk factors	
ACC	ESC
History of ischemic heart disease	History of ischemic heart disease
History of compensated or prior heart failure	History of compensated or prior heart failure
Diabetes mellitus	Diabetes mellitus requiring insulin therapy
Renal insufficiency	Renal insufficiency
History of cerebrovascular disease	History of cerebrovascular disease

TABLE 3 - Surgical risk

	ACC	ESC
High (>5%)	Aortic and other major vascular surgery Peripheral vascular surgery	Aortic and other major vascular surgery Peripheral vascular surgery Endovascular aneurysm repair
Intermediate (1-5%)	Intraperitoneal and intrathoracic surgery Carotid endarterectomy Head and neck surgery Orthopedic surgery Prostate surgery	Abdominal and pulmonary surgery Carotid endarterectomy Head and neck surgery Orthopedic- major (hip and spine surgery) Urologic - major Neurological Renal / liver transplant
Low (<1%)	Cataract surgery Breast surgery Ambulatory surgery Endoscopic procedures Superficial procedure	Eye surgery Breast surgery Gynaecologic Reconstructive Orthopedic – minor (knee surgery) Urologic - minor Dental Endocrine

## RECOMMENDATIONS ON BETA-BLOCKER USE

### Continuation of beta-blockers

Preoperative beta-blocker withdrawal is associated with increased mortality as reported in observational studies.<sup>9,10</sup> Therefore, both guidelines give a IC recommendation to continue beta-blocker therapy in the perioperative period (Table 1). The ESC guidelines add that beta-blockers should not be withdrawn in patients treated for stable heart failure due to LV systolic dysfunction (IIaC). In decompensated heart failure, beta-blocker therapy may need to be reduced, or temporarily omitted.<sup>11</sup>

### Contraindications

The ACC/AHA guidelines include a class III recommendation on beta-blockers in patients with absolute contraindications. Although no separate recommendation with class and level of evidence, the ESC guidelines clearly state that contra-indications to beta-blockers (asthma, severe conduction disorders, symptomatic bradycardia, and symptomatic hypotension) should be respected. Furthermore, these guidelines also highlight that beta-blockers are not contra-indicated in patients with intermittent claudication, nor are cardioselective beta-blockers in patients with chronic obstructive pulmonary disease (COPD) undergoing vascular surgery.<sup>12,13</sup>

### Initiation of beta-blocker therapy and dose titration

Both guidelines advocate careful dose titration to achieve adequate heart rate control with maximizing the benefits of beta-blockade and minimizing the associated risks for adverse outcome. The regimen of the Dutch Echographic Cardiac Risk Evaluating Applying Stress Echo (DECREASE) studies, titrated rate control to maintain a heart rate of 60 to 70 bpm with systolic blood pressure >100 mmHg, has demonstrated efficiency.<sup>14,15</sup> On the other hand, the POISE (PeriOperative Ischemic Evaluation) trial showed that routine administration of high-dose beta-blockers without titration is not useful for patients undergoing noncardiac surgery and may be harmful to beta-blocker naïve patients undergoing surgery.<sup>16</sup> The positive effects on cardiac death, MI, or cardiac arrest were accompanied by a 33% increase in total mortality (3.1% vs. 2.3%,  $P=0.03$ ) and a 2-fold increase risk in stroke (1.0 vs. 0.5%,  $P=0.0005$ ). Stroke was associated with perioperative bradycardia, hypotension, and bleeding in patients randomized to metoprolol succinate with a diseased cerebrovascular tree. Post-hoc analysis also showed that hypotension had the largest population-attributable risk for death and stroke. This highlights the importance of preventing overtreatment with fixed high initial doses without titration, for which both guidelines give a class III recommendation.

### High-risk

The different surgical risk categories explain a large part of the heterogeneity observed across the trials assessing the effectiveness of beta-blockers in non-cardiac surgery.<sup>17</sup> In line, Lindenauer et al. performed a large retrospective cohort study drawn from a quality of care database including 663,635 patients undergoing non-cardiac surgery (30% high risk surgery).<sup>18</sup> They observed a relationship between cardiac risk and the effect of perioperative beta-blocker use. Beta-blocker use was associated with a significant decrease in mortality when the Lee index was  $\geq 3$ . No significant difference was observed for a Lee index of 1 or 2. Mortality was increased in the lowest risk group (Lee index of 0).

Vascular surgery is in both guidelines defined as high-risk surgery. Importantly, it should be acknowledged that the long-term prognosis of vascular surgery patients is estimated to be significantly worse than for patients with CAD.<sup>19</sup> The ESC guidelines give vascular surgery patients a class IB recommendation for beta-blockers, while the ACC guidelines give mainly IIa recommendations. Three randomized trials including >40% vascular surgery patients demonstrated, however, a beneficial effect of beta-blockers on cardiovascular complications.<sup>15,16,20</sup> The Dutch Echographic Cardiac Risk Evaluating Applying Stress Echo (DECREASE) trial selected 112 out of 1,453 vascular surgery patients who combined at least 1 clinical risk factor and positive DSE, excluding patients with extensive wall motion abnormalities.<sup>15</sup> There was an 89% reduction in cardiac mortality and/or MI in the bisoprolol group (3.4% vs. 34%,  $P<0.001$ ), which was sustained for up to 3 years. The POISE (PeriOperative Ischemic Evaluation) trial randomized more than 8000

patients to controlled-release oral metoprolol succinate or placebo.<sup>16</sup> Inclusion criteria were age  $\geq 45$  years and known cardiovascular disease, at least 3 out of 7 clinical risk factors, or undergoing major vascular surgery (41%). The POISE trial initiated randomized treatment of controlled-release metoprolol just before surgery, and the maximum recommended therapeutical dose (400 mg) could already be achieved within the first day of surgery. The primary endpoint of cardiac death, MI, or cardiac arrest was reduced in the metoprolol group, compared to placebo (5.8% vs. 6.9%, hazard ratio 0.83, 95%CI 0.70-0.99,  $P=0.04$ ). However, the 30% decrease of non-fatal MI (3.6 vs. 5.1%,  $P=0.0008$ ) was accompanied by a 33% increase in total mortality (3.1% vs. 2.3%,  $P=0.03$ ) and a twofold increase risk in stroke (1.0 vs. 0.5%,  $P=0.0005$ ). In contrast, some trials did not show an effect. The PeriOperative Beta-Blockade (POBBLE) trial included 103 low-risk patients undergoing elective infra-renal vascular surgery, randomized to metoprolol tartrate or placebo.<sup>21</sup> The incidence of cardiovascular events at 30 days did not differ between the metoprolol and placebo groups (13% and 15%, respectively,  $P=0.78$ ). Patients were at low cardiac risk and those with a history of MI within the previous two years were excluded. In the Metoprolol after Vascular Surgery (MaVS) trial, 497 patients undergoing abdominal or infra-inguinal vascular surgery were randomized to metoprolol succinate or placebo.<sup>22</sup> The combined cardiovascular endpoint at 30 days did not differ between the metoprolol and placebo groups (10% and 12%, respectively,  $P=0.57$ ). Important to note is that in the MAVS trial most patients were at low risk for complications as The Lee index was  $\leq 2$  in 90% of patients and  $\leq 1$  in 60%.

### Intermediate risk

Both the POISE as well as DECREASE IV trial included many intermediate risk patients.<sup>16,23</sup> In DECREASE IV, Intermediate-risk patients were defined by an estimated risk of perioperative cardiac death and myocardial infarction of 1-6%, using clinical data and type of surgery. Patients randomized to bisoprolol ( $N=533$ ) had a lower incidence of the primary efficacy endpoint than those randomized to bisoprolol-control therapy (2.1% vs. 6.0% events, HR 0.34, 95% CI 0.17-0.67). The Diabetes Postoperative Mortality and Morbidity (DIPOM) trial selected 921 patients with diabetes, age  $> 39$  years, and a duration of surgery of more than one hour (39% low-risk surgery).<sup>24</sup> Patients were randomized to receive metoprolol succinate or placebo. The combined cardiovascular endpoint at 30 days did not differ between metoprolol and placebo groups (6% and 5%, respectively,  $P=0.66$ ). However, only 54% of the patients had a history of IHD, or an additional cardiac risk factor, and underwent high- or intermediate-risk surgery. In contrast to the guidelines, in this study major non-cardiac surgery was defined as surgery with an expected duration over one hour. The ESC guidelines have a IIaB recommendation while the ACC/ AHA guidelines have same the same class only level C (Table 1).

TABLE 3 - Summary table randomized clinical trials

Study	N	Vascular surgery	Beta-blocker Type	Onset (before surgery)	Duration (days after surgery)	Dose titration	Patient selection according to cardiac risk	Main findings
Mangano et al <sup>20</sup>	200	40%	atenolol	30 min	7	no	IHD or ≥2 risk factors	Atenolol treatment can reduce mortality and the incidence of cardiovascular complications as long as 2 years after surgery
DECREASE <sup>5</sup>	112	100%	bisoprolol	7 days	30	yes	Positive DSE	Bisoprolol reduces the perioperative incidence of cardiovascular mortality and nonfatal MI
POBBLE <sup>21</sup>	103	100%	metoprolol tartrate	<24 h	7	no	No	Metoprolol did not seem to reduce 30-day cardiovascular events in patients receiving metoprolol treatment. Time from surgery to discharge was decreased
MaVS <sup>22</sup>	496	100%	metoprolol succinate	2 h	5	no	No	Metoprolol was not effective in reducing the 30-day and 6-month postoperative cardiac events.
DIPOM <sup>24</sup>	921	7%	metoprolol succinate	12 h	8	no	Diabetes	Metoprolol did not significantly affect mortality and cardiac morbidity.
BBSA <sup>35</sup>	219	5%	bisoprolol	> 3 h	10	yes	IHD or ≥2 risk factors	Bisoprolol did not affect cardiovascular outcome.
POISE <sup>16</sup>	8351	41%	metoprolol succinate	2-4 h	30	no	IHD or atherosclerosis or major vascular surgery or ≥3 risk factors	Metoprolol prevents nonfatal MI but increases the risk of nonfatal stroke
DECREASE IV <sup>23</sup>	1066	0	bisoprolol	34 days	30	yes	Estimated risk of perioperative cardiac death and MI of +1.6%, using clinical data and type of surgery	Bisoprolol was associated with a significant reduction of 30-day cardiac death and nonfatal MI.

IHD, ischemic heart disease; MI, myocardial infarction

### Low risk

Large cohort studies suggest that perioperative beta-blockade does not decrease the risk of cardiac complications in low risk patients. In the aforementioned large retrospective cohort study of Lindenauer et al showed no significant difference was observed for a Lee index of 1 or 2. Mortality was increased in the lowest risk group (Lee index of 0). Because of the few evidence, ESC guidelines have a IIb recommendation for patients with risk factor undergoing low risk surgery. The ACC/AHA guidelines lack specific guidelines for low risk surgery in their recommendation table.

In conclusion, both guidelines have comparable recommendations for perioperative beta-blockers use. Both recommend continuation of beta-blockers in the perioperative period. Beta-blockers are recommended for high-risk patients similar to the non-surgical setting. In patients evaluated prior to surgery the main theme is: can secondary prevention for cardiovascular disease be initiated safely prior to surgery? The dose of beta-blockers should be titrated, which requires that treatment be initiated optimally between 30 days and at least one week before surgery. It is recommended that treatment start with a daily dose of 2.5 mg of bisoprolol or 50 mg of metoprolol succinate which should then be adjusted before surgery to achieve a resting heart rate of between 60 and 70 beats per minute with systolic blood pressure >100 mmHg. The goal for heart rate is the same during the whole perioperative period, using intravenous administration when oral administration is not possible. If insufficient time is available, only the initial first step of a dose titration scheme should be started, in order to prevent overtreatment with beta-blockers during surgery. If dose titration schemes can be applied in the preoperative period, beta-blockers are safe and improve outcome. For patients without risk factors or proven cardiovascular disease, similar to the non-surgical population, beta-blockers are not recommended. Future randomized trials are needed to further evaluate the value of beta-blocker therapy, with focus on starting time and dose titration, and strengthen the evidence.



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# CHAPTER

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## Should the ACC/AHA guidelines be changed in patients undergoing vascular surgery?

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**This editorial refers to ‘Vascular surgery patients: perioperative and long-term risk according to the ACC/AHA guidelines, the additive role of postoperative troponin evaluation’ by Bursi et al.<sup>4</sup>**

In Western countries annually about 4-10% of the population is scheduled for noncardiac surgery. Patients undergoing vascular surgery are known to be at increased risk of perioperative mortality and other cardiac complications due to underlying (a)symptomatic coronary artery disease (CAD). Although the overall perioperative event rate has declined over the past 30 years, 30 day cardiovascular mortality still remains as high as 3 to 5%.<sup>1</sup> Myocardial infarction (MI) accounts for 10-40% of postoperative fatalities and can therefore be considered as the major determinant of perioperative mortality associated with noncardiac surgery.<sup>2</sup>

The pathophysiology of a perioperative MI (PMI) is not entirely clear. However, similar to MI's occurring in the nonoperative setting, coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion is suggested as an important causative mechanism.<sup>3</sup> Surgery is an important stress factor leading to an increase in the incidence of plaque rupture. In patients with significant CAD, PMI may also be caused by a sustained myocardial supply/demand imbalance due to prolonged hemodynamic stress inducing sustained myocardial ischemia. Both factors, acute thrombus formation and sustained myocardial ischemia, probably contribute equally to the pathophysiology of PMI.

In order to improve postoperative outcome, the ACC/AHA developed guidelines for preoperative cardiac risk evaluation.<sup>3</sup> They provide an algorithm for a stepwise approach. Patients are divided into three groups; those who underwent a previous coronary revascularization, previous cardiac testing and all other remaining patients. If patients underwent a coronary revascularization in the past 5 years and if the clinical status has remained stable without recurrent symptoms or signs of myocardial ischemia, further cardiac testing is not indicated and the patient can directly send for surgery. Similarly, patients who underwent noninvasive testing or coronary angiography in the past two years, in the absence of unfavourable results and without new symptoms, can also send for surgery without further evaluation. All other patients are analyzed according to the presence of major, intermediate and minor clinical risk factors (Table 1) and by addition of procedural risk the individual risk can be assessed. In patients with major risk factors, surgery should be postponed until these symptoms are adequately treated. Patients with no or only minor risk predictors represent a low-risk population and further evaluation is only necessary for those with a poor functional capacity undergoing vascular surgery. However, patients with intermediate risk predictors, additional noninvasive evaluation is recommended to assess the presence of myocardial ischemia and to determine further perioperative management.

The present study of Bursi et al.<sup>4</sup> reported that despite preoperative risk stratification according to the ACC/AHA guidelines, patients undergoing elective major vascular surgery are

still at high risk of MI and death. Event rates were as high as 45%, 23% and 9% in patients with previous revascularization without recurrent symptoms or signs of CAD, with intermediate and those with minor or no clinical predictors, respectively. These findings question the current recommendations, and moreover indicate that the ACC/AHA guidelines are of limited use to preoperative risk stratification in vascular surgery patients.

**TABLE 1 - Clinical predictors of increased perioperative cardiovascular risk<sup>3</sup>**

**MAJOR**

Unstable coronary syndromes

Acute or recent myocardial infarction with evidence of important ischemic risk by clinical symptoms or noninvasive study

Unstable or severe angina (Canadian class III or IV)

Decompensated heart failure

Significant arrhythmias

High-grade atrioventricular block

Symptomatic ventricular arrhythmias in the presence of underlying heart disease

Supraventricular arrhythmias with uncontrolled ventricular rate

Severe valvular disease

**INTERMEDIATE**

Mild angina pectoris (Canadian class I or II)

Previous myocardial infarction by history or pathological Q waves

Compensated or prior heart failure

Diabetes mellitus (particularly insulin-dependent)

Renal insufficiency

**MINOR**

Advanced age

Abnormal ECG (left ventricular hypertrophy, left bundle-branch block, ST-T abnormalities)

Rhythm other than sinus (e.g., atrial fibrillation)

Low functional capacity (e.g., inability to climb one flight of stairs with a bag of groceries)

History of stroke

Uncontrolled systemic hypertension

The high event rates in a small sub-population of patients who underwent previous revascularization without signs of CAD, might be explained by an incomplete or failed revascularization or silent ischemia. These pitfalls should be taken into account when stratifying these patients. In addition, it should be noted that atherosclerosis is an ongoing disease and that plaque progression and vulnerability is unpredictable and is responsible for 50% of all PMIs. This also has important implications for the current guideline stating that the subgroup of patients who have undergone (non)invasive coronary evaluation in the past two years, in the absence of unfavourable stress test results or changes of symptoms, can undergo surgery without further evaluation. Because of the unpredictable character of CAD, this two year time lap may be much too long.



The high event rates in patients with minor or intermediate risk factors can partly be explained by change of more sensitive diagnostic tools for PMI over time. Nowadays, diagnosis of PMI requires a rise and fall of troponin with or without clinical or ECG findings, while in the past ECG abnormalities, CK/CK-MB changes and clinical symptoms indicated a PMI. This resulted in a substantial increase of patients being diagnosed as having MI as also seen in the current study of Bursi et al.<sup>4</sup> Prior studies have questioned the value of a positive troponin in the perioperative setting and even suggested a false positive value especially in patients with renal insufficiency or massive CK enzyme release. However, a recent study confirmed the prognostic value of troponin elevations in postoperative patients.<sup>5</sup> Same results were demonstrated in the current paper of Bursi et al.<sup>4</sup> which showed that cTnI elevations were independent predictors of subsequent death and/or MI.

Available data suggests that beta-blockers may be underused and yet unpublished results from a survey in The Netherlands also show only 60% use of beta-blockers during vascular surgery.<sup>6</sup> In the present study only 62% of patient with intermediate clinical risk received perioperative a beta-blocker which may adversely influence outcome. Statins and beta-blockers use may reduce those devastating complications associated with noncardiac surgery.<sup>7,8</sup> Statins may prevent plaque instability and thrombosis, due to their pleiotropic effects, as improvement of endothelial function, reduction of inflammation, and stabilizing atherosclerotic plaques. Beta-blockers can restore the supply/demand mismatch, by a reduction of myocardial oxygen use by decreasing sympathetic tone and myocardial contractility. When beta-blockers are used in the perioperative period, timing and dose adjustment for heart rate control is important as shown by the study of Raby et al.<sup>8</sup> Furthermore, treatment should not be interrupted during the perioperative period and prolonging beta-blocker therapy beyond the surgical procedure seems to be essential since the risk of myocardial infarction remains high in the first postoperative week. Besides beta-blockers and statins, aspirin might be considered to provide optimal medical therapy.

### **Should the ACC/AHA guidelines be changed in patients undergoing vascular surgery?**

Vascular surgery patients probably represent the highest risk population because of the underlying CAD. Basically, the stepwise approach of the guidelines is valid for preoperative cardiac screening. However, considering above findings, we would like to give the following recommendations:

1. The warranty of previous revascularization might be questioned and therefore risk stratification should be considered independently of previous coronary revascularization.
2. Following the recent publication of Lindenauer et al.<sup>10</sup>, beta-blocker therapy appeared to be harmful in low-risk patients, neutral in patients at intermediate risk, and beneficial in high-risk patients.<sup>10</sup> This further strengthens the beneficial effects of beta-blockers in high-risk patients and therefore we recommend initiation of beta-blocker therapy in vascular surgery patients. Adjustment of beta-blocker dose is recommended to assure a heart rate between 60-70 bpm.

3. In addition, until the results of DECREASE-II are available, which studies the effect of noninvasive screening in patients undergoing vascular surgery without any or few cardiac risk factors, we believe it is appropriate to screen noninvasively all vascular surgery patients, including carotid surgery, for myocardial ischemia. Recently, the CARP trial demonstrated that coronary revascularization before elective vascular surgery did not significantly alter the incidence of PMI among patients with stable CAD.<sup>11</sup> Therefore screening of high-risk patients for ischemia is not essential for revascularization but primary to optimize perioperative patient management, which includes optimal medical therapy with beta-blockers and statins, monitoring and aggressive treatment of myocardial ischemia, and if possible endovascular treatment. In patients with exclusions criteria of the CARP trial: >50% stenosis of the left main coronary artery, left ventricular ejection fraction <20% and severe valvular aortic stenosis the optimal preoperative treatment is yet not defined and treatment should therefore be individualized using a combination of minimal invasive surgery in combination with medical therapy and coronary revascularization, if postponement of the index surgery can be accepted.

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# CHAPTER

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## Indications of prophylactic revascularization in patients undergoing major vascular surgery; the saga continues.

# 8

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### **ACC/AHA Guidelines**

When considering a patient for major vascular surgery, a careful preoperative clinical risk evaluation and subsequent risk-reduction strategies are essential to improve post-operative outcome. The ACC/AHA TaskForce published therefore Practice Guidelines for Perioperative Cardiovascular Evaluation for Non-cardiac Surgery in 1996 and an update in 2002.<sup>1</sup> Furthermore, due to increasing evidence of the beneficial effect of beta-blocker use in the perioperative period, the guidelines section on perioperative beta-blocker therapy is recently updated.<sup>2</sup> The core of the ACC/AHA guidelines is an algorithm, which summarizes the stepwise evaluation of clinical parameters used to assess the need for further cardiac testing. According to the algorithm, after assessing the urgency of the surgery and the cardiac status of patients having previous coronary revascularization within 5 years or previous cardiac evaluation within 2 years, the patients are classified as major, intermediate or minor clinical predictors of increased perioperative cardiovascular risk. The need for cardiac testing is then determined by an assessment of the functional status of the patient and the surgery-specific risk. Patients scheduled for major vascular surgery with only minor clinical predictors and adequate functional capacity represent a low-risk population and further evaluation is unnecessary. However, in patients with intermediate clinical predictors or patients with minor clinical predictors and reduced functional capacity, additional noninvasive evaluation should be considered before undergoing major vascular surgery.

The main purpose of performing preoperative cardiac risk assessment is to identify patients at high risk for perioperative cardiac events. In general, two strategies have been used in an attempt to reduce the incidence of perioperative myocardial infarctions and other cardiac complications: preoperative coronary revascularization and pharmacological treatment. With respect to prophylactic coronary revascularization, ACC/AHA guidelines recommend coronary revascularization only for subgroups of high-risk patients with unstable cardiac symptoms or those for whom coronary artery revascularization offers a long-term benefit.

### **Risk stratification**

Landesberg et al. developed a long term survival score (LTSS) comprised of seven predictors that independently determine long-term survival: age $\geq$ 65, diabetes, cerebrovascular disease, ischaemic heart disease, congestive heart failure, ST-depression on preoperative ECG, and renal insufficiency.<sup>3</sup> They validated their LTSS score with bootstrapping and demonstrated that LTSS score is a good prognostic factor for 3-year and long-term mortality. On the basis of their LTSS, all patients in the study were divided into low, intermediate, and high risk groups (0-1, 2-3,  $\geq$ 4 predictors, respectively). This LTSS has a considerable number of risk factors in common with the well accepted Revised Cardiac Risk Index<sup>3</sup>, which is a commonly used perioperative risk-stratification approach in the selection of noninvasive cardiac testing and medical treatment in

the intermediate-risk patients. Although this Revised Cardiac Risk Index is nowadays a commonly accepted risk stratification tool, the current ACC/AHA guidelines do not incorporate this risk score. The addition of age, as suggested in the LTSS of Landesberg et al., is known to make a more valid prediction of cardiovascular mortality in noncardiac surgery.<sup>5</sup>

### **Prophylactic coronary revascularization**

Current guidelines are based on different retrospective studies that assessed the overall benefit of coronary revascularization for decreasing perioperative cardiac risk of noncardiac surgery.<sup>6,7</sup> Recently, a large, multiple-centre, randomized clinical trial (Coronary Artery Revascularization Prophylaxis (CARP) trial) was conducted by McFalls et al.<sup>8</sup> to evaluate the benefit of coronary revascularization before elective vascular surgery. All patients scheduled for elective vascular surgery were randomized after undergoing coronary angiography to revascularization or no revascularization. Importantly, patients with left main disease and poor LV function were excluded. The incidence of morbid cardiac events during the revascularization phase of the trial was 1.7% and they found no overall difference in death rate after 2.7 years. In contrast, this study of Landesberg et al. demonstrated that the intermediate-risk group (LTSS 2-3) had better long-term survival following preoperative coronary revascularization (hazard ratio 0.48; 95% confidence interval (CI) 0.31 to 0.75). However, no statistically significant effect of preoperative coronary revascularization was observed in the perioperative period, at 6-months or at 1-year follow-up in this group. Preoperative coronary revascularization showed also no beneficial effect at short or long term in both the low-risk patients (LTSS 0-1) and high risk patients (LTSS  $\geq 4$ ). As the authors mention, their study is limited by its retrospective nature and large randomized trials are needed to give exclusive recommendations in this area.

These results are in line with the recently published results of the DECREASE-II study.<sup>9</sup> This randomized, multicenter study was conducted to assess the value of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight heart rate control. Patients assigned to no testing had similar incidence of cardiac death or myocardial infarction at 30 days as those assigned to testing (1.8% vs 2.3%; odds ratio 0.78; CI 0.28 to 2.1). These studies demonstrate that intermediate-risk patients undergoing major vascular surgery are at relatively low perioperative risk and do not benefit from preoperative cardiac testing and revascularization in the short-term follow-up.

It has to be noted that preoperative revascularization can even be harmful for the patient because of progression of coronary artery disease during stress of surgery<sup>10</sup> and postponement of the noncardiac procedure. Importantly, the cumulative risk of prophylactic coronary revascularization and noncardiac surgery has to balance the risk of noncardiac surgery alone. An important implication of the study of Landesberg et al. and other described studies is that



coronary revascularisation may be safely postponed to the postoperative period for selective patients, because no beneficial effect of preoperative coronary revascularization was seen in the immediate postoperative period. A shift from preoperative to postoperative management is therefore recommended in these patients in order to prevent cardiac complications in the long term. An accurate postoperative risk score consisted of weighted risk factors based on regression coefficients and the addition of biomarkers as B-type natriuretic peptide and high-sensitive CRP may be effective for better postoperative risk stratification and subsequent adapted care.<sup>11</sup> We would like to stress that postoperative patients at high risk of cardiac complications should be seen by the physician on a regular basis to optimize treatment with medical therapy and if necessary revascularization.

### **Guidelines in practice**

Successful perioperative evaluation and management of patients undergoing noncardiac surgery requires careful teamwork and communication between surgeon, anaesthesiologist, cardiologist and the patient's primary care physician. With this respect, guidelines play an essential role and should be straightforward, uniform and based on recent scientific evidence. The algorithm proposed in the ACC/AHA guidelines had to rely predominantly on observational data and expert opinion because there were no randomized trials to help define the process. It is important to update guidelines on a regularly basis to reflect the most recent clinical evidence and furthermore, guidelines should be easy to use in clinical care.

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# CHAPTER

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## **Fluvastatin and perioperative events in patients undergoing vascular surgery**



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## ABSTRACT

**Background:** Adverse cardiac events are common after vascular surgery. We hypothesized that perioperative statin therapy would improve postoperative outcome.

**Methods:** In this double-blind, placebo-controlled trial, we randomly assigned patients who had not previously been treated with a statin to receive, in addition to a beta-blocker, either 80 mg of extended-release fluvastatin or placebo once daily before undergoing vascular surgery. Lipid, interleukin-6, and C-reactive protein were measured at the time of randomization and prior to surgery. The primary endpoint was the occurrence of myocardial ischemia, defined as transient ECG abnormalities and troponin T release within 30 days after surgery. The secondary endpoint was the composite of cardiac death and myocardial infarction.

**Results:** Two hundred fifty patients were assigned to fluvastatin and 247 to placebo. Interleukin-6 and C-reactive protein levels remained unchanged in the placebo group (-4% and +3% respectively) and decreased in the fluvastatin group (-33% and -21% respectively,  $P < 0.001$ ). The incidence of myocardial ischemia in the fluvastatin and placebo groups was, respectively, 10.8% vs. 19.0%, hazard ratio 0.55; 95% confidence interval [CI] 0.34 to 0.88. The incidence of cardiac death or myocardial infarction was 4.8% vs. 10.1%, hazard ratio 0.47; 95% CI 0.24 to 0.94. Importantly, fluvastatin use was not associated with an increased risk for myopathy, liver dysfunction or all-cause death.

**Conclusions:** In patients undergoing vascular surgery, fluvastatin therapy is associated with an improved postoperative cardiac outcome and a reduction of inflammation activity.

## INTRODUCTION

Patients with atherosclerotic vascular disease who undergo noncardiac vascular surgery are at high risk for postoperative cardiac events, such as myocardial infarction and death from cardiovascular causes. Cardiac events occur in up to 24% of patients in high-risk cohorts<sup>1</sup> and are related to the high incidence of underlying coronary artery disease. Hertzner et al., performing routine coronary angiography in 1000 patients scheduled for vascular surgery, found that only 8% had a normal coronary-artery tree.<sup>2</sup>

Although the pathophysiology of perioperative myocardial infarction is not entirely understood, it is well accepted that rupture of coronary plaque, leading to thrombus formation and subsequent vessel occlusion, plays an important role. The surgical stress response elicits a surge of catecholamine, with associated hemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation, and consequent hypercoagulability.<sup>3</sup> Inflammatory processes in general and monocyte-derived macrophages in particular play a critical role in the progression and destabilization of coronary plaque.

Large trials involving the nonsurgical population have shown a beneficial role of long-term statin therapy on cardiac outcome.<sup>4</sup> These effects are related to a reduction of low-density lipoprotein (LDL) cholesterol levels and inflammation.<sup>5</sup> Reduction in inflammation might, independently of patients' cholesterol levels, prevent destabilization of coronary plaque induced by the stress of surgery. To our knowledge, no placebo-controlled trial has been published that assesses the effect of statins on the 30-day postoperative outcome.<sup>6</sup>

We conducted the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography III (DECREASE III) trial to address this issue. We hypothesized that perioperative statin therapy would reduce the postoperative incidence of adverse cardiac events in patients undergoing elective vascular surgery.

## METHODS

The DECREASE III trial was conducted at the Erasmus Medical Center, Rotterdam, the Netherlands. The trial was designed by the authors and approved by the medical ethics committee at Erasmus Medical Center. Novartis contributed to the support of the study. Neither Novartis nor any other organization supporting the study had a role in the design, or conduct of the trial, analysis of data, or reporting of the results. Study medication was provided by Novartis. The authors vouch for the accuracy and completeness of the data and the analyses.

### Study Patients

All patients who were older than 40 years of age and were scheduled for noncardiac vascular surgery at Erasmus Medical Center from June 2004 through April 2008 were candidates for inclusion in the trial. Patients had to be scheduled for abdominal aortic aneurysm repair, distal aortoiliac reconstruction, lower-limb arterial reconstruction, or carotid-artery endarterectomy. Patients were required to have at least 51 points on a prespecified risk index that was designed for this trial. All study patients provided written informed consent.

Patients were excluded from the trial if they were currently being treated with a statin, had a contraindication for statin therapy, were undergoing surgery that could interfere with continuous 12-lead electrocardiographic (ECG) recording, were undergoing emergency surgery, were undergoing reoperation within 30 days after a previous surgical procedure, had unstable coronary artery disease, or had extensive stress-induced myocardial ischemia suggestive of left main coronary artery disease or its equivalent.

Patients who were enrolled and were already receiving long-term beta-blocker therapy continued their medication. For patients not already taking a beta-blocker, bisoprolol, at a dose of 2.5 mg once a day, was initiated at the screening visit. Beta-blocker therapy was adjusted as previously described for the DECREASE II study.<sup>7</sup>

### Study Treatment

Patients were randomly assigned to receive either extended-release fluvastatin (Novartis) at a dose of 80 mg, or an identical-appearing placebo, once daily. The study drug was started at the outpatient clinic on the day of randomization and was continued for at least 30 days after surgery. A computer-generated randomization list was obtained by the study statistician and given to the pharmacy department. Independent pharmacists dispensed either active study drugs or placebo according to the list. Study personnel and patients were unaware of the group assignments for the duration of the study.

### Study Outcomes

The primary study outcome was the occurrence of myocardial ischemia, defined as either transient ECG signs of ischemia, release of troponin T, or both. ECG monitoring was performed using continuous ECG recording in the 48 hours after surgery and 12-lead ECG recording on days 3, 7, and 30. Troponin T measurements were performed on days 1, 3, 7, and 30. For patients who were discharged before day 7, troponin T was measured at the day of discharge.

ECG data were initially processed by a technician and analyzed by two experienced cardiologists who were unaware of the patient's clinical data. For the continuous ECG recordings, a ST-segment trend was generated after excluding all abnormal QRS complexes. Episodes of ischemia were



defined as periods of reversible ST-segment changes lasting at least 1 minute on continuous ECG recording and shifting from the baseline value by more than 0.1 mV (1 mm). The ST-segment change was measured 60 msec after the J point occurred, unless the J point fell within the T wave, in which case the ST-segment change was measured 40 msec after the J point occurred. Ischemia on standard 12-lead ECG recording was defined as the presence of a reversible ST-segment change, measured 60 msec after the J point occurred.

The principal secondary end point was the composite of death from cardiovascular causes and nonfatal myocardial infarction. All deaths were classified as being from either cardiovascular or noncardiovascular causes. Death from cardiovascular causes was defined as any death with a cardiovascular diagnosis as the primary or secondary cause, including death after myocardial infarction, cardiac arrhythmia, resuscitation, heart failure, or stroke. Sudden death in a previously stable patient was considered to be a death from cardiovascular causes.<sup>8</sup> A nonfatal myocardial infarction was diagnosed if any two of the following three criteria were present: characteristic ischemic symptoms lasting more than 20 minutes, ECG changes (new left bundle-branch block, new T-wave inversion persisting for at least 24 hours, new ST-segment depression persisting for at least 24 hours, or acute ST-segment elevation followed by appearance of Q waves or loss of R waves), or a positive troponin T level with a characteristic pattern of rising and falling values.<sup>9</sup>

The other secondary study outcome was the effect of fluvastatin therapy on levels of biomarkers including lipids, high-sensitivity C-reactive protein, and interleukin-6. These markers were measured before initiation of the study drug and on the day of admission for the surgical procedure.

Safety outcome measures included serum creatine kinase and alanine aminotransferase levels and development of clinical myopathy and rhabdomyolysis. Blood samples were obtained before randomization, on the day of hospital admission, and on days 1, 3, 7, and 30 after surgery. The study drug was withheld if alanine aminotransferase levels were more than three times the upper limit of the normal range, if creatine kinase levels were more than 10 times the upper limit of the normal range, or if patients had myopathy or rhabdomyolysis.

### **Sample Size**

On the basis of preliminary data from the DECREASE II registry<sup>7</sup>, the anticipated incidence of the primary end point, perioperative myocardial ischemia, was 18.0% in the placebo group. Treatment with fluvastatin was expected to be associated with a 50% reduction in the relative risk of the primary end point.<sup>10,11</sup> We estimated that a sample of 500 patients — 250 in each study group — would yield a statistical power of more than 80% to detect the anticipated 50% risk reduction associated with fluvastatin therapy, with a two-sided alpha level of 0.05.

### Statistical Analysis

The time to the first occurrence of the primary efficacy end point was determined according to the Kaplan–Meier method, and the difference in this time between the two groups was evaluated using the log-rank statistic. The Cox proportional-hazards model was used to determine the effects of each study drug on the primary and principal secondary efficacy end points, which are presented as hazard ratios and 95% confidence intervals. The assumption of proportional hazards was verified through visual assessment of log-minus-log survival plots. These plots demonstrated reasonably parallel lines, indicating that the proportional-hazards assumption was not violated. Analyses of other end points were based on Mann–Whitney U tests, independent-samples t-tests, and chi-square tests. Results of exploratory analyses for the primary outcome were evaluated with the use of tests for interaction of study-drug effect with baseline features. All analyses were performed according to the intention-to-treat principle. All statistical tests were two-sided, and a P-value of less than 0.05 was considered to indicate statistical significance.

## RESULTS

### Study Subjects

Of 1669 patients assessed for trial eligibility, 1172 were excluded: 356 because they did not meet inclusion criteria, 798 because they were already taking a statin, and 18 for other reasons. Of the 497 patients who were enrolled, 250 were assigned to fluvastatin and 247 to placebo. Baseline characteristics of the patients are presented in Table 1. The mean age was 66 years, and 74.8% of the patients were male. The surgical procedure performed was carotid-artery surgery in 69 (13.9%), abdominal aortic surgery in 236 (47.5%), and lower-limb arterial surgery in 192 (38.6%) (Table 1). The median interval between initiation of the study drug and surgery was 37 days (interquartile range, 21 to 54). Between the time of randomization and the surgical procedure, no patient had an adverse cardiac outcome.

Four patients did not receive the intended study drug: three who had been assigned to fluvastatin did not take it and one who had been assigned to placebo mistakenly received preoperative statin treatment because of elevated cholesterol levels. A total of 34 patients (6.8%) discontinued the study drug because of side effects: 16 (6.4%) in the fluvastatin group and 18 (7.3%) in the placebo group. After surgery, the study drug was temporarily discontinued in 115 patients (23.1%) because of an inability to take the study drug orally.

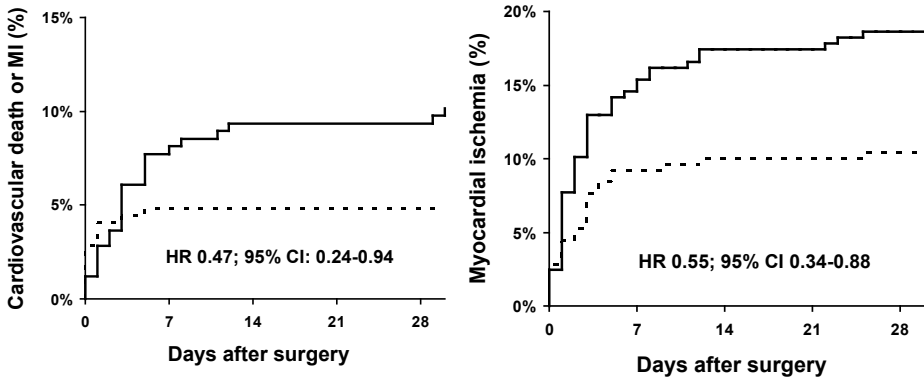
**TABLE 1 - Clinical characteristics, medication use, and type of surgery\***

	Placebo N=247	Fluvastatin N=250
Age – yr	65.8 ± 11.5	66.0 ± 10.5
Male – no. (%)	178 (72)	194 (78)
<b>Risk factors</b>		
Myocardial infarction – no. (%)	66 (27)	73 (29)
Angina pectoris – no. (%)	59 (24)	52 (21)
Congestive heart failure – no. (%)	19 (8)	13 (5)
Diabetes mellitus – no. (%)	42 (17)	55 (22)
Stroke or TIA – no. (%)	66 (27)	75 (30)
Renal insufficiency – no. (%)	31 (13)	23 (9)
Hypertension – no. (%)	143 (58)	142 (57)
COPD – no. (%)	71 (29)	74 (30)
<b>Medication use</b>		
Beta-blocker – no. (%)	247 (100)	250 (100)
Antiplatelet therapy – no. (%)	146 (59)	160 (64)
Anticoagulant therapy – no. (%)	73 (30)	62 (25)
ACE-inhibitor – no. (%)	73 (30)	76 (30)
Calcium antagonist – no. (%)	59 (24)	56 (22)
A-II antagonist – no. (%)	37 (15)	40 (16)
Nitrates – no. (%)	23 (9)	20 (8)
Prednison – no. (%)	63 (26)	54 (22)
Diuretics – no. (%)	78 (32)	64 (25)
<b>Surgery</b>		
Carotid artery surgery – no. (%)	32 (13)	37 (15)
Abdominal aortic surgery – no. (%)	115 (47)	121 (48)
Open surgery – no. (%)	54 (22)	58 (23)
Endovascular surgery – no. (%)	61 (25)	63 (25)
Lower limb arterial surgery – no. (%)	100 (41)	92 (37)
*Plus-minus values are means±SD. TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme and A-II angiotensin II.		

### Primary Outcome

A total of 27 of the 250 patients (10.8%) in the fluvastatin group had evidence of myocardial ischemia within 30 days after surgery, as compared with 47 of the 247 patients (19.0%) in the placebo group (hazard ratio, 0.55; 95% confidence interval [CI], 0.34 to 0.88;  $P=0.01$ ) (Figure 1A). Hence, the number of patients who would need to be treated to prevent 1 patient from having myocardial ischemia was 12.

During the 30-day period of follow-up after surgery, perioperative myocardial ischemia (the primary outcome) occurred in 27 of the 250 patients (10.8%) in the fluvastatin group and 47 of the 247 patients (19.0%) in the placebo group (hazard ratio with fluvastatin, 0.55; 95% confidence interval [CI], 0.34 to 0.88;  $P=0.01$ ). During the 30-day period of follow-up after surgery, perioperative death from cardiovascular causes or nonfatal myocardial infarction (the secondary outcome) occurred in



**FIGURE 1** - Kaplan-Meier Estimates of the Cumulative Probabilities of the Primary and Secondary Outcomes.

During the 30-day period of follow-up after surgery, perioperative myocardial ischemia (the primary outcome) occurred in 27 of the 250 patients (10.8%) in the fluvastatin group and 47 of the 247 patients (19.0%) in the placebo group (hazard ratio with fluvastatin, 0.55; 95% confidence interval [CI], 0.34 to 0.88;  $P=0.01$ ). During the 30-day period of follow-up after surgery, perioperative death from cardiovascular causes or nonfatal myocardial infarction (the secondary outcome) occurred in 12 of the 250 patients (4.8%) in the fluvastatin group and 25 of the 247 patients (10.1%) in the placebo group (hazard ratio with fluvastatin, 0.47; 95% CI, 0.24 to 0.94;  $P=0.03$ ).

12 of the 250 patients (4.8%) in the fluvastatin group and 25 of the 247 patients (10.1%) in the placebo group (hazard ratio with fluvastatin, 0.47; 95% CI, 0.24 to 0.94;  $P=0.03$ ).

### Secondary Outcomes

A total of six patients receiving fluvastatin died, with four of the deaths due to cardiovascular causes. In contrast, 12 patients receiving placebo died, with 8 deaths due to cardiovascular causes. In addition, 8 patients in the fluvastatin group and 17 in the placebo group had a nonfatal myocardial infarction. The combined end point of death from cardiovascular causes or nonfatal myocardial infarction occurred in 12 of 250 patients (4.8%) receiving fluvastatin, as compared with 25 of 247 (10.1%) receiving placebo. Hence, fluvastatin therapy was associated with a 53% relative reduction in the incidence of death from cardiovascular causes or nonfatal myocardial infarction (hazard ratio, 0.47; 95% CI, 0.24 to 0.94;  $P=0.03$ ) (Figure 1B). The number of patients who would need to be treated to prevent the composite end point of death from cardiovascular causes or nonfatal myocardial infarction in 1 patient was 19.

**TABLE 2** - Levels of lipids and inflammatory markers during the study, according to study group.\*

Marker	Placebo	Fluvastatin	P-value
<b>At baseline</b>			
Cholesterol (mmol/l)			
Total	5.30 ± 1.20	5.40 ± 1.14	0.34
LDL	3.26 ± 0.93	3.36 ± 1.06	0.27
HDL	1.53 ± 0.70	1.61 ± 0.81	0.27
Triglycerides (mmol/l)			
Median	1.46	1.63	0.67
IQR	1.07 to 2.32	1.28 to 2.30	
High-sensitive C-reactive protein (mg/l)			
Median – interquartile range	5.80	5.93	0.32
IQR	3.00 to 10.40	2.42 to 10.89	
Interleukin-6 (pg/ml)			
IQR	8.76	8.55	0.80
Median – interquartile range	2.54 to 15.66	1.26 to 16.59	
<b>At time of surgery</b>			
Cholesterol (mmol/l)			
Total	5.09 ± 1.16	4.32 ± 0.79	<0.001
LDL	3.16 ± 0.91	2.55 ± 0.84	<0.001
HDL	1.55 ± 0.51	1.59 ± 0.53	0.40
Triglycerides (mmol/l)			
Median	1.62	1.64	0.90
IQR	1.18 to 2.40	1.26 to 2.36	
High-sensitive C-reactive protein (mg/l)			
Median	6.00	4.66	0.02
IQR	2.90 to 11.90	1.99 to 8.83	
Interleukin-6 (pg/ml)			
Median	8.45	5.75	0.005
IQR	2.28 to 15.35	1.00 to 11.41	
<b>Percent change between baseline and surgery†</b>			
Cholesterol (mmol/l)			
Total	-3.9 ± 4.6	-19.0 ± 9.6	<0.001
LDL	-3.1 ± 6.4	-23.2 ± 11.4	<0.001
HDL	4.3 ± 14.8	2.5 ± 16.1	0.20
Triglycerides (mmol/l)			
Median	0	1.0	0.58
IQR	-10.2 to 19.4	-23.8 to 32.1	
High sensitive C-reactive protein (mg/l)			
Median	3.3	-20.5	<0.001
IQR	-20.5 to 30.3	-26.8 to -12.0	
Interleukin-6 (pg/ml)			
Median	-4.2	-32.7	<0.001
IQR	-16.7 to 10.2	-42.3 to -21.6	

\* Plus–minus values are means ±SD. To convert values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert values for triglycerides to milligrams per deciliter, divide by 0.01129.

CRP, C-reactive protein; HDL, highdensity lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.

† The percent change from baseline is the value at the time of surgery minus that at baseline, reflecting the change over the period of study treatment (median, 37 days).

Baseline lipid levels were similar in the two groups (Table 2); 253 patients (50.9%) had a baseline total cholesterol level of less than 5.5 mmol per liter (213 mg per deciliter) and 194 patients (39.0%) had a baseline LDL cholesterol level of less than 3.0 mmol per liter (116 mg per deciliter). At the time of surgery, the mean total cholesterol and LDL cholesterol levels were reduced from the baseline levels by 1.08 mmol per liter (42 mg per deciliter) (20%) and 0.81 mmol per liter (31 mg per deciliter) (24%), respectively, in the fluvastatin group, as compared with 0.21 mmol per liter (8 mg per deciliter) (4%) and 0.10 mmol per liter (4 mg per deciliter) (3%), respectively, in the placebo group ( $P<0.001$  for both comparisons). Changes in high-density lipoprotein cholesterol and triglyceride levels were not significant, nor did they differ significantly between the two study groups.

The median baseline high-sensitivity C-reactive protein level was 5.93 mg per liter in the fluvastatin group and 5.80 mg per liter in the placebo group (Table 2). At the time of surgery, the median decrease in the high-sensitivity C-reactive protein level from the baseline level was 1.27 mg per liter (21%) in the fluvastatin group, whereas there was a median increase of 0.20 mg per liter (3%) in the placebo group ( $P<0.001$ ). The median interleukin-6 levels at baseline were similar in the fluvastatin group (8.55 pg per milliliter) and the placebo group (8.76 pg per milliliter) and by the time of surgery had decreased by significantly more in the fluvastatin group ( $-2.80$  [ $-33\%$ ]) than in the placebo group ( $-0.31$  [ $-4\%$ ]) ( $P<0.001$ ).

### Adverse Events

The proportion of patients who had an increase in creatine kinase of more than 10 times the upper limit of the normal range was 4.0% in the fluvastatin group and 3.2% in the placebo group (Table 3). The median peak creatine kinase level was 141 U per liter in the fluvastatin group and 113 U per liter in the placebo group ( $P=0.24$ ). The proportion of patients with an increase in alanine aminotransferase levels to more than three times the upper limit of the normal range was 3.2% in the fluvastatin group and 5.3% in the placebo group. The median peak alanine aminotransferase level was 24 U per liter in the fluvastatin group and 23 U per liter in the placebo group ( $P=0.43$ ). There were no reports of myopathy or rhabdomyolysis within 30 days after surgery in either study group.

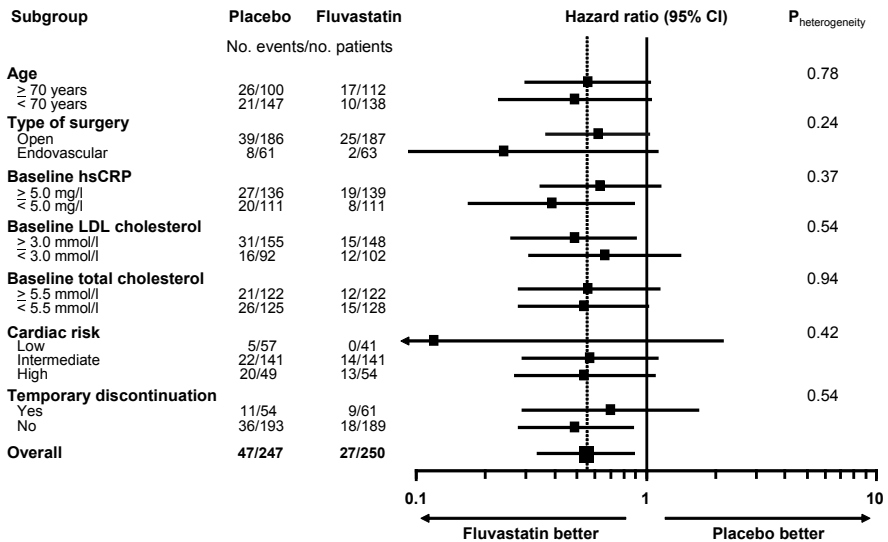
### Exploratory Findings

The relative difference in the incidence of the primary outcome, perioperative myocardial ischemia, persisted in exploratory analyses of multiple subgroups (Figure 2). In light of recent concerns about the safety of perioperative use of beta-blockers, we also evaluated the incidence of stroke. Three patients suffered a nonfatal postoperative stroke: two (0.8%) in the placebo group and one (0.4%) in the fluvastatin group.

**TABLE 3 - Adverse events, according to study group\***

	Placebo N=247	Fluvastatin N=250	P-value
Discontinuation of treatment – no. (%)			
Temporarily	54 (22)	61 (24)	0.53
Permanently	18 (7.3)	16 (6.4)	0.73
Peak creatinine kinase			
>10x ULN – no. (%)	8 (3.2)	10 (4.0)	0.81
Units per liter - median (IQR)	113 (66-369)	141 (77-380)	0.24
Peak alanine aminotransferase			
>3x ULN – no. (%)	13 (5.3)	8 (3.2)	0.27
Units per liter - median (IQR)	23 (15-37)	24 (17-50)	0.43
Death – no. (%)			
From any cause	12 (4.9)	6 (2.4)	0.14
From noncardiovascular cause	4 (1.6)	2 (0.8)	0.40

\*No patients in either group had myopathy or rhabdomyolysis.  
IQR, interquartile range and ULN, upper limit of the normal range.



**FIGURE 2 - Hazard Ratios for the Primary Outcome of Myocardial Ischemia, According to Post Hoc Specified Baseline Characteristics.** Cardiac risk was defined as in the DECREASE II (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography II) study.<sup>7</sup> To convert values for cholesterol to milligrams per deciliter, divide by 0.02586. CRP, C-reactive protein, and LDL, low-density lipoprotein.

## DISCUSSION

In the DECREASE III trial, we compared extended-release fluvastatin, at a dose of 80 mg once daily, initiated at a median of 37 days before vascular surgery, with placebo in patients who had not previously been treated with a statin and who had a mean total cholesterol level of 5.35 mmol per liter (207 mg per deciliter). We found that fluvastatin reduced the risk of perioperative myocardial ischemia. Though the trial was not powered for this end point, we also found a reduction in the risk of death from cardiovascular causes or nonfatal myocardial infarction. Fluvastatin treatment was associated with significant decreases in serum lipid levels and inflammatory activity (reflected by a reduction in high-sensitivity C-reactive protein and interleukin-6 levels).

The pathophysiology of perioperative cardiac events remains unclear. Autopsy studies suggest that approximately half of fatal myocardial infarctions in this context are attributable to a sustained mismatch between myocardial oxygen supply and demand, whereas coronary-plaque rupture is accountable for the other half.<sup>12,13</sup> It is thought that statins might be particularly suitable for reducing the risk of rupture-induced myocardial infarction by stabilizing unstable coronary plaques. The risk of plaque rupture is related to two factors: intrinsic morphologic features of plaque and extrinsic forces triggering plaque disruption.<sup>14</sup> Although it has been proved that statins are capable of positively altering morphologic characteristics of plaque, it appears implausible that this would occur within a few weeks. However, statins might play a pivotal role in counteracting the extrinsic factors causing plaque disruption. The pleiotropic effects of statins include several plaque-stabilizing effects, such as increased expression of endothelial nitric oxide synthase, reduced production of endothelin-1 and reactive oxygen species, an improvement of the thrombogenic profile, and importantly, a reduction in inflammation through reduced expression of inflammatory cytokines, chemokines, and adhesion molecules.<sup>15,16</sup> We found that fluvastatin reduced inflammatory activity within weeks, even in patients without hypercholesterolemia. Whether the decrease in inflammation is responsible for the beneficial clinical effects of perioperative statin use is unclear.

Our findings on the perioperative benefits of statins are in line with those in previous retrospective studies and one small, double-blind, randomized trial involving a total of 100 patients assigned to either 20 mg of atorvastatin, or placebo, once a day for 45 days.<sup>17</sup> In that trial, vascular surgery was performed, on average, 31 days after randomization. During the 6-month follow-up period, atorvastatin significantly reduced the incidence of cardiac events (8%, vs. 26% in the placebo group;  $P=0.03$ ). Though the trial was not powered to assess 30-day postoperative outcomes, there was a trend suggesting a beneficial effect of statins: three patients (6%) receiving atorvastatin had nonfatal myocardial infarction or death from cardiovascular causes, as compared with nine patients (18%) receiving placebo (odds ratio, 0.23; 95% CI, 0.09 to 1.30). Several retrospective



studies have also reported a potential beneficial effect of perioperative statin use with respect to various cardiovascular outcomes, with odds ratios for active treatment ranging from 0.22 to 0.71<sup>10,11,18,19</sup>; the DECREASE III findings are consistent with these results. We found no heterogeneity of effect among patients in subgroups characterized by various baseline characteristics, including cardiac risk, cholesterol levels, type of surgery, and levels of inflammatory markers.

One concern with perioperative statin treatment is the necessity of treatment interruption when oral administration is not feasible during the early postoperative period. Such interruption is potentially hazardous, as sudden withdrawal of statins in the nonsurgical setting has been associated with a diminished benefit.<sup>20,21</sup> In the present study, fluvastatin had to be interrupted in approximately a quarter of the patients for a median of 2 days. However, when the analysis was corrected for baseline characteristics and type of surgery, we did not find a significant increase in the rate of adverse outcomes among patients in whom fluvastatin was interrupted as compared with those who continued to receive the drug (odds ratio, 1.1; 95% CI, 0.48 to 2.52). These findings support the hypothesis that treatment with extended-release fluvastatin is robust to a gap in therapy of 1 to 2 days after surgery, when oral intake is not yet feasible.

Recent guidelines from the American College of Cardiology and the American Heart Association (ACC/AHA)<sup>22</sup> and the TransAtlantic Inter-Society Consensus on the management of peripheral arterial disease<sup>23</sup> indicate that statin use is appropriate in patients undergoing vascular surgery, regardless of whether they have other clinical risk factors. These guidelines are based on retrospective studies; the results of the current prospective trial confirm these recommendations.

It should also be noted that current guidelines state that long-term treatment with a statin is indicated in all patients with peripheral arterial disease.<sup>23,24</sup> However, the timing of initiation of statin therapy has been a matter of debate. The clinical advisory of the ACC, AHA, and the National Heart, Lung, and Blood Institute on the use and safety of statins suggests that there is an increased risk of statin-associated myopathy during the perioperative period, indicating that “it may be prudent to withhold statins” during hospitalization for major surgery.<sup>24</sup> The results of the DECREASE III trial suggest that the benefits of perioperative statin use outweigh the risks and that long-term statin therapy in patients with peripheral arterial disease may be prudently initiated during the perioperative period.

In conclusion, we compared fluvastatin and placebo in patients undergoing vascular surgery. Fluvastatin therapy was associated with an improved postoperative cardiac outcome and a reduction in serum lipid levels and levels of markers of inflammation.

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# CHAPTER

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## The impact of cardioselective beta-blockers on mortality in patients with chronic obstructive pulmonary disease and atherosclerosis

# 10

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## ABSTRACT

**Background:** Beta-blocker use is associated with improved health outcomes in patients with cardiovascular disease. There is a general reluctance to prescribe beta-blockers in patients with chronic obstructive pulmonary disease (COPD) because they may worsen symptoms. We investigated the relationship between cardioselective beta-blockers and mortality in patients with COPD undergoing major vascular surgery.

**Methods:** We evaluated 3,371 consecutive patients who underwent major vascular surgery at one academic institution between 1990 and 2006. The patients were divided into those with and without COPD based on symptoms and spirometry. The major endpoints were 30-day and long-term mortality after vascular surgery. Patients were defined as receiving low-dose therapy if the dosage was less than 25% of the maximum recommended therapeutic dose; dosages higher than this were defined as intensified dose.

**Results:** There were 1,265 (39%) patients with COPD of whom 462 (37%) received cardioselective beta-blocking agents. Beta-blocker use was associated independently with lower 30-day (odds ratio, 0.37; 95% confidence interval, 0.19-0.72) and long-term mortality in patients with COPD (hazards ratio, 0.73; 95% confidence interval, 0.60-0.88). Intensified dose was associated with both reduced 30-day and long-term mortality in COPD patients, whereas low dose was not.

**Conclusions:** Cardioselective beta-blockers were associated with reduced mortality in patients with COPD undergoing vascular surgery. In carefully selected patients with COPD, the use of cardioselective beta-blockers appears to be safe and associated with reduced mortality.



## INTRODUCTION

During the last decade, beta-blocker therapy has become an increasingly important treatment in patients undergoing noncardiac surgery. Several studies have shown that peri-operative beta-blocker therapy can reduce the incidence of peri- and post-operative cardiac complications, including sudden death, angina and myocardial infarction in patients undergoing noncardiac vascular surgery.<sup>1-5</sup> Accordingly, the American College of Cardiology and the American Heart Association recommend the use of beta-blockers in patients undergoing major vascular surgery.<sup>6</sup> Many patients with cardiovascular disease (CVD) have co-existing chronic obstructive pulmonary disease (COPD) and vice versa possibly because they share the same risk factor, cigarette smoking.<sup>7</sup> In patients with COPD, approximately 30% of all deaths are from CVD.<sup>8</sup> Beta-blockers are, however, frequently withheld from COPD patients with co-existing CVD because of the concern that beta-blockers may induce bronchoconstriction from blockade of beta-2-adrenoreceptors. Although nonselective beta-blockers act on the beta-2-adrenoreceptors to inhibit bronchodilation,<sup>9</sup> there is substantial evidence that cardioselective beta-blockade is likely safe and beneficial in patients with COPD and CVD.<sup>10-18</sup> Additional concern regarding use of beta-blockers in COPD is the potential for insensitivity. COPD is associated with systemic inflammation, which may accelerate metabolism of beta-blockers, leading to reduced efficacy. Patients are particularly vulnerable to cardiac events during and after major vascular surgery.<sup>19</sup> The primary aim of the present study was to investigate the association between cardioselective beta-blockers and 30-day and long-term mortality in patients with COPD who undergo major vascular surgery. The secondary objective was to determine the relationship between low and intensified dosage and mortality. Some of the results of this study have been previously reported in the form of an abstract.<sup>20</sup>

## METHODS

### Study population

This observational retrospective study included 3,371 consecutive patients undergoing elective vascular surgery between 1990 and 2006 at the Erasmus Medical Center Rotterdam, The Netherlands. The surgical procedures included abdominal aortic surgery (comprising aortic-to-aortic or aortic-bifurcation prostheses procedures, removal of infected prostheses, and other operations of the abdominal aorta), carotid endarterectomy (including reconstruction or desobstruction of the carotid artery), and lower limb arterial reconstruction procedure (including iliac-femoral, femoral-popliteal, femoral-tibial artery bypass procedures, removal of infected prostheses, peripheral desobstruction and other elective peripheral arterial surgical reconstructions). Vascular reconstructions due to trauma and ruptured abdominal aortic aneurysms were excluded.

Abstracted variables included patient demographics (age and sex) and cardiac risk factors, including the following: hypertension (defined as a blood pressure  $\geq 140/90$  mm Hg), hypercholesterolemia (total cholesterol of  $>5.2$  mmol/L), diabetes mellitus (presence of fasting blood glucose of  $\geq 140$  mg/dl or treatment with insulin or oral hypoglycemic agents), serum creatinine renal dysfunction (baseline serum creatinine  $>1.5$  mg/dl), current smoking status and body mass index (BMI) calculated as weight divided by height squared ( $\text{kg}/\text{m}^2$ ). The patient's cardiovascular history was assessed and included the following: previous myocardial infarction, coronary revascularization (coronary artery bypass graft and/or percutaneous coronary intervention), heart failure (defined according to the New York Heart Association classification), angina pectoris, stroke and/or transient ischemic attack. The use of bronchodilators and corticosteroids at baseline was captured. Cardiac medications at baseline were also evaluated. These included beta-blockers, statins, angiotensin-converting enzyme inhibitors, diuretics, aspirin, anticoagulants, nitrates and calcium channel blockers. Almost all (97%) of the prescribed beta-blockers were cardioselective beta-blocking agents: metoprolol, bisoprolol and atenolol. To evaluate the association of low and intensified beta-blocker dose with mortality, we converted the beta-blocker dosage at initial hospitalization. Low dose was defined as patients using less than 25% of the maximum recommended therapeutic dose, whereas intensified dose was defined as an average dose exceeding or equal to 25% of maximum recommended therapeutic dose. For metoprolol, a maximum recommended therapeutic dose of 400 mg was used, for bisoprolol 10 mg was used, and for atenolol 100 mg was used.

### Pulmonary Function Testing

A diagnosis of COPD was based on post-bronchodilator spirometric values in conjunction with a history of cough, sputum production and/or dyspnea. COPD was defined according to the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) ( $\text{FEV}_1$  to FVC ratio less than 70%<sup>21</sup>). Disease severity was classified into three groups: I = mild COPD ( $\text{FEV}_1/\text{FVC} < 0.70$  and  $\text{FEV}_1 \geq 80\%$  of the predicted  $\text{FEV}_1$ ), II = moderate COPD ( $\text{FEV}_1/\text{FVC} < 0.70$  and  $\text{FEV}_1 50\% \leq \text{FEV}_1 < 80\%$  of the predicted  $\text{FEV}_1$ ), and III = severe COPD ( $\text{FEV}_1/\text{FVC} < 0.70$  and  $\text{FEV}_1 30\% \leq \text{FEV}_1 < 50\%$  of the predicted  $\text{FEV}_1$ ).<sup>21</sup> We used the equation of Quanjer and colleagues<sup>22</sup>, adjusted for age, sex, and height, to calculate the predicted  $\text{FEV}_1$  value, which has demonstrated to make an accurate prediction.<sup>23</sup> The equation for males is  $4.30 \times \text{height (m)} - \text{age} \times 0.029 - 2.49$  and for women is  $3.95 \times \text{height (m)} - \text{age} \times 0.025 - 2.60$ .<sup>22</sup> In 82% of the patients with COPD, a preoperative spirometry was performed. The patients without a preoperative pulmonary function test were classified as having no COPD if they were free of pulmonary complaints (cough and dyspnea), and not currently receiving pulmonary medications (i.e., bronchodilators and corticosteroids) and demonstrated normal arterial blood gases on room air ( $\text{Pco}_2 < 6.4$  kPa and  $\text{Po}_2 > 10.0$  kPa).

### Follow-up and Endpoints

Follow-up was complete in 96% of the study patients, with a median follow-up of 5 years. Survival status was obtained from the municipal civil registries. Clinical baseline characteristics were retrieved from the hospital medical records. Endpoints of the study were 30-day and long-term (10-yr) mortality regardless of the cause.

### Statistical analysis

Continuous data are presented as mean  $\pm$  SD and compared using the Student's *t* test. Categorical variables among the patient groups are expressed as percentages and compared using  $\chi^2$  tests. Univariate and multivariate logistic regression analyses were used to determine the relationship of cardioselective beta-blockers and their dose with 30-day mortality. Cox proportional hazards models were used to analyze the impact of these drugs on long-term mortality, adjusted for salient covariates, including age, sex, hypertension, hypercholesterolemia, diabetes mellitus, renal dysfunction, current smoking status, BMI, type of surgery, year of surgery, and cardiovascular history. In addition, a composite variable of statins, aspirin and angiotensin-converting enzyme inhibitors was included. Patients who received non-selective beta-blockers ( $n=112$ ; 3%) were excluded from the analysis. In addition, using a multivariate logistic regression model, we developed a propensity score to adjust for the likelihood of receiving beta-blockers in subjects with COPD and non-COPD subjects. The variables in this model included: age, sex, COPD, hypertension, hypercholesterolemia, diabetes mellitus, renal dysfunction, current smoking status, BMI, type of surgery, year of surgery, all variables on cardiovascular history, all cardiac and pulmonary medications (Table 1). The fit of the propensity score model was assessed using c-statistics and the Hosmer-Lemeshow goodness-of-fit-test. In all comparative analysis of beta-blockers, patients who were not on beta-blocker therapy were used as the reference group. Odds ratios (ORs) and hazard ratios (HRs) were calculated from these models along with their 95% confidence intervals (CIs). For all tests, a two-sided *P* value of less than 0.05 was considered significant. All statistical analyses were performed using SPSS 15.0 for Windows (SPSS, Inc., Chicago, IL).

# RESULTS

## Baseline characteristics

TABLE 1 - Baseline characteristics according to COPD and beta-blocker use

	COPD (n=1,265)		P-value	No COPD (n=1,994)		P-value
	Beta-blocker (n=462)	No beta-blocker (n=803)		Beta-blocker (n=567)	No beta-blocker (n=1,427)	
<b>Demographics</b>						
Mean age, yr (SD)	69 (9)	69 (10)	0.61	65 (11)	63 (13)	0.01
Male sex (%)	82	78	0.07	70	68	0.30
Type of surgery (%)			<0.001			<0.001
AAA	54	43		37	24	
CEA	15	13		31	31	
LLR	31	44		32	46	
<b>Cardiovascular history (%)</b>						
Myocardial infarction	33	21	<0.001	31	14	<0.001
Coronary revascularization*	25	14	<0.001	22	11	<0.001
Heart failure	7	5	0.22	5	4	0.29
Angina pectoris	26	11	<0.001	23	9	<0.001
Stroke or TIA	24	20	0.14	35	35	0.76
<b>Clinical characteristics (%)</b>						
Hypertension	49	36	<0.001	54	28	<0.05
Diabetes Mellitus	17	12	<0.05	18	14	0.08
Hypercholesterolemia	26	11	<0.001	28	14	<0.001
Renal dysfunction	9	8	0.43	10	4	<0.001
Body mass index (SD)	26 (4)	25 (4)	<0.05	26 (4)	25 (4)	<0.05
Current smoking status	35	33	0.41	27	24	0.21
<b>Cardiac medication (%)</b>						
Statins	49	11	<0.001	46	14	<0.001
ACE-inhibitors	31	19	<0.001	34	18	<0.001
Calcium antagonists	28	22	<0.05	33	16	<0.001
Diuretics	28	19	<0.05	23	11	<0.001
Aspirin	47	30	<0.001	58	37	<0.001
Anti-coagulants	32	38	<0.05	41	42	0.84
Nitrates	17	11	<0.05	18	7	<0.001
<b>Pulmonary medication (%)</b>						
Bronchodilators	13	18	<0.05	0	0	0.85
Corticosteroids	23	11	<0.001	1	1	0.88

AAA, abdominal aortic surgery; ACE, angiotensin-converting enzyme; CEA, carotid endarterectomy; COPD, chronic obstructive pulmonary disease; LLR, lower limb arterial reconstruction; TIA, transient ischemic attack.

\*Coronary artery bypass graft or percutaneous coronary intervention.

Of the 3,371 patients (mean age  $66 \pm 12$  yr; 73% male), 1,029 (31%) received cardioselective beta-blockers at their initial hospitalization (Table 1). The commonly used beta-blockers were bisoprolol at 50% (n=514), atenolol at 15% (n=151) and metoprolol at 32% (n=325). Patients with beta-blockers were more likely to have underlying history of cardiac disease, hypertension, and hypercholesterolemia (all  $P < 0.001$ ). The percentage of beta-blocker use was not significantly different among the COPD severity groups (mild COPD, 39%; moderate COPD, 35%; and severe COPD, 33%;  $P = 0.20$ ).

### Association between cardioselective beta-blockers and mortality

Overall, there were 1,265 (39%) patients with COPD. Of these patients, 462 (37%) used cardioselective beta-blocking agents. In comparison, 567 (28%) of the patients who did not have COPD used beta-blockers. Within 30 days of surgery, 16 (4%) patients with COPD who were receiving beta-blockers died. In contrast, 66 (8%) patients who did not use beta-blockers died during the same period of time ( $P = 0.001$ ). Over the entire follow-up period, 184 (40%) patients with COPD who were and 532 (67%) were not on beta-blocker therapy died ( $P < 0.001$ ). Cardioselective beta-blockers were independently associated with reduced 30-day mortality in patients with (OR, 0.37; 95% CI, 0.19-0.72) and without COPD (OR, 0.34; 95% CI, 0.17-0.66) (Table 2). Over the entire follow-up period, cardioselective beta-blocking agents reduced long-term mortality in patients with COPD (HR, 0.73; 95% CI, 0.60-0.88). In the long-term, a trend was observed in patients without COPD, although it did not achieve statistical significance (HR, 0.84; 95% CI, 0.69-1.02). A sensitivity analysis was performed using propensity score measurements for adjustment of various factors, including severity of disease to address the issue of confounding by indication. In this analysis, the relationship of cardioselective beta-blockade with mortality in patients with COPD was similar to the main analysis (OR, 0.41; 95% CI, 0.20-0.81 and HR, 0.75; 95% CI, 0.61-0.91).

**TABLE 2** - The association between cardioselective beta-blockers and mortality

	30 day mortality				Long-term mortality			
	Univariate		Multivariate		Univariate		Multivariate	
	OR	[95% CI]	OR	[95% CI]	HR	[95% CI]	HR	[95% CI]
BBL								
Total	0.45	[0.30-0.66]	0.35	[0.22-0.57]	0.84	[0.74-0.95]	0.78	[0.68-0.89]
No COPD	0.46	[0.26-0.81]	0.34	[0.17-0.66]	0.86	[0.73-1.02]	0.84	[0.69-1.02]
COPD	0.40	[0.23-0.70]	0.37	[0.19-0.72]	0.74	[0.63-0.88]	0.73	[0.60-0.88]
Mild	0.45	[0.21-0.98]	0.46	[0.18-1.16]	0.70	[0.54-0.92]	0.68	[0.50-0.93]
Moderate/ severe	0.34	[0.15-0.78]	0.32	[0.12-0.85]	0.79	[0.64-0.98]	0.82	[0.64-1.05]

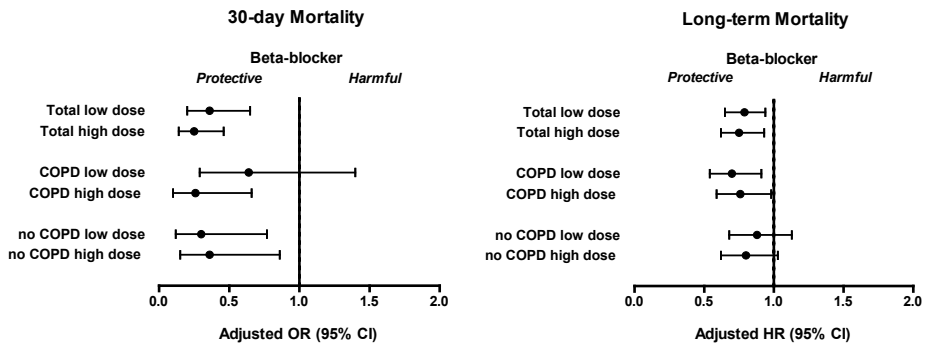
Definition of abbreviations: COPD, chronic obstructive pulmonary disease; HR, hazard ratio; OR, odds ratio.

In patients without COPD, a significant association was found between beta-blocker use and 30-day mortality (OR, 0.36; 95% CI, 0.18-0.72). Similar to the main analysis, a trend was observed with the long-term mortality, although the relationship was not significant (HR, 0.88; 95% CI, 0.72-1.07).

The relationship between beta-blockers and mortality across different COPD severity groups is also summarized in Table 2. Even in moderate to severe group, beta-blocker therapy was associated with reduced mortality in the short and long-term.

### Cardioselective beta-blocker dose and mortality

Of the patients using cardioselective beta-blockers, 41% received low-dose beta-blocker therapy at the time of surgery and 59% received an intensified dose. These percentages were similar among patients with COPD, with 42% of the patients on a low-dose and 58% on an intensified dose. In patients with COPD, an intensified but not low-dose was associated with reduced 30-day mortality (OR, 0.26; 95% CI, 0.10-0.66) (Figure 1). However, in the long-term, both dosing regimens were associated with reduced mortality (low dose: HR, 0.70; 95% CI, 0.54-0.91 and intensified dose: HR, 0.76; 95% CI, 0.59-0.98). In patients without COPD, both low and intensified dosing regimens were associated with reduced 30-day mortality (OR, 0.30; 95% CI, 0.12-0.77 and OR, 0.36; 95% CI, 0.15-0.86, respectively). The relationships became insignificant for low-dose beta-blockers when long-term mortality was considered, although a trend for reduced mortality was still observed in non-COPD patients who were treated with an intensified dose (HR, 0.80; 95% CI, 0.62-1.03).



**FIGURE 1 - The association between low and intensified cardioselective beta-blocker dose and mortality.**

\*Adjusted for age, sex, hypertension, hypercholesterolemia, diabetes mellitus, renal dysfunction, current smoking status, BMI, type of surgery, year of surgery and cardiovascular history. CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; OR = odds ratio.

## DISCUSSION

The present study demonstrated that cardioselective beta-blockers were associated with reduced 30-day and long-term mortality in patients with COPD who underwent major vascular surgery. We also found that an intensified dosing regimen appeared to be superior to low-dose therapy in terms of its impact on 30-day mortality.

These findings are consistent with other studies that demonstrated the beneficial effects of beta-blockers in patients with COPD who recently experienced myocardial infarction.<sup>13,15,18</sup> A major limitation of the previous studies was that there was no or little information on lung function and as such the diagnosis of COPD could not be confirmed. We extend these findings by demonstrating among a large group of well-characterized patients with COPD, defined both clinically and spirometrically, that beta-blockers were safe and indeed beneficial in prolonging survival after major vascular surgery. There is evolving evidence showing that cardioselective beta-blockade probably does not induce bronchospasm in patients with COPD.<sup>11,12,14,16,17</sup> In addition, a meta-analysis of Salpeter and colleagues that evaluated the relationship between cardioselective beta-blockers and COPD found no significant differences in FEV<sub>1</sub> or respiratory symptoms between those who were treated with a cardioselective beta-blockers or those treated with placebo, even in patients with severe COPD.<sup>24</sup> In a study of patients with congestive heart failure, patients with and without COPD had similar rates of withdrawal from beta-blockers because of intolerance.<sup>25</sup> These data suggest that COPD does not increase the rate of adverse reactions to cardioselective beta-blockers (leading to withdrawal). In view of the observed beneficial effect of cardioselective beta-blockers in our study, we believe that cardioselective beta-blocking agents may be used cautiously in patients with COPD with underlying ischemic vascular disease. Because cardioselective beta-blocking agents have some (although minor) effects on the beta-2-adrenergic receptors, such patients should be monitored very closely for any adverse effects. Moreover, although we found that intensified dose was superior to low-dose therapy with regard to 30-day mortality, we believe that it may be prudent to initiate therapy at the lowest dose feasible and to gradually increase the dose to the target range over several weeks to ensure safety.

Why beta-blockers would be effective in COPD is largely unknown; however, it is well established that CVD is an important comorbidity in COPD. In the Lung Health Study, for instance, which studied 5,887 smokers, aged 35 to 60 years, with GOLD stage 1 and 2 disease (FEV<sub>1</sub>  $\geq$ 50% predicted), CVDs were primarily responsible for 22% of all deaths<sup>26</sup> and cardiovascular events accounted for 42% of the first hospitalizations and 48% of the second hospitalizations.<sup>27</sup> The increased CVD risk in COPD may, in part, be related to excess adrenergic activity. Using microneurography of the peroneal nerve, Heindl and colleagues showed that patients with COPD have a marked increase in peripheral sympathetic discharge compared with control subjects<sup>28</sup>, which was inversely related to

the patients' oxyhemoglobin saturation ( $r = 0.54$ ).<sup>29</sup> Patients with COPD also demonstrate reduced cardiac accumulation of meta-iodobenzylguanidine, an analog of guanetidide, a higher washout rate from the heart, and increased plasma norepinephrine levels than control subjects, indicating excess activity of the sympathetic nervous system with increased norepinephrine turnover than do control subjects.<sup>30</sup> In patients who demonstrate excess sympathetic nervous activity such as those with chronic heart failure or previous myocardial infarction, the use of beta-adrenoceptor blockers, which attenuate sympathetic nervous activity, improves cardiac function and reduces CVD morbidity and mortality.<sup>31</sup> In addition, beta-blockers may reduce peri- and postoperative cardiac complications by attenuating cardiac workload and myocardial ischemia through beta-blockade. Beta<sub>1</sub>-blockade may also inhibit catecholamine-induced necrosis and apoptosis of the myocardium, which may confer additional benefits to the stressed heart.<sup>32</sup>

Our finding that an intensified dosing regimen was superior to a low-dose regimen in reducing 30-day mortality is consistent with those from a previous study which examined the effect of low- and intensive-dose therapy in vascular surgery patients.<sup>19</sup> It is also consistent from the findings of the MOCHA (Multicenter Oral Carvedilol Heart Failure Assessment), SENIORS (Study of the Effects of Nebivolol Intervention on Outcome and Rehospitalization in Seniors with Heart Failure), and the COMET (Carvedilol or Metoprolol European Trial) trials, which also demonstrated a dose-related reduction in mortality.<sup>33-35</sup> Conversely, the MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure) trial and the CIBIS (Cardiac Insufficiency Bisoprolol Study) II trial failed to demonstrate this dose-dependent effect.<sup>36,37</sup> However, all these trials were conducted in patients with heart failure and should therefore be carefully compared with our study. Unfortunately, in most of these trials, patients with COPD were excluded because of concerns about bronchoconstriction, which makes cross-comparisons difficult. To our knowledge, the present study is the first of its kind to investigate the dose-dependent association between beta-blockers and mortality in vascular surgery patients with COPD.

There were limitations to the study. First, we could not fully rule out the possibility that some individuals with COPD also had asthma. However, although bronchial hyper-responsiveness is more common (and more severe) in asthma than in COPD, over 70% of patients with COPD also demonstrate bronchial hyper-responsiveness. Thus, in reality, a clear separation is not always possible in clinical practice.<sup>38</sup> Second, this was an observational study and not a clinical trial, which raises the possibility of confounding. To mitigate this possibility, we carefully collected salient clinical and demographic information and used sophisticated statistical modelling and inclusion of lung function measurements. We calculated a propensity score for beta-blocker use and included this propensity score in the multivariable analysis to correct for the conditional probability of receiving the medication. We found that this made no material difference to the overall results. Although we cannot entirely rule out confounding by reverse indication, the adjustments of these



factors including spirometric data suggest that these findings are not spurious and unlikely due to treatment selection. Nevertheless, additional prospective studies are needed to validate these early findings. Third, the prescription of beta-blockers increased during 10 years of follow-up. To minimize the effect of this potential bias, we adjusted for the year of surgery in the analysis. Moreover, although we found that beta-blocker therapy was associated with both short- and long-term survival, our measure of beta-blocker exposure occurred at one-time point. We did not have follow-up data on beta-blocker use, which may have led to exposure misclassification. However, it is likely that patients who were prescribed beta-blockers at baseline were more likely to have received similar therapy in subsequent periods of follow-up.<sup>39</sup> Thus, the long-term benefits of beta-blocker therapy are likely on the basis of ongoing use of these medications as an outpatient.

In summary, our results suggest that cardioselective beta-blockers are beneficial in patients with COPD undergoing vascular surgery, with an intensive dose being most effective in the reduction of 30-day mortality. Therefore, cardioselective beta-blocking agents should not be withheld from patients with COPD undergoing vascular surgery.

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**Closing**

# PART III

## The Gap





# CHAPTER

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**Guidelines for cardiac management in noncardiac surgery are poorly implemented in clinical practice. Results from a peripheral vascular survey in The Netherlands**

11

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## ABSTRACT

**Background:** The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for Perioperative Cardiovascular Evaluation for Noncardiac Surgery recommend an algorithm for a stepwise approach to preoperative cardiac assessment in vascular surgery patients. The authors' main objective was to determine adherence to the ACC/AHA guidelines on perioperative care in daily clinical practice.

**Methods:** Between May and December 2004, data on 711 consecutive peripheral vascular surgery patients were collected from 11 hospitals in The Netherlands. This survey was conducted within the infrastructure of the Euro Heart Survey Programme. The authors retrospectively applied the ACC/AHA guideline algorithm to each patient in their dataset and subsequently compared observed clinical practice data with these recommendations.

**Results:** Although 185 of the total 711 patients (26%) fulfilled the ACC/AHA guideline criteria to recommend preoperative noninvasive cardiac testing, clinicians had performed testing in only 38 of those cases (21%). Conversely, of the 526 patients for whom noninvasive testing was not recommended, guidelines were followed in 467 patients (89%). Overall, patients who had not been tested, irrespective of guideline recommendation, received less cardioprotective medications, whereas patients who underwent noninvasive testing were significantly more often treated with cardiovascular drugs (beta-blockers 43% vs 77%, statins 52% vs 83%, platelet inhibitors 80% vs 85%, respectively; all *P*-values <.05). Moreover, the authors did not observe significant differences in cardiovascular medical therapy between patients with a normal and patients with an abnormal test result.

**Conclusion:** This survey showed poor agreement between ACC/AHA guideline recommendations and daily clinical practice. Only one out of each 5 patients underwent noninvasive testing when recommended. Furthermore, patients who had not undergone testing despite recommendations received as little cardiac management as the low risk population.

## INTRODUCTION

Patients undergoing vascular surgery are known to be at increased risk of perioperative mortality and other cardiac complications due to frequently underlying (a)symptomatic coronary artery disease. Mortality rates of 1.5%-2% for endovascular procedures and 3%-4% for surgical repair have been reported.<sup>1,2</sup> Myocardial infarction accounts for 10-40% of postoperative fatalities and can therefore be considered as the major determinant of perioperative mortality associated with noncardiac surgery.<sup>3,5</sup> Furthermore, a nonfatal myocardial infarction in the perioperative period is associated with a 20-fold increased risk of late mortality.<sup>6</sup>

When considering a patient for vascular surgery, a careful preoperative clinical risk evaluation and subsequent risk-reduction strategies are essential to reduce post-operative cardiac complications. The American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines, which are commonly used in clinical practice in The Netherlands, recommend an algorithm for a stepwise approach to preoperative cardiac assessment (Figure 1).<sup>7</sup> This decision-making process integrates clinical markers, early coronary evaluation, functional capacity and the type of surgery planned. According to the guidelines, preoperative noninvasive testing is recommended for all patients undergoing high-risk procedures and patients with intermediate clinical predictors of perioperative complications and poor functional capacity undergoing intermediate-risk surgery.

Several studies showed that this stepwise approach to the assessment of significant coronary artery disease is both efficacious and cost-effective.<sup>8,9</sup> However, the use of such preoperative cardiac evaluation does not seem to predict or improve outcome.<sup>10-12</sup> In addition, little is known about the adherence to the ACC/AHA guidelines in daily clinical practice and the effect on patient outcome. Therefore, the primary aim of this study was to determine to what extent the ACC/AHA guidelines are followed in routine clinical practice.

## MATERIALS AND METHODS

### Study population

Between May and December 2004, a survey of routine clinical practice was conducted in 11 hospitals in The Netherlands. This survey was conducted within the infrastructure of the Euro Heart Survey Programme in The Netherlands, which evaluates the implementation of guidelines in daily clinical practice. Five hospitals were located in the central part of the country, three in the northern region and three in the southern region. Two centres were university hospitals, which act as tertiary referral centres.

All consecutive patients who were admitted to the vascular surgery department of the participating hospital were screened. Patients above the age of 18 who were undergoing peripheral vascular repair were eligible for participation in the survey, except those undergoing thoracic or brain surgery. The total study population consisted of 711 patients. Patients had to provide informed consent. The medical ethics committees of the participating hospitals approved the study.

### **Data collection**

Trained research assistants obtained data on patient characteristics, applied diagnostic procedures, cardioprotective treatment and the surgical procedure from the patients' hospital charts. All data were entered into the electronic Case Record Form and transferred regularly to the central database at the Erasmus Medical Center (Rotterdam, The Netherlands) via the Internet. Data entered into the electronic Case Record Form were automatically checked for completeness, internal consistency and accuracy. The data management staff at the Erasmus Medical Center performed additional edit checks. If necessary, queries were resolved with the local research assistants.

### **ACC/AHA guidelines**

The ACC/AHA TaskForce published Practice Guidelines for Perioperative Cardiovascular Evaluation for Noncardiac Surgery in 1996 and an update in 2002.<sup>7</sup> The core of the ACC/AHA guidelines is an algorithm, that summarizes the stepwise process leading to practical recommendations as performing noninvasive testing. (Figure 1)<sup>7</sup> According to this algorithm, after the urgency of the surgery and the cardiac status of patients having previous coronary revascularization within 5 years or previous cardiac evaluation within 2 years are assessed, the patients have to be classified at major, intermediate or minor perioperative cardiovascular risk. Major, intermediate, and minor clinical predictors of risk, together with surgical risk and degree of functional capacity can be determined as predictors of perioperative cardiac complications. Patients with only minor or intermediate clinical predictors and adequate functional capacity represent a low-risk population, irrespective of type of surgery, and further evaluation is unnecessary. However, if any of the clinical markers of cardiac risk present, additional noninvasive evaluation should be considered.

The main purpose of performing preoperative cardiac risk assessment is to identify patients at high risk for perioperative cardiac events. In general, two strategies have been used to reduce the incidence of perioperative MIs and other cardiac complications: preoperative coronary revascularization and pharmacological treatment. The ACC/AHA guidelines recommend beta-blockers for patients at high cardiac risk. Evidence for statins and beta-blockers in intermediate risk patients is less clearly described.

We applied the ACC/AHA guideline definitions to the study population. Because the guidelines were not explicit on the definition of advance age, we defined it as older than 70 yr. Poor functional capacity was defined as a patient being unable to walk 4 blocks on level ground or climb two flights of stairs without symptomatic limitation. Procedures were divided into high, intermediate and low surgery-specific risk. High-risk procedures included major vascular surgery and intermediate risk procedures carotid endarterectomy. Endovascular procedures were defined as low-risk procedures.

### **End points**

This survey was designed to evaluate the application of guidelines in patients undergoing peripheral vascular surgery. We specifically looked at noninvasive imaging, cardiovascular medication (beta-blockers, statins, and antiplatelet therapy) and preoperative revascularization. Antiplatelet therapy included aspirin, dipyridamole, clopidogrel or any of combination of these agents. All-cause mortality and adverse events were reported at 30-days and 1-year after surgery by the local research assistants. Cardiovascular complications were defined as cardiac death, myocardial infarction, cardiac arrhythmias, congestive heart failure, cerebrovascular events, or revascularization.

### **Data analyses**

For each patient in our dataset, we retrospectively determined whether ACC/AHA guidelines were followed. We described the number of patients for whom guidelines were followed with percentages and corresponding confidence intervals. Differences in following guidelines were analysed with chi-square tests and Fisher exact test, when appropriate. Mortality rates were only described with percentages and confidence intervals (CIs) because small subgroup sample sizes limited statistical power for statistical testing. All statistical analyses were undertaken using version 13.0 of the SPSS program for Windows (SPSS Co., Chicago, IL). In all analyses, a *P*-value less than 0.05 was considered statistically significant.

## **RESULTS**

The mean age of the total 711 patients was 67 years (*SD*=10), with many patients having a history of associated risk factors (Table 1). When stratified into surgery-specific risk categories according to the ACC/AHA guidelines, 328 (46%) underwent high-risk procedures, 29 patients (4%) underwent intermediate-risk procedures and 354 (50%) underwent low-risk procedures. The 328 open vascular procedures included infrainguinal arterial reconstruction (52%), abdominal aortic surgery (42%), and 21 other procedures (6%).

## Risk evaluation

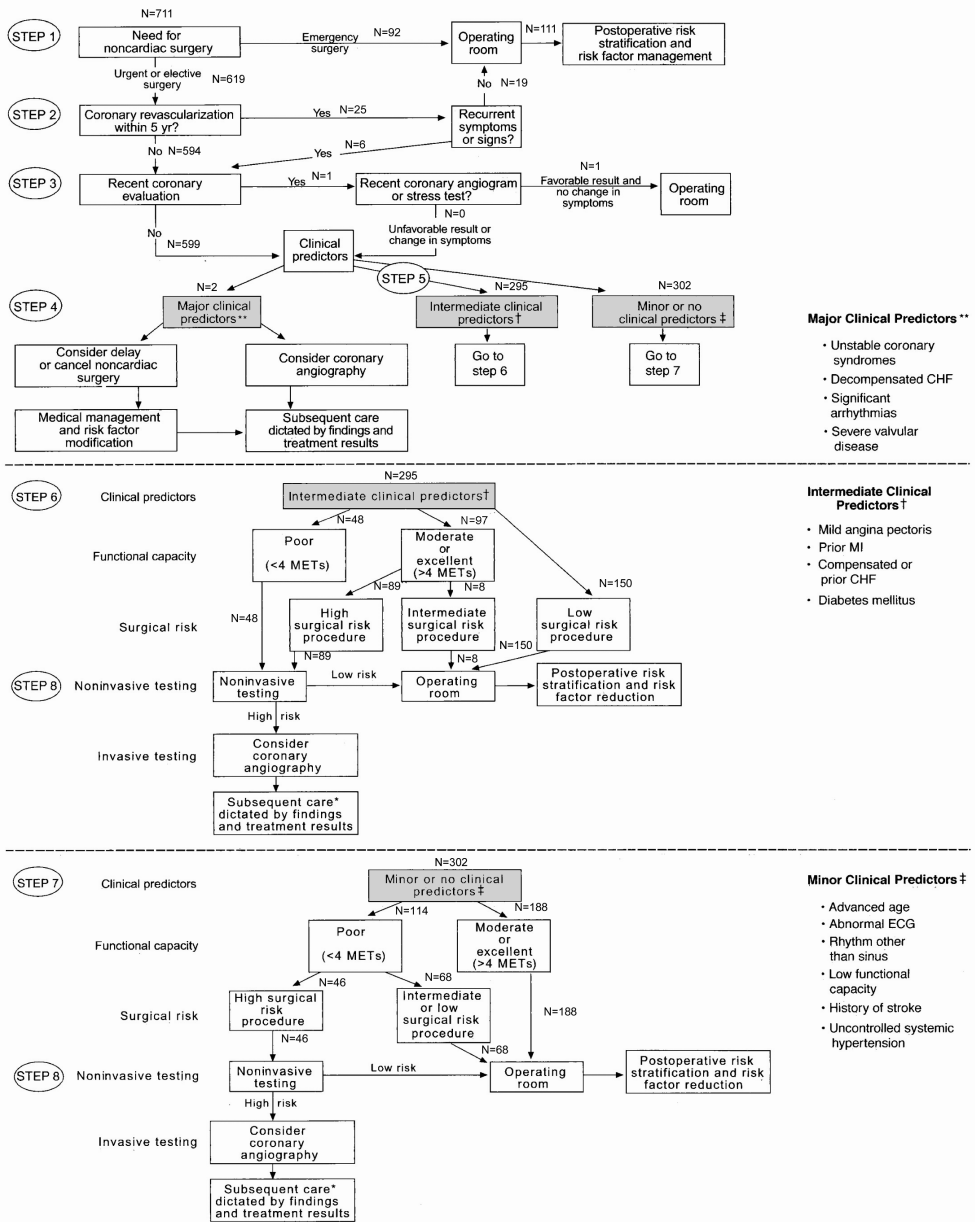
As shown in the algorithm in Figure 1, 92 of the total 711 patients (13%) underwent emergency surgery. Of the 619 patients undergoing urgent or elective surgery, 25 patients (4%) underwent recent coronary revascularization, of which 19 patients had no recurrent symptoms or signs. One other patient had a recent coronary evaluation without recurrent symptoms or unfavourable results. According to the ACC/AHA guidelines algorithm, those patients can undergo surgery directly without previous noninvasive testing. The remaining 599 patients were classified according to the guidelines as having major (n=2), intermediate (n=295) and minor or no clinical risk predictors (n=302). Depending on this clinical risk profile, functional capacity and surgical risk profile, noninvasive testing is recommended as shown in the algorithm and outlined in Table 2.

For example, within the 295 patients with intermediate clinical risk factors, 48 patients had a poor functional capacity and are recommended to undergo noninvasive testing, whereas the 150 patients undergoing low-surgical-risk-procedures can go directly to surgery.

**TABLE 1** · Baseline characteristics

N=711	
<b>Demographics</b>	
Mean age ±SD, yr	67±10
Male gender, n (%)	496 (70)
<b>Cardiovascular history, n (%)</b>	
Angina pectoris	99 (14)
Myocardial infarction	106 (15)
Heart failure	38 (5)
Stroke or tia	123 (17)
Arrhythmia	77 (11)
Valvular disease	50 (7)
Previous revascularization	116 (16)
<b>Clinical risk factors, n (%)</b>	
Obesity	77 (11)
Current smoker	256 (36)
Hypertension	273 (38)
Diabetes mellitus	149 (21)
Renal insufficiency	51 (7)
COPD	101 (14)
<b>Procedure, n (%)</b>	
Low-risk	354 (50)
Intermediate-risk	29 (4)
High-risk	328 (46)
<b>Functional capacity, n (%)</b>	
Poor	240 (34)
Moderate	471 (66)

COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack.



**FIGURE 1 - Application of The American College of Cardiology/American Heart Association algorithm for perioperative cardiovascular evaluation for noncardiac surgery to the study population.** Adapted from ACC/AHA Guidelines for the Perioperative Cardiovascular Evaluation for Noncardiac Surgery.<sup>7</sup> CHF = congestive heart failure; ECG = electrocardiogram; MI = myocardial infarction.

TABLE 2 - Agreement with the ACC/AHA guidelines regarding noninvasive testing

Clinical category	ACC/AHA Guideline Category	Surgical Risk	Functional Capacity	Expected according to guidelines		Noninvasive testing recommended		Observed in clinical practice
				Yes	No	Yes	No	
Emergency								
Revascularization <5 years								
Recent coronary evaluation								
Major				2	1 (50%)	92	13 (68%)	89 (97%)
Intermediate		Low				19	1	128 (85%)
Intermediate	Poor			48	9 (19%)	150		
Intermediate	Moderate/excellent	Intermediate				8		6 (75%)
Intermediate	Moderate/xcellent	High		89	20 (33%)			
Minor or no	Poor	Intermediate/low				68		64 (94%)
Minor/no	Poor	High		46	8 (17%)			
Minor/no	Moderate/excellent					188		166 (88%)
<b>Total</b>				<b>185</b>	<b>38 (21%)</b>	<b>526</b>		<b>467 (89%)</b>

ACC, The American College of Cardiology; AHA, American Heart Association



In total, 185 patients (26%) fulfilled the criteria to recommend preoperative noninvasive cardiac testing. However, clinicians had performed testing in only 38 of those cases (21% (95% CI: 15-28%)). Of those 38 patients, 17 (45%) had abnormal test results. Conversely, of the 526 patients for whom testing was not recommended, guidelines were followed in 467 patients (89% (95% CI: 86-91%)) in clinical practice, as shown in the last columns of Table 2. So 59 (11% (95% CI: 9-14%)) patients were noninvasively tested while not recommended. As inherent to the algorithm, the 185 patients who fulfilled the guideline criteria to undergo noninvasive cardiac testing had a significantly higher cardiac risk profile than the patients for whom testing was not recommended (Table 3). In clinical practice, a sex difference was observed as 84% of those patients who underwent noninvasive testing were men, compared to 68% males in the not-tested group ( $P=.002$ ). Furthermore, tested patients were more likely to have evidence of an ischemic heart disease. Regarding the procedural risk, we observed a clear difference between guideline recommendation and clinical practice, because one third of the tested patients underwent a low-risk procedure, whereas testing was hardly recommended in this group.

### **Risk modification**

Regarding the above guideline based risk evaluation, differences were observed in cardiovascular medical therapy among different subgroups of patients. Overall, patients who had not been tested, irrespective of guideline recommendation, received less cardioprotective medications, whereas patients who underwent noninvasive testing were significantly more often treated with cardiovascular drugs (beta-blockers 43% versus 77%, statins 52% versus 83%, platelet inhibitors 80% versus 85%, respectively; all  $P$ -values  $<.05$ ). No differences in medical treatment were observed between patients who had not been tested in accordance and discordance to the guidelines (beta-blockers 42% versus 48%, statins 52% versus 52%, platelet inhibitors 80% versus 78%, respectively; all  $P$ -values  $>.20$ , Figure 2).

Moreover, we did not observe significant differences in cardiovascular medical therapy between patients with a normal and patients with an abnormal test result. For example, in the 38 patients who were tested according to the guidelines, the percentage beta-blocker users was 71% and 77% for patients with normal and abnormal test results, respectively ( $P$ -value = .73). These percentages are in line with the group tested while not recommended, 78% in patients with a normal test result and 83% in patients with an abnormal result ( $P= .60$ ). Preoperative revascularization was observed in a small number of patients.

Thirty-six patients (5%) had cardiovascular complications within 30 days after surgery. In patients treated according to the guidelines with respect to noninvasive testing, the percentage complications at 30 day was 7% (95% CI: 5-9%). In contrast, the complication rate was 4% (95% CI: 1-7%) in patients tested in discordance to the guidelines. After 1 year total mortality was 11%. Mortality was 11% (95% CI: 8-14%) in patients tested according to the guidelines and 12% (95% CI: 8-16%) in patients who were tested in discordance with the guidelines.

**TABLE 3 - Differences in baseline characteristics**

	Guideline recommendation			Observed in clinical practice		
	Testing not recommended (N=526)	Testing recommended (N=185)	P-value	Testing not performed (N=614)	Testing performed (N=97)	P-value
<b>Demographics</b>						
Mean age (±SD)	67±11	68±9	.084	67±11	67±9	.716
Male gender (%)	360 (68)	136 (73)	.196	415 (68)	81 (84)	.002
<b>Cardiovascular history, n (%)</b>						
Angina pectoris	59 (11)	40 (22)	<.001	72 (12)	27 (28)	<.001
Myocardial infarction	68 (13)	38 (21)	.012	83 (14)	23 (24)	.009
Heart failure	27 (5)	10 (5)	.886	37 (6)	1 (1)	.046
Stroke or tia	99 (19)	24 (13)	.070	109 (18)	14 (14)	.422
Arrhythmia	44 (8)	33 (18)	<.001	69 (11)	8 (8)	.378
Valvular disease	31 (6)	19 (10)	.045	44 (7)	6 (6)	.726
Previous revascularisation	83 (16)	33 (18)	.515	89 (15)	27 (28)	.001
<b>Clinical risk factors, n (%)</b>						
Obesity	53 (10)	24 (13)	.275	63 (10)	14 (14)	.219
Current smoker	188 (36)	68 (37)	.805	229 (37)	27 (28)	.071
Hypertension	181 (34)	92 (50)	<.001	232 (38)	41 (42)	.399
Diabetes Mellitus	90 (17)	59 (32)	<.001	131 (21)	18 (19)	.532
Renal insufficiency	33 (6)	18 (10)	.117	44 (7)	7 (7)	.986
COPD	70 (13)	31 (17)	.248	86 (14)	15 (16)	.702
<b>Procedure, n (%)</b>						
Low-risk	353 (67)	1 (1)		320 (52)	34 (35)	
Intermediate-risk	29 (6)	0		23 (4)	6 (6)	
High-risk	144 (27)	184 (99)		271 (44)	57 (59)	
<b>Functional capacity, n (%)</b>						
Poor	146 (28)	94 (51)	<.001	208 (34)	32 (33)	.795
Moderate	380 (72)	91 (49)		406 (66)	65 (67)	

COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack.

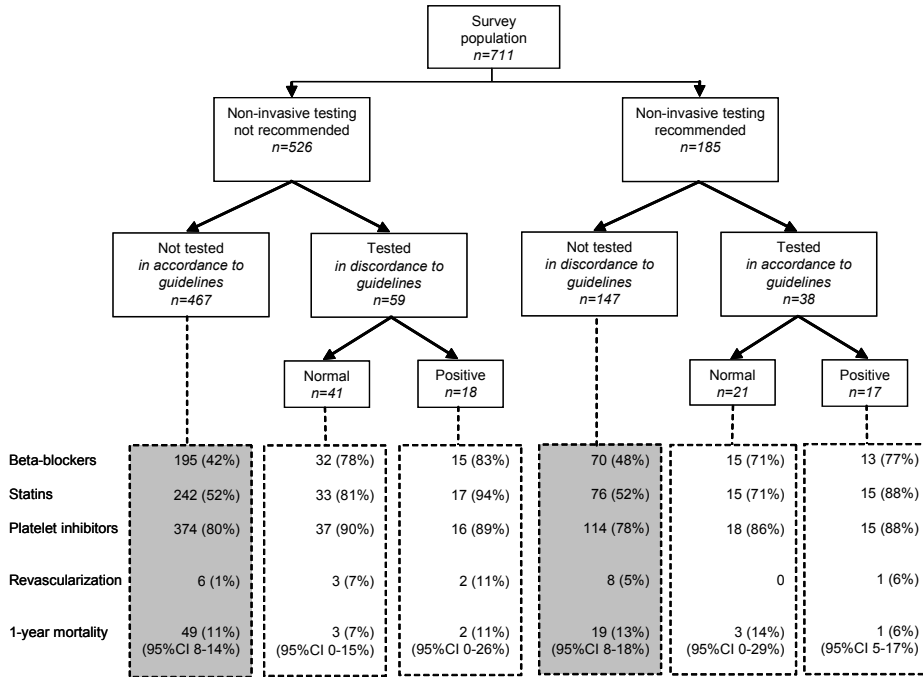


FIGURE 2 - Risk evaluation and modification.

## DISCUSSION

The value of using the ACC/AHA guidelines in patients undergoing vascular surgery is still under debate. Whereas some demonstrated improved risk stratification<sup>8,9</sup> and decreased resource use<sup>13</sup>, others showed that this did not result in a beneficial outcome.<sup>10-12,14</sup> Our study demonstrated poor agreement between clinical practice and the ACC/AHA guideline recommendations for perioperative cardiovascular evaluation for noncardiac surgery. Only one out of each 5 patients underwent noninvasive testing when recommended. Furthermore, high risk patients defined by ACC/AHA guidelines who did not undergo testing although recommended, received as little cardiac management as the low risk population.

The core of the ACC/AHA guidelines is an algorithm, which summarizes the stepwise process leading to practical recommendations as performing noninvasive cardiac testing. In general, two strategies have been used to reduce the incidence of perioperative MIs and other cardiac complications: preoperative coronary revascularization and pharmacological treatment. In recent years, more attention has focused on the role of pharmacological treatment, whereas

controversy remains to the appropriate management of patients identified preoperatively as having significant but correctable coronary artery disease. In our study population, only a small number of patients underwent preoperative coronary revascularization. Recently, the Coronary Artery Revascularization Prophylaxis trial demonstrated that in short term there is no reduction in the number of post-operative myocardial infarctions, deaths or duration of stay in the hospital, or in long-term outcomes in patients who underwent preoperative coronary revascularization compared with patients who received optimized medical therapy.<sup>15</sup> These findings apply to patients with stable coronary artery disease, but the optimal perioperative management for patients with left main disease, severe left ventricular dysfunction, unstable angina pectoris, and aortic stenosis has to be investigated in controlled clinical trials.

Besides coronary revascularization, an extensive preoperative cardiac evaluation with noninvasive cardiac testing might improve outcome by inciting an improvement in medical management in the perioperative period. Perioperative beta-blockers and statins have in this way shown a significant benefit in decreasing perioperative cardiac mortality and morbidity.<sup>16-18</sup> Because of increasing evidence of the beneficial effect of beta-blocker in the perioperative period, recently the guidelines section on perioperative beta-blocker therapy is updated.<sup>19</sup> Results on beta-blocker use from this survey, published before, showed an underuse of beta-blockers in vascular surgery patients, also in high-risk patients.<sup>20</sup> In the current study, we found that patients who had not been tested, irrespective of guideline recommendation, received less cardioprotective medications compared with patients who underwent noninvasive testing. All of these patients were apparently regarded as a low-risk population and consequently received less medical treatment. Thus, high-risk patients in whom testing was recommended but who did not undergo testing received comparable low medical therapy as the real low risk population. That is, under-diagnosis seems to lead to under-treatment. Conversely, patients who were tested while it was not recommended were medically treated as high risk patients. This was irrespective of the test result.

A variety of barriers to guideline adherence have been pointed out: out-of-date guidelines, lack of awareness, agreement, or self-efficacy, lack of outcome expectancy, the inertia of previous practice, and external barriers.<sup>21</sup> It should also be noted that the treatment of individual patients is more complex than simply following guidelines. In addition, the algorithm proposed in the guidelines had to rely predominantly on observational data and expert opinion because there were no randomized trials to help define the process. Several of those barriers may be responsible for the poor adherence to guidelines as we observed. For example, the ACC/AHA guidelines do not incorporate the Revised Cardiac Risk Index, which is nowadays a commonly used perioperative risk-stratification approach in the selection of noninvasive cardiac testing and medical treatment in the intermediate-risk patients. Furthermore, the recent DECREASE-II study showed that cardiac testing for intermediate-risk patients before major vascular surgery, as recommended by the

guidelines of the ACC/AHA, provided no benefit in patients receiving beta-blocker therapy with tight heart rate control.<sup>22</sup> Additionally, the ACC/AHA guidelines recommend that the patient's functional capacity should be incorporated into the overall risk assessment. Although many studies have indeed shown that better functional capacity indicates a better long-term survival,<sup>23</sup> good exercise tolerance does not necessarily signify the absence of significant coronary disease. Furthermore, patients with severe peripheral artery disease frequently suffer from intermittent claudication that can give limitations to the assessment of functional capacity and could therefore not be a very good discriminative factor in this patient population. Another reason for the poor adherence to guidelines we observed may be a lack of agreement between guidelines. In addition to the ACC/AHA guidelines, the American College of Physicians also developed guidelines for preoperative risk assessment. A recent study reported that the recommendations for preoperative cardiac testing significantly differed when applying these two different guidelines.<sup>24</sup> Successful perioperative evaluation and management of high-risk cardiac patients undergoing noncardiac surgery requires careful teamwork and communication between surgeon, anaesthesiologist, cardiologist and the patient's primary care physician. In addition, the algorithm of the ACC/AHA guidelines could be too complicated for use in routine care, as evident by several publications of the ACC/AHA algorithm as a simplified formula.<sup>25</sup> This reflects that guidelines must be straightforward, simple to use, uniform and based on recent scientific evidence.

The limitations of this study are those inherent to observational studies involving voluntarily participating hospitals. Although we included a wide spectrum of hospitals, the results could be biased towards better than average practices. Nevertheless, because patient inclusion was consecutive in all participating sites, we trust that the survey depicts ongoing clinical practice. It should be noted also that our study was limited by its sample size, reflected by the limited number of patients in the subgroups. Larger studies are needed to confirm observed findings.

In conclusion, our study showed poor agreement between ACC/AHA guideline recommendations and daily clinical practice for both noninvasive testing and cardiac management.

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# CHAPTER

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## **Increase of 1-year mortality after perioperative beta-blocker withdrawal in endovascular and vascular surgery patients**

# 12

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# ABSTRACT

**Objective:** To assess the relation between beta-blocker use, underlying cardiac risk, and 1-year outcome in vascular surgery patients, including the effect of beta-blocker withdrawal.

**Design:** Prospective survey

**Materials:** 711 consecutive peripheral vascular surgery patients from 11 hospitals in The Netherlands between May and December 2004

**Methods:** Patients were evaluated for cardiac risk factors, beta-blocker use and 1-year mortality. Low and high risk was defined according to the Revised Cardiac Risk Index. Propensity scores for the likelihood of beta-blocker use were calculated and regression models were used to study the relation between beta-blocker use and mortality.

**Results:** 285 patients (40%) received beta-blockers throughout the perioperative period (continuous users). Only 52% of the 281 high risk patients received continuous beta-blocker therapy. Beta-blocker therapy was started in 29 and stopped in 21 patients, respectively. One-year mortality was 11%. After adjustment for potential confounders and the propensity of its use, continuous beta-blocker use remained significantly associated with a lower 1-year mortality compared to nonusers (HR=0.4; 95%CI=0.2-0.7). In contrast, beta-blocker withdrawal was associated with an increased risk of 1-year mortality compared to nonusers (HR=2.7; 95%CI=1.2-5.9).

**Conclusions:** We demonstrated an underuse of beta-blockers in vascular surgery patients, even in high-risk patients. Perioperative beta-blocker use was independently associated with a lower risk of 1-year mortality compared to non-use, while perioperative withdrawal of beta-blocker therapy was associated with a higher 1-year mortality.

## INTRODUCTION

Patients with peripheral vascular disease frequently have underlying (a)symptomatic coronary artery disease (CAD). When undergoing vascular repair they are at increased risk of life-threatening peri- and postoperative cardiac complications, especially myocardial infarction (MI).<sup>1,3</sup> In order to improve postoperative outcome of noncardiac surgery patients, the American College of Cardiology (ACC) and the American Heart Association (AHA) developed guidelines for perioperative cardiac risk evaluation and risk reduction.<sup>4</sup> As far as risk reduction strategies are concerned, guidelines recommend beta-blocker therapy in all high-risk patients, since several randomised clinical trials demonstrated a significant reduction in perioperative cardiac death or MI by such therapy.<sup>5,6</sup> In contrast to high cardiac risk patients, evidence in favour of beta-blocker use in patients with low or intermediate risk is less clear.

The pathophysiology of a perioperative MI (PMI) is not entirely clear. In patients with severe CAD, PMI may be caused by a sustained myocardial supply/demand imbalance due to prolonged tachycardia and increased myocardial contractility. Beta-blockers can restore the supply/demand mismatch through a reduction of myocardial oxygen consumption by decreasing sympathetic tone and myocardial contractility. At the other hand, it has been suggested that sudden withdrawal of beta-blockers around the time of peripheral vascular surgery may increase the risk of PMI.<sup>7,8</sup> The occurrence of withdrawal syndromes after withdrawal of beta-blocker use in patients with CAD have been widely reported.<sup>9-12</sup> In contrast, this phenomenon is still unclear in vascular surgery patients.

Although guidelines recommend beta-blocker therapy, little is known about the application of beta-blockers in patients undergoing vascular surgery in clinical practice. Available data suggests that beta-blockers are underused in patients undergoing vascular repair.<sup>13-16</sup>

The objective of the study was to assess the relation between the prescription of beta-blockers, underlying cardiac risk, and 1-year mortality in consecutive peripheral vascular surgery patients. We were especially interested in the effect of beta-blocker withdrawal.

## METHODS

### Study population

Between May and December 2004, a survey of clinical practice was conducted in 11 hospitals in The Netherlands. This survey was an integrated part of the infrastructure of the survey program supported by The Netherlands Heart Foundation in the context of the Euro Heart Survey Programme. Five hospitals were located in the centre part of the country, three centres in the

northern region and three in the southern region. The participating sites included 2 small centers (<400 beds), 5 of intermediate size (400 to 800 beds) and 4 large centers (>800 beds). Two centres were university hospitals, which act as tertiary referral centers.

All patients who were admitted to the vascular surgery department of the participating hospitals were screened. Patients undergoing peripheral vascular repair were eligible for participation in the survey. We excluded patients below the age of 18 years. Patients had to provide informed consent. The medical ethics committees of the participating hospitals approved the study.

### **Data collection**

Trained research assistants obtained data on patient characteristics, applied diagnostic procedures, cardioprotective treatment and the surgical procedure from the patients' hospital charts. All data were entered into the electronic Case Record Form (eCRF) and transferred regularly to the central database at Erasmus MC via the Internet. Data entered into the eCRF were automatically checked for completeness, internal consistency and accuracy. The data management staff at Erasmus MC performed additional edit checks. If necessary, queries were resolved with the local research assistants.

### **Endpoints**

This survey was designed to evaluate the application of guidelines in patients undergoing peripheral vascular surgery. Outcome and adverse events were reported at 30-days and 1-year after surgery by the local research assistants, and not adjudicated by an independent endpoint committee. Since we realise the survey design is susceptible to observer bias, especially with regard to "soft" endpoints, we choose the incidence of all-cause mortality at one year after surgery as endpoint of this study.

### **Data analysis**

We determined the cardiac risk score for each patient in our dataset, according to the Revised Cardiac Risk index that was developed by Lee et al.<sup>17</sup>, and one point was assigned to each of the following characteristics: open vascular surgery, history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, insulin therapy for diabetes mellitus and renal failure. Hypertension was recorded if patients presented with a blood pressure  $\geq 140/90$  mm Hg or if patients were medically treated for hypertension. Diabetes mellitus was recorded if patients presented with a fasting glucose level  $\geq 7.0$  mmol/l, or in those who required treatment. Renal insufficiency was recorded if patients presented with a serum creatinine level  $\geq 2.0$  mg/dl or in those who required dialysis. Obesity was defined as having a Body Mass Index  $\geq 30$ .

We defined four categories of beta-blocker use (Table 1): continuous users, who used beta-blockers throughout the in-hospital period; stoppers, who used and subsequently stopped the beta-blocker in the perioperative period; starters, who started the beta-blocker postoperatively; and nonusers, who didn't receive a beta-blocker.

Dichotomous data are described as numbers and percentages, and continuous data are presented as means with standard deviations (SD). Differences in baseline characteristics between beta-blocker users were evaluated by analysis of variances (ANOVA) and Chi-square tests, where appropriate.

We developed a propensity score for the likelihood of receiving continuous beta-blocker therapy, and used applied multivariable logistic regression analysis to calculate the propensity score. The variables included in the model were: age, gender, obesity, smoking, hypertension, arrhythmia, valvular disease, COPD, Revised Cardiac Risk Index, statins, calcium-channel blockers, ACE-inhibitors, angiotensin-receptor blockers, diuretics, heparins, oral nitrates, folium acid, antibiotics, vitamin K antagonists, antiplatelet agents. The performance of the propensity score model was studied with respect to discrimination and calibration. Discrimination refers to the ability to distinguish beta-blocker users from nonusers; it was quantified by the c-statistic. Calibration refers to whether the predicted probability of beta-blocker use is in agreement with the observed probability and was measured with the Hosmer-Lemeshow goodness-of-fit-test.

The method of Kaplan-Meier was used to describe the incidence of death over time. A log-rank test was applied to study differences in survival between continuous users, stoppers, starters and nonusers. These relations were further evaluated by multivariable Cox' proportional hazard regression analysis, with adjustment for confounders and propensity score. All potential confounders (age, gender, obesity, smoking, hypertension, arrhythmia, valvular disease, COPD and the Revised Cardiac Risk Index) were entered in the multivariable model to ensure giving an unbiased as possible estimate for the relation between beta-blocker use and one-year mortality. Crude and adjusted Odds and Hazard ratios are reported with corresponding 95% confidence intervals (CI). For all tests, a *P*-value <0.05 (two-sided) was considered significant. All statistical analyses were performed using SPSS statistical software.

## RESULTS

Of the total of 711 patients, 285 patients (40%) received a beta-blocker throughout the perioperative period, i.e. the continuous users (Table 1). Beta-blocker therapy was started in 29 patients and stopped in 21 patients, respectively. In 19% of those 21 stoppers the beta-blocker was stopped on the day of intervention. Overall, 376 patients (53%) didn't use a beta-blocker at all.

TABLE 1 - Definitions of beta-blocker use						
	Use at day of surgery	Use at discharge*	N	In-hospital mortality	30 day mortality	1-year mortality
Beta-blockers						
Continuous users**	Yes	Yes	285	5 (2%)	5 (2%)	17 (6%)
Stoppers	Yes	No	21	5 (24%)	5 (24%)	8 (38%)
Starters	No	Yes	29	0 (0%)	0 (0%)	3 (10%)
Non users	No	No	376	17 (5%)	18 (5%)	49 (13%)

\*Discharge home or in-hospital death  
 \*\*For example, continuous users were defined as receiving beta-blockers at the day of surgery until the day of discharge

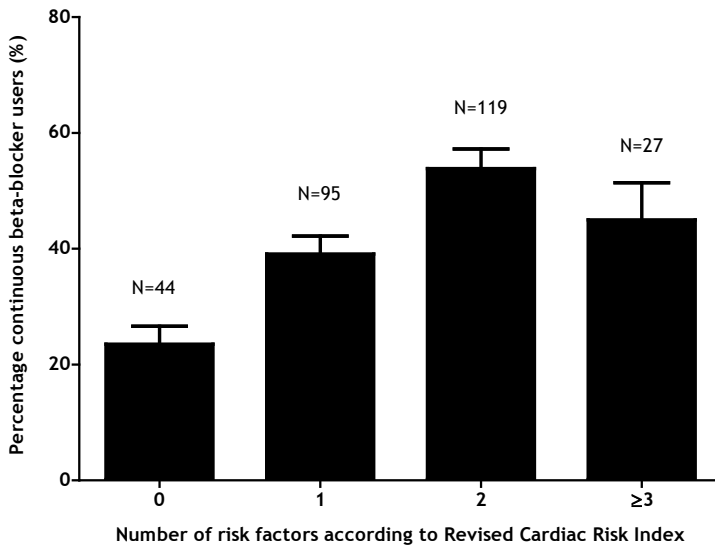


FIGURE 1 - Continuous beta-blocker use by the Revised Cardiac Risk Index.

As shown in Figure 1, continuous beta-blocker was positively associated with the Revised Cardiac Risk Index. However, only 52% of patients at high cardiac risk, with 2 or more risk factors, received continuous beta-blocker therapy. As shown on the Kaplan-Meier curve (Figure 2), not receiving beta-blocker therapy was associated with a high mortality rate but withdrawal of beta-blocker therapy was associated with an even worse survival. Log rank test gave a significant overall difference in mortality among the different beta-blocker categories ( $P < .001$ ).

Table 2 shows the baseline characteristics according to the four beta-blocker categories. The mean age of the study population was 67 years, and 70% were men. Half of patients underwent an endovascular procedure ( $n=354$ ), 328 patients (46%) had open surgery and 29 patients (4%) underwent carotid endarterectomy. The nonusers represent a low cardiac risk group with 71% having no or only one risk factor according to the Revised Cardiac Risk Index. In contrast, about half of the continuous users (51%) and stoppers (52%) had 2 or more risk factors.



TABLE 2 - Baseline characteristics

	Continuous users (n=285)	Stoppers (n=21)	Starters (n=29)	Nonusers (n=376)	P-value*
<b>Demographics</b>					
Mean age (±SD)	67 ± 9	66 ± 11	68 ± 9	72 ± 11	Ns
Male gender	209 (73)	19 (91)	24 (83)	244 (65)	.006
<b>Cardiovascular history</b>					
Angina pectoris	62 (22)	1 (5)	4 (14)	32 (9)	<.001
Myocardial infarction	66 (23)	4 (19)	5 (17)	31 (8)	<.001
Heart failure	15 (6)	2 (12)	1 (4)	19 (6)	Ns
Stroke or tia	59 (21)	3 (14)	6 (21)	55 (15)	Ns
Arrhythmia	37 (13)	1 (5)	3 (10)	36 (10)	Ns
Valvular disease	25 (9)	3 (14)	3 (10)	19 (5)	.050
Previous revascularisation	68 (24)	2 (10)	9 (31)	37 (10)	<.001
<b>Clinical risk factors</b>					
Obesity	41 (14)	1 (5)	0	35 (9)	.049
Current smoker	95 (33)	7 (33)	11 (38)	143 (38)	Ns
Hypertension	135 (47)	7 (33)	10 (34)	121 (32)	<.001
Diabetes mellitus	64 (23)	3 (14)	8 (28)	74 (20)	Ns
Renal insufficiency	22 (8)	3 (14)	1 (3)	25 (7)	Ns
COPD	39 (14)	5 (24)	3 (10)	54 (14)	Ns
<b>Surgical procedure</b>					
Endovascular	131 (46)	2 (9)	10 (34)	211 (56)	.010
Carotid endarterectomy	16 (6)	1 (5)	2 (7)	10 (3)	
Open	138 (48)	18 (86)	17 (59)	155 (41)	
<b>Revised Cardiac Risk Index<sup>a</sup></b>					
0	44 (15)	1 (5)	4 (14)	138 (37)	<.001
1	95 (33)	9 (43)	11 (38)	128 (34)	
2	119 (42)	7 (33)	10 (35)	85 (22)	
≥3	27 (10)	4 (19)	4 (14)	25 (7)	

COPD, chronic obstructive pulmonary disease; Ns, not significant

\*Overall difference between groups

<sup>a</sup> Variables included in the Revised Cardiac Risk Index; open surgical procedure, ischaemic heart disease, history of congestive heart failure, history of cerebrovascular disease, insulin therapy for diabetes mellitus and renal failure

Postoperative in-hospital mortality occurred in 27 patients (4%) and at 1-year follow-up total mortality was 11%, of which 21% died of cardiovascular causes. Table 3 shows the univariable and multivariable associations between beta-blocker use and 1-year mortality. Continuous beta-blocker use in the perioperative period remained an independent predictor for one-year survival (HR=0.3 (95%CI=0.2-0.6)). In contrast, perioperative withdrawal of beta-blockers was independently associated with an increasing risk of one year mortality (HR=2.6 (95%CI=1.2-5.6)) compared to non-use. When the propensity score was included in the model with all the covariates to adjust also for the chance of prescription of beta-blockers, the effect of continuous beta-blocker therapy and withdrawal was comparable to the analysis adjusted for covariates.

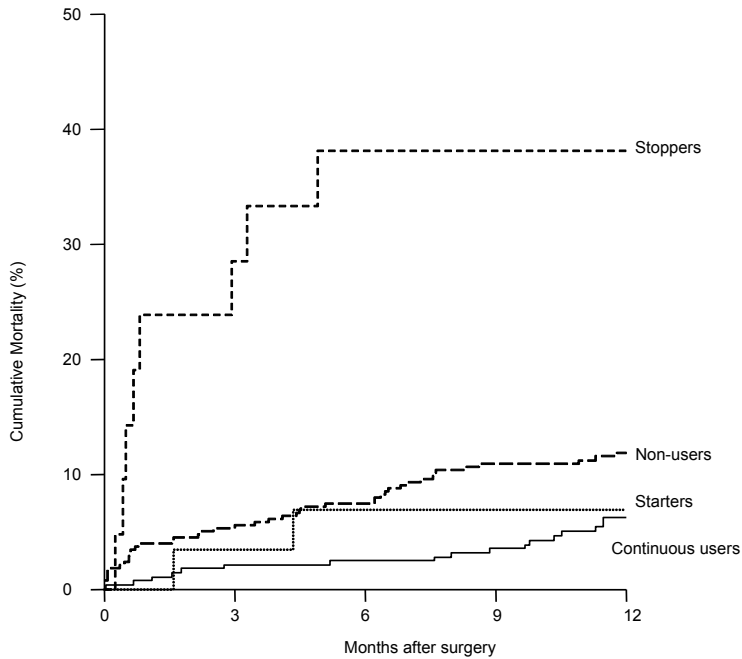


FIGURE 2 - Kaplan-estimate of 1-year mortality, stratified according to the use of beta-blockers.

TABLE 3 - Multivariable associations of beta-blocker use and 1-year mortality

	Unadjusted		Adjusted for confounders <sup>a</sup>		Adjusted for confounders and propensity score <sup>b</sup>	
	HR	95% CI	HR	95% CI	HR	95% CI
<b>Beta-blocker use</b>						
No use	Reference		Reference		Reference	
Continuous	0.4	0.3-0.8	0.3	0.2-0.6	0.4	0.2-0.7
Stoppers	3.7	1.8-7.9	2.6	1.2-5.6	2.7	1.2-5.9
Starters	0.8	0.2-2.4	0.6	0.2-1.9	0.6	0.2-1.9
C-index	0.63		0.81		0.82	

<sup>a</sup> Adjusted for age, gender, obesity, smoking, hypertension, arrhythmia, valvular disease, COPD and the Revised Cardiac Risk Index

<sup>b</sup> Variables included in the propensity score model were: age, gender, arrhythmia, valvular disease, obesity, smoking, hypertension, COPD, Revised Cardiac Risk Index, statins, calcium-channel blockers, ACE-inhibitors, angiotensin-receptor blockers, diuretics, heparins, oral nitrates, folium acid, antibiotics, vitamin K antagonists, antiplatelet agents.

## DISCUSSION

Guidelines on perioperative care recommend that high cardiac risk patients should receive a beta-blocker.<sup>4</sup> The present survey results of beta-blocker use in daily clinical practice, however, provide evidence for an underuse of beta-blockers in vascular surgery, even in patients at high cardiac risk. Continuous beta-blocker use is associated with a lower risk of mortality, while an adverse effect of perioperative withdrawal of beta-blockers was observed.

The survey shows a clear relationship between beta-blocker use and cardiac risk stratification according to the Revised Cardiac Risk Index: the higher the cardiac risk, the higher the prescription rate of beta-blockers. These results are in line with the guidelines which recommend beta-blocker therapy in especially high-risk patients. However, improvement is necessary because still a sizeable proportion of patients are not treated according to the guidelines. Identified barriers in following clinical guidelines, such as lack of awareness, lack of agreement with the guidelines, difficult to use (not concise enough), and so on, might partly explain the limited adherence to guidelines in clinical practice.<sup>18,19</sup>

Our study demonstrated that continuous beta-blocker use during the perioperative period is independently associated with a better postoperative outcome. This result is partly in contrast to the study of Lindenauer who assessed the association between the perioperative use of beta-blockers and in-hospital mortality and found that beta-blockers were harmful in low-risk patients, neutral in patients at intermediate risk, and beneficial in high-risk patients.<sup>20</sup> However, this observed adverse effect in the low risk population has been questioned because beta-blockers may have been prescribed in response to a cardiac complication, rather to prevent one.<sup>21</sup> Further randomised controlled trials are needed to assess the benefits of beta-blocker use in patients at low or intermediate cardiac risk.

Patients in whom beta-blockers were perioperatively stopped have an increased risk of mortality compared to both continuous users and nonusers. This finding clearly reveals the high risk of beta-blocker withdrawal. Similar results were found by Shammash et al. who reported that discontinuing beta-blockers immediately after surgery may increase the risk of postoperative cardiovascular morbidity and mortality.<sup>7</sup> However, the sample size of this study was very small. A possible mechanism for the explanation of the observed withdrawal phenomenon is that exposure to a beta-blocker produces an increased number of postsynaptic beta-receptors and subsequent withdrawal is likely to result in a state of hypersensitivity.<sup>12</sup> Continuation of beta-blocker therapy is very important and if oral intake is impossible early after surgery intravenous administration is a good alternative.

This study clearly reveals the need for more awareness of routine and continued beta-blocker therapy in the peri- and postoperative period. To improve this awareness, protocols could

be developed and implemented in clinical practice.<sup>22,23</sup> Future surveys are important to assess improvement of beta-blocker therapy over time, as shown in the comparison of Euroaspire I and II, and to explore reasons for discontinuing recommended treatment strategies.<sup>24</sup>

An important limitation of this observational study is that the use of beta-blockers was not randomised and therefore subject to confounding by indication. However, giving the evidence supporting the adverse effects of beta-blocker withdrawal, a randomised trial of beta-blocker withdrawal may be considered unethical. Propensity analysis was performed to adjust as much as possible for the bias inherent in the decision about beta-blocker therapy.<sup>25</sup> Another limitation of this study is the small number of patients who stopped beta-blocker therapy. Further research with more patients is necessary to confirm our findings.

In conclusion, this study demonstrates an underuse of beta-blocker therapy in patients undergoing vascular repair, even in patients at high cardiac risk. Continued beta-blocker use in those patients is associated with a lower risk of mortality. However, withdrawal of beta-blocker therapy prior to surgery is accompanied with a higher risk of mortality compared to nonusers. Further research is necessary in this area and subsequent effective strategies are needed to implement guidelines and results of clinical trials in clinical practice.

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# CHAPTER

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## **Statin use in the elderly: results from a peripheral vascular survey in The Netherlands**

# 13

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## ABSTRACT

**Background:** The prevalence of death due to cardiovascular disease increases steeply in vascular surgery patients with increasing age. Observational data in coronary heart disease and heart failure patients suggest that elderly patients are less optimally treated compared to younger patients. The aim of this study was to examine the differences in clinical characteristics and medical therapy of the elderly compared to younger patients in vascular surgery. Furthermore, we assessed the effect of statins on 1-year mortality in an unselected patient population.

**Methods:** Data on 711 consecutive peripheral vascular surgery patients were collected from 11 hospitals in The Netherlands in 2004. Elderly patients were defined as patients with an age above 70 years. Multivariable logistic regression analysis was used to identify clinical characteristics and medical therapy associated with older age. The effect of statins on 1-year mortality was assessed with Cox proportional hazard regression analysis.

**Results:** The mean age was  $67 \pm 10$  years and 299 (42%) patients were older than 70 years of age. Elderly patients showed a significant higher cardiac risk profile according to the Lee Cardiac Risk Index (Lee-Index) ( $\geq 2$  risk factors: 50% vs. 32% in younger patients,  $P < .001$ ). Multivariable analysis showed that older patients presented with a significant higher Lee Index, a higher incidence of cardiac arrhythmias (OR=1.9; 95% CI=1.1-3.3) and chronic obstructive pulmonary disease (COPD) (OR=2.8; 95%CI=1.7-4.7). However, smoking (OR=0.5; 95%CI=0.3-0.7) was less common in the elderly. Statins were significantly less often prescribed in the elderly (OR=0.6; 95%CI=0.3-0.8), although a beneficial effect of statins on 1-year mortality (HR=0.4, 95%CI=0.1-0.7) was observed.

**Conclusion:** Elderly patients undergoing vascular surgery had a higher cardiac risk profile than younger patients. Despite this high cardiac risk and the beneficial effect, our study demonstrated that statins were less often used in elderly patients.

## INTRODUCTION

Cardiovascular disease remains the major cause of death and morbidity across Europe. The global ageing phenomenon will even further increase the burden of cardiovascular disease. Overall, approximately 40% of deaths are caused by cardiovascular diseases, with a prevalence of up to 50% in the elderly.<sup>1,2</sup>

Ageing of the world's population can be seen as an indicator of improving global health. A high standard of living and the good quality of health care have contributed to the increased life expectancy.<sup>1</sup> On the other hand, ageing also enforces a change in health care toward the elderly population. In contrast to the past, major surgical interventions are increasingly performed in the elderly. Furthermore, a recent study performed in 1351 patients undergoing noncardiac surgery showed that the rate of cardiac events increased with advanced age, independent of other clinical variables, in patients with myocardial perfusion abnormalities during stress scintigraphy.<sup>3</sup> Despite this increased cardiovascular risk in the elderly, available data from surveys in cardiology suggest that evidence-based therapies are less frequently used in the elderly population.<sup>4,6</sup> A major point of discussion in this context is the effectiveness of medical therapy in the elderly. More research is conducted in the elderly these days and, for example, statins have shown to be also beneficial in the increasing group of coronary artery disease patients with advanced age.<sup>7</sup>

The aim of this study was to examine the differences in clinical characteristics and medical therapy of the elderly compared to younger patients in vascular surgery. Furthermore, we assessed the effect of statins on 1-year mortality in an unselected patient population.

## METHODS

### Study population

Between May and December 2004, a survey of clinical practice was conducted in 11 hospitals in The Netherlands.<sup>8</sup> A total of 711 patients were consecutively enrolled. This survey was an integral part of the infrastructure of the survey program supported by The Netherlands Heart Foundation in the context of the Euro Heart Survey Programme. All patients who were admitted to the vascular surgery department of the participating hospitals were screened. Patients undergoing peripheral vascular repair were eligible for participation in the survey. The medical ethics committees of the participating hospitals approved the study and patients provided informed consent.

### Data collection

Trained research assistants obtained data on patient characteristics, diagnostic procedures,

cardioprotective treatment, and the surgical procedure from the patients' hospital charts. All data were entered into an electronic Case Record Form (eCRF) and transferred regularly to the central database at Erasmus MC via the Internet. Data entered into the eCRF were automatically checked for completeness, internal consistency and accuracy. The data management staff at Erasmus MC performed additional edit checks. If necessary, queries were resolved with the local research assistants.

### **Clinical characteristics**

In this study, advanced age was defined as above 70 years of age. We determined the cardiac risk score for each patient in our dataset, according to the Lee Cardiac Risk Index<sup>9</sup>, and one point was assigned to each of the following characteristics: open vascular surgery, history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, insulin-dependent diabetes mellitus and renal insufficiency. Hypertension was recorded if patients presented with a blood pressure  $\geq 140/90$  mm Hg or if patients were medically treated for hypertension. Diabetes mellitus was recorded if patients presented with a fasting glucose level  $\geq 7.0$  mmol/l, or in those who required treatment. Renal insufficiency was recorded if patients presented with a serum creatinine level  $\geq 2.0$  mg/dl or in those who required dialysis. Obesity was defined as having a Body Mass Index  $\geq 30$  kg/m<sup>2</sup>.

### **Follow-up**

The endpoint of this study was 1-year mortality after surgery.

### **Statistical Analyses**

Dichotomous data are described as numbers and percentages. Differences in baseline characteristics between young and elderly patients were evaluated by Chi-square tests. Logistic regression analysis was used to identify clinical characteristics and medical therapy (statins, beta-blockers, antiplatelet agents) associated with advanced age as the dependent variable. The clinical characteristics included in the model were: gender, obesity, smoking, hypertension, arrhythmia, valvular disease, chronic obstructive pulmonary disease (COPD) and Lee-Index. Interaction terms were included if statistically significant. Furthermore, the effect of statins on 1-year mortality in a consecutive cohort was evaluated with Cox proportional hazard regression analysis including an interaction term of statin therapy and advanced age. Odds ratios (OR) and Hazard ratios (HR) are reported with corresponding 95% confidence intervals (CI). For all tests, a P-value  $< 0.05$  (two-sided) was considered significant. All statistical analyses were performed using SPSS statistical software (Chicago, Ill).

## RESULTS

The mean age of the 711 patients was 67±10 years and 299 (42%) patients were older than 70 years of age (Table 1). Half of the patients underwent an endovascular procedure (n=354), 328 patients (46%) had open surgery and 29 patients (4%) underwent carotid endarterectomy. Elderly patients showed a significant higher cardiac risk profile according to the Lee Risk Index (≥2 risk factors: 50% vs. 32%,  $P<.001$ ). The main contributable factors in the Lee Index were history of ischemic heart disease (42% vs. 30%,  $P=.001$ ), heart failure (9% vs. 3%,  $P<.001$ ) and a history of a cerebrovascular event (21% vs. 15%,  $P=.024$ ).

Logistic regression analysis with advanced age as the dependent variable showed that elderly patients presented with a significant higher Lee Risk Index (1 risk factor: OR=1.2, 95%CI=0.8-1.9; 2 risk factors: OR=2.0, 95%CI=1.3-3.1; ≥2 risk factors: OR=2.8, 95%CI= 1.5-5.4) compared to younger patients. Also a higher incidence of cardiac arrhythmias (OR=1.9, 95%CI=1.1-3.3) and COPD (OR=2.8; 95%CI=1.7-4.7) was observed in the elderly. However, smoking (OR=0.5, 95%CI=0.4-0.7) was less common in the elderly. A significant interaction term was observed between smoking and COPD (OR=0.2; 95%CI=0.04-0.6). These numbers are visualized in Figure 1.

TABLE 1 - Baseline characteristics

	Age <70 years 412	Age ≥70 years 299	P-value
Male gender, n (%)	285 (69)	211 (70)	.690
Current smoker, n (%)	176 (43)	80 (27)	<.001
Hypertension, n (%)	157 (38)	116 (39)	.852
Diabetes mellitus, n (%)	82 (20)	67 (22)	.418
Renal insufficiency, n (%)	18 (4)	33 (11)	.001
Angina pectoris, n (%)	54 (13)	45 (15)	.460
Myocardial infarction, n (%)	50 (12)	56 (19)	.015
Heart failure, n (%)	11 (3)	27 (9)	.001
Stroke or TIA, n (%)	60 (15)	63 (21)	.024
Previous revascularisation, n (%)	57 (14)	59 (20)	.036
COPD, n (%)	43 (10)	58 (19)	.001
Lee Risk Index <sup>a</sup> , n (%)			<.001
0	127 (31)	60 (20)	
1	152 (37)	91 (30)	
2	108 (26)	113 (38)	
≥3	25 (6)	35 (12)	

TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease.

<sup>a</sup>Variables included in the Lee Risk Index: open surgical procedure, ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, insulin therapy for diabetes mellitus, and renal insufficiency.

TABLE 2 - Medical treatment			
	Age <70 years	Age ≥70 years	P-value
	412	299	
Beta-blockers, n (%)	183 (44)	157 (53)	.033
Statins, n (%)	247 (60)	151 (51)	.012
Platelet inhibitors, n (%)	335 (81)	240 (80)	.727

Of the total population, 48% received beta-blockers, 56% statins, 81% antiplatelets and 59% anticoagulants. Beta-blockers were more often prescribed in elderly patients (53% vs. 44%,  $P=.033$ ), while statins were less common used in these patients (51% vs. 60%,  $P=.012$ ; Table 2). Analysis adjusted for patient characteristics showed that statins were significantly less often prescribed in the elderly ( $OR=0.6$ ;  $95\%CI=0.4-0.8$ ), whereas no differences in prescription of other cardiovascular drugs were observed (Figure 2). As shown in Figure 3, statin use was clearly associated with age. Until the age of 60, we observed an evident increase of statin prescription, whereas afterwards a decline was noticed.

The use of statins was associated with a beneficial effect on 1-year mortality ( $HR=0.3$ ,  $95\%CI=0.1-0.7$ ). No significant interaction was observed between advanced age and statin therapy.

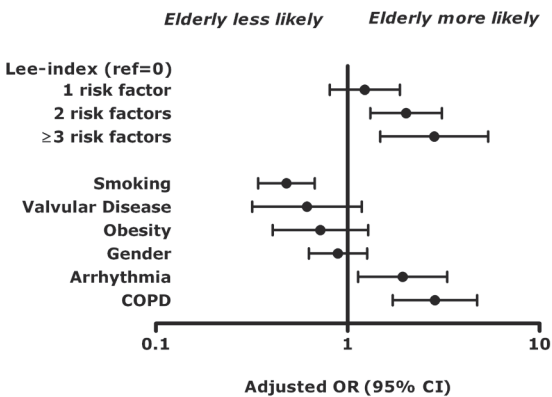


FIGURE 1 - Clinical risk factors associated with elderly age.

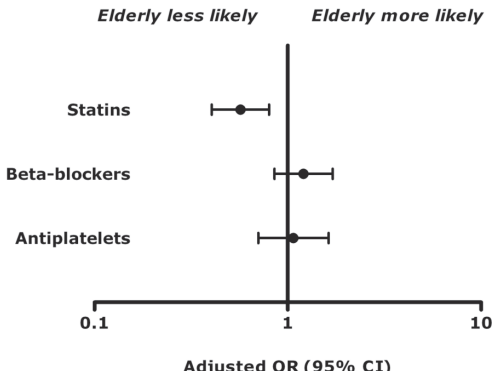


FIGURE 2: Association of the prescription of medical with elderly age.

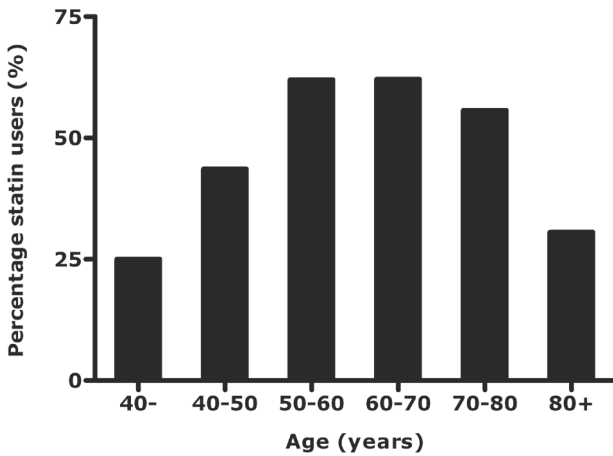


FIGURE 3 - Proportion of patients with statin therapy by age groups.

## DISCUSSION

Elderly patients undergoing vascular surgery had a higher cardiac risk profile than younger patients. Despite this high cardiac risk and the observed beneficial effect of statins, our study demonstrated that statins were less often prescribed in elderly patients.

An important observation of our study is that 42% of our vascular surgery patients consisted of patients over the age of 70. This number clearly reflects the overall ageing phenomenon and also emphasizes the increasing proportion of elderly undergoing surgery. Advanced age has shown to be an important predictor of adverse outcome in patients undergoing vascular surgery.<sup>10,11</sup> Boersma et al. demonstrated that adding advanced age to the Lee Risk Index increased its predictive

value of cardiovascular mortality. The combination of the high incidence of comorbidities in the elderly and the effect of aging itself poses this elderly population as a high risk group. Our study confirms that patients with advanced age have a higher cardiac risk profile according to the Lee Risk Index as compared to the younger group. Furthermore, beyond the Lee Index, COPD and cardiac arrhythmias were significantly associated with advanced age in our study which is also well-known from literature.<sup>12</sup> Evidently, this elderly population is an increasing high risk population which should get extra attention in the coming years.

Statins are widely prescribed in patients with or at risk for coronary heart disease (CHD) because of their well-established lipid lowering capacity. Beyond this property, effects of statins as atherosclerotic plaque stabilization, oxidative stress reduction, and a decrease of vascular inflammation may stabilize coronary artery plaques and thereby prevent plaque rupture and subsequent MI in the perioperative period.<sup>13</sup> Several studies indeed showed a beneficial effect of statins in the vascular surgery patients.<sup>14-18</sup> Our observational study in a consecutive cohort of patients seen in daily clinical practice confirms that the use of statins is associated with reduced mortality. Based on this accumulating evidence, the recently published guidelines on perioperative cardiovascular evaluation and care recommend statin treatment in all patients undergoing vascular surgery.<sup>19</sup>

Despite the benefits of statins on cardiovascular events, we observed that statins were significantly less often prescribed in elderly patients undergoing vascular surgery. Patients with advanced age were almost two times less likely to receive statins in the perioperative period. To our knowledge, this is the first study reporting on underuse of statins in elderly patients undergoing vascular surgery. This in contrast to CHD and heart failure patients where the undertreatment phenomenon in the elderly is widely described.<sup>5,20-22</sup> A secondary prevention study showed that CHD patients aged 65-74 years were half as likely to receive statins as those aged under 65 years while patients aged 75 years were nine times less likely.<sup>21</sup> Moreover, an overall increase in prescription of statins in CHD patients was shown over time in different studies, but importantly, the substantial age inequalities in statin use changed little in the last decade.<sup>5,22</sup>

Different factors may contribute to the low prescription rates in the elderly. First, an important reason is the shortage of evidence in the elderly population as a result of a historical under-representation of this group in randomized controlled trials. These highly selective trial populations lessen generalizability to clinical practice which represents a rather heterogeneous population. A recent study investigating the underutilization of statins in elderly coronary heart disease patients revealed that the primary reason why elderly patients not receiving statins were perceived lack of indication.<sup>23</sup> In recent years, however, more research is conducted in the elderly. To answer the question of statins in elderly patients with CHD, Afilalo et al. conducted a hierarchical bayesian meta-analysis including nine randomized trials with an age range of 65 to 82 years.<sup>7</sup> They



demonstrated a beneficial effect of statins in the elderly and reported a relative reduction of 22% over 5 years (RR=0.8, 95%CI=0.7-0.9) for all causes of mortality. In addition, statins reduced CHD mortality, non-fatal MI, need for revascularization and stroke. Furthermore, a large cohort study indicated that statin therapy was beneficial across all age groups up to 97 years of age with the greatest absolute benefit in the very elderly patients.<sup>20</sup> Importantly, our study in an unselected cohort of vascular surgery patients indicated a comparable significant effect of statin therapy in the elderly compared to younger patients. Although limited by the observational nature of this study, these results hint to extend the effect of statins to patients with advanced age undergoing vascular surgery. As elderly patients have a higher baseline risk, which is also demonstrated in this study, this comparable effect of statins in the elderly will logically result in a greater absolute risk reduction. Furthermore, baseline risk has shown to outweigh potential age-related variations in the efficacy of treatment for the absolute benefits of treatment.<sup>24</sup>

There may also be a greater fear of side-effects in the elderly population, mainly because of polypharmacy and comorbidities. The LIPID study and the Cholesterol Reduction in Seniors Program, however, showed a comparable incidence of adverse events in young and elderly patients.<sup>25,26</sup> Results of the Study Assessing goals in the Elderly (SAGE) indicated that statins were well tolerated in older patients.<sup>27</sup> Furthermore, the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial showed no effect of polypharmacy on pravastatin functioning.<sup>28</sup> And again, because of the high baseline risk in the elderly, the treatment-related adverse effects exert relatively little influence on the net benefits associated with treatment.

Cost-effectiveness may be another point of concern which may relate to the under use of statins. Studies indicate, however, that statin therapy is reasonably cost-effective in the elderly and at least comparable to younger patients. The estimated cost-effectiveness ratio of statin therapy in patients aged 75 to 84 years of age with a history of MI was 18,800 per quality-adjusted life year.<sup>29</sup> This number is quite similar to the ratio in younger patients.<sup>30</sup> Important to note is that cost-effectiveness is also a function of baseline risk, i.e. the high baseline risk of the elderly patient will lead to more favourable cost-effectiveness ratios because of a greater absolute number events would be prevented.

To summarize, our study shows a high proportion of elderly undergoing vascular surgery and indicates that statin therapy seems to be as beneficial in elderly patients as compared to younger patients. This is a crucial fact in a future with increasing life expectancy and rising number of the elderly population. Despite the increased risk of the elderly and the observed beneficial effect of statins in this population, our study revealed that statins were significantly less often used in elderly patients undergoing vascular surgery. More research is needed to further investigate the effect of statin therapy in the elderly in randomized controlled trials and guideline implementation strategies should be improved to increase the prescription of statins in this high risk population.

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# CHAPTER

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## Medication underuse during long-term follow-up in patients with peripheral arterial disease

# 14

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## ABSTRACT

**Background:** Patients with peripheral arterial disease (PAD) constitute a high-risk population. Guideline-recommended medical therapy use is therefore of utmost importance. The aims of our study were to establish the patterns of guideline-recommended medication use in patients with PAD at the time of vascular surgery and after 3 years of follow-up, and to evaluate the effect of these therapies on long-term mortality in this patient group.

**Methods and Results:** Data on 711 consecutive patients with PAD undergoing vascular surgery were collected from 11 hospitals in The Netherlands (enrollment between May and December 2004). After  $3.1 \pm 0.1$  years of follow-up, information on medication use was obtained by a questionnaire ( $n=465$ , 84% response rate among survivors). Guideline-recommended medical therapy use for the combination of aspirin and statins in all patients and beta-blockers in patients with ischemic heart disease was 41% in the perioperative period. The use of perioperative evidence-based medication was associated with a reduction of 3-year mortality after adjustment for clinical characteristics (hazard ratio=0.65; 95%CI=0.45-0.94). After 3 years of follow-up, aspirin was used in 74%, statins in 69% and beta-blockers in 54% of the patients respectively. Guideline-recommended medical therapy use for the combination of aspirin, statins, and beta-blockers was 50%.

**Conclusions:** The use of guideline recommended therapies in the perioperative period was reduction in long-term mortality. However, the proportion of patients receiving these evidence-based treatments - both at baseline and 3 years after vascular surgery - was lower than expected based on the current guidelines. These data highlight a clear opportunity to improve the quality of care in this high-risk group of patients.

## INTRODUCTION

Peripheral arterial disease (PAD) is a common condition, and its prevalence is expected to increase because of the ageing population.<sup>1</sup> Importantly, only 1 out of 9 patients with PAD are symptomatic, but vascular morbidity and mortality is estimated to be similar in patients with symptomatic or asymptomatic PAD.<sup>2,3</sup> This poses PAD to be a major health burden. Patients with PAD undergoing vascular surgery are known to be at risk for both early and late cardiovascular events.<sup>4,5</sup> Hertzner's landmark study in 1000 consecutive patients undergoing surgery for PAD who underwent preoperative cardiac catheterizations reported that only 8% had normal coronary arteries, and approximately one third had severe-correctable or severe-inoperable ischemic heart disease (IHD).<sup>6</sup> The estimated cardiovascular risk in PAD is as high as in IHD.<sup>5,7</sup> Adequate risk reduction management is clearly of utmost importance in these patients. The international prospective Reduction of Atherothrombosis for Continued Health (REACH) Registry demonstrated a substantial gap between guideline recommendation and clinical practice throughout the atherothrombotic spectrum.<sup>8</sup> In addition, the REACH registry demonstrated that optimal risk factor control was associated with fewer cardiovascular events. Patients with PAD scheduled for surgery are an even higher risk population. Data are limited in this specific population about the application of risk factor control. Earlier studies have shown that the implementation of guidelines in the perioperative period is rather poor but data is lacking about medication use in vascular surgery patients at late follow-up.<sup>9,10</sup> From observational studies it is known that these patients benefit from long-term medical treatment.<sup>11,12</sup> However, the composite effect of perioperative guideline recommended medication in vascular surgery patients on long-term outcome is not well established in daily clinical practice.

The first aim of our study was to investigate whether recommended medication is used in patients with PAD 3 years after vascular surgery. In addition, we evaluated the effect of guideline recommended perioperative medication use on long-term outcome.

## METHODS

### Study population

Between May and December 2004, a survey of clinical practice in vascular surgery patients was conducted in 11 hospitals in The Netherlands.<sup>9,13</sup> The total study population consisted of 711 consecutively enrolled patients undergoing peripheral vascular surgery. Five hospitals were located in the central part of the country, 3 were located in the northern region, and 3 were located in the southern region. Two centers were university hospitals, which act as tertiary referral

centers. This survey was an integral part of the infrastructure of the survey program supported by The Netherlands Heart Foundation in the context of the Euro Heart Survey Programme. All patients who were admitted to the vascular surgery department of the participating hospitals were screened. Endovascular surgery procedures included aortic endografts or peripheral angioplasties with or without stenting. The open procedures comprised abdominal aortic surgery, carotid endarterectomy or infrainguinal arterial bypass grafting. All patients provided informed consent before participation. The 11 participating hospitals met the requirements for ethical approval based on local standards. After 3 years, follow-up information on vital status was obtained through the civil registries. Patient status could be determined in 701 patients (99%), of whom 149 patients (21%) died during 3-year period. All 552 survivors were contacted to complete questionnaires including medical treatment and the occurrence of cardiovascular events during the 3-year period. Of these, 87 (16%) patients did not respond, leaving 465 (84%) patients for further analysis at 3-year follow-up. The median follow-up time of these patients was 3.1 years (interquartile range 3.07 to 3.19).

### **Data collection**

Baseline measurements, patient characteristics and risk factors, were collected by trained research assistants. The hospital charts were searched for information on the relevant clinical characteristics, such as cardiovascular history, diabetes, and renal insufficiency. Furthermore, the following medication use was noted: aspirin, statins, beta-blockers, angiotensin converting enzyme inhibitors (ACE), angiotensin II receptor blockers, antithrombotics, calcium-channel blockers, and diuretics. Clinical data including the presence of IHD and cerebrovascular disease (CVD) were updated at 3 years after surgery. Polyvascular disease was defined as coexistent arterial disease in 1 or 2 other territories (coronary or cerebral) within each patient with PAD. Ischemic heart disease was defined as history of myocardial infarction, angina, or previous coronary revascularization. Cerebrovascular disease was defined as a previous ischemic cerebrovascular accident.

### **Guideline-recommended medical therapy use**

All patients with PAD were considered candidates for aspirin and statins in this study. Beta-blockers were indicated in patients with known IHD. These indications are based on national and international guidelines for patients with PAD.<sup>14-17</sup> Guideline-recommended medical therapy for the combination of aspirin, statins and beta-blockers was considered to be present when 1) aspirin, statins as well as beta-blockers were used in patients with IHD, or 2) aspirin and statins were used in patients without IHD, irrespective of beta-blockers. The extent of guideline recommended medical treatment was quantified by the absolute number of used drugs, i.e. 0 to 1, 2 or all 3 drugs per individual patient (aspirin, statins, beta-blockers).



## Outcome

The main outcome measure of this study was all-cause mortality within 3 years after vascular surgery.

## Statistical Analyses

Clinical characteristics are described as numbers and percentages for dichotomous variables and the continuous variable age was reported as mean with standard deviation. Comparisons between categorical variables were performed using Pearson Chi-square tests. Trend tests were used to calculate the *P*-value for trend across the number of vascular beds. The relation between guideline-recommended medical therapy use in the perioperative period and 3-year mortality was evaluated by multivariable Cox proportional hazard regression analysis with adjustment for confounders. All potential confounders (age, gender, IHD, heart failure, CVD, diabetes, renal insufficiency and type of surgery) were entered in the multivariable model to ensure giving an as unbiased as possible estimate for the relation between medical therapy use and long-term mortality. Sensitivity analyses were performed using a hierarchical model with hospital as random effect. Kaplan-Meier survival curves were calculated to assess the relation between the extent of guideline compliant medical treatment and long-term survival and compared with a log-rank test. For all tests, a *P*-value <0.05 (two-sided) was considered significant. All statistical analyses were performed using SPSS 15.0 statistical software.

## RESULTS

Of the 711 included patients, 149 (21%) died during the 3-year follow up period. Baseline characteristics are presented in Table 1. Half of the patients underwent an endovascular procedure (*n*=354), 328 patients (46%) had open surgery and 29 patients (4%) underwent carotid endarterectomy.

Three-year mortality rates increased from 18% in PAD only to 28% in patients with 3 affected vascular beds (trend *P*=.014). Nonresponder data analysis showed that responders did not differ significantly from nonresponders with regard to age, sex and other cardiovascular risk factors.

### Baseline medication

Of the initial 711 patients, 28% had IHD and 17% had CVD at baseline. Polyvascular disease was present in 41%. Aspirin was used in 534 patients (75%), 398 (56%) used statins and 340 (48%) used beta-blockers in the perioperative period (Table 2). Beta-blocker use in patients with IHD (*n*=201) was 69%. Overall, guideline-recommended medical therapy use for the combination of aspirin and statins in all patients and beta-blockers in patients with IHD was 41%.

TABLE 1 - Patient characteristics

	All patients	Deceased	3-year follow-up	
			Non-responders*	Responders
N	711	149	97	465
<b>Demographics</b>				
Age (mean±SD), y	66.9 ± 10.4	73.9 ± 8.9	64.9 ± 11.0	65.1 ± 9.9
Male gender, n (%)	496 (69.8)	108 (72.5)	65 (67.0)	323 (69.5)
<b>Cardiovascular history, n (%)</b>				
IHD, n (%)	201 (28.3)	46 (30.9)	20 (20.6)	135 (29.0)
Myocardial infarction	106 (14.9)	30 (20.1)	9 (9.3)	67 (14.4)
Angina	99 (13.9)	16 (10.7)	10 (10.3)	73 (15.7)
Previous revascularization	116 (16.3)	27 (18.1)	12 (12.4)	77 (16.6)
Heart failure, n (%)	38 (5.4)	18 (12.1)	2 (2.1)	18 (3.9)
CVD, n (%)	123 (17.3)	38 (25.5)	16 (16.5)	69 (14.8)
<b>Risk factors, n (%)</b>				
Diabetes	149 (21.0)	41 (27.5)	12 (12.4)	96 (20.6)
Renal insufficiency	51 (7.2)	24 (16.1)	3 (3.1)	24 (5.2)
<b>Affected vascular beds, n (%)</b>				
PAD only	432 (59.5)	75 (50.3)	64 (66.0)	284 (61.1)
PAD + (IHD or CVD)	252 (35.4)	64 (43.0)	30 (30.9)	158 (34.0)
PAD + IHD + CVD	36 (5.1)	10 (6.7)	3 (3.1)	23 (4.9)

IHD, ischemic heart disease; CVD, cerebrovascular disease; PAD, peripheral arterial disease

\*Nonresponders include 10 patients with missing survival status and 87 patients who didn't respond to the questionnaire

Patients with guideline-recommended medical therapy use were younger (66 years vs. 68 years,  $P=.019$ ) had more often a history of CVD (21% vs. 15%,  $P=.040$ ) and polyvascular disease (46% vs 37%,  $P=.014$ ) compared to patients without this treatment (Table 3). Three-year mortality in patients with or without guideline compliant medical treatment was 15% and 26%, respectively ( $P<.001$ ). The use of evidence-based medication was associated with a significant reduction in long-term mortality after adjustment for clinical characteristics (HR=0.65; 95%CI=0.45-0.94). Sensitivity analyses using a hierarchical model with hospital as random effect revealed comparable results. Furthermore, there was a clear relationship between the increasing number of guideline indicated drugs and long-term outcome (Figure 1).

TABLE 2 - Medical treatment at baseline and at 3-year follow-up

	Baseline	3 year follow-up
N	711	465
Aspirin, n (%)	534 (75.1)	344 (74.0)
PAD only	308/423 (72.8)	187/ 251 (74.5)
IHD	162/201 (80.6)	116/ 163 (71.2)
CVD	92/123 (74.8)	62/ 82 (75.6)
Statins, n (%)	398 (56.0)	321 (69.0)
PAD only	204/ 423 (48.2)	163/ 251 (64.9)
IHD	143/ 201 (71.1)	115/ 163 (70.6)
CVD	80/ 123 (65.0)	69/ 82 (84.1)
Beta-blockers, n (%)	340 (47.8)	251 (54.0)
PAD only	160/ 423 (37.8)	111/ 251 (44.2)
IHD	138/ 201 (68.7)	112/ 163 (68.7)
CVD	68/ 123 (55.3)	51/ 82 (62.2)
Any antithrombotic therapy, n (%)	618 (86.9)	413 (88.8)
PAD only	347/ 423 (82.0)	221/ 251 (88.0)
IHD	194/ 201 (96.5)	145/ 163 (89.0)
CVD	111/ 123 (90.2)	76/ 82 (92.7)
ACE-inhibitors, n (%)	219 (30.8)	143 (30.8)
Calcium channel blockers, n (%)	168 (23.6)	102 (21.9)
Diuretics, n (%)	211 (29.7)	144 (31.0)

IHD, ischemic heart disease; CVD, cerebrovascular disease; PAD, peripheral arterial disease; ACE, angiotensin-converting enzyme

Numbers are presented in total population and in patients with PAD only, IHD and CVD, respectively

Presence of IHD/ CVD at time of baseline or 3 year follow-up respectively.

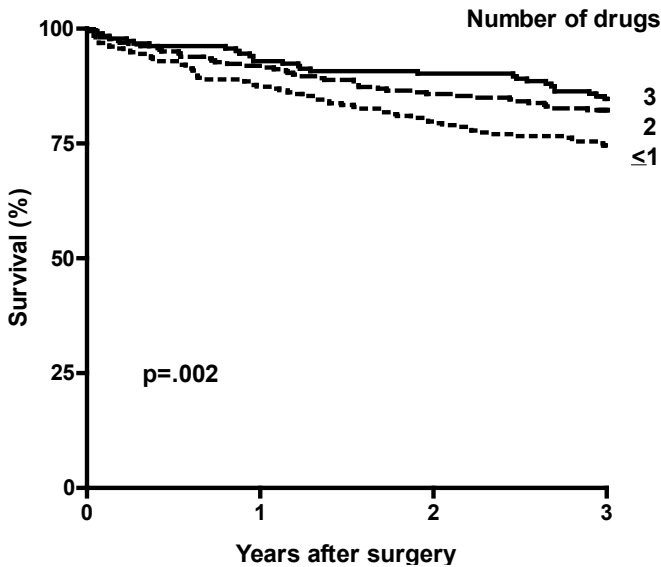
### Follow-up medication use

Of the 465 patients at 3-year follow-up, mean age at was 68 years with 70% male. A history of IHD at 3-year follow-up was present in 163 patients (35%) and CVD in 82 (18%). In total, 251 (54%) patients had “PAD only”, 183 (39%) had PAD in combination with one other affected vascular bed (IHD or CVD) and 31 (7%) had 3 affected vascular beds. The percentage of medication use at long-term follow-up was still low (Table 2). Aspirin was used in 74% of patients, statins in 69% and beta-blockers in 54% of patients after 3 years. In patients with “PAD only”, statin use increased from 48% to 65% in the 3-year period. This increase was also observed in CVD patients. Guideline-recommended medical therapy use for the combination of aspirin and statins in all patients and beta-blockers in patients with IHD was only 50%. A clear relationship between medication use and number of vascular beds was observed (Figure 2). Patients with “PAD only” were treated less intensively with statins (trend  $P=.016$ ) and beta-blockers (trend  $P<.001$ ), compared to patients with more affected vascular beds.

**TABLE 3** - Patient characteristics stratified by the use of guideline recommended perioperative medication use

	Guideline recommended perioperative medication use		P-value
	Yes	No	
N	288	423	
<b>Demographics n, (%)</b>			
Age, yrs ± SD	65.8 ± 9.5	67.7 ± 11.0	.019
Male gender	198 (68.8)	298 (70.4)	.628
<b>Cardiovascular history n, (%)</b>			
IHD	92 (31.9)	109 (25.8)	.073
Myocardial infarction	51 (17.7)	55 (13.0)	.084
Angina	45 (15.6)	54 (12.8)	.280
Previous revascularization	56 (19.4)	60 (14.2)	.062
Heart failure	9 (3.1)	29 (6.9)	.030
CVD	60 (20.8)	63 (14.9)	.040
<b>Risk factors n, (%)</b>			
Diabetes	65 (22.6)	84 (19.9)	.383
Renal insufficiency	19 (6.6)	32 (7.6)	.623
<b>Affected vascular beds n, (%)</b>			
PAD only	155 (53.8)	268 (63.4)	
PAD + (IHD or CVD)	114 (39.6)	138 (32.6)	
PAD + IHD + CVD	19 (6.6)	17 (4.0)	

IHD, ischemic heart disease; CVD, cerebrovascular disease; PAD, peripheral arterial disease; ACE, angiotensin-converting enzyme.



**FIGURE 1** - Survival according to the number of evidence-based medications (i.e. aspirin and statins and beta-blockers).

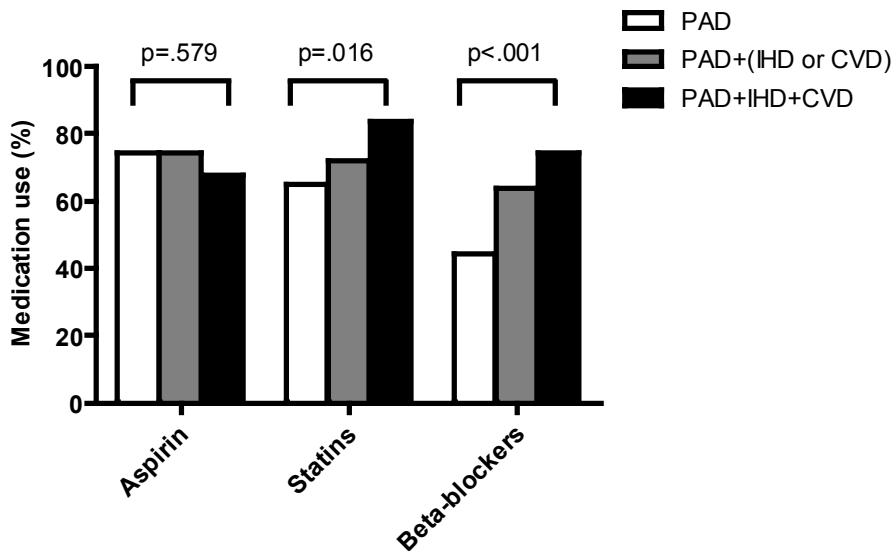


FIGURE 2 - Medication use at 3-year follow-up according to the number of affected vascular beds.

## DISCUSSION

Perioperative and long-term use of medication in vascular surgery patients proved to be lower than expected based on current guidelines. However, we noticed a clear relationship between greater evidence-based medication use and increasing number of affected vascular beds. Importantly, we also observed a significantly lower 3-year mortality in patients who were treated according to the guidelines. These data clearly indicate the need of both initiating optimal medical treatment during perioperative assessment and improving the rates of long term evidence-based medication use.

Risk factors for atherosclerotic disease are common in patients with PAD. The prognosis of patients with PAD is predominantly determined by the presence and extent of the underlying IHD.<sup>5</sup> Consequently, IHD is the most common cause of death in patients with PAD. Our results indicated that 1 out of 3 patients with PAD had underlying IHD. Thus, atherosclerotic risk factor control and optimal pharmacological treatment are key elements of perioperative and long-term management of patients with PAD. Importantly, our survey demonstrated a graded relationship between that greater use of evidence-based therapies in the perioperative period and lower mortality after 3 years of follow-up in consecutive PAD patients seen in daily clinical practice. Our data are in accordance with studies in IHD patients, which also showed significant associations between guideline adherence and better outcomes.<sup>18,19</sup> Our findings suggest that adherence to guideline-

recommended therapies during hospitalization for vascular surgery might serve as a marker of quality of care.

Adherence to evidence-based guidelines appears to be an important component in improve cardiovascular outcomes in PAD patients. Data from observational studies and registries, however, show that the use of evidence-based medical therapy in the perioperative period remains suboptimal in this high-risk population.<sup>10,13,20,21</sup> Our results are in line with previous findings regarding disparities in risk factor management among patients with atherothrombotic disease. McDermott and colleagues previously reported that PAD patients received less intensive drug treatment compared to IHD patients, irrespective of comparable risk.<sup>22</sup> Additionally, in a large risk factor matched population, patients with IHD received more cardiovascular medications, compared with PAD patients.<sup>5</sup> The observed poor medical control of PAD patients may explain the worse outcome of PAD patients compared with IHD patients as observed by the study of Welten et al.<sup>5,22</sup> The reason for this poor medical control seems to be multifactorial. First, national physician surveys have reported deficiencies in physician knowledge and attitudes regarding the importance of atherosclerotic risk factor reduction in PAD patients.<sup>23-25</sup> Furthermore, data from the REACH registry demonstrated substantial variation in patients' medication use by physician speciality.<sup>26</sup> For example, statin prescription was 79% among cardiologists and 49% among vascular surgeons and same differences were observed for beta-blockers (70 vs. 34 respectively). In addition, patients themselves are also known to underestimate the cardiovascular risks associated with PAD. A population-based survey showed major knowledge gaps regarding PAD.<sup>27</sup> Only 1 out of 4 PAD patients were aware of the fact that PAD is associated with increased risk of myocardial infarction and stroke. Atherosclerotic vascular disease and its risks constitute a chronic condition, with consequences for life-long attention to vascular risks. There is a significant opportunity to improve the use of secondary preventive therapy in these high-risk patients and improve patient compliance.

Our data showed a clear relationship between the number of vascular beds and medical treatment. Patients with "PAD only" were treated less intensively compared to patients with more affected vascular beds. Polyvascular disease is highly prevalent in the PAD population.<sup>7,8</sup> The results of our study indicated 40% having polyvascular disease. Three 3-year mortality rates increased from 18% in PAD only to 28% in patients with 3 affected vascular beds. These results are in keeping with the REACH registry which showed that cardiovascular outcome increased in a stepwise fashion with the number of symptomatic vascular beds.<sup>7</sup> The combined 1-year outcome of atherothrombotic events ranged from 17% in patients with PAD as a single affected vascular bed to 26% in patients with 3 diseased vascular beds. As patients with PAD constitute a high risk group and there is a clear care gap between guideline recommendation and clinical practice, more attention should be focussed at initiating evidence-based therapy, especially in patients with PAD only.

The discrepancy between daily clinical practice and guideline recommendation demonstrates the need for improving perioperative and long-term care of patients with PAD. In cardiac patients it has been demonstrated that in-hospital initiation of medication has an impressive effect on long-term treatment rates and patients compliance.<sup>28</sup> The preoperative visits to the hospital related to the intended vascular procedure in patients with PAD can be considered as an ideal opportunity to initiate medical therapy and lifestyle changes with achievement of treatment targets according to the guidelines. Furthermore, long-term care should be provided by all involved cardiovascular principles. Increased efforts should be focussed on implementing guideline recommendation in both the perioperative and long-term period. This can potentially be achieved by implementing disease management programs including critical pathways, patient education, and multidisciplinary hospital teams.<sup>29</sup> Programs such as American College of Cardiology Guidelines Applied in Practice (GAP) and the American Heart Association Get With The Guidelines (GWTG) program are examples of successful quality improvement programs that are designed to improve guideline adherence through tools and system redesign strategies. The GAP project resulted in increased adherence to key treatments in the administration of aspirin and beta-blockers on admission and the use of aspirin and smoking cessation counselling at discharge.<sup>30</sup> The GWTG coronary artery disease program was also associated with improved guideline adherence.<sup>31</sup> The use of beta-blockers, ACE-inhibitors, statins, aspirin, and smoking cessation counselling were significantly increased.<sup>32</sup> Our findings highlight the need to implement similar programs in patients with PAD and study their impact on adherence to guideline-recommended therapies and subsequent patient outcomes.

Our study needs to be considered in the context of several limitations. First, although adjustments were made for known covariates, there is the possibility of residual confounding by unmeasured factors. Second, we relied on patient report for assessment of long-term medication use. Third, we did not have the data regarding potential contraindications to guideline-recommended treatments. Therefore, we could not determine the rates of medication use among “ideal candidates”. Another potential limitation of our work is that the response rate of our study was not 100%. A response rate of 84%, however, is regarded as quite good and importantly, nonresponder analyses revealed no differences between the patients who responded and those who did not.

In conclusion, we showed that perioperative guideline-recommended medical treatment is associated with improved survival in patients with PAD. However, the rates of evidence-based medication use remain low in these high-risk patients - both at baseline and during long-term follow-up. These results highlight an important potential opportunity to improve the quality of care in patients with PAD.

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# CHAPTER

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## High prevalence of smoking 3 years after vascular intervention

# 15

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## ABSTRACT

**Objectives:** Smoking is the most important risk factor for peripheral artery disease (PAD) and moreover, associated with disease progression and adverse outcome after vascular intervention. This study aimed to investigate the prevalence of smoking before and after a vascular intervention and its relation to the number of affected vascular beds.

**Methods:** Between May and December 2004, data on 711 consecutive PAD patients undergoing vascular surgery were collected from 11 hospitals in the Netherlands. After  $3.1 \pm 0.1$  years of follow-up, information on smoking status was obtained by means of a questionnaire which was sent to all 552 living patients of whom 465 (84%) responded and were included in the analysis.

**Results:** At time of surgery, 95% of the patients had a history of smoking with 53% smokers within 1 year before surgery. Three years after the vascular intervention, still 39% of all patients were current smokers. A clear inverse relationship between smoking status and polyvascular disease was observed after follow-up: the more affected vascular beds, the lower the smoking rate ( $P < .001$ ).

**Conclusions:** The prevalence of smoking in PAD patients after vascular surgery is remarkably high. In addition, a relationship between smoking and the number of affected vascular beds was observed. There is a high need for the development and implementation of effective smoking cessation programmes in vascular surgery patients.

## INTRODUCTION

Peripheral artery disease (PAD) is a common chronic disorder and associated with an increased risk of cardiovascular events. Management of these patients should focus both on lifestyle modification and pharmacological treatment. Data from observational studies and registries demonstrates a substantial gap between guideline recommendation and clinical practice in PAD patients.<sup>1,3</sup> Importantly, Mc Dermott and colleagues reported in 1997 that PAD patients received less intensive drug treatment compared to ischemic heart disease (IHD) patients, irrespective of comparable risk.<sup>4</sup> Additionally, in a large risk factor matched population, patients with IHD received more secondary medical treatment, compared with PAD patients.<sup>5</sup> The observed poor medical control of PAD patients may be an explanation for the worse outcome of PAD patients compared with IHD patients as observed by the study of Welten et al.<sup>5,6</sup>

Information about lifestyle management in vascular surgery patients is less well established. Smoking increases the risk of lower extremity PAD, aortic aneurysms, and carotid artery disease.<sup>7,8</sup> Current smokers with PAD also have increased risk of amputation and increased risk of postoperative complications and mortality.<sup>9</sup> Therefore, European Guidelines on Cardiovascular Disease Prevention in clinical practice emphasize the importance of smoking cessation in cardiovascular patients.<sup>10</sup> The European Society of Cardiology has adopted the 5 A's (ask, assess, advise, assist, arrange) as an effective strategy to promote smoking cessation. These guidelines also highlight that the momentum for smoking cessation is particularly strong at the time of diagnosing arterothrombotic cardiovascular disease and in connection with an invasive treatment such as vascular surgery. The combination of support (motivational, social) and pharmacotherapy has shown to be the most effective treatment.<sup>11,12</sup>

This study aimed to investigate the prevalence of smoking before and after a vascular intervention. Furthermore, we expected a relation between smoking and the number of affected vascular beds.

# METHODS

## Study population

Between May and December 2004, a survey of clinical practice in vascular surgery patients was conducted in 11 hospitals in the Netherlands.<sup>3,13</sup> The total study population consisted of 711 consecutively enrolled patients undergoing peripheral vascular surgery. Five hospitals were located in the central part of the country, 3 were located in the northern region, and 3 were located in the southern region. Two centers were university hospitals, which act as tertiary referral centers. This survey was an integral part of the infrastructure of the survey program supported by the Netherlands Heart Foundation in the context of the Euro Heart Survey Programme. All patients who were admitted to the vascular surgery department of the participating hospitals were screened. Endovascular surgery procedures included aortic endografts or peripheral angioplasties with or without stenting. The open procedures comprised abdominal aortic surgery, carotid endarterectomy or infrainguinal arterial bypass grafting. All patients provided informed consent before participation. The 11 participating hospitals met the requirements for ethical approval based on local standards. After 3 years, follow-up information on vital status was obtained through the Civil Registries. Patient status could be determined in 701 patients (99%) of whom 149 patients (21%) died during 3 year period. All 552 survivors were contacted to complete questionnaires including smoking status. Of these, 87 (16%) patients did not respond, leaving 465 (84%) patients for further analysis at 3 years follow-up. The median follow-up time of these patients was 3.1 years (interquartile range 3.07-3.19).

## Data collection

Baseline measurements, patient characteristics and risk factors, were collected by trained research assistants. The hospital charts were searched for information on the relevant clinical characteristics, such as cardiovascular history, smoking, diabetes, and renal insufficiency. At 3-year follow-up, questionnaires were sent to the patients including smoking status, medical treatment and the occurrence of cardiovascular events during the 3-year period. Patients were characterized as quitters if they stopped smoking between baseline and three years of follow-up. Patients were considered as persistent smokers if they smoked from one year before surgery and still smoked at three years of follow-up, patients who never smoked were classified as never smokers, while patients who quit smoking before measurement at baseline, were considered as former smokers. Clinical data including the presence of IHD and cerebrovascular disease (CVD) were updated at 3 years after surgery. Polyvascular disease was defined as coexistent arterial disease in



1 or 2 other territories (coronary or cerebral) within each patient with PAD. Ischemic heart disease was defined as history of myocardial infarction, angina or previous coronary revascularization. Cerebrovascular disease was defined as a previous ischemic cerebrovascular accident.

### Statistical Analyses

Clinical characteristics are described as numbers and percentages for dichotomous variables and the continuous variable age was reported as mean with standard deviation. Comparisons between categorical variables were performed using Pearson Chi-square tests. For all tests, a *P*-value <0.05 (two-sided) was considered significant. All statistical analyses were performed using SPSS 15.0 statistical software.

## RESULTS

Table 1. Patient characteristics

	Baseline		3-year follow-up	
	All patients	Deceased	Non-responders	Responders
N	711	149	97*	465
<b>Demographics, n (%)</b>				
Age, yrs ± SD	66.9 ± 10.4	73.9 ± 8.9	64.9 ± 11.0	65.1 ± 9.9
Male gender	496 (69.8)	108 (72.5)	65 (67.0)	323 (69.5)
<b>Risk factors (baseline), n (%)</b>				
IHD	201 (28.3)	46 (30.9)	20 (20.6)	135 (29.0)
Myocardial infarction	106 (14.9)	30 (20.1)	9 (9.3)	67 (14.4)
Angina	99 (13.9)	16 (10.7)	10 (10.3)	73 (15.7)
Previous revascularization	116 (16.3)	27 (18.1)	12 (12.4)	77 (16.6)
Heart failure	38 (5.4)	18 (12.1)	2 (2.1)	18 (3.9)
CVD	123 (17.3)	38 (25.5)	16 (16.5)	69 (14.8)
Perioperative smokers**	335 (47.1)	41 (27.5)	50 (51.5)	244 (52.5)
Diabetes	149 (21.0)	41 (27.5)	12 (12.4)	96 (20.6)
Renal insufficiency	51 (7.2)	24 (16.1)	3 (3.1)	24 (5.2)
<b>Number of affected vascular beds, n (%)</b>				
PAD only	423 (59.5)	75 (50.3)	64 (66.0)	284 (61.1)
PAD + (IHD or CVD)	252 (35.4)	64 (43.0)	30 (30.9)	158 (34.0)
PAD + IHD + CVD	36 (5.1)	10 (6.7)	3 (3.1)	23 (4.9)

IHD, ischemic heart disease; CVD, cerebrovascular disease; PAD, peripheral arterial disease

\*Nonresponders include 10 patients with missing survival status and 87 patients who did not respond to the questionnaire

\*\*Perioperative smokers are defined as patients who smoked within 1 year before surgery

Of the 711 included patients, 149 (21%) died during the 3-year follow up period. After 3 years, information about smoking status could be obtained in 465 (84%) of the survivors. Baseline characteristics are presented in Table 1. Nonresponder data analysis at 3-year follow-up showed that responders did not differ significantly from nonresponders with regard to age, sex, smoking and other cardiovascular risk factors.

Of the 465 patients, 244 (53%) smoked within one year before surgery (Table 1). At 3-year follow-up, 24 (5%) patients were classified as never smokers while 180 (39%) patients still smoked (Table 2). Of the patients who smoked within 1 year before surgery, the proportion who stopped smoking after vascular surgery was 26% (64/244). Approximately all (95%) patients with PAD undergoing surgery were current or former smokers at 3-year follow-up. Significant differences in cardiovascular risk factors were observed between the different smoking categories, except for angina, heart failure and renal insufficiency.

A clear relationship between the number of affected vascular beds and smoking status at 3-year follow-up was observed. The percentage smokers at 3-year decreased with increasing number of affected vascular beds: PAD: 43%, PAD+IHD/CVD: 34% and PAD+IHD+CVD: 18% (Figure 1).

**TABLE 2** - Patient characteristics and smoking behaviour after 3 years (n=465)

	Never smokers	Persistent smokers	Quitters	Former smokers	P-value
N	24	180	64	197	
<b>Demographics n, (%)</b>					
Age, yrs± SD	66.5 ± 14.7	62.7 ± 9.4	61.7 ± 8.0	68.4 ± 9.2	<.001
Male gender	7 (29.2)	123 (68.3)	42 (65.6)	151 (76.6)	<.001
<b>Risk factors n, (%)</b>					
IHD	5 (20.8)	44 (32.6)	12 (18.8)	74 (37.6)	.005
Myocardial infarction	1 (4.2)	18 (10.1)	8 (12.5)	40 (20.3)	.014
Angina	4 (16.7)	24 (13.3)	6 (9.4)	39 (19.8)	.157
Previous revascularization	4 (16.7)	24 (13.3)	4 (6.3)	45 (22.8)	.008
Heart failure	3 (12.5)	6 (3.3)	1 (1.6)	8 (4.1)	.118
CVD	8 (33.6)	19 (10.6)	10 (15.6)	32 (16.2)	.024
Diabetes	11 (47.8)	29 (16.3)	14 (21.9)	41 (20.8)	.006
Renal insufficiency	2 (8.7)	4 (2.2)	4 (6.3)	14 (7.1)	.150
<b>Number of affected vascular beds n, (%)</b>					
PAD only	13 (54.2)	122 (67.8)	43 (67.2)	106 (53.8)	
PAD + (IHD or CVD)	9 (37.5)	53 (29.4)	20 (31.3)	76 (38.6)	
PAD + IHD + CVD	2 (8.3)	5 (2.8)	1 (1.6)	15 (7.6)	

IHD, ischemic heart disease; CVD, cerebrovascular disease; PAD, peripheral arterial disease

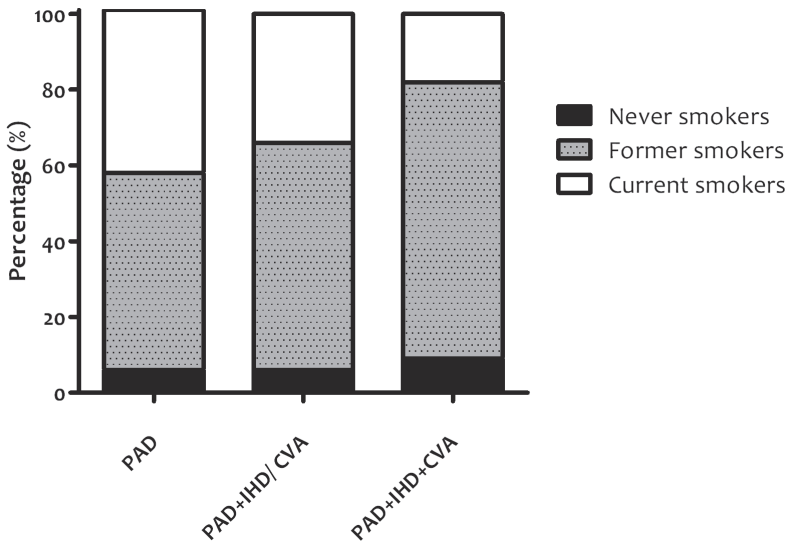


FIGURE 1 - Prevalence of smoking 3 years after surgery.

## DISCUSSION

The prevalence of smoking is very high in vascular surgery patients in the perioperative period and at long-term follow-up. Furthermore, an inverse relationship between smoking and the number of affected vascular beds was observed.

Smoking is a risk factor for six of the eight leading causes of death in the world. Consequently, tobacco use is the leading preventable cause of death worldwide.<sup>14</sup> The risk factors for PAD are highly similar to those for IHD.<sup>15,16</sup> Notably, cigarette smoking is a stronger risk factor for PAD than CAD. The Edingburgh Artery Study showed an adjusted relative risk (RR) for PAD comparing heavy smokers with nonsmokers of 2.72 (1.13-6.53) as compared with CAD (1.61 (0.91-2.85)).<sup>17</sup> Besides a higher prevalence of PAD among smokers and former smokers, those who smoke more heavily were also found to have an increased incidence of symptomatic instead of asymptomatic PAD.<sup>16</sup> Smoking is also a strong risk factor for progression of disease and a poor outcome. Smokers with PAD have twice the amputation rate of nonsmokers, an increased risk of graft failure following femoro-popliteal bypass surgery and increased postoperative mortality.<sup>9,18</sup>

Smoking cessation has been shown to not only reduce disease progression but also the morbidity and mortality in PAD.<sup>19</sup> In addition to beneficial effects on long-term health, smoking cessation also has immediate benefits to surgical patients by reducing the risk of perioperative

complications.<sup>20</sup> Furthermore, smoking is associated with many drug interactions (for example beta-blockers) which cause smokers to require larger doses of certain drugs through an increase in plasma clearance, a decrease in absorption, enzyme induction or a combination of these factors.<sup>21</sup> Smokers with PAD have twice the amputation rate of nonsmokers, an increased risk of graft failure following femoro-popliteal bypass surgery.

The prevalence of smoking is high in the total cardiovascular spectrum, although reported even higher in patient with PAD. In our study, 39% smoked 3 years after vascular surgery. The Euroheart survey of coronary heart disease patients reported 21% smoking 1.5 year after first diagnosis or cardiac intervention.<sup>22</sup> The REACH registry including patients with PAD reported a prevalence of smokers of 22% in patients with PAD.<sup>1</sup> Smoking cessation rate in this cohort was significantly lower compared in PAD patients to patients without PAD.

Unfortunately smoking cessation is not part of routine practice for many physicians. Lifestyle changes should not be secondary to pharmacological interventions. Smoking is not recognized as a disorder of dependence but simply as a “bad habit” or a “lifestyle choice”. Given that smoking is intrinsically linked to PAD in most patients, much of the risk reduction strategy should be directed to smoking cessation. The PARTNERS programme found only half of patients with PAD who smoked were prescribed interventions for smoking cessation, indicating a missed opportunity for prevention.<sup>23</sup> It has been shown that smokers are more likely to succeed with the help and support from healthcare professionals, and that combining nicotine replacement therapy and brief advice can improve long-term cessation rates.<sup>11</sup> Motivational counselling is emerging as an effective and efficient catalyst of behaviour change. One of the central features is to help patients explore and resolve ambivalence. Trained nurses can assist in smoking cessation and provide more support and follow-up counselling.

The European Guidelines on Cardiovascular Disease Prevention in clinical practice emphasize the importance of smoking cessation and the momentum for smoking cessation at the time of diagnosing arterothrombotic cardiovascular disease and in connection with an invasive treatment.<sup>10</sup> A hospital admission provides an opportunity to help patients stop smoking. In this respect, surgery has been shown to be a “teachable moment” for smoking cessation.<sup>24</sup> The term “teachable moment” relates to the fact that health events can motivate people to spontaneously change health behaviours.<sup>25</sup> The impact of these major health events on smoking is also demonstrated in the current study. The percentage current smokers was lowest in patients with three affected vascular beds while highest in patients with “only” PAD. So if patients with PAD also had a myocardial infarction and/or a cerebrovascular attack in the past, they are more likely to have stopped smoking already. There should be increased awareness for lifestyle management including smoking cessation in patients with PAD, especially in patients with “PAD only”. This is in line with evidence from cardiovascular surveys. A stroke survey showed better secondary

prevention in patients admitted with ischemic stroke compared to outpatients with mostly TIA's.<sup>26</sup> Additionally, the second EUROASPIRE demonstrated that the proportion of stopped smokers was higher in patients who were hospitalized for myocardial infarction and low in those hospitalized for ischemia.<sup>22</sup> Both physicians and patients should be more aware of the seriousness of the disease and the importance of appropriate lifestyle changes. The evident power of the surgery as a teachable moment suggests that this is an opportune time to intervene and further increases cessation rates. A recent systematic review including 33 trials concluded that offering smoking cessation counselling is effective as long as supportive contacts continue for more than 1 month after discharge.<sup>11</sup> Nicotine replacement therapy will enhance smoking cessation. Clinicians should encourage patients to stop smoking, especially in the period around the vascular surgery when smokers are more willing to stop smoking. Even after a major cardiovascular event, it is not too late to stop smoking.

The results of this study should be interpreted with some caution. First, smoking status was assessed by means of self-report. However, the concurrence rate between objectively assessed smoking status and self-report has shown to be high with 80%.<sup>27</sup> A second limitation were the nonresponders although this percentage was low and patient characteristics did not differ between responders and nonresponders.

In conclusion, the prevalence of smoking in PAD patients after vascular surgery is remarkably high. In addition, a relationship between smoking and the number of affected vascular beds was observed. There is a high need for the development and implementation of effective smoking cessation programmes in vascular surgery patients, also in patient with "only PAD". These data indicate the need for increasing awareness for smoking cessation in vascular surgery patients and professionals.

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**Outcome**



# **PART IV**

# **Aessment**



# CHAPTER

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## Further validation of the Peripheral Artery Questionnaire: results from a peripheral vascular surgery survey in The Netherlands

# 16

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## ABSTRACT

**Objectives:** Peripheral arterial disease (PAD) is associated with adverse cardiovascular events and can significantly impair patients' health status. Recently, marked methodological improvements in the measurement of PAD patients' health status have been made. The Peripheral Artery Questionnaire (PAQ) was specifically developed for this purpose. We validated a Dutch version of the PAQ in a large sample of PAD-patients.

**Design:** Cross-sectional study.

**Methods:** The Dutch PAQ was completed by 465 PAD patients (70% men, mean age 65±10 years) participating in the Euro Heart Survey Programme. Principal components analysis and reliability analyses were performed. Convergent validity was documented by comparing the PAQ with EQ-5D scales.

**Results:** Three factors were discerned; Physical Function, Perceived Disability, and Treatment Satisfaction (factor loadings between 0.50 and 0.90). Cronbach's  $\alpha$  values were excellent (mean  $\alpha=0.94$ ). Shared variance of the PAQ domains with EQ-5D scales ranged from 3 to 50%.

**Conclusions:** The Dutch PAQ proved to have good measurement qualities; assessment of Physical Function, Perceived Disability, and Treatment Satisfaction facilitates the monitoring of patients' perceived health in clinical research and practice. Measuring disease-specific health status in a reliable way becomes essential in times where a wide array of treatment options are available for PAD patients.

## INTRODUCTION

Patients with peripheral arterial disease (PAD) constitute a high-risk group that needs stringent risk management and monitoring. Atherosclerotic processes underlying the disease affect different vascular beds simultaneously and predispose PAD patients to a variety of cardiovascular conditions such as claudication, myocardial infarction, and stroke.<sup>1</sup> Increasing awareness of PAD and its consequences is especially needed in lower-extremity PAD.<sup>2,3</sup> Apart from the disease burden itself,<sup>4</sup> patients are confronted with multiple challenges due to the chronic nature of their disease and the multifaceted risk management and treatment options that are available to them. PAD patients should be routinely offered stringent risk management treating associated conditions such as hypertension and hyperlipidemia and, where indicated, endovascular procedures and surgery may bring relief.<sup>1</sup> When it comes to the evaluation of medical therapy and existing revascularization procedures, quantifying PAD patients' health status becomes an important issue.<sup>5</sup> In fact, unlike the use of percutaneous revascularization in the setting of an acute myocardial infarction where treatment may improve survival, the primary goal of revascularization procedures in PAD is to improve patients' symptoms, function and quality of life. In order to monitor patients' health status in a reliable way, a sensitive disease-specific instrument is needed.

Recently, marked methodological improvements in the measurement of PAD patients' health status (their symptoms, function and quality of life) have been made. The psychometrically-sound Peripheral Artery Questionnaire (PAQ), a disease-specific measure, was developed for this purpose.<sup>6</sup> This instrument already proved to be useful to quantify improvement in health status after peripheral endovascular revascularization.<sup>5</sup> However, the PAQ is only available in an English-language version, and the dimensions it measures were created to represent a clinical framework for quantifying patients' health status and no empiric data supporting a patient-centered framework of the data has been performed. In order to make wider use of the PAQ possible, and to facilitate comparisons of PAD care and outcomes across different healthcare systems, we translated and validated a Dutch version of the PAQ in a large sample of Dutch PAD patients. More specifically, its validity and reliability was examined; convergent validity was tested against the EQ-5D, a standardized and widely used health outcome instrument.<sup>7,8</sup>

## METHODS

### Participants and design

This study was part of a survey of clinical practice that was conducted between May and December 2004 in 11 hospitals across The Netherlands. The study was performed within the infrastructure of

the Euro Heart Survey Programme, a project that evaluates the implementation of guidelines in daily clinical practice. Details of the participating centers and information about data collection are described elsewhere.<sup>9</sup> All consecutive patients included in this survey were seen at the participating vascular surgery departments and were undergoing noncardiac elective vascular repair (endovascular or open procedures). Endovascular procedures included aortic endograft repair and peripheral angioplasties with and without stenting. Open procedures included: elective abdominal aortic surgery, carotid endarterectomy, or infrainguinal arterial reconstruction. Patients below the age of 18 years and patients undergoing thoracic or brain surgery were excluded. The study was approved by the local ethics committees of the participating centers and all patients provided informed consent. After three years, information on vital status was obtained from the civil registries. All survivors were contacted to complete health status questionnaires.

### **Translation of the instrument**

Forward and backward translation according to the World Health Organization translation method was applied.<sup>10</sup> Forward translations were made by two different translators whose native language was Dutch. These translations were combined for making a first agreed-upon forward translation. Two other members of the bilingual group then evaluated the quality of this first version regarding clarity and readability, and checked for further inconsistencies in the translation. Adaptations upon this evaluation were amended where appropriate. Next, monolingual individuals were asked to read the first forward translation version through and check for comprehensibility. These individuals were PAD patients recruited at the vascular outpatient clinic of a teaching hospital at the St.-Elisabeth Hospital, The Netherlands. Comments of the monolingual group that were compatible with the meaning of the original document were inserted in the first forward translation version. Subsequently, a back-translated version was obtained from a professional translator. Finally, the original and back-translated documents were side-by-side by the bilingual expert group and were reviewed for accuracy and equivalence of the translation. The final version of the Dutch translation is presented in appendix A and information about the interpretation of scores is added in appendix B.

### **Measures**

#### ***Demographic and clinical variables***

Demographic variables included age and sex. Patients' medical history was documented by their hospital charts at the time of inclusion and included previous cardiovascular history (angina pectoris, myocardial infarction, heart failure, stroke/transient ischemic attack, arrhythmia, valvular disease, and previous revascularization), clinical risk factors (obesity, current smoking,

hypertension, diabetes mellitus, renal insufficiency, and chronic obstructive pulmonary disease), and type of surgery (endovascular, open). Obesity was defined as having a Body Mass Index  $\geq 30$ . Hypertension was recorded in patients presenting with a blood pressure of  $\geq 140/90$  mm Hg or who were treated for hypertension. Diabetes mellitus was recorded if patients had a fasting glucose level of  $\geq 7.0$  mmol/l, or if they received treatment for diabetes. Renal insufficiency was recorded in patients with a serum creatinine level  $\geq 2.0$  mg/dl or in those who required dialysis.

### **Health status**

Disease-specific health status was measured by the translated Dutch version of the PAQ; the instrument consists of 20 items with one item identifying the most symptomatic leg and the other items being answered along variable Likert response scales with equidistant gradations of response. Six domains were initially discerned in the PAQ: Physical Function, Symptoms, Symptom Stability, Social Limitation, Treatment Satisfaction, and Quality of Life.<sup>6</sup> Given that the response categories are different across items, standardized scoring algorithms are applied to obtain scale scores ranging from 0 to 100, with high scores indicating good health status.<sup>6</sup> Previously, the instrument proved to be internally reliable (Cronbach's  $\alpha$  ranging from 0.80 to 0.94) and sensitive to clinical improvement in a study with patients undergoing elective percutaneous peripheral revascularization.<sup>6</sup> The convergent validity of the PAQ was established against existing health status questionnaires, including the Walking Impairment Questionnaire, the 36-item Short-Form Health Survey (SF-36), and an exercise treadmill test.<sup>6</sup>

To assess the convergent validity of the Dutch PAQ, the Dutch version of the EQ-5D was used, a standardized, generic instrument for describing and valuing health that was designed by the EuroQol Group (an international research network established in 1987).<sup>11,12</sup> The EQ-5D consists of a descriptive system that defines health along five dimensions and a visual analogue scale (EQ VAS). The five dimensions include: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension can be rated on three levels, ranging from no problems to extreme problems and this score can be dichotomized. The EQ VAS asks respondents to rate their perception of their overall health on a vertical visual analogue scale with the endpoints ranging from 0 to 100 (0 = 'worst imaginable health state' and 100 = 'best imaginable health state'). In this study, the EQ VAS, the EQ-5D index, and the dichotomous dimension scores (1=no problems, 0=some or extreme problems) were used in the analyses.<sup>13</sup> The EQ-5D index, a single summary index, calculated in this study was based on value sets derived from the Dutch population.<sup>14,15</sup>

### **Statistical analysis**

Baseline characteristics were described for the total sample and differences between responders and nonresponders regarding these variables were examined using Student's t-tests for continuous

variables and chi-square tests for dichotomous variables to assess for potential selection biases among those who participated in the current study. Missing values were also checked on item-level for the PAQ. To assess the suitability of the data for factor analysis, Bartlett's test of sphericity and the Kaiser-Meyer-Olkin measure of sampling adequacy were checked. Principal components analysis (PCA) was applied to determine the number of factors present in the PAQ. Factors with an eigenvalue of 1.0 or more were retained for further investigation. Varimax rotation was used to interpret the pattern of loadings on the identified factors. Internal consistency of the factors was examined by performing reliability analyses. Cronbach's alpha coefficients were used as indicators of internal consistency. Convergent validity of the PAQ was evaluated by correlating the extracted PAQ subscales and Summary score with the dichotomized subscales of the EQ-5D (point-biserial correlations), the EQ VAS, and the EQ-5D index and by calculating the shared variance ( $r^2$  in %) between the PAQ and the EQ domains. In addition, PAQ summary and domain scores were stratified by dichotomized EQ-5D subscales (Student's *t*-tests). All analyses were performed using SPSS for Windows, version 14.0.1 (SPSS Inc., Chicago, Illinois).

## RESULTS

The total study population consisted of 711 patients. Patient status could be determined in 701 (99%) of the original 711 respondents revealing that 149 (21%) of patients died in the three year period since the original survey. All 552 survivors were contacted to complete health status questionnaires (EQ-5D and PAQ), 465 (84%) of whom responded and comprised the final study group.

The current sample ( $n=465$ ) included 70% ( $n=323$ ) male patients and the mean age was 65 years ( $SD=10$  years). There were 245 (52.7%) of patients who underwent an endovascular procedure; 27 patients underwent an aortic endograft procedure, 216 peripheral angioplasties with or without stenting, and 2 others. A total of 220 (47.3%) patients underwent an open procedure; 22 patients underwent carotid endarterectomy, infrainguinal arterial reconstruction  $n=101$ , abdominal aortic surgery  $n=88$  and 9 other open procedures. Information about associated risk factors and procedure information is presented in Table 1.

Responders did not differ from nonresponders, except for current smoking (52.9% in nonresponders vs. 35.5% in responders,  $P=.002$ ) and the presence of arrhythmia (16.1% in nonresponders vs. 6.5% in responders,  $P=.002$ ). The total of missings on the PAQ items ranged from 2.8 to 14.2% (mean=5.5%), with the questions concerning treatment satisfaction yielding the largest amount of missings.



**TABLE 1** - Characteristics of the total sample (N = 465)

<b>Demographics</b>		
Mean age $\pm$ SD, year	65	$\pm$ 10
Male sex, n (%)	323	(70)
<b>Cardiovascular history, n (%)</b>		
Angina pectoris	73	(16)
Myocardial infarction	67	(14)
Heart failure	18	(4)
Stroke or TIA	69	(15)
Arrhythmia	30	(7)
Valvular disease	23	(5)
Previous revascularization	77	(17)
<b>Clinical risk factors, n (%)</b>		
Obesity	57	(12)
Current smoker	165	(36)
Hypertension	177	(38)
Diabetes mellitus	96	(21)
Renal insufficiency	24	(5)
COPD	49	(11)
<b>Surgical procedure, n (%)</b>		
Endovascular	245	(53)
Open	220	(47)

TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease.

### Measurement qualities of the PAQ

Factor analyses were performed on all PAQ items (except for the first item that indicates the most symptomatic leg) for the total sample (n=465). Three factors explained the most of the variance in the observed data (using the criterion of eigenvalues above 1.0) and therefore three factors were retained in the final model (Table 2). The first factor explained 58%, the second 10%, and the third 5%. A more than three factor solution did not significantly add to the interpretability of the data (explaining only residual variance between 4 and 0.4%). Items are presented and numbered according to the order of the original instrument. All PAQ items had factor loadings ranging from 0.50 to 0.90. Two out of three factors corresponded almost exactly with the original Physical Function domain (items 2a-2f) and exactly with the Treatment Satisfaction scale (items 7-9). The new factor was a combination of the original Symptom, Symptom Stability, Social Limitation, and Quality of Life domains (items 3-13c). This new domain was called 'Perceived Disability' because these items require patients to evaluate their disabilities. Items with double loadings (4, 11, 13 a-c) were allocated according to their original domain in order to preserve the 'clinical' framework of the original instrument (Table 2).<sup>6</sup> The Summary score was computed by averaging the Physical Function and Perceived Disability scores.

Reliability was documented using Cronbach's  $\alpha$ ; Cronbach's  $\alpha$  for the Physical Function domain was 0.95, for the Perceived Disability domain 0.93, and for the Treatment Satisfaction domain 0.91. The Cronbach's  $\alpha$  for the Summary scale was 0.96. Mean inter-item correlation for the Physical Function domain was 0.76, for the Perceived Disability 0.58, for Treatment Satisfaction 0.78, and for the Summary score 0.71.

TABLE 2 - Sample Pattern Matrices of PAQ Scale Items as Indicated by Principal Component Analyses<sup>a</sup>

	Total (N = 465)		
	Factor I Physical Function	Factor II Perceived Disability	Factor III Treatment Satisfaction
<b>Physical Function</b>			
2a-Walking around your home	<b>0.70</b>	0.34	0.19
2b-Walking 1-2 blocks on level ground	<b>0.85</b>	0.30	0.16
2c-Walking 1-2 blocks up a hill	<b>0.88</b>	0.22	0.19
2d-Walking 3-4 blocks on level ground	<b>0.88</b>	0.24	0.15
2e-Hurrying or jogging	<b>0.87</b>	0.15	0.20
2f-Vigorous work or exercise	<b>0.87</b>	0.19	0.19
<b>Perceived Disability</b>			
3-Symptoms of PAD have changed	0.29	<b>0.66</b>	0.01
4-How often PAD symptoms	0.54	<b>0.54</b>	0.31
5-How much has PAD bothered you	0.55	<b>0.63</b>	0.31
6-Awakened with PAD symptoms	0.26	<b>0.56</b>	0.28
10-Limited enjoyment of life	0.42	<b>0.63</b>	0.42
11-Spend rest of life with PAD like it is now	0.41	<b>0.50</b>	0.50
12-Felt discouraged or down in the dumps	0.38	<b>0.62</b>	0.40
13a-Limited participation in hobbies, recreation	0.59	<b>0.57</b>	0.32
13b-Limited participation in visiting family, friends	0.56	<b>0.59</b>	0.18
13c-Limited participation in working or doing household chores	0.62	<b>0.56</b>	0.23
<b>Treatment Satisfaction</b>			
7-Satisfied that everything possible is being done	0.19	0.21	<b>0.85</b>
8-Satisfied with explanations	0.14	0.10	<b>0.90</b>
9-Satisfied with current treatment	0.19	0.21	<b>0.85</b>

<sup>a</sup> Varimax rotation; loadings of items assigned to a factor are presented in bold face.

### Convergent validity of the PAQ

Correlations between the PAQ subscales, PAQ Summary score, and the dichotomized subscales of the EQ-5D, the EQ VAS, and the EQ-5D index are presented in Table 3. Shared variance between the PAQ Physical Function domain and the EQ-5D scales ranged from 10 to 49%. The shared variance of the Perceived Disability domain scores of the PAQ and the EQ-5D scores ranged from 14 to 50%. The Treatment Satisfaction domain and the EQ-5D domains only shared 3 to 22% of variance. The shared variance between the Summary PAQ score and the EQ-5D scores ranged from 12 to 50%. The intercorrelations of the PAQ are also presented in Table 3 (shared variance between 18 and 92%). The intercorrelations with the Treatment Satisfaction scale, were relatively smaller (0.43 to 0.60) as compared with the intercorrelations of the other domains and the Summary score (0.78-0.96).

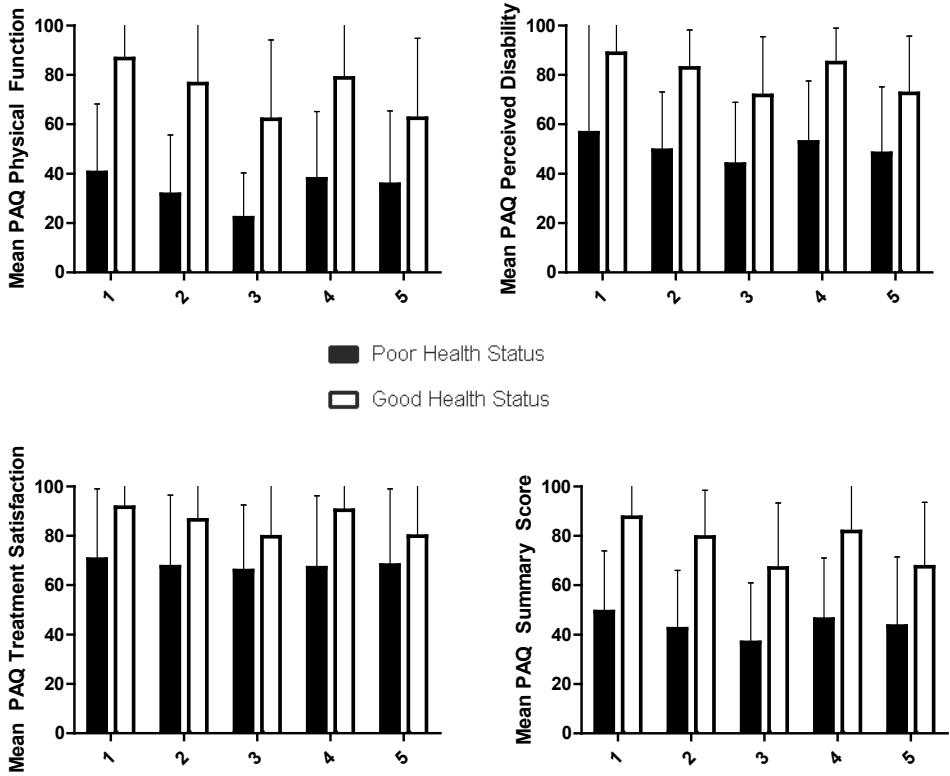
Mean PAQ Summary scores and PAQ domain scores were significantly different ( $P < .0001$ ) for high vs. low health status patients groups that were created by stratifying the total sample according to the five dichotomized subscales of the EQ-5D (Figure 1).

**TABLE 3** - Correlation Matrix of the PAQ Scales and EQ-5D Scales (N = 465)

	Correlation matrix <sup>a</sup>			
	PAQ Physical Function	PAQ Perceived Disability	PAQ Treatment Satisfaction	PAQ Summary Score
<b>PAQ</b>				
Physical Function	-			
Perceived Disability	0.78	-		
Treatment Satisfaction	0.43	0.60	-	
Summary Score	0.96	0.93	0.54	-
<b>EQ-5D</b>				
Mobility	0.66	0.59	0.36	0.64
Daily Activities	0.67	0.65	0.35	0.66
Self Care	0.40	0.38	0.18	0.38
Pain	0.61	0.61	0.42	0.62
Anxiety/Depression	0.32	0.38	0.17	0.35
EQ-5D Index	0.65	0.67	0.38	0.66
EQ-VAS	0.70	0.71	0.47	0.71

PAQ, Peripheral Artery Questionnaire; EQ-5D, EuroQol; VAS, visual analogue scale.

All correlations were significant at the 0.01 level.



**FIGURE 1 - Mean PAQ Domain and Summary Scores and Standard Deviations Stratified by Dichotomized EQ-5D Subscales (n=465).** All differences were significant at the  $P < .0001$  level. (1) Mobility, (2) Daily Activities, (3) Self Care, (4) Pain, (5) Anxiety/Depression.

## DISCUSSION

In order to make wider use of the PAQ possible, the questionnaire was translated into Dutch and validated in a study of Dutch PAD patients that was performed within the infrastructure of the Euro Heart Survey. It is the first translated version of the PAQ that was developed and the first study that evaluated its factorial structure within a relatively large study sample. A high response rate and the missing analysis on item-level showed that the PAQ was well accepted in the current sample of PAD patients. Unlike in the original instrument, three factors were discerned in the Dutch version of the PAQ, explaining most of the variance in the observed data. Two factors overlapped completely with the previously proposed Physical Function and Treatment Satisfaction scales of the original instrument. The other original domains (Symptom, Symptom Stability, Social Limitation, and Quality of Life) were combined in a new domain, which we labeled the Perceived

Disability domain in our study. As we chose to stay close to the clinically interpretable domains that were defined in the original instrument, we accordingly allocated double-loaded items. Future studies therefore need to replicate our work in both American and European samples to get an internationally agreed-upon factor structure. The three domains identified in this study were internally reliable. The convergent validity was established using a well standardized generic health status questionnaire, the EQ-5D.<sup>7</sup> Convergent validity of the PAQ domains was documented by medium to large correlations with the EQ-5D and by comparisons of the mean scores of the PAQ scales with the stratified EQ-5D domains. Both the intercorrelations of the PAQ domains and the correlations of the Treatment Satisfaction domain with the EQ-5D scales pointed to the uniqueness of the Treatment Satisfaction domain. Intercorrelations of the PAQ domains Perceived Disability and Physical Function were all high, indicating that the domains were strongly related to the construct that the questionnaire purported to measure, namely disease-specific health status.

Measuring disease-specific health status in a reliable way becomes essential in times where a wide array of treatment options are available for PAD patients. Recent technological advances have also resulted in a shift from open surgical procedures toward lower-morbidity catheter-based interventional therapies.<sup>16,17</sup> Although the use of these catheter-based interventions has increased significantly, the results regarding long-term patency rates of these interventions are mixed.<sup>18</sup> Due to the variety in treatment options and their variable success rates, PAD management has become a complex and challenging task. Treatment should therefore be tailored to the individual patient and should take into account the patients' perspective. To facilitate such discussions with patients, patient-based outcomes also need to be included in randomized trials evaluating revascularization procedures and medication use in PAD patients. Generic health status instruments are not sensitive enough to provide clinicians and researchers with useful information that makes adequate evaluation of PAD treatments possible.<sup>6,19,20</sup> Several disease-specific health status measures are developed for this purpose, with the PAQ being an excellent example of a valid and sensitive instrument that could be used both in clinical practice and as a treatment outcome in clinical PAD trials.<sup>5,6</sup>

The term 'health status' was chosen to refer to the construct that the PAQ intends to measure. However, the items that are contained in the PAQ do not all fully correspond with the definition of health status: "physical, mental, and social functioning assessment, but without the subjective evaluation of the patient".<sup>21</sup> The questionnaire is actually a mixture of items that deal with patients' health status and items that assess quality of life, with quality of life referring to patients' personal evaluation of their functioning, disease, and treatment.<sup>22,23</sup>

The Physical Function domain of the PAQ is an example of a scale measuring health status; it indicates whether PAD caused limitations and classifies the levels of such limitations.<sup>22</sup> In the second domain, called Perceived Disability in our study, a more subjective and evaluative character

is attributed to items 10 to 13c (e.g., *If you had to spend the rest of your life with your PAD the way it is right now, how would you feel about this?*). The third domain in our study also refers to the personal evaluation of the treatment that the patient received and is therefore more related to the genuine quality of life concept.<sup>23</sup> For clinical decision making, both health status or the registration of limitations, and quality of life, the extent to which these limitations actually hamper the patient, need to be considered and in this respect, the PAQ may offer insight in both. Other disease-specific outcome measures that are available suffer from predominantly focussing on the registration of limitations and do not stress the subjective experience of the disease and its limitations. The Walking Impairment Questionnaire, for example, only assesses the degree of physical limitation that the PAD patient experiences<sup>24</sup> and although the developers of the Intermittent Claudication Questionnaire claim to measure quality of life, thirteen out of sixteen items only register limitations with physical, mental and social functioning and do not evaluate the degree of dissatisfaction with these limitations.<sup>25</sup> The Vascular Quality of Life Questionnaire, on the other hand, contains items that tap both the patients' health status and quality of life, but the instrument contains both questions for PAD patients with intermittent claudication and critical leg ischemia, making this instrument more generic.<sup>26</sup>

This study has some limitations that should be considered when interpreting our results. The most important limitation is the cross-sectional nature of this study. We only assessed patients' health status with the PAQ on a single point of time and issues regarding reproducibility and sensitivity to change were not examined. On the other hand, previous studies with the PAQ convincingly showed that the instrument had a good test-retest reliability and that the instrument was sensitive to clinical improvement.<sup>5,6</sup> Another limitation is that our study population only consisted of PAD patients that underwent vascular surgery, which may limit the generalizability of scores to PAD patients that received conservative treatment. In spite of these limitations, potential strengths of our study were the large sample size and the fact that our study population consisted of patients of different hospitals across The Netherlands. Furthermore, this study was the first to extensively document on the factorial validity of the PAQ and was able to reduce the number of factors from six to three, further facilitating its use in clinical practice.

In sum, the Dutch version of the PAQ was found to be a reliable and valid instrument to assess the health status of PAD patients. In contrast with the six domains of the original instrument, a three-factor solution was sufficient to explain most of the variance in the health status scores of the present study. The next step is to perform additional research to establish the validity of the PAQ with relevant clinical indices, such as walking performance and standardized disease-specific risk classifications, and to monitor the performance of the questionnaire in evaluating the benefit of PAD treatments, as perceived by the individual patient. These efforts should all contribute to the tailor-made management of PAD patients, in this era of multifaceted risk management and treatment options that are available to them.

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3. Vergeleken met 4 weken geleden, zijn uw klachten die te maken hebben met uw **perifeer vaatlijden** (ongemak, vermoeidheid, pijn, zeurende pijn of krampen in uw kuiten (of billen) veranderd?  
Mijn klachten zijn...

Veel verergerd	Een beetje verergerd	Onveranderd gebleven	Een beetje verbeterd	Veel verbeterd	Ik heb geen klachten gehad in de afgelopen 4 weken
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. In de afgelopen 4 weken, hoeveel keer had u **ongemak, vermoeidheid, pijn, zeurende pijn of krampen in uw kuiten (of billen)**?

Altijd	Meerdere keren per dag	Minimaal 1 keer per dag	3 of meer keer per week, maar niet elke dag	1 à 2 keer per week	Minder dan 1 keer per week	Geen enkele keer in de afgelopen 4 weken
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5. In de afgelopen 4 weken, hoeveel hinder heeft uw **ongemak, vermoeidheid, pijn, zeurende pijn of krampen in uw kuiten (of billen)** u bezorgd?

Het bezorgde me...

<b>Ernstige</b> hinder	<b>Matige</b> hinder	<b>Enigszins</b> hinder	<b>Lichte</b> hinder	<b>Helemaal geen</b> hinder	Ik heb <b>geen ongemak in mijn benen</b> gehad
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

6. In de afgelopen 4 weken, hoe vaak bent u wakker geworden met **pijn, zeurende pijn of krampen in uw benen of voeten**?

Elke nacht	3 of meer keer per week, maar niet elke nacht	1 à 2 keer per week	Minder dan 1 keer per week	Nooit in de afgelopen 4 weken
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

7. Hoe tevreden bent u dat al het mogelijke voor u wordt gedaan om uw **perifeer vaatlijden** te behandelen?

Helemaal niet tevreden	Grotendeels ontevreden	Een beetje tevreden	Grotendeels tevreden	Helemaal tevreden
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

8. Hoe tevreden bent u met de uitleg die uw dokter u heeft gegeven over uw **perifeer vaatlijden**?

Helemaal niet tevreden	Grotendeels ontevreden	Een beetje tevreden	Grotendeels tevreden	Helemaal tevreden
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

9. Over het algemeen, hoe tevreden bent u over de huidige behandeling van uw **perifeer vaatlijden**?

Helemaal niet tevreden	Grotendeels ontevreden	Een beetje tevreden	Grotendeels tevreden	Helemaal tevreden
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

10. In de afgelopen 4 weken, hoeveel heeft uw **perifeer vaatlijden** u beperkt in uw levensvreugde?

Het heeft mijn levensvreugde <b>heel veel</b> beperkt	Het heeft mijn levensvreugde <b>veel</b> beperkt	Het heeft mijn levensvreugde <b>matig</b> beperkt	Het heeft mijn levensvreugde <b>een beetje</b> beperkt	Het heeft mijn levensvreugde <b>niet</b> beperkt
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

11. Als u de rest van uw leven verder moest leven met uw perifeer vaatlijden zoals het op dit ogenblik is, hoe zou u zich hierover voelen?

Helemaal niet tevreden	Grotendeels ontevreden	Een beetje tevreden	Grotendeels tevreden	Helemaal tevreden
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

12. In de afgelopen 4 weken, hoe vaak heeft u zich ontmoedigd gevoeld of in de put gezeten vanwege uw **perifeer vaatlijden**?

Ik voelde me zo <b>heel de tijd</b>	Ik voelde me zo <b>meestal</b>	Ik voelde me <b>soms</b> zo	Ik voelde me <b>zelden</b> zo	Ik voelde me <b>nooit</b> zo
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

13. In hoeverre beïnvloedt uw perifeer vaatlijden uw levensstijl? Geef aan hoe uw ongemak, vermoeidheid, pijn, zeurende pijn of krampen in uw kuiten (of billen) u van deelname aan de volgende activiteiten hebben beperkt in de afgelopen 4 weken.

Plaatst u a.u.b. een X in één hokje op elke lijn.

Activiteit	Ernstig beperkt	Nogal beperkt	Matig beperkt	Licht beperkt	Helemaal niet beperkt	Niet van toepassing of nam niet deel door andere redenen
a. Hobby's, ontspannende activiteiten	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Familie of vrienden gaan bezoeken	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Werken of huishoudelijke taken verrichten	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

## APPENDIX B

Interpretation of Raw Scores – Patients Undergoing Vascular Surgery in The Netherlands (N=465). The following table can be used for the interpretation of raw scores on the PAQ scales.

	Mean (SD)	33 Percentile cut-off scores to indicate poor health status
Physical Function	56.4 (33.5)	≤33
Perceived Disability	67.2 (25.9)	≤57
Treatment Satisfaction	77.4 (27.5)	≤75
Summary Score	62.0 (28.2)	≤47



# CHAPTER

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## **Clinical validity of a disease-specific health status questionnaire: the Peripheral Artery Questionnaire**

# 17

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## ABSTRACT

**Background:** Measuring patient-centered outcomes is becoming increasingly important in patients with peripheral arterial disease (PAD), both as a means of determining the benefits of treatment and as an aid for disease management. In order to monitor health status in a reliable and sensitive way, the disease-specific measure Peripheral Artery Questionnaire (PAQ) was developed. However, to date, its correlation with traditional clinical indices is unknown. The primary aim of this study was to better establish the clinical validity of the PAQ by examining its association with functional indices related to PAD. Furthermore, we hypothesized that the clinical validity of this disease-specific measure is better as compared with the EuroQol-5-dimensional (EQ-5D), a standardized generic instrument.

**Methods:** Data on 711 consecutive PAD patients undergoing surgery were collected from 11 Dutch hospitals in 2004. At 3-year follow-up, questionnaires including the PAQ, EQ-5D and EuroQol-Visual Analogue Scale (EQ VAS) were completed in 84% of survivors. The PAQ was analyzed according to three domains, as established by a factor analyses in the Dutch population, and the summary score. Baseline clinical indices included the presence and severity of claudication intermittent (CI) and the Lee Cardiac Risk Index.

**Results:** All three PAQ domains (Physical Function, Perceived Disability, Treatment Satisfaction) were significantly associated with CI symptoms ( $P$ -values  $<.001-.008$ ). Patients with claudication had significant lower PAQ summary scores as compared with asymptomatic patients ( $58.6 \pm 27.8$  vs.  $68.6 \pm 27.8$ ,  $P \leq .001$ ). Furthermore, the PAQ summary score and the subscale scores for Physical Functioning and Perceived Disability demonstrated a clear dose-response relation for walking distance and the Lee Risk Index ( $P$ -values  $<.001-.031$ ). With respect to the generic EQ-5D, the summary EQ-5D index was associated with CI ( $0.81 \pm 0.20$  vs.  $0.76 \pm 0.24$ ,  $P = .031$ ) but not with walking distance ( $P = .128$ ) nor the Lee Risk Index ( $P = .154$ ). The EQ VAS discriminated between the clinical indices ( $P$ -values  $<.01$ ), although a clear dose-response relation was lacking.

**Conclusions:** The clinical validity of the PAQ proved to be good as the PAQ subscales discriminated well between patients with or without symptomatic PAD and its severity as defined by walking distance. Furthermore the PAQ subscales were directly proportional to the presence and number of risk factors relevant for PAD. For studying outcomes in PAD patients, the disease-specific PAQ is likely to be a more sensitive measure of treatment benefit as compared with the generic EQ VAS, although the latter may still be of value when comparing health status across different diseases. Regarding disease management, we advocate the use of the disease-specific PAQ as its greater sensitivity and validity will assist its translation into clinical practice.



## INTRODUCTION

Peripheral arterial disease (PAD) is a common chronic condition and is associated with increased cardiovascular morbidity and mortality.<sup>1</sup> The global aging phenomenon will further increase the burden of cardiovascular diseases, including PAD.<sup>2</sup> It is well accepted that PAD adversely affects patients' health status and quality of life (QoL).<sup>3</sup> Patients not only perceive that their physical functioning is affected by lower-extremity symptoms, but a PAD diagnosis and its associated symptoms also affect patients' psychological well-being and mental health.<sup>4,6</sup>

The primary treatment goals of patients with PAD are to relieve pain, to improve health status and QoL, and to prolong survival. Sensitive patient-centered outcome measures are increasingly used in order to quantify the benefits of different treatment strategies and their cost-effectiveness.<sup>7</sup> From a methodological perspective these measures are important because the discriminative power of mortality as an outcome measure is poor, especially in PAD where mortality is more often due to the associated coronary and cerebrovascular disease rather than the PAD itself. As such, treatment of PAD is more often directed towards the goal of improving symptoms and its associated health impact, rather than survival. In addition to using health status in outcomes research, health status measurements can be used in disease management as a tool to identify patients who are suffering more from their PAD or who are at higher risk for adverse outcomes.<sup>8</sup> Identification of these high-risk patients may lead to more invasive treatment and more intensive follow-up.

Health status and QoL can be assessed using either generic or disease-specific instruments. Available data suggests a better construct validity of disease-specific instruments as compared with generic instruments.<sup>9</sup> Key advantages of disease-specific instruments are the focus on specific symptoms of a disease and their correspondingly greater sensitivity and responsiveness to clinical changes. Furthermore, the information received from disease-specific instruments can also be more easily translated into clinical practice as compared with information derived from generic questionnaires. On the other hand, advantages of using generic instruments are their simplicity and the ability of comparing patients' health status across different diseases.

In order to monitor health status in a reliable way, a new disease-specific measure, the Peripheral Artery Questionnaire (PAQ), was developed in US patients undergoing percutaneous peripheral revascularization and afterwards translated and validated in Dutch using a vascular surgery population in The Netherlands.<sup>10</sup> Although its psychometric properties<sup>10,11</sup> and sensitivity to change after revascularization<sup>12</sup> were adequately documented, there is limited insight into the ability to discriminate between asymptomatic and symptomatic disease and its correlation with traditional clinical indices of disease severity.<sup>10,12</sup> This study was designed to further document its validity by contrasting PAQ scores in patients with asymptomatic and symptomatic disease and

by comparing PAQ scores with PAD-related indices, such as walking disease and an established cardiac risk algorithm. More specifically, clinical validity was studied both in this disease-specific instrument and the EQ-5D, a standardized generic instrument applicable in a wide range of medical conditions, containing a five dimensional descriptive health status system (EQ-5D) and a visual analogue scale (EQ VAS).<sup>13,14</sup> We hypothesized that the clinical validity of the disease specific PAQ would be better than the generic EQ-5D.

## METHODS

### Study Population

Between May and December 2004, a survey of clinical practice was conducted in 11 hospitals in The Netherlands.<sup>15</sup> This survey was an integral part of the infrastructure of the survey program supported by The Netherlands Heart Foundation in the context of the Euro Heart Survey Programme. All consecutive patients included in this survey were seen at the participating vascular surgery departments and were undergoing noncardiac vascular repair (endovascular or open procedures). Endovascular procedures included aortic endograft procedures and peripheral angioplasties with and without stenting. Open procedures included abdominal aortic surgery, carotid endarterectomy, or infrainguinal arterial reconstruction. Patients below the age of 18 years and patients undergoing thoracic or brain surgery were excluded. The total study population consisted of 711 consecutively enrolled patients undergoing peripheral vascular repair. After three years follow-up, information on survival status was obtained through the Civil Registries. Patient status could be determined in 701 (99%) of the original 711 respondents revealing that 149 (21%) of patients had died in the three year period since the original survey. All 552 survivors were contacted to complete health status questionnaires (EQ-5D and PAQ), 465 (84%) of whom responded and comprised the final study group.

### Data Collection

#### *Clinical Characteristics*

Trained research assistants obtained data on patient characteristics, cardiac treatments and the surgical procedure from the patients' hospital charts. We determined the cardiac risk score for each patient in our dataset, according to the Lee Risk Index<sup>16</sup>, in which one point is assigned to each of the following characteristics: open vascular surgery, history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, insulin therapy for diabetes and renal failure. Furthermore, the presence of claudication and its severity were assessed by quantifying

patients' maximum walking distance. Walking distance was scored as <50 meter, 50-100 meters or >100 meters. More details on the study population and methods of data collection can be found in an earlier publication on this survey.<sup>15</sup>

### **Health Status**

Health status was measured at three years of follow-up by the translated Dutch version of the PAQ, a disease-specific instrument for assessing health status in patients with PAD.<sup>11</sup> The instrument consists of 20 items with one item identifying the most symptomatic leg and the other items being answered along variable Likert scales with equidistant gradations of response. Although the term 'health status' was chosen to refer to the construct that the PAQ intends to measure, the questionnaire contains both items that assess health status (i.e. registration of limitations) and QoL (patients' personal evaluation of their functioning, disease, and treatment). A previous validation study of the Dutch PAQ revealed three overarching domains: physical limitation (corresponding to the original PAQ physical limitation domain), perceived disability (corresponding to the original PAQ symptom, symptom stability, social limitation and QoL domains), and treatment satisfaction (corresponding to the original PAQ treatment satisfaction domain). Given that the response categories are different across items, standardized scoring algorithms are applied to obtain scale scores ranging from 0 to 100, with high scores indicating good health status.<sup>10</sup> A summary score can be obtained by combining the physical limitation and perceived disability subscale scores. The PAQ and its scoring instructions can be obtained from <http://www.cvoutcomes.org/>.

The Dutch version of the EQ-5D was used as a standardized, generic instrument for describing and valuing health.<sup>13,14</sup> This instrument was developed by the EuroQol group and has been used to assess health status across a wide range of chronic conditions, including cardiovascular disease.<sup>17</sup> The EQ-5D contains both an EQ-5D descriptive system that defines health along five dimensions and an EQ VAS. The five dimensions of the descriptive system consist of mobility, self-care, usual activities, pain or discomfort, and anxiety/depression. Each of these dimensions has three levels of severity corresponding to "no problems", "moderate problems" and "severe problems". Theoretically, 243 different health states can be generated by the descriptive system. A single summary index (EQ-5D index) representing the patient's self-rated health can be calculated by applying scores from a standard set of general population weights. The ratings can be analyzed on an individual level using health-state utility scores. Scores <0 are regarded as worse than death and 1 representing full health, from the perspective of the general population. The EQ-5D index in this study was obtained on value sets derived from the Dutch population by the time trade-off valuation technique.<sup>14</sup> In addition, the EQ VAS asks respondents to rate their perception of their overall health on a vertical visual analogue scale with the endpoints ranging from 0 to 100 (0 = 'worst imaginable health state' and 100 = 'best imaginable health state'). The EQ-5D and its scoring

instructions can be obtained from <http://www.euroqol.org/>. The results of the EQ-5D in this study will be presented using the weighted index of the 5-dimensional descriptive system (EQ-5D index) and using the EQ VAS as a measure of overall self-rated health status.

### **Clinical validity**

Clinical validity assesses the ability of scores to discriminate among groups of patients defined according to clinical severity. Patients who have a good clinical status (i.e., asymptomatic disease, fewer risk factors, and longer walking distance) should score well on the questionnaire, and patients who have a poor clinical status (i.e., symptomatic disease, more risk factors, and shorter walking distance) should score poorly. A high degree of clinical validity is suggested by a high correlation between health status and clinical indicators.

### **Statistical Analyses**

Baseline characteristics were described as numbers and percentages. Health status scores were described as means and standard deviations and compared using t-tests for dichotomous data and analysis of variance (ANOVA) for multiple categories. Linear regression analysis was used to assess multivariable association between the clinical indicators for PAD and health status scores. For all tests, a  $P$ -value  $<0.05$  (two-sided) was considered significant. All statistical analyses were performed using SPSS 15.0 statistical software (SPSS for Windows, Chicago: SPSS Inc).

## **RESULTS**

Of the 465 participating patients, 454 had sufficient health status information to generate PAQ summary scores with a mean score of  $62.0 \pm 28.2$ . Missing data analysis showed that respondents did not differ significantly from nonrespondents with regard to age, gender and Lee Risk Index. As shown in Table 1, most cardiovascular risk factors compromising the Lee Risk Index were associated with lower PAQ summary scores. Furthermore, the presence of COPD ( $53.3 \pm 26.8$  vs.  $63.0 \pm 28.2$ ,  $P=.024$ ) and obesity ( $50.8 \pm 29.0$  vs.  $63.6 \pm 27.8$ ,  $P=.001$ ) was associated with lower PAQ summary scores.

As shown in Table 1 and Figure 1, patients with claudication had significantly lower PAQ summary scores as compared with asymptomatic patients ( $58.6 \pm 27.8$  vs.  $68.6 \pm 27.8$ ,  $P \leq .001$ ). The differences in the PAQ summary score reflect the observed differences in the underlying PAQ domains Physical Functioning and Perceived Disability. Furthermore, the Treatment Satisfaction domain successfully discriminated between those who were symptomatic and those with asymptomatic PAD ( $75.0 \pm 28.1$  vs.  $82.5 \pm 25.7$ ,  $P=.008$ ). With respect to the generic EQ-5D, both the

EQ-5D index and the EQ VAS scores were lower for patients with claudication.

Of the 305 patients with claudication, information on walking distance was available in 202 (73%) patients with 25% classified as 0-50 meters, 29% 50-100 meters and 46% more than 100 meters. As shown in Figure 2, PAQ scores were proportional higher with increasing walking ability. The EQ VAS did also differ significantly between the groups, while the differences in EQ-5D index lacked significance.

PAQ summary score and subscale scores for the Physical Functioning domain and the Perceived Disability domain demonstrated a clear dose-response relationship with the Lee Risk Index, i.e. PAQ scores were lower with increasing cardiac risk (Figure 3). The Treatment Satisfaction domain was not associated with the Lee Risk Index. The EQ-5D index did not differ significantly between the risk groups; while the EQ VAS did ( $P=.008$ ) although the clear dose-response relation was lacking.

In addition, multivariable linear regression analysis revealed that after adjusting for other clinical characteristics, the independent association between CI, Lee Risk Index, and PAQ scores (Physical Functioning, Perceived Disability and PAQ summary score) remained (all  $P$ -values  $<.05$ ).

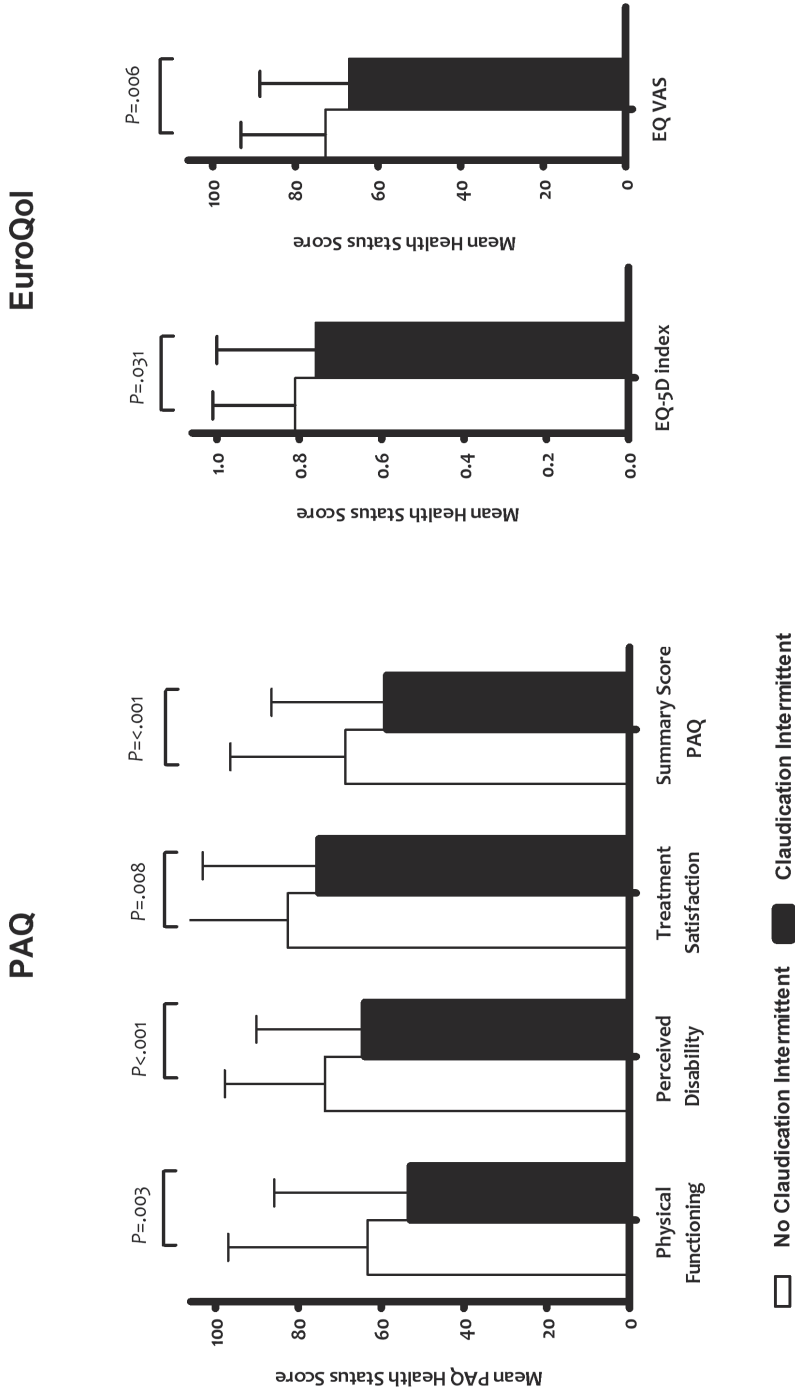


FIGURE 1 – Health status according to the presence of claudication intermittent symptoms. PAQ, Peripheral Artery Questionnaire; EQ-5D, EuroQoL-5-dimensions; EQ VAS, EuroQoL visual analogue scale.

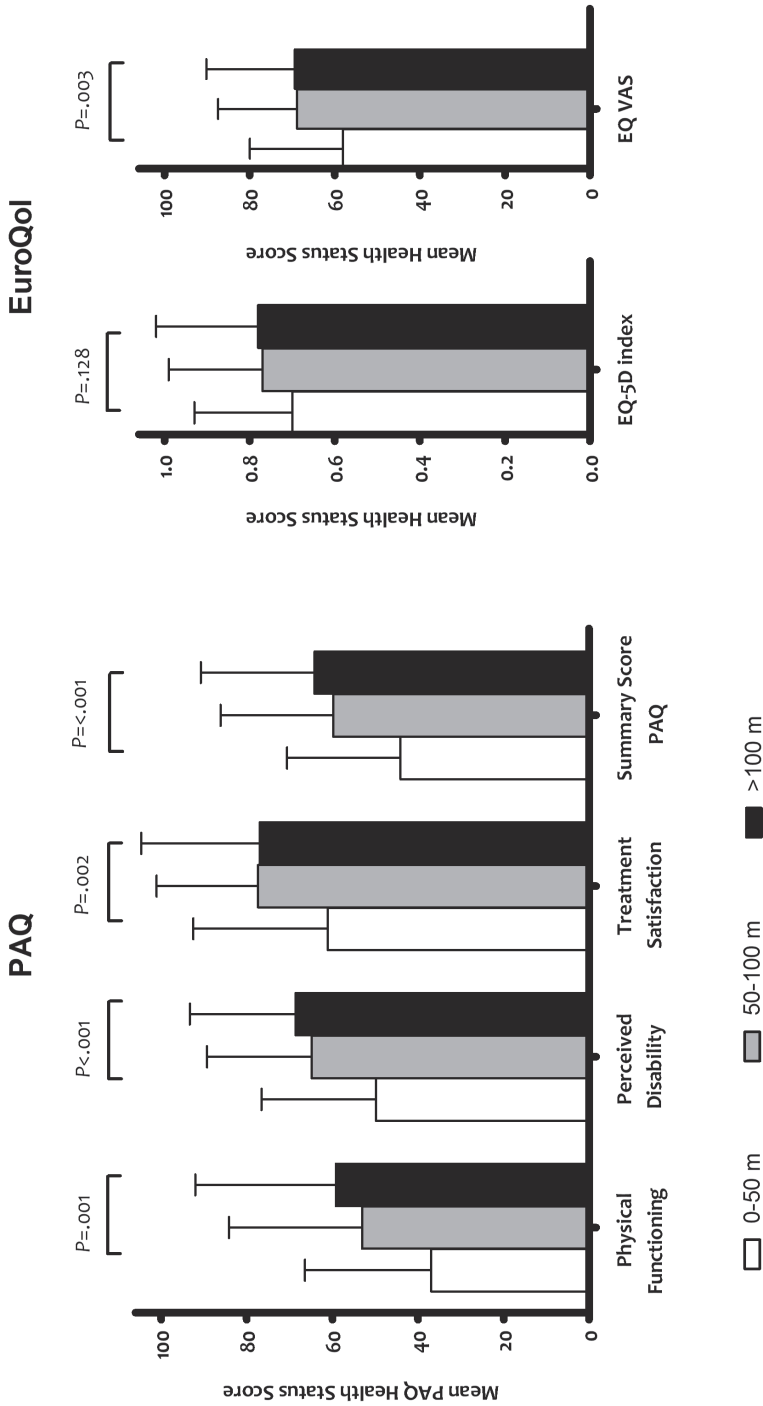


FIGURE 2 – Health status according to walking distance. Information on walking distance was available in 202 (73%) of the 305 patients with intermittent claudication. PAQ, Peripheral Artery Questionnaire; EQ-5D, EuroQoL-5-dimensions; EQ VAS, EuroQoL visual analogue scale.

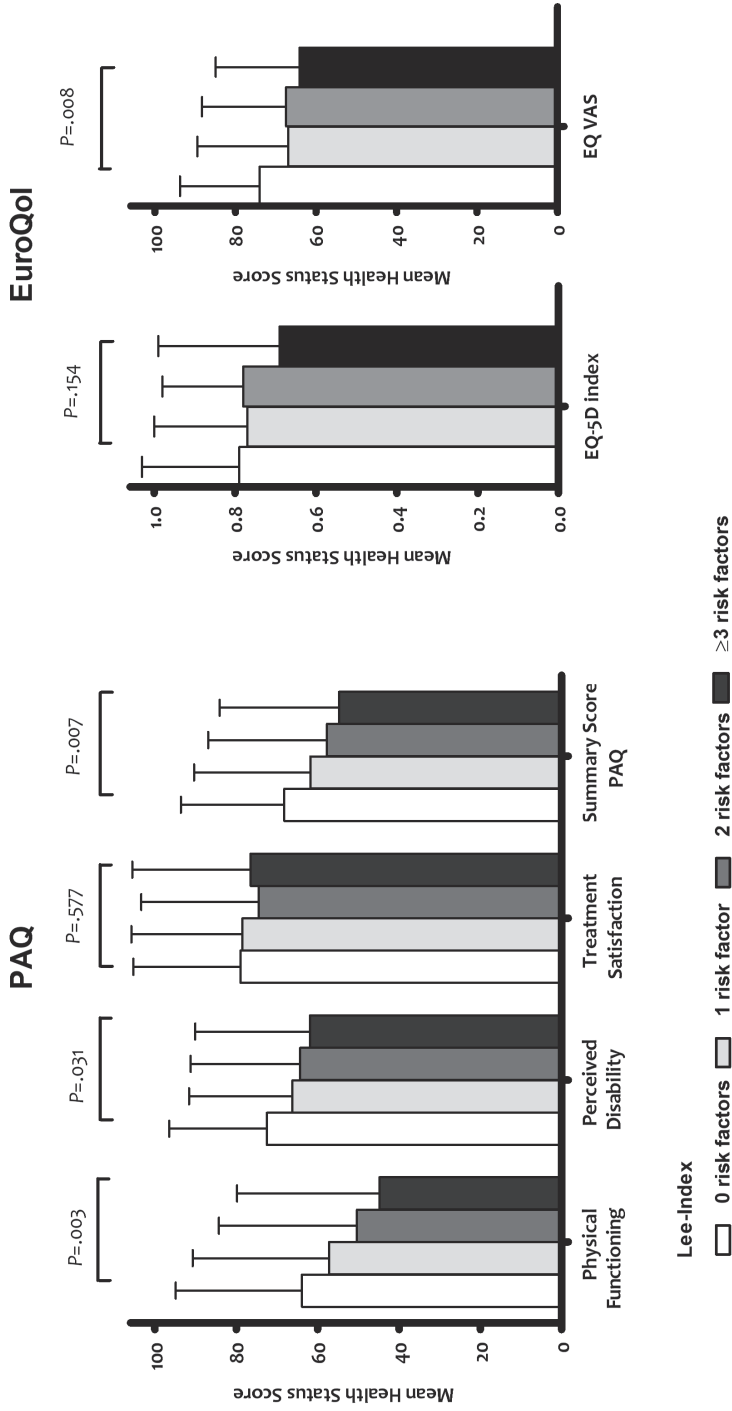


FIGURE 3 – Health Status According to the Lee Cardiac Risk Index. Abbreviations: PAQ, Peripheral Artery Questionnaire; EQ-5D, EuroQol-5-dimensions; EQ-VAS, EuroQol visual analogue scale.



## DISCUSSION

This study demonstrated good clinical validity of the PAQ with traditional clinical indices of PAD severity. In specific, all PAQ subscales discriminated well between patients with or without symptomatic PAD and its severity. Moreover, it was sensitive to the presence of risk factors relevant for PAD and demonstrated a clear dose-response relationship between the number of risk factors and patients' experienced health status. Although the EQ-5D index and EQ VAS scale could differentiate between asymptomatic and symptomatic disease, the EQ indices were not able to display the clear dose-response relationship between the number of risk factors and worsening of health status. These findings have important potential implications for disease management programs and future clinical trials.

An important issue to be addressed regarding the development and use of health status instruments in vascular medicine are their reliability and validity. Internal reliability of the three domains quantified by Cronbach's  $\alpha$  was reported high for the Dutch PAQ (mean  $\alpha=0.94$ ) and the original instrument.<sup>10</sup> Previous studies also showed that the PAQ had a good test-retest reliability and sensitivity to change.<sup>10,12</sup> In addition, an important issue for the use of disease-specific measures in clinical practice is that they focus on aspects that are relevant for a specific patient population. Our results of the PAQ instrument clearly show the disease-specific nature of this measure, with the PAQ discriminating well between different clinical indices. The strongest association of PAD symptoms that we observed were with pain and physical limitations, i.e. the PAQ sub domains of Physical Functioning and Perceived Disability. This observation confirms earlier research demonstrating the impact of symptomatic disease on physical health and QOL in PAD patients.<sup>5,18</sup> PAD is also often accompanied by comorbid diseases, which may pose an extra burden on patients' health status. The results in this report showed that the cardiac risk profile of PAD patients, as described by the Lee Cardiac Risk Index, was highly correlated with patients' health status. Increasing risk was proportionally reflected in decreasing PAQ scores on the Physical Functioning and Perceived Disability domains and, Summary score.

The management of patients with PAD has changed in the last decade with the introduction of endovascular techniques and other treatment modalities.<sup>19</sup> In general, the principal aim of medical treatment is to relieve symptoms related to the specific disease and to improve the patients' health status and prognosis. Traditionally, treatment success is measured with clinical measures, such as the ankle-brachial index, patency rates, and survival. The question regarding the impact of the intervention on the patients' ability to function in daily life remains, however, when only relying upon these technical measures.<sup>7</sup> Since the patients' main concerns are for symptom relief and improvement in their daily functioning, treatment should also be assessed by its success in improving patients' health status. Furthermore, clinical measures, as the ankle-brachial index are

known to correlate poorly with changes in health status scores,<sup>9,20</sup> which also supports the use of direct, patient-centered assessments of the effects of treatment on patients' health status. As such, health status is increasingly being assessed in clinical research studies comparing different treatment options.<sup>20,21</sup> Moreover, patient-based outcome measures can provide substantial insights into related clinical factors and processes of care that are useful in assessing healthcare quality.<sup>22</sup> Traditional metrics for evaluating healthcare have been mortality and morbidity, but these measures often lack the sensitivity to differentiate providers and omit a major outcome from the perspective of patients.

While there is a choice in how best to quantify patients' health status, important advantages of disease-specific, as compared with generic, instruments are their focus on specific symptoms of a disease and the sensitivity and responsiveness to clinically relevant changes conferred by treatment. Previous studies have demonstrated a better discriminative ability of disease-specific versus generic questionnaires to detect changes in QOL in PAD patients,<sup>23</sup> congruent with the findings of our study, which demonstrated that the PAQ discriminated better between the clinical indices than the generic EQ-5D index. The EQ-5D is known for its ceiling effect, i.e. the score distribution tends to be skewed to higher scores, which could potentially be related to having only three response categories and its generic character. In our study, 25% of the patients had a maximum score. Except for patients with more than three risk factors according to Lee Risk Index, mean scores of the EQ5D were all higher than 0.75 and did not differ substantially. On the other hand, the EQ VAS was more sensitive for clinical indices, although its discriminative ability appeared to be less than the PAQ in this study. For studying outcomes in PAD patients, the disease-specific PAQ, therefore, seems to be the preferred choice. The EQ VAS may still be a valuable secondary choice, as generic health status questionnaires are known to be broad and multidimensional instruments and, therefore, apt for use when comparing health status across different diseases or when calculating utility values in economic analysis are important study goals.

In addition to using health status measures as outcome measure, health status measurements may provide prognostic information to guide clinical decision-making. In this way, impaired health status has been shown to be an independent predictor of mortality in cardiac patients<sup>24-26</sup> and predicted invasive treatment in a prospective PAD population.<sup>27</sup> Health status measurements can therefore potentially be used in clinical practice to identify patients who are at relatively high risk for adverse outcomes. These patients may benefit from more aggressive treatment, including pharmacological, invasive or behavioural interventions. Of note, the performance of the EQ VAS score was acceptable when discriminating between symptomatic vs. asymptomatic disease and suboptimal when relating the index to walking distance and the presence of risk factors. Although it seems attractive in terms of time, effort and resources to use this simple instrument to assess the patients' health status, its role in disease management is minor. The PAQ describes clear and

clinically-relevant domains that can give clinicians important insights with which to better manage patients' PAD; including patients' physical limitations due to their PAD and their personal evaluation of their limitations related to PAD. These nuances can not be captured by generic questionnaires and by instruments that only focus on physical limitations, rather than concentrating on the subjective evaluations of patients' physical functioning. Although information received from generic instruments are hard to interpret and to translate into clinical practice, the EQ VAS may be used as an initial screening tool to further identify vulnerable patients with disease-specific questionnaires, such as the PAQ.

The limitations of this study are those inherent to observational studies and the fact that all patients underwent vascular interventions. Although the study cohort seems to be a relatively high risk population, the PAQ was still able to discriminate well between the clinical indices. Moreover, it has to be noted that compared to clinical trials, our study comprises a rather heterogeneous population and is more representative of daily clinical practice. Further research has to be performed to ascertain the clinical validity of PAQ in an overall PAD population treated with a range of therapeutic options. Another potential limitation of our work is that the response rate of our study was not 100%. A response rate of 84%, however, is regarded as quite good and importantly nonresponder analyses revealed no differences between the patients who responded and those who did not. Furthermore, it should be noted that the assessment of the validity of questionnaires is not straightforward as there is no golden standard for outcome measurement in PAD patients. In this study, we used clinical indices retrospectively obtained from chart review, including the presence of claudication and the Lee Risk Index as criterion measures for clinical validity. This limitation should be kept in mind together with the fact that no baseline health status measurements were available when interpreting our results. Future studies using the PAQ, should further elaborate on the clinical relevance of this disease-specific instrument tracking clinical indices, such as the ankle-brachial index, and aspects of lower-extremity functioning together with patients' health status.

In conclusion, this study demonstrated good clinical validity of the PAQ as the instrument discriminated well between patients with or without symptomatic PAD and its severity and was sensitive to the presence of risk factors relevant for PAD. We would like to strengthen the importance of disease-specific health status measures like the PAQ and advocate their use as outcome measure and disease management tool in PAD management, rather than relying on clinical measures alone. After all, outcome and risk assessment should be evaluated from the patients' perspective. Health status measures will play an increasingly important role in the evaluation of diverse therapeutic strategies and in clinical decision making in the field of vascular medicine.

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# CHAPTER

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## Health-related quality of life predicts long-term survival in patients with peripheral artery disease

# 18

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## ABSTRACT

**Objectives:** We examined whether HRQoL predicts long-term survival in patients with peripheral artery disease (PAD) independent of established prognostic risk factors.

**Methods:** In 2004, data on 711 consecutive patients with PAD undergoing vascular surgery were collected from 11 hospitals in the Netherlands. After one year, patients were contacted to complete the EuroQol Questionnaire (EQ-5D), of which 503 (79%) complied. HRQoL assessed by the EQ-5D was divided into tertiles, i.e. poor, intermediate and good HRQoL. Mortality was subsequently assessed three years after surgery.

**Results:** Of the 503 patients, 55 (11%) died during follow-up. Mortality was 21% in patients with poor HRQoL, 8% in patients with intermediate HRQoL, and 5% in patients with good HRQoL. Patients with poor HRQoL (HR=5.4; 95%CI 2.3–12.5) had a worse survival compared to patients with a good HRQoL, after adjusting for established prognostic factors.

**Conclusions:** Poor HRQoL predicts long-term survival in patients with PAD, and provides prognostic value above established risk factors.



## INTRODUCTION

Peripheral artery disease (PAD) is a marker of generalized atherosclerosis affecting multiple vascular beds simultaneously.<sup>1</sup> This polyvascular disease phenomenon frequently leads to conditions such as intermittent claudication, myocardial infarction (MI), dementia, and stroke.<sup>1,2</sup>

PAD is associated with increased cardiovascular morbidity, poor physical functioning, and adverse health outcomes.<sup>3,4</sup> Long-term survival after vascular surgery in patients with PAD is predominantly determined by the associated risk of coronary artery disease (CAD).<sup>5</sup> Despite the known risk patients with PAD do not achieve comparable risk control as patients with other cardiovascular diseases.<sup>6,7</sup> Patients with PAD have poor long-term survival even more so than patients with CAD only.<sup>8</sup> Taken together, patients with PAD constitute a high-risk group that needs stringent risk management and monitoring.<sup>2</sup>

Health related quality of life (HRQoL) reflects patients physical, mental and social beliefs and perceptions in relation to health. HRQoL has been shown to have prognostic value in predicting adverse clinical events independent of conventional risk factors in CAD.<sup>9,12</sup> Prognostic information is pertinent for providing tailored patient management. Importantly, information about HRQoL and health status, as perceived by the patient, can help optimize patient-centred care in clinical practice.<sup>13</sup> In addition, poor HRQoL has been shown to predict poor prognosis independent of indicators of disease severity in patients with CAD and heart failure.<sup>14</sup> Although HRQoL and the risk of mortality in patients with PAD are generally comparable to that of patients with CAD<sup>15</sup>, the impact of HRQoL on mortality in PAD has not yet been investigated. HRQoL might help to identify patients with PAD at high risk for adverse health outcomes and may provide independent prognostic information, other than established biomedical risk factors, as shown in a recent systematic review of the the impact of HRQoL on survival in CAD and congestive heart failure.<sup>14</sup> Hence, the objective of the present study was to examine if HRQoL predicts long-term survival in patients with PAD beyond established biomedical risk factors.

## METHODS

### Study population

The study population was derived from the Netherlands Heart Foundation Health Care Programme, entitled Peripheral Arterial Disease Survey. Details are only reported here as relevant to the current analyses. More details on the study population and methods of data collection can be found in an earlier publication on this survey.<sup>16</sup> Between May and December 2004, data on 711 patients with PAD undergoing noncardiac vascular surgery were collected from 11 hospitals

in the Netherlands. The consecutively enrolled patients were seen at the participating vascular surgery departments when undergoing endovascular or open procedures. Endovascular surgery procedures included aortic endografts or peripheral angioplasties with and without stenting. The open procedures comprised abdominal aortic surgery, carotid endarterectomy, or infrainguinal arterial reconstruction. All patients were asked for informed consent before participation. The 11 participating hospitals met the requirements for ethical approval based on local standards.

One year after surgery, 634 of 711 (89%) patients were still alive. Survivors were sent the EuroQol Questionnaire and questions concerning their cardiovascular events by mail, which they were asked to complete.

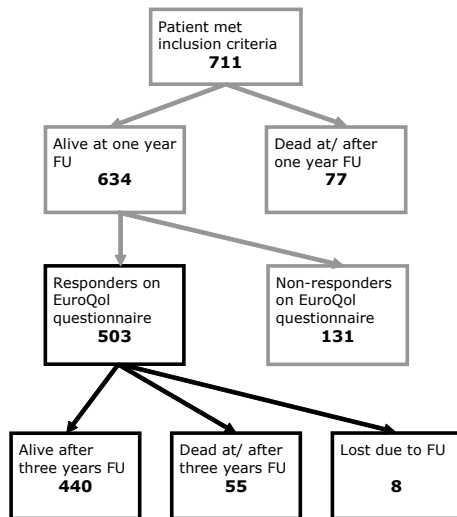


FIGURE 1 - Flowchart of patient selection.

### Data collection

Baseline measurements, patient characteristics and risk factors, were collected before surgery by trained research assistants. The hospital charts were searched for information on relevant clinical characteristics, such as history of chronic obstructive pulmonary disease (COPD), diabetes mellitus, and renal insufficiency as cardiovascular morbidity. Data with respect to the incidence of angina pectoris (AP), MI, history of revascularization, prior arrhythmias, history of congestive heart failure, and history of cerebrovascular disease were once again updated one year after surgery. All data were entered into the electronic Case Record Form and transferred regularly via the Internet to the central database at the Erasmus Medical Centre, Rotterdam, the Netherlands. Three years after surgery, survival status (all-cause mortality) was obtained through the civil registries.

### Health-related Quality of Life

HRQoL was measured one year after surgery with the Dutch version of the EuroQoL Questionnaire.<sup>17,18</sup> This instrument consists of two facets, the EQ-5D and the EQ visual analogue scale. To intensively investigate the clinical application of HRQoL assessment, the focus of this cohort was on the EQ-5D. The validated EQ-5D is a standardized, generic measure of self-reported HRQoL which has been used in patients with PAD<sup>16</sup> and other cardiovascular diseases.<sup>9</sup> The EQ-5D descriptive system assesses the following five clinically relevant dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of these dimensions has three levels of severity, corresponding to “no problems”, “moderate problems” and “severe problems”. Patients were asked which statement best described their health. More details on and instructions for the EQ-5D can be found on <http://www.euroqol.org/>.

### Statistical analyses

Descriptive statistics included count plus percentages for nominal variables, and mean values with corresponding standard deviations for continuous variables. Responders were compared with nonresponders by use of Pearson chi-square tests. Differences between survivors and deceased patients on demographic and clinical characteristics in relation to survival were compared by use of univariable Cox regression analysis. The five dimensions of the EQ-5D were computed to form a utility score using a standard set of general population weights. These scores can range from -0.594 to 1, with a score <0 regarded as a HRQoL that is worse than death and 1 representing full health, from the perspective of the general population. The general population weights were obtained on value sets derived from the Dutch population by the time trade-off valuation technique.<sup>17</sup> To examine the effect of a high score on the EQ-5D versus one that is lower in rank, the utility scores were divided into tertiles for parsimony, i.e. poor HRQoL, intermediate HRQoL, and good HRQoL. Kaplan-Meier curves were computed for each tertile with all-cause mortality as the endpoint. To investigate the prognostic ability of the individual dimensions of the EQ-5D, the dimensions were dichotomized into: “no problems” vs. a cluster of “moderate problems” and “severe problems”, prior to statistical analyses. Univariable Cox regression analyses were conducted to determine the prognostic ability of HRQoL utility score, tertiles, and individual dimensions on mortality. Multivariable Cox regression analyses were performed to adjust for potential confounders based on univariate analysis ( $P < .001$ ) including age, prior arrhythmias, history of congestive heart failure, COPD and renal insufficiency. Sensitivity analyses were performed to adjust for 1) medication use (statins, aspirins, beta-blockers) and 2) the entity of PAD (i.e., peripheral occlusive disease of the lower limbs, abdominal aortic aneurysms and carotid stenosis). Results from the Cox regression analyses are presented as hazard ratios (HR) with 95% confidence intervals (CI). For all tests, a  $P < .05$  (two-sided) was considered significant. All statistical analyses were performed with SPSS statistical software, version 15.0 (SPSS Inc, Chicago, Ill).

# RESULTS

## Patient characteristics of survey responders versus nonresponders

Of the 634 1-year survivors, 503 (79%) completed the questionnaire, comprising the sample available for statistical analyses in this study (Figure 1). The characteristics of the patients who did not complete the EuroQol Questionnaire (21%) were compared with the sample included in the analyses. Comparison of the responders (n=503) versus the nonresponders (n=131) showed great similarities, with the exception of non-responders being less likely to be males (73.2% vs. 57.3%;  $P<.001$ ) but more likely to have congestive heart failure (3.4% vs. 7.6%;  $P=.021$ ).

**TABLE 1** - Clinical characteristics\* of the total sample and stratified by survival status.

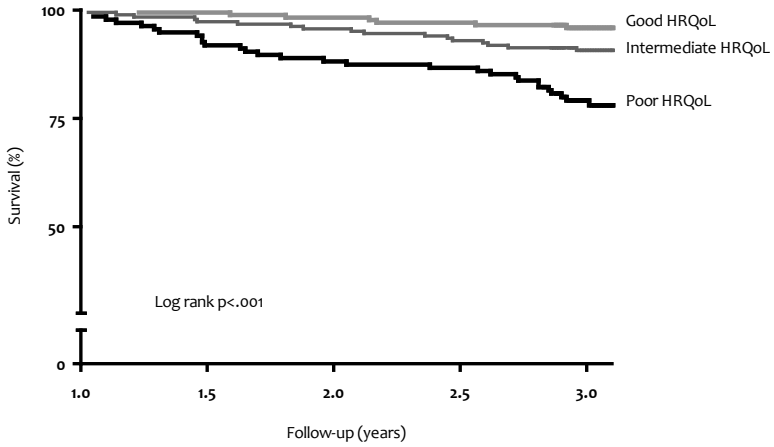
Characteristics	Total	N(%)	Alive	N(%)	Dead	N(%)	Univariate HR (95% CI) for mortality
N	503	(100%)	440	(88%)	55	(11%)	
Age (yrs):							
Age (Mean $\pm$ SD)	67 $\pm$ 10		66 $\pm$ 10		74 $\pm$ 10		1.1 (1.0 - 1.1)
$\geq$ 70 years	208	(41%)	167	(38%)	39	(71%)	3.6 (2.0 - 6.5)
Gender, male	368	(73%)	320	(73%)	43	(78%)	1.2 (0.7 - 2.4)
COPD	65	(13%)	49	(11%)	15	(27%)	2.8 (1.5 - 5.1)
Diabetes mellitus	93	(19%)	79	(18%)	13	(24%)	1.4 (0.8 - 2.7)
Renal insufficiency	28	(6%)	20	(5%)	8	(15%)	3.2 (1.5 - 6.8)
Stroke or TIA	83	(17%)	72	(16%)	9	(16%)	1.0 (0.5 - 2.1)
Arrhythmias	51	(10%)	39	(9%)	11	(20%)	2.3 (1.1 - 4.5)
Heart failure	26	(5%)	19	(4%)	7	(13%)	2.6 (1.1 - 6.1)
Angina pectoris	75	(15%)	68	(16%)	7	(13%)	0.7 (0.3 - 1.6)
Myocardial infarction	80	(16%)	69	(16%)	11	(20%)	1.2 (0.6 - 2.4)
Previous coronary revascularization	90	(18%)	76	(17%)	13	(24%)	1.5 (0.8 - 2.8)

\*Clinical characteristics of the patients at time of HRQoL measurement

N, number; SD, standard deviation; HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease.

## Baseline characteristics for the total sample and stratified by survival status

The mean age of the 503 included patients was 67 $\pm$ 10 years and 73% were male. During the follow-up period, 55 (11%) patients died. Patients who died during follow-up had in general more risk factors compared to survivors (Table 1). Univariable Cox regression analysis revealed significant increased risk for mortality for age  $\geq$ 70 years (HR=3.6; 95%CI 2.0–6.5), COPD (HR=2.8; 95%CI 1.5–5.1), renal insufficiency (HR=3.2; 95%CI 1.5–6.8), prior arrhythmias (HR=2.3; 95%CI 1.1–4.5), and history of congestive heart failure (HR=2.6; 95%CI 1.1–6.1).



Number at risk

	1.0	1.5	2.0	2.5	3.0
Good HRQoL	172	172	170	168	113
Intermediate HRQoL	184	180	177	172	120
Poor HRQoL	135	125	120	118	75

FIGURE 2 - Survival stratified by differences in HRQoL.

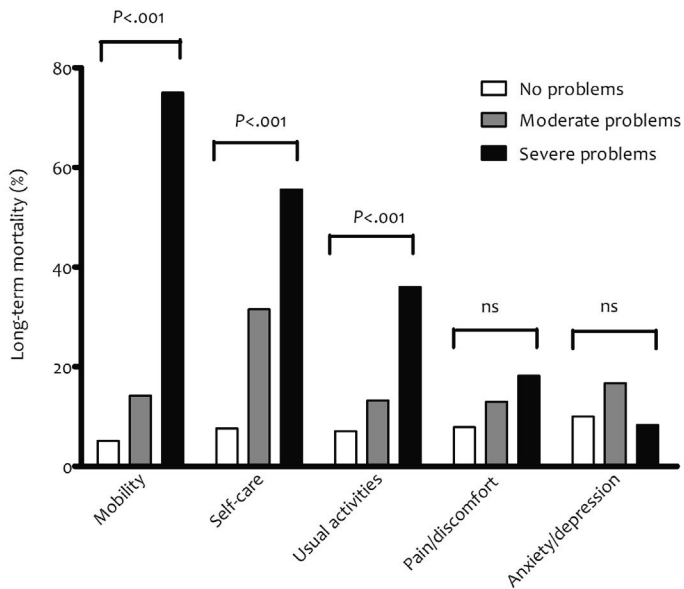


FIGURE 3 - Long-term mortality, according to severity of reported problems on the EuroQol dimensions.

### Impact of Health Related Quality of Life

There was a clear relationship between HRQoL and mortality. Mean utility scores were  $0.79 \pm 0.22$  in survivors versus  $0.64 \pm 0.27$  in those who died ( $P < .001$ ). The mean utility score and range of the individual tertiles were  $0.48 \pm 0.24$  (-0.26-0.77) for poor HRQoL,  $0.80 \pm 0.03$  (0.78-0.86) for intermediate HRQoL, and  $0.97 \pm 0.05$  (0.90-1.00) indicating good HRQoL. Mortality was 21% in patients with poor HRQoL, 8% in patients with intermediate HRQoL, and 5% in patients with good HRQoL. Kaplan-Meier curves revealed similar results, i.e. patients with poor HRQoL had the poorest prognosis, followed by intermediate HRQoL (Figure 2). To examine if HRQoL predicts mortality beyond conventional clinical risk factors, analyses were adjusted for potential confounders. The adjusted analyses showed impaired HRQoL as a predictor of mortality, i.e. poor vs. good HRQoL (HR=5.3; 95%CI 2.3–12.1) and intermediate vs. good HRQoL (HR=2.0; 95%CI 0.8–4.9). Age  $\geq 70$  years (HR=2.6; 95%CI 1.4–4.8), COPD (HR=3.2; 95%CI 1.7–6.2), renal insufficiency (HR=3.2; 95%CI 1.4–7.2), AP (HR=0.4; 95%CI 0.1–0.9) were also significant predictors of mortality in the adjusted analyses. Sensitivity analysis adjusting for medication use (statins, aspirins, beta-blockers) revealed comparable results, poor vs. good HRQoL (HR=5.2; 95%CI 2.3–12.0) and intermediate vs. good HRQoL (HR=1.9; 95%CI 0.8–4.7). Additionally, sensitivity analysis adjusting for the entity of PAD showed also similar results, poor vs. good HRQoL (HR=5.3; 95%CI 2.3–12.1) and intermediate vs. good HRQoL (HR=2.0; 95%CI 0.8–4.9).

There was also a clear relationship between the severity of impairment on the individual dimensions of the EQ-5D and long-term mortality. The more severely impaired the HRQoL dimension, the lower the survival rate (Figure 3). Multivariable analyses revealed significant associations between reporting problems and long-term mortality for the dichotomized dimensions of the EQ-5D. Patient-rated problems reached statistical significance for mortality in all of the dimensions of the EQ-5D. The results of the adjusted analyses were significant for mobility (HR=2.7; 95%CI 1.3-5.6), self-care (HR=4.4; 95%CI 2.5-7.8), usual activities (HR=2.3; 95%CI 1.3-4.1), pain/discomfort (HR=1.8; 95%CI 1.0-3.3), and for anxiety/depression (HR=2.0; 95%CI 1.1–3.7) (Table 2).

TABLE 2 - Comparison of symptom reports on the EuroQol Questionnaire and stratified by survival status

EQ-5D	Total	N(%)	Alive	N(%)	Dead	N(%)	Univariate HR (95% CI) for mortality	Multivariate HR (95% CI) for mortality
N	503	(100%)	440	(88%)	55	(11%)		
Mean ±SD	.77±.23		.79±.22		.64±.27		1.2 (1.1- 1.3) <sup>a</sup>	1.2 (1.1- 1.4) <sup>a</sup>
<b>Tertiles:</b>								
Good	178	(35%)	166	(38%)	9	(16%)	1	1
Intermediate	187	(37%)	168	(38%)	17	(31%)	2.3 (1.0 - 5.6) <sup>b</sup>	2.0 (0.8 - 4.9) <sup>b</sup>
Poor	138	(27%)	106	(24%)	29	(53%)	5.8 (2.5 -13.2) <sup>b</sup>	5.3 (2.3 - 12.1) <sup>b</sup>
<b>Mobility</b>							3.3 (1.6 - 6.8) <sup>c</sup>	2.7 (1.3 - 5.6) <sup>c</sup>
no problems	196	(39%)	185	(42%)	10	(18%)		
moderate problems	303	(60%)	254	(58%)	42	(76%)		
severe problems	4	(1%)	1	(0%)	3	(6%)		
<b>Self-care</b>							5.7 (3.3 - 9.8) <sup>c</sup>	4.4 (2.5 - 7.8) <sup>c</sup>
no problems	439	(87%)	399	(91%)	33	(60%)		
moderate problems	55	(11%)	37	(8%)	17	(31%)		
severe problems	9	(2%)	4	(1%)	5	(9%)		
<b>Usual activities</b>							2.5 (1.4 - 4.5) <sup>c</sup>	2.3 (1.3 - 4.1) <sup>c</sup>
no problems	272	(54%)	247	(56%)	19	(35%)		
moderate problems	205	(41%)	177	(40%)	27	(49%)		
severe problems	26	(5%)	16	(4%)	9	(16%)		
<b>Pain/discomfort</b>							2.0 (1.1 - 3.7) <sup>c</sup>	1.8 (1.0 - 3.3) <sup>c</sup>
no problems	219	(44%)	199	(45%)	17	(31%)		
moderate problems	249	(50%)	214	(49%)	32	(58%)		
severe problems	35	(7%)	27	(6%)	6	(11%)		
<b>Anxiety/depression</b>							1.7 (0.9 - 3.0) <sup>c</sup>	2.0 (1.1 - 3.7) <sup>c</sup>
no problems	405	(81%)	359	(82%)	40	(73%)		
moderate problems	86	(17%)	70	(16%)	14	(26%)		
severe problems	12	(2%)	11	(3%)	1	(2%)		

N, number; SD, standard deviation; HR, hazard ratio; CI, confidence interval.

<sup>a</sup> Hazard per 0.1 decline in EQ-5D utility score.

<sup>b</sup> References group for analyses is the tertile that represents a good HRQoL.

<sup>c</sup> To examine the relationship between reporting problems on the EQ-5D dimensions and survival by use of Cox regression, the three levels of severity were dichotomised in: “no problems” vs. reporting problems (a cluster of “moderate problems” and “severe problems”).

## DISCUSSION

To our knowledge this is the first study to investigate the relationship between HRQoL and mortality in PAD. This study demonstrates HRQoL, as measured by the EQ-5D, to be strongly associated with long-term survival in patients with PAD. After adjusting for other established risk factors, poor HRQoL remained an independent predictor of mortality, with the risk being 5-fold compared to patients with a good HRQoL. The risk factors that were adjusted for in multivariable analyses are known for being the most important predictors of mortality in patients with PAD.<sup>7</sup> In addition, impaired health status assessed by the EQ-5D has previously been shown to independently predict mortality in CAD patients as well.<sup>9</sup>

HRQoL assessments provide unique information about the impact of the disease as perceived by the patient, which was confirmed in the current study, as poor HRQoL had predictive value in addition to established biomedical risk factors. Quality of life assessed by questionnaires such as the Short Form Health Survey 36 (SF-36), the 46-item Patient Concerns Checklist, and the quality-of-life Index-Cardiac Version have also shown to be independent predictors of mortality in patients with CAD and congestive heart failure.<sup>10,14</sup>

The primary goal of therapy in patients with PAD is to improve HRQoL and morbidity/mortality. In previous research, surrogates of objective measures of disease, including the ankle-brachial index, has been shown to correlate weakly with HRQoL.<sup>19</sup> In addition, physician evaluated health status of cardiac patients are known to have limited reproducibility and sensitivity with regard to clinical changes.<sup>13,20</sup> Routine clinical practice often does not assess directly unobservable components such as self-care, social functioning, general health perception and coping with illness that are imbedded in self-rated health. Therefore, it is important to assess HRQoL as rated by the patient.

Taken together, due to the unique prognostic value of patient-rated HRQoL, it may be timely to adopt HRQoL assessments in clinical practice in order to guide treatment and enhance secondary prevention in patients with cardiovascular disease.<sup>9,10,14,21</sup> The prognostic ability of HRQoL may complement traditional clinical practice, by identifying patients at high risk for mortality independent of biomedical factors. Further research is warranted to investigate the mechanisms that may be responsible for the relationship between HRQoL and mortality. Thus far, depression and the distressed (Type D) personality have been shown to predict impaired HRQoL and poor survival independent of disease status.<sup>22,23</sup> In addition, depression is associated with poor medication adherence independent of somatic sensations due to disease as experienced by the patient.<sup>24</sup> Nevertheless, even if there is still no clear evidence concerning the mechanisms, patients with impaired HRQoL may benefit from more aggressive medical treatment. These high-risk patients should be monitored more carefully and be invited to clinical follow-ups more frequently,



and may also profit from more aggressive disease management. Such disease management should probably be multi-factorial, consisting of adjustment in medication, exercise training, behavioural intervention, and the adoption of a confronting coping strategy, which have been shown to improve HRQoL.<sup>25-27</sup> Smoking cessation and following a careful diet may also be beneficial.

The major advantage of the EQ-5D is its brevity, making the transition to implement, understand, and use HRQoL as an additional tool in clinical practice less taxing both for health-care professionals and patients. The EQ-5D consists of five questions, whereas most other HRQoL measures predicting mortality are much more lengthy.<sup>10-12</sup> Despite its brevity, the EQ-5D clearly differentiated between PAD patients with a poor versus good survival in the current study. Furthermore, the EQ-5D has shown to have a comparable sensitivity and specificity to more lengthy questionnaires, such as the generic questionnaire SF-36 and the disease-specific questionnaire the Vascular Quality of Life in preoperative patients with PAD.<sup>28</sup>

The results of the current study should be interpreted with some caution. First, the study may be subject to selection bias, as only survivors at one year were included in our analyses (excluding deceased patient, n=77). Furthermore, an inherent limitation of cohort studies is non-response. Nevertheless, responder versus nonresponder baseline characteristics analyses showed almost no differences. Second, we had no information on socio-economic status that may serve as a confounder on the relationship between HRQoL and mortality. Third, the use of tertiles and dichotomization of HRQoL is arbitrary, even though dichotomization enhances the clinical applicability of the results.<sup>29</sup> Fourth, despite the link between HRQoL and long-term mortality in patients with PAD, we do not know whether HRQoL is a risk marker for a third variable on the causal pathway between HRQoL and mortality, nor which mechanisms, e.g. behavioral or biological, that may explain the link with mortality. Finally, although this cohort demonstrates HRQoL as predictor of long-term survival in patients with PAD, there was no data available on HRQoL prior to surgery, so we still need to know the effect of HRQoL on different time points.

In conclusion, patients with PAD constitute a high-risk group that needs stringent risk management and monitoring. Patient-rated HRQoL, as measured by the EQ-5D, identifies patients with PAD at high risk for mortality independent of established biomedical risk factors. The EQ-5D could be used in clinical practice to identify patients at high risk, who may benefit from more aggressive treatment, behavioural intervention and support but also as a performance measure to enhance the quality of care in clinical practice, as advocated by others.<sup>13</sup>

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# CHAPTER

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**Process of care partly explains the variation  
in mortality between hospitals after  
peripheral vascular surgery.**

# 19

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## ABSTRACT

**Background:** Postoperative mortality rates often serve as a measure to compare hospital quality.

**Aim:** The aim of this study is to investigate whether variation in mortality at hospital level reflects differences in quality of care of peripheral vascular surgery patients.

**Design:** Observational study

**Methods:** In 11 hospitals in the Netherlands, 711 consecutive vascular surgery patients were enrolled. Multilevel logistic regression models were used to relate patient characteristics, structure and process of care to mortality at 1 year. The models were constructed by consecutively adding age, sex and Lee index, then remaining risk factors, followed by structural measures for quality of care and finally selected process of care parameters. Sensitivity analyses were performed with 30-day and 3-year mortality as outcome.

**Results:** Total 1-year mortality was 11%, ranging from 6% to 26% in different hospitals. Large differences in patient characteristics and quality indicators were observed between hospitals (e.g. age >70 years: 28% to 58%; beta-blocker therapy: 39% to 87%). The adjusted analyses showed that a large part of variation in mortality was explained by age, gender and the Lee-index (AIC=59,  $P<.001$ ). Another substantial part of the variation was explained by process of care (AIC=5,  $P=.001$ ). Sensitivity analyses with 30-day and 3-year mortality revealed comparable results.

**Conclusions:** Differences between hospitals exist in patient characteristics, structure of care, process of care and mortality. Even after adjusting for the patient population at risk, a substantial part of the variation in mortality can be explained by differences in process measures of quality of care.

## INTRODUCTION

Assessing quality of care is becoming more and more important in contemporary medical practice. In general, performance profiling has two primary objectives. First, to stimulate and promote internal quality assurance at the level of the hospitals and physicians, and second to promote an efficient market economy in health care.<sup>1</sup>

The widely accepted Donabedian's classic paradigm of assessing quality of care is based on a three-component approach; structure, process, and outcome.<sup>2</sup> Structural measures refer to inherent characteristics of the provider that are believed to be associated with quality of care. Process measures of quality of care reflect the extent to which a provider complies with evidence-based guidelines. Postoperative mortality rates serve as an outcome-based measure to compare hospital quality of surgical care. However, it has been shown that hospital variations in mortality rates are not exclusively related to differences in quality of care but also to differences in case-mix.<sup>3,5</sup> Accordingly, Rutherford has emphasized the need for risk-adjustment for disease severity and other case-mix characteristics for adequately comparing outcomes for vascular surgery.<sup>6</sup> Furthermore, differences in the ascertainment and definition of data could cause variation in outcome. Indeed, a study in patients undergoing aortic surgery concluded that unadjusted mortality rates used as an indicator of performance are subject to bias and distortion owing to the collection of incorrect information, variation in patient selection between hospitals and case-mix differences.<sup>7</sup> Finally, beyond chance, differences in outcome may reflect genuine differences in structure and process of care. The association of procedure volume as a structural measure with outcome is often described in surgery.<sup>8,9</sup> However, less evidence exist regarding the relation between process of care and outcome in vascular surgery.

In order to study whether variation in mortality at hospital level reflects differences in quality of care, data from the Netherlands Peripheral Vascular Disease Survey were used, in which detailed data on patient characteristics, structure and process of care and outcome are available.

## METHODS

### Study population

Between May and December 2004, a survey of clinical practice was conducted in 11 hospitals in the Netherlands.<sup>10</sup> This survey was an integral part of the infrastructure of the survey program supported by the Netherlands Heart Foundation in the context of the Euro Heart Survey Programme. The objective of the Euro Heart Survey was to evaluate clinical practice, adherence to guidelines, differences in the management, and outcome of patients and to assess to what

extent the patients of daily practice are represented in randomized clinical trials. Five hospitals were located in the centre part of the country, three hospitals in the northern region and three in the southern region. The participating sites included 2 small centres (<400 beds), 5 of intermediate size (400 to 800 beds) and 4 large centers (>800 beds). Two centres were university hospitals, which act as tertiary referral centres.

Patients undergoing peripheral vascular repair were eligible for participation in the survey. All consecutive patients included in this survey were seen at the participating vascular surgery departments and were undergoing noncardiac vascular repair (endovascular or open procedures). Endovascular procedures included aortic endograft procedures and peripheral angioplasties with and without stenting. Open procedures included: elective abdominal aortic surgery, carotid endarterectomy, or infrainguinal arterial reconstruction. The total study population consisted of 711 consecutively enrolled patients. The medical ethics committees of the participating hospitals approved the study. All patients provided informed consent.

### **Data collection**

Trained research assistants obtained data on patient characteristics, diagnostic procedures, cardioprotective treatment and the surgical procedure from the patients' hospital charts. All data were entered into the electronic Case Record Form (eCRF) and transferred regularly to the central database at Erasmus MC via the Internet. Data entered into the eCRF were automatically checked for completeness, internal consistency and accuracy. The data management staff at Erasmus MC performed additional edit checks. If necessary, queries were resolved with the local research assistants. At 1 year and 3 years, survival status was obtained through the Civil Registries. Follow-up was complete in 98.5%. More details on the study population and methods of data collection can be found in an earlier publication on this survey.<sup>10</sup>

### **Clinical characteristics**

We determined the cardiac risk score for each patient in our dataset, according to the Lee-index<sup>11</sup>, and one point was assigned to each of the following characteristics: open vascular surgery, history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, insulin therapy for diabetes mellitus and renal insufficiency. Hypertension was recorded if patients presented with a blood pressure  $\geq 140/90$  mm Hg or if patients were medically treated for hypertension. Diabetes mellitus was recorded if patients presented with a fasting glucose level  $\geq 7.0$  mmol/l, or in those who required treatment. Renal insufficiency was recorded if patients presented with a serum creatinine level  $\geq 2.0$  mg/dl or in those who required dialysis. Obesity was defined as having a Body Mass Index  $\geq 30$ .



### **Structure of care**

Structural measures refer to inherent characteristics of the provider that are believed to be associated with quality of care. High volume, university centre and preoperative anaesthesiology outpatient clinic were used as structural measures for quality of care in this study. We approximated the volume of the hospitals by the volume of abdominal aortic aneurysm procedures in 2004 and high volume was defined as more than 80 procedures per year.<sup>12</sup>

### **Process of care**

Process measures of quality of care reflect the extent to which a provider complies with evidence-based guidelines. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for perioperative care were the guided choice for quality of care parameters in this survey.<sup>13</sup> These parameters included noninvasive testing, beta-blocker therapy, antiplatelet therapy and cholesterol lowering therapy. Application of all recommended procedures and treatments were derived from the hospital records. When nothing was reported in the hospital record, the procedure or treatment was considered as not applied.

### **Outcome measures**

Mortality was obtained at 30-days, 1 year and 3 years after surgery through the civil registries. Patient status was complete in 99%. We defined 1-year all-cause mortality as the primary endpoint in this study. Sensitivity analyses were performed with the alternative outcome measures.

### **Statistical Analyses**

To assess the differences in outcome between hospitals in patient characteristics, structure of care and process of care, hospitals were divided in tertiles based on the percentage of patients who died in the first year. Dichotomous data are described as numbers and percentages, and continuous data are presented as means with standard deviations (SD). Differences in patient characteristics, structure of care, process of care and outcome between hospitals were evaluated by analysis of variances (ANOVA) and Chi-square tests, where appropriate.

Stepwise logistic regression analysis was performed to investigate the relationship between clinical characteristics, structure of care, process of care and outcome. The database has a hierarchical structure with patients operated in different hospitals. To account for the different sources of variation (patient level and center level) in observed mortality rates at different centers, we used a multilevel model with hospital as a random effect. In the first step of the multilevel model we included only age, sex and the Lee-Index. Secondly, other clinical characteristics were added: obesity, smoking, hypertension, arrhythmia, valvular disease and chronic obstructive pulmonary disease (COPD). Structural measures were added in the third step. In the final step

selected process of care measures were added to the model. The contribution of each step was expressed by Akaike's information criterion (AIC) which corresponds to the  $\chi^2$  of the step (or the difference in -2 log likelihood between the model with and without that step) minus 2x the degrees of freedom.<sup>14</sup> Analysis was performed using SPSS 14.0 for Windows and R statistical software. Multilevel regression models were constructed with the Laplace method using the LME4 package of R. For all tests, a *P*-value <0.05 (two-sided) was considered significant.

## RESULTS

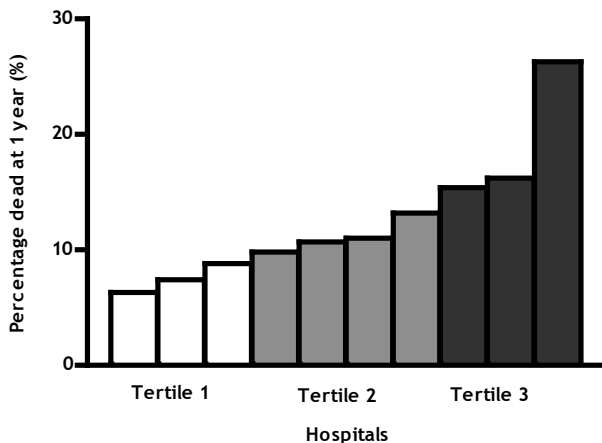
### Outcome

The study population consisted of 711 patients undergoing vascular repair. Of all patients, 4% died during hospital stay (Table 1). At 1 year, 77 patients died (11%), ranging from 6% to 26% between hospitals (Figure 1). The mean mortality rate was 8% in tertile 1, 11% in tertile 2 and 17% in tertile 3. A total of 149 (21%) patients died within 3 years of follow-up.

**TABLE 1.** Variation in percentage 1-year mortality by hospital

	Total	Hospital Tertiles based on patient outcome (% dead at 1 year)*		
		1 (lowest)	2	3 (highest)
Number of patients	711	300	247	164
Number of hospitals	11	3	4	4
30-day mortality	28 (4%)	4% (2-5)	3% (1-7)	5% (0-11)
1-year mortality	77 (11%)	8% (6-9)	11% (10-11)	17% (13-26)
3-year mortality	149 (21%)	18% (11-22)	21% (17-25)	28% (24-37)

\* Hospitals were divided into tertiles based on the percentage of patients that were dead at 1 year.



**FIGURE 1** - One-year mortality after vascular repair by hospital and tertile division.

## Clinical characteristics

The mean age was 67 years (SD=10) and 70% were male. Of the total patient population, 26% had no risk factors, 34% only 1, 31% had 2 risk factors and 8% had 3 or more risk factors according to the Lee-Index. Differences in clinical characteristics between the hospital tertiles were observed (Table 2). For example, percentage males varied from 72% to 67% ( $P < 0.05$ ) and percentage patients with good functional capacity from 70% to 60% ( $P < 0.05$ ). The percentage patients with no risk factors ranged from 28% in the lowest tertile to 24% in the highest tertile. The percentage high risk patients (2 or more risk factors) varied between hospitals from 13% to 63% ( $P < 0.001$ ) as illustrated in Figure 2.

**TABLE 2** - Variation in patient characteristics by hospital

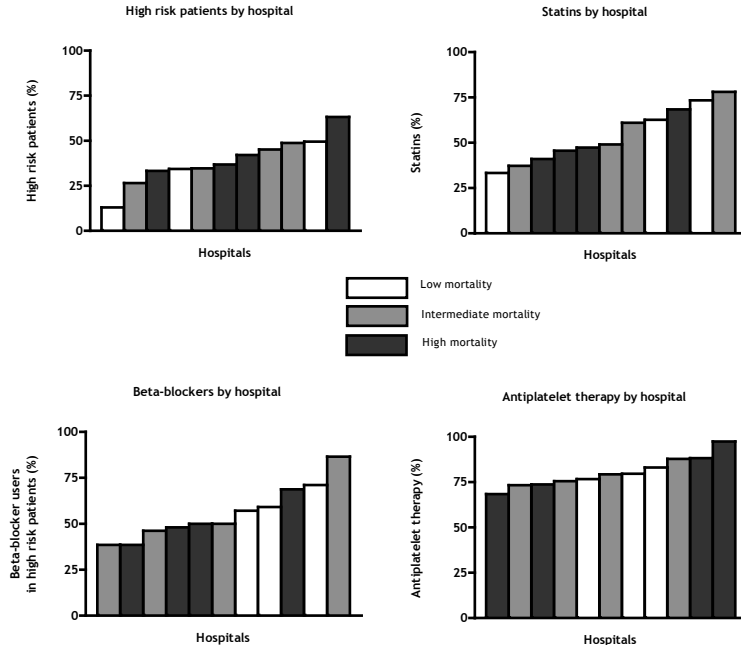
	Total	Hospital Tertiles based on patient outcome (% dead at 1 year)*			P-value <sup>b</sup>
		1 (lowest)	2	3 (highest)	
Number of patients	711	300	247	164	
Number of hospitals	11	3	4	4	
Age >70	299 (42%)	40% (28-46)	42% (39-49)	46% (38-58)	ns
Male gender	496 (70%)	72% (56-79)	69% (65-73)	67% (49-90)	<.05
Current smoker	256 (36%)	35% (28-46)	35% (28-49)	40% (26-47)	<.05
Hypertension	273 (38%)	31% (2-70)	53% (2-81)	31% (21-74)	<.001
Diabetes mellitus	149 (21%)	21% (20-22)	21% (17-31)	21% (15-26)	ns
Renal insufficiency	51 (7%)	8% (2-10)	7% (3-12)	7% (2-21)	<.05
Angina pectoris	99 (14%)	12% (10-16)	16% (12-20)	15% (10-21)	ns
Myocardial infarction	106 (15%)	17% (14-18)	13% (12-15)	14% (10-21)	ns
Heart failure	38 (5%)	5% (4-6)	8% (2-13)	3% (0-5)	ns
Stroke or TIA	123 (17%)	16% (6-18)	16% (2-29)	23% (15-28)	<.05
Previous revascularisation	116 (16%)	20% (9-26)	17% (12-20)	9% (3-16)	<.05
COPD	101 (14%)	10% (2-12)	20% (16-29)	14% (11-21)	<.05
Good functional capacity	471 (66%)	71% (65-73)	65% (37-90)	60% (46-76)	<.001
Open surgical procedure	357 (50%)	47% (20-56)	47% (36-81)	60% (43-100)	<.001
Elective procedure	619 (87%)	82% (75-96)	90% (85-96)	91% (84-100)	<.001
Lee-Index <sup>a</sup>					<.001
0	187 (26%)	28% (18-46)	26% (15-31)	24% (0-37)	
1	243 (34%)	33% (27-41)	35% (28-47)	35% (27-47)	
2	221 (31%)	31% (11-38)	30% (18-38)	32% (23-47)	
≥3	60 (8%)	9% (2-12)	9% (7-15)	8% (5-16)	

COPD, chronic obstructive pulmonary disease

\* Hospitals were divided into tertiles based on the percentage of patients that were dead at 1 year

<sup>a</sup> Variables included in the Lee-Index; open surgical procedure, ischaemic heart disease, history of congestive heart failure, history of cerebrovascular disease, diabetes mellitus and renal insufficiency)

<sup>b</sup>  $\chi^2$  for differences between 11 hospitals



**FIGURE 2 - Variation in patient characteristics and process of care parameters by hospital and mortality based tertile division.**

Across the tertiles of hospital mortality, these percentages were 40%, 39% and 40%, respectively ( $P=.959$ ). Half of the patients underwent an open surgical procedure. The 357 open vascular procedures included infrainguinal arterial reconstruction (52%), abdominal aortic surgery (42%), and 21 (6%) other procedures. The percentage of patients undergoing open surgical procedure varied also widely between the centres (20% to 100%,  $P<.001$ ).

**TABLE 3 - Variation in structure of care by hospital**

	Total	Hospital Tertiles based on outcome (% dead at 1 year)*			P-value <sup>a</sup>
		1 (lowest)	2	3 (highest)	
Number of patients	711	300	247	164	
Number of hospitals	11	3	4	4	
High volume hospital	3	1	1	1	<.001
Preoperative anaesthesiology outpatient clinic	8	2	3	3	<.001
University hospital	2	0	2	0	<.001

\* Hospitals were divided into tertiles based on the percentage of patients that were dead at 1 year

<sup>a</sup>  $\chi^2$  for differences in presence of structure of care parameter between 11 hospitals

## Process of care

Although 185 of the total 711 patients (26%) fulfilled the ACC/AHA guideline criteria to recommend preoperative noninvasive cardiac testing, clinicians had performed testing in only 38 of those cases (21%). As shown in Table 4, this percentage varied from 12% to 30% across the hospital tertiles ( $P=0.06$ ). Overall, 304 patients (48%) received beta-blocker therapy, 398 patients (56%) statin therapy and 575 patients (81%) antiplatelet therapy in the perioperative period. These proportions differed significantly between the hospital tertiles: 52% to 34% for beta-blockers ( $P<.001$ ) and 60% to 48% for statins ( $P=0.039$ ). The percentage beta-blocker users in the 281 high risk patients, i.e.  $\geq 2$  risk factors according to the Lee-Index, was 62%. This proportion varied also widely across the hospitals tertiles in the same trend as the overall proportions (68% to 52%,  $P=.084$ ).

**TABLE 4** - Variation in process of care by hospital

	Total	Hospital Tertiles based on outcome (% dead at 1 year)*			P-value <sup>a</sup>
		1 (lowest)	2	3 (highest)	
Number of patients	711	300	247	164	
Number of hospitals	11	3	4	4	
Diagnostic investigations					
Noninvasive test	38/185 (21%)	22% (0-55)	12% (0-35)	30% (20-33)	<.05
Medical therapy					
Beta-blockers	340 (48%)	52% (33-61)	52% (35-77)	34% (21-45)	<.001
In high-risk patients	174/281 (62%)	68% (57-71)	62% (39-87)	52% (39-69)	<.05
Statins	398 (56%)	60% (33-73)	57% (37-78)	48% (41-68)	<.001
In high-risk patients	180/281 (64%)	67% (43-77)	63% (39-78)	61% (56-67)	ns
Antiplatelet therapy	575 (81%)	81% (77-83)	78% (37-88)	85% (68-97)	<.05

\* Hospitals were divided into tertiles based on the percentage of patients that were dead at 1 year

a)  $\chi^2$  for differences between 11 hospitals

## Relation between clinical characteristics, quality of care and outcome

Age, sex and the Lee-Index explained a large part of the variation in mortality (step 1; AIC=59,  $P<.001$ ) (Table 5a). A relatively small part was explained by other risk factors (step 2; AIC=-1,  $P=.102$ ). After adjusting for all these risk factors in step 1 and 2, structure of care explained a non-significant part of the variation on mortality (step 3; AIC=-4,  $P=.285$ ). In contrast, on top of clinical characteristics and structural measures, process measures of quality of care explained a relatively large part of the variation in mortality (step 4; AIC=5,  $P=.001$ ). The area under the curve of the model with only age, sex and the Revised Cardiac Risk Index was .74 and increased to .81 for the complete model.

## Sensitivity analyses

Results were not affected by changing the dependent variable of the logistic regression analysis into 30-day mortality (Table 5b). Step 1 and 4 explained most of the variation in mortality (AIC=44,  $P < .001$  and AIC=16,  $P = .003$ ). Consistent results were obtained with 3-year mortality.

**TABLE 5 A** - Multilevel stepwise logistic analysis: Predictors of 1-year mortality

	Contribution of each step			
	$\chi^2$	Df	AIC	P-value
Step 1: Age, sex and Lee-index	69	5	59	<.001
Step 2: Risk factors	11	6	-1	.102
Step 3: Structure of care	2	3	-4	.285
Step 4: Process of care	13	4	5	.001

**TABLE 5 B** - Multilevel stepwise logistic analysis: Predictors of 30-day mortality

	Contribution of each step			
	$\chi^2$	Df	AIC*	P-value
Step 1: Age, sex and Lee-index	44	5	34	<.001
Step 2: Risk factors	5	6	-7	.554
Step 3: Structure of care	2	3	-4	.438
Step 4: Process of care	16	4	8	.003

## DISCUSSION

In this survey we observed large variations in patient characteristics, quality of process and structure of care and mortality. Even after adjusting for the patient population at risk, a substantial part of the variation in mortality between hospitals can be explained by differences in process of care.

In recent years more attention is given to relating structure and process of care to outcome. Literature reveals diverse conclusions regarding the association of process and outcome in different subsets of patients. For example in stroke patients, the considerable variation in patient outcome which was observed between hospitals could not be explained by the differences in quality of process of care.<sup>15,16</sup> Mainly differences in case-mix contributed to the observed variation in patient outcome. On the other hand, a recent study in acute coronary syndrome patients showed a significant association between process of care and outcomes.<sup>17</sup> Their study used 9 ACC/AHA guideline recommendations to assess whether composite adherence was related to adjusted in-hospital mortality. In this paper, the 2002 ACC/AHA guideline recommendations outlining diagnostic and therapeutic interventions for patients undergoing noncardiac surgery were used to select process of care measures.<sup>13</sup> Our study demonstrated a significant association between process of care and patient outcome.

Process of care in terms of adherence to guideline criteria seems logical to serve as a marker of quality of care.<sup>18-20</sup> Difficulties arise however when the evidence for diagnostics and treatment is less clear, as is the case for the guidelines on perioperative care. Recently, new guidelines have been published in this area but the recommendations are still based on limited randomized controlled trials.<sup>21</sup> These new guidelines do however strengthen the recommendation of statins and beta-blockers in vascular surgery patients. Highly evidence-based and well-formulated guidelines are fundamental for good implementation.

Secondly, although randomized controlled trials have shown effectiveness of guideline recommendations in selected patients and controlled settings, few data is however available about the performance of these quality measures in daily clinical practice. Furthermore, it is known that disparity exists between patients in clinical practice and patients in whom the studies that provide the evidence for treatment guidelines are performed.<sup>22</sup> Thirdly, the choice of process measure should be relevant. For example, a recent study examined the association of performance measures and clinical outcomes for patients hospitalized with heart failure but found little relationship. They claimed that additional measures like beta-blocker therapy at hospital discharge may be required to more effectively quantify the quality of care provided to these patients.<sup>23</sup> Fourthly, studies reported lack of strong correlation between several individual process measures.<sup>17,24</sup> For example, modest correlation was observed between use of aspirin and beta-blockers at discharge in patients with acute coronary syndromes.<sup>17</sup> These results emphasize the need for accurately identifying a broad range of quality indicators.

The association between the structural component volume and outcome is often investigated in surgical care. For example, in abdominal aortic aneurysm surgery several studies described an inverse volume outcome effect relationship.<sup>8,9</sup> In contrast, we did not observe a relation between volume and outcome. Shackley et al. demonstrated that adjusting for case-mix tends to diminish the relationship between volume and outcome in peripheral vascular surgery which might also explain our results.<sup>25</sup> Other explanations for this could be the small number of included hospitals and patients in our study. In addition, the definition of high volume of abdominal aortic aneurysm operations, which we used in our study, may be not a good indicator for the volume effect. Furthermore, as argued by others, the vascular procedures could be too heterogeneous to detect real differences. However, it has to be noticed that volume is clearly a proxy measure for other characteristics because there exists no direct link between volume and outcome. For example, in a study including myocardial infarction patients, differences in process of care explained one third of the survival advantage attributed to high-volume hospitals.<sup>26</sup> Evidence regarding the underlying explanations is not well investigated. With regard to quality improvement, it is also important to note that structural measures are difficult to change, while the key advantage of process measures is the relatively actionable nature.<sup>27</sup> Our results indicate the urge for improving and evaluating

process of care at hospital level as we observed a clear relationship between these quality measures and mortality in patients undergoing vascular surgery. Effective quality improvement efforts such as benchmarking of hospitals on process measures like beta-blockers and statins are necessary to increase quality of care in low-performance hospitals.<sup>28</sup>

Using 1-year mortality as the primary endpoint in this study might be a point of discussion. Importantly, sensitivity analyses using 30 days and 3-year mortality did not change the observed relationship between process of care and outcome. These results strengthen the role of process indicators in vascular surgery demonstrated in this study. In the era of increasing pay-for-performance and focus on measurement of quality of care, future research is needed to establish accurate and valid performance measures in vascular surgery.

In conclusion, we observed that patient outcome varies widely between hospitals. A substantial part of this observed variation in mortality was explained by differences in process of care, on top of patient characteristics. An important implication of these results is that improvement of patient outcome per hospital can be achieved by targeting process of care parameters.



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# Summary &

# Discussion



## PREOPERATIVE RISK ASSESSMENT

Atherosclerosis is a generalized disease with symptoms ranging from angina pectoris, myocardial infarction, stroke to claudication. The prognosis of patients with peripheral arterial disease (PAD) is predominantly determined by the presence and extent of the underlying ischemic heart disease (IHD). Patients with PAD undergoing vascular surgery are at high risk for postoperative cardiac complications (**chapters 1 & 2**). Importantly, we observed that 1 out of 3 patients with PAD undergoing surgery had symptomatic IHD. Another important observation of our study is that 42% of the vascular surgery patients consisted of patients >70 years (**chapter 13**). This number clearly reflects the overall ageing phenomenon and emphasizes the increasing proportion of elderly undergoing surgery. Advanced age has shown to be an important predictor of adverse outcome in patients undergoing vascular surgery.<sup>1,2</sup> The combination of the high incidence of comorbidities in the elderly and the effect of ageing itself poses this elderly population as a high-risk population which should get extra attention in the coming years.

In general, risk stratification tools are designed to identify patients in clinical practice who are at relatively high risk for adverse outcomes. The widely used Lee Risk Index was introduced to assess perioperative cardiac risk.<sup>3</sup> In our large consecutive cohort of PAD patients undergoing vascular surgery, the Lee Risk Index proved not only an important prognostic factor for in-hospital outcome but also for late mortality and impaired health status in patients with PAD (**chapter 3**). Once the assessment of risk factors indicates an increased cardiac perioperative risk, or if there is a suspicion of coronary artery disease upon examination, further cardiac evaluation is warranted (**chapter 4**). Together with effective disease management programs specific for patients with PAD, better long term clinical outcome and patient-centered outcome may be achieved in the upcoming years.

Health status measurements may provide prognostic information to guide clinical decision-making. In this way, impaired health status has shown to be an independent predictor of mortality in cardiac patients<sup>4,5</sup> and predicted invasive treatment in a prospective PAD population.<sup>6</sup> Health status measurements can therefore potentially be used in clinical practice to identify patients who are at relatively high risk for adverse outcomes. These patients may benefit from more aggressive treatment, including pharmacological, invasive or behavioural interventions. In **chapter 18** we demonstrate that health related quality of life (HRQoL), as measured by the EQ-5D, is strongly associated with long-term survival in patients with PAD. After adjusting for other established risk factors, poor HRQoL remained an independent predictor of mortality, with the risk being 5-fold compared to patients with a good HRQoL.

## GUIDELINES

Successful perioperative evaluation and management of patients undergoing noncardiac surgery requires careful teamwork and communication between surgeon, internist, pulmonologist, anaesthesiologist, cardiologist and the patients' primary care physician. By translating the best available scientific evidence into specific recommendations, guidelines can serve as useful tools to achieve effective and efficient patient care.<sup>7</sup> The recently published new guidelines of the European Society of Cardiology (ESC) on perioperative cardiac care provide valuable tools for daily clinical practice (**chapter 5**). **Chapter 6** discusses the recommendations for beta-blocker use in the ESC and ACC/AHA guidelines. It is important to update guidelines on a regularly basis to reflect the most recent clinical evidence and furthermore, guidelines should be easy to use in clinical care (**chapters 7 & 8**).

The new ESC guidelines on perioperative care also include the evidence from two important studies on medical therapy. First in **chapter 9** the results of the DECREASE III trial are described. In this double-blind, placebo-controlled trial, statin naïve patients were randomly assigned to receive, in addition to beta-blocker, either statin once daily, or placebo, starting 37 days prior to surgery. The incidence of myocardial ischemia in the statin group was significantly lower compared to the placebo group, 10.8% vs. 19.0%, respectively.

Second, as shown in **chapter 10**, cardioselective beta-blockers were associated with reduced mortality in patients with chronic obstructive disease (COPD) undergoing vascular surgery. These agents are frequently withheld from COPD patients with co-existing cardiovascular disease because of the concern that beta-blockers may induce bronchoconstriction from blockade of beta<sub>2</sub>-adrenoreceptors. In carefully selected patients with COPD, the use of cardioselective beta-blockers appears to be safe and, more importantly associated with reduced mortality.

## CLOSING THE GAP BETWEEN GUIDELINES AND CLINICAL PRACTICE

### Exploring the gap

Atherosclerotic risk factor control, lifestyle improvement and optimal pharmacological treatment are key elements of perioperative and long-term management of patients with PAD. The core of the ACC/AHA guidelines is an algorithm, which summarizes the stepwise process leading to practical recommendations. In general, two strategies have been used in an attempt to reduce the incidence of perioperative myocardial infarctions and other cardiac complications: pharmacological treatment and preoperative coronary revascularization. In recent years, most attention has been



given on the role of pharmacological treatment, whereas controversy remains about prophylactic coronary revascularization. Our study demonstrated poor agreement between clinical practice and the ACC/AHA guideline recommendations for perioperative cardiovascular evaluation for noncardiac surgery (**chapter 11**). Only 1 out of each 5 patients underwent noninvasive testing when recommended, whereas we observed no difference in cardiac management according to the test result. In addition, high risk patients defined by ACC/AHA guidelines who did not undergo testing although recommended, received as little cardiac management as the low risk population.

An extensive preoperative cardiac evaluation might also improve outcome by inciting an improvement in medical management in the perioperative period. In **chapter 12** we show a clear relationship between beta-blocker use and cardiac risk stratification according to the Lee Risk Index: the higher the cardiac risk, the higher the prescription rate of beta-blockers. In general, the results of our survey provide evidence for a gap between daily clinical practice and guideline recommendations in patients undergoing vascular surgery. Guideline-recommended medical therapy use for the combination of aspirin and statins in all patients and beta-blockers in patients with IHD was 41% in the perioperative period (**chapter 14**). **Chapter 13** shows a high proportion of patients >70 years undergoing vascular surgery and indicates that statin therapy seems to be as beneficial in elderly patients as compared to younger patients. Although randomized controlled trials have shown effectiveness of medical therapies in selected patients and controlled settings, few data is available about the performance of these therapies in daily clinical practice. Furthermore, it is known that disparity exists between patients in clinical practice and patients in whom the studies that provide the evidence for treatment guidelines are performed.<sup>8</sup> Despite the increased risk of the elderly and the observed beneficial effect of statins in this population, our study revealed that statins were significantly less often used in elderly patients undergoing vascular surgery.

At the long term, use of medication in patients with PAD 3 years after vascular surgery proved to be lower than expected based on current guidelines. After 3 years of follow-up, aspirin was used in 74%, statins in 69% and beta-blockers in 54% of the patients respectively. Guideline-recommended medical therapy use for the combination of aspirin, and statins in all, and beta-blockers in IHD patients was 50% (**chapter 13**). Another observation of the survey was that continuous perioperative beta-blocker use is associated with a lower risk of mortality, while an adverse effect of perioperative withdrawal of beta-blockers was observed (**chapter 14**).

With respect to lifestyle management, we observed a high prevalence of smoking before and after the vascular procedure (**chapter 15**). In addition, a relationship between smoking and the number of affected vascular beds was observed. There is a high need for the development and implementation of effective smoking cessation programmes in vascular surgery patients, also in patient with “only PAD”. These data indicate the need for increasing awareness for smoking cessation in vascular surgery patients and professionals.

Our results are in line with previous findings regarding disparities in risk factor management among patients with atherothrombotic disease. The international prospective Reduction of Atherothrombosis for Continued Health (REACH) Registry evaluated the cardiac risk factor control and outcomes in outpatients with atherothrombotic disease. In general, this large international database demonstrated a substantial gap between guideline recommendation and clinical practice throughout the atherothrombotic spectrum.<sup>9</sup> These and our result point to the fact that improvement is necessary because still a sizeable proportion of patients are not treated according to the guidelines.

### **Explaining the gap**

A variety of barriers to guideline adherence have been pointed out by others: out-of-date guidelines, lack of awareness, agreement, or self-efficacy, lack of outcome expectancy, the inertia of previous practice, and external barriers.<sup>10</sup> This reflects that guidelines must be straightforward, simple to use, uniform and based on recent scientific evidence. The reason for the observed gap between guideline recommendation and clinical practice in patients with PAD seems to be multifactorial. At first, national physician surveys reported deficiencies in physician knowledge and attitudes regarding the importance of atherosclerotic risk factor reduction in PAD patients.<sup>11-13</sup> Furthermore, data from the REACH registry demonstrated substantial variation in patients' medication use by physician speciality.<sup>14</sup> For example, statin prescription was 79% among cardiologists and 49% among vascular surgeons. Similar differences were observed for beta-blockers (70% vs. 34%, respectively). In addition, patients themselves also underestimate the cardiovascular risks associated with PAD. A population-based survey showed major knowledge gaps regarding PAD.<sup>15</sup> Only 1 out of 4 PAD patients were aware of the fact that PAD is associated with increased risk of myocardial infarction and stroke. Atherosclerotic vascular disease and its risks constitute a chronic condition, with consequences for life-long attention to vascular risks. There is a significant opportunity to improve the use of secondary prevention therapy in these high-risk patients and improve patient compliance.

### **Closing the gap improves outcome**

Importantly, our survey demonstrated that the use of evidence-based therapy in the perioperative period was indeed associated with a reduction of postoperative mortality in consecutive patients seen in daily clinical practice (**chapter 14**). This is in accordance with studies in IHD patients which also showed significant associations between guideline adherence and outcomes.<sup>16</sup> These data indicate that process of care in terms of adherence to guidelines might serve as a marker of quality of care.

## OUTCOME ASSESSMENT

### Health status

In order to quantify the benefits of different treatment strategies and their cost-effectiveness, sensitive patient-centered outcome measures are increasingly adopted in outcomes research with cardiovascular patients. Recently, a disease-specific measure of PAD patients' health status (their symptoms, function and quality of life), the Peripheral Artery Questionnaire (PAQ), was developed.<sup>17</sup> In order to make wider use of the PAQ possible, the questionnaire was translated into Dutch and validated in a study of Dutch PAD patients (**chapter 16**). A high response rate and the analysis of missing values on item-level showed that the PAQ was well accepted in the current sample of PAD patients. Important issues to be addressed regarding the development and use of health status instruments are their reliability and validity. Internal reliability of the three domains quantified by Cronbach's  $\alpha$  was reported high for the Dutch PAQ (mean  $\alpha=0.94$ ) and the original instrument (**chapter 16**). Previous studies also showed that the PAQ had a good test-retest reliability and sensitivity to change.<sup>17,18</sup> Our results of the PAQ instrument clearly show the disease-specific nature of this measure as the PAQ demonstrated good clinical validity with traditional clinical indices of PAD severity (**chapter 17**).

We would like to strengthen the importance of disease-specific health status measures like the PAQ and advocate their use as outcome measure and disease management tool in PAD management, rather than relying on clinical measures alone. Health status measures will play an increasingly important role in the evaluation of therapeutic strategies and in clinical decision making in the field of vascular medicine.

### Quality of care

Assessing quality of care is becoming more and more important in contemporary medical practice. In general, performance profiling has two primary objectives. First, to stimulate and promote internal quality assurance at the level of the hospitals and physicians, and second to promote an efficient market economy in health care.<sup>19</sup> The widely accepted Donabedian's classic paradigm of assessing quality of care is based on a three-component approach; structure, process, and outcome.<sup>20</sup> Structural measures refer to inherent characteristics of the provider that are believed to be associated with quality of care. Process measures of quality of care reflect the extent to which a provider complies with evidence-based guidelines. With regard to quality improvement, it is also important to note that structural measures are difficult to change, while the key advantage of process measures is the relatively actionable nature.<sup>21</sup> Postoperative mortality rates serve as an outcome-based measure to compare hospital quality of surgical care. However, it has been shown that hospital variations in mortality rates are not exclusively related to differences in quality of care

but also to differences in case-mix.<sup>22-24</sup> We observed that patient outcome varies widely between hospitals (**chapter 19**). A substantial part of this observed variation in mortality was explained by differences in process of care parameters of which guidelines indicated importance, on top of patient characteristics (**chapter 19**). An important implication of these results is that improvement of patient outcome per hospital can be achieved by targeting process of care parameters. Our results indicate the urge for improving and evaluating process of care at hospital level as we observed a clear relationship between these quality measures and mortality in patients undergoing vascular surgery. Effective quality improvement efforts such as benchmarking of hospitals on process measures like beta-blockers and statins are necessary to increase quality of care in low-performance hospitals.<sup>25</sup> In the era of increasing pay for performance and focus on measurement of quality of care, future research is needed to establish accurate and valid performance measures in vascular surgery.

## LIMITATIONS

Several limitations should be taken into account when interpreting our results. First, the PAD survey was an observational study. Although adjustments were made for known covariates, there is the possibility of residual confounding by unmeasured factors. Unfortunately, only limited data were available on the decision making process and reasons for not performing or not prescribing evidence-based treatment was underexposed. Furthermore, adherence to the prescribed medications by the patients themselves was not assessed, which has probably caused an underestimation of the underuse in patients with PAD. It should also be noted that participating centres were not selected at random; therefore, a selection bias cannot be ruled out. Nevertheless, a wide range of both university and nonacademic hospitals across The Netherlands participated. Another important limitation was the absence of on-site monitoring and source document verification. However, data-quality was checked electronically through queries for missing data. Although we observed that many patients in clinical practice were treated in accordance with guidelines, areas for improvement were identified. Adding this information to future survey programmes would reveal even more important information.

## FURTHER PERSPECTIVES

The discrepancy between daily clinical practice and guideline recommendation demonstrates the high need for improving perioperative and long-term care of patients with PAD. Developing

evidence-based guidelines alone does not guarantee improved quality of care. Effective implementation should ensure guideline adherence in practice and subsequently lead to improved patient outcomes. The PDSA (Plan - Do - Study - Act) cycle is a process model for continuous quality improvement that has been used extensively in the health care field, especially for working with clinical practice guidelines. Monitoring (Study) like the PAD survey serves the important functions of providing feedback for the implementation cycle, creating accountability for guideline implementation, and assessing the effects of the guideline on quality of care. Increased efforts should be focussed on implementing guideline recommendation in vascular surgery patients. This can potentially be achieved by implementing disease management programs including critical pathways, patient education, and multidisciplinary hospital teams.<sup>26</sup> Programs such as ACC Guidelines Applied in Practice (GAP) and the AHA Get With The Guidelines (GWTG) program are examples of successful quality improvement programs that are designed to improve guideline adherence through tools and system redesign strategies. The GAP project resulted in increased adherence to key treatments in the administration of aspirin and beta-blockers on admission and the use of aspirin and smoking cessation counselling at discharge.<sup>27</sup> The GWTG coronary artery disease program was also associated with improved guideline adherence.<sup>28</sup> The use of beta-blockers, ACE-inhibitors, statins, aspirin, and smoking cessation counselling were significantly increased.<sup>29</sup> A comparable approach is needed in patients with PAD, as atherosclerosis is a systemic disease affecting all vascular beds. A well-coordinated multidisciplinary program addressing clinical risk factors may enhance both survival and health status in patients with PAD. The preoperative visits to the hospital related to the intended vascular procedure in patients with PAD can be considered as a “golden opportunity” to initiate medical therapy and lifestyle changes with achievement of treatment targets according to the guidelines. Furthermore, long-term care should be provided by all involved cardiovascular disciplines.

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**SAME**

**NVATTING**



## RISICOSTRATIFICATIE

Bij patiënten met perifere arterieel vaatlijden is vaak sprake van onderliggend (a)symptomatisch coronairlijden. Wanneer zij een vaatingreep moeten ondergaan, hebben zij een verhoogd risico op perioperatieve complicaties. Het optreden van een hartinfarct is de meest voorkomende complicatie. Risicofactoren voor atherosclerose of aderverkalking komen vaak voor bij patiënten met perifere vaatlijden (PAD) (**hoofdstuk 1, 2 & 4**). Om perioperatieve complicaties bij deze patiënten te voorkomen, is het belangrijk om een goede inschatting van het risico te maken. Op basis van deze risico-inschatting kan de juiste therapie worden ingesteld. Voor bepaling van het perioperatieve complicatierisico is de Lee Risk Index een geaccepteerde vragenlijst. **Hoofdstuk 3** laat zien dat de preoperatieve Lee Risk Index niet alleen een belangrijke prognostische factor is in het voorspellen van uitkomsten tijdens opname, maar ook voor lange termijn mortaliteit en een verslechterde kwaliteit van leven bij patiënten met PAD die een vaatchirurgische operatie ondergaan. In **hoofdstuk 18** wordt aangetoond dat kwaliteit van leven ook onafhankelijk geassocieerd is met lange termijn overleving van patiënten met PAD.

## RICHTLIJNEN

Succesvolle perioperatieve evaluatie en management van patiënten die een operatie ondergaan vereist een nauwe samenwerking tussen de chirurg, internist, longarts, neuroloog, anesthesioloog, cardioloog en de huisarts. Om klinici van dienst te zijn bij het nemen van beslissingen over de beste behandeling voor hun patiënten, worden door onder andere de European Society of Cardiology (ESC) richtlijnen ontwikkeld en verbeterd. Deze richtlijnen zijn gebaseerd op de resultaten van gerandomiseerde klinische studies, observationele studies en consensus van experts. Om het beloop van chirurgische patiënten te verbeteren, ontwikkelde de ESC onlangs de eerste richtlijnen voor perioperatieve cardiovasculaire risico evaluatie voor niet-cardiale chirurgie (**hoofdstukken 5 & 6**). Het is belangrijk om richtlijnen op regelmatige basis te toetsen zodat zij het meest recente wetenschappelijk bewijs reflecteren (**hoofdstukken 7 & 8**). De nieuwe ESC richtlijnen bevatten verschillende belangrijke studies omtrent de medicamenteuze therapie in de perioperatieve zorg. Twee van deze studies zijn opgenomen in dit proefschrift. De resultaten van een recente dubbelblinde, placebogecontroleerde studie zijn beschreven in **hoofdstuk 9** en laten zien dat perioperatieve behandeling met een statine leidt tot een betere cardiale uitkomst bij patiënten die een vaatchirurgische operatie ondergaan. **Hoofdstuk 10** toont aan dat cardioselectieve bètablokkers geassocieerd zijn met een verminderde mortaliteit bij patiënten met chronische obstructieve longziekten (COPD) die vaatchirurgie ondergaan.

## KLINISCHE PRAKTIJK

Om de behandeling van patiënten met PAD die een operatie ondergaan te evalueren is in Nederland de Euro Heart Survey perifeer vaatlijden uitgevoerd. Opeenvolgende patiënten (n=711) die een vaatinterventie ondergingen, werden in dit observationele onderzoek geïncludeerd. Deze studie laat zien dat de dagelijkse klinische praktijk aanzienlijk verschilt van wat de richtlijnen adviseren. Zo onderging slechts één op de vijf patiënten voor wie een niet-invasieve cardiale test geïndiceerd was, daadwerkelijk de test (**hoofdstuk 11**). In **hoofdstuk 12** wordt aangetoond dat er sprake is van ondergebruik van beta-blokkers in de periode rondom vasculaire chirurgie, zelfs bij patiënten met een hoog complicatierisico. Het gebruik van beta-blokkers bleek onafhankelijk geassocieerd te zijn met een betere uitkomst, terwijl het stoppen van beta-blokkers in de perioperatieve periode juist een vergrote kans gaf op sterfte binnen 1 jaar. In de perioperatieve periode was het percentage medicamenteuze therapie gebruik volgens de richtlijnen, namelijk de combinatie van aspirine en statinen bij alle patiënten en beta-blokkers bij patiënten met kransslagaderlijden, slechts 41% (**hoofdstuk 14**). **Hoofdstuk 13** toont aan dat, ondanks het toegenomen risico bij ouderen en het aangetoonde beschermend effect van statines bij deze groep, statines significant minder vaak gebruikt werden in oudere vaatchirurgische patiënten.

Op de lange termijn (3 jaar na operatie) bleek het medicatiegebruik van patiënten met PAD lager te zijn dan op basis van de richtlijnen verwacht zou worden. Een andere belangrijke conclusie uit onze studie is dat het gebruik van evidence-based therapie in de perioperatieve periode, bij opeenvolgende patiënten gezien in de dagelijkse klinische praktijk, inderdaad geassocieerd is met een afname van de mortaliteit na drie jaar (**hoofdstuk 14**). Deze resultaten indiceren dat het zorgproces, in termen van het volgen van de richtlijnen, kan dienen als een marker voor de kwaliteit van de zorg.

**Hoofdstuk 15** laat zien dat de prevalentie roken vóór en na een vaatoperatie hoog is. Tevens zagen we een relatie tussen roken en het aantal aangedane vaatbedden. Zowel patiënten als professionals moeten zich meer bewust worden van de noodzaak van het stoppen met roken.

## UITKOMST

Mortaliteit bij PAD wordt vaak veroorzaakt door geassocieerd kransslagaderlijden en cerebrovasculaire ziekten, in plaats van door de PAD zelf. De behandeling van PAD is daarom gericht op het verminderen van symptomen en de hiermee samenhangende kwaliteit van leven, in plaats van op overleving alleen. Om die reden worden sensitieve patiëntgerichte uitkomstmaten steeds vaker toegepast in onderzoek naar uitkomsten bij cardiovasculaire patiënten. In **hoofdstuk**

16 beschrijven we de vertaling en validatie van de Peripheral Arterial Questionnaire (PAQ), een ziektespecifieke vragenlijst over de kwaliteit van leven bij patiënten met PAD. De PAQ laat ook een goede klinische validiteit met traditionele klinische indices voor de ernst van PAD zien (**hoofdstuk 17**). Alle PAQ-subschalen hadden een goede onderscheidende waarde voor patiënten met of zonder symptomatische PAD en voor de ernst van de PAD.

**Hoofdstuk 19** laat zien dat er grote variatie is tussen de ziekenhuizen. Het verschil in sterftepercentages op ziekenhuisniveau hing zowel met klinische karakteristieken samen als met de kwaliteit van zorg. Het meten van de kwaliteit van zorg wordt steeds belangrijker in de huidige medische praktijk en vraagt om verdere validatie van prestatieindicatoren.

## AANBEVELINGEN

De discrepantie tussen de dagelijkse klinische praktijk en de aanbevelingen uit de richtlijnen toont aan dat er een noodzaak is voor het verbeteren van de perioperatieve en lange termijn zorg van patiënten met PAD. Tevens willen wij het belang van ziektespecifieke kwaliteit van leven instrumenten zoals de PAQ onderstrepen. Wij pleiten voor het gebruik van dergelijke instrumenten als uitkomstmaat en ziektemanagement instrument in de behandeling van PAD, in plaats van aangewezen te zijn op klinische maten alleen. Maten voor kwaliteit van leven verdienen binnen de vasculaire geneeskunde een belangrijke rol en bij de evaluatie van verschillende therapeutische strategieën en klinische besluitvorming.

Bij ischemische hartziekten en beroerten zijn artsen bekend met een scala aan multidisciplinaire behandelprogramma's, met bewezen effectiviteit in het verbeteren van klinische uitkomsten en kwaliteit van leven. Programma's zoals de ACC Guidelines Applied in Practice (GAP) en het AHA Get With The Guidelines (GWTG) programma zijn voorbeelden van succesvolle programma's om het volgen van richtlijnen te stimuleren. Een vergelijkbare benadering wordt in dit proefschrift aanbevolen voor patiënten met PAD, aangezien atherosclerose een systemische aandoening is die alle vaatbedden aantast. De preoperatieve bezoeken van de patiënt aan het ziekenhuis, gerelateerd aan de geplande vaatoperatie, zijn een uitgelezen moment om te starten met medicamenteuze behandeling en veranderingen in levensstijl zoals aanbevolen in de richtlijnen. Een goed gecoördineerd multidisciplinair programma, dat zich richt op klinische risicofactoren, kan zowel de overleving als de kwaliteit van leven van patiënten met PAD verbeteren. Implementeren van dergelijke behandelprogramma's, waaronder critical pathways, educatie van de patiënt en multidisciplinaire teams in het ziekenhuis, zal leiden tot een verbeterde klinische en patiëntgerichte uitkomst in de toekomst.

**DAN**



**KWOORD**

Dan is het nu tijd voor het laatste en ongetwijfeld meest gelezen gedeelte van dit proefschrift: Het dankwoord.

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# CURRICU

# LUM VITAE

Sanne Elisabeth Hoeks was born in Eersel on the 12th of July 1980. After finishing secondary school at Rhythovius College in Eersel in 1998, she started studying Biology at the University of Utrecht. She obtained her MSc degree in Biology in 2004. Next, she worked as a research statistician at the Department of Clinical Epidemiology of the Thoraxcenter, Erasmus Medical Center in Rotterdam. In the beginning of 2006, she started a Ph.D.-project at the Erasmus MC under supervision of prof.dr. Don Poldermans and dr. Wilma Scholte op Reimer. She completed the Master of Science in Epidemiology programme as part of The Netherlands Institute for Health Sciences (NIHES) curriculum of the Erasmus University in 2007.



# PhD Portfolio

Name PhD student: Sanne Hoeks

PhD period: 2006-2010

Erasmus MC Department: Anesthesiology

Promotor: Prof.dr. D. Poldermans

Research School: COEUR

Supervisor: dr. W.J.M. Scholte op Reimer

## 1. PhD training

	Year	Workload (ECTS)
<b>Courses</b>		
- NIHES "Diagnostic Research"	2009	9
- Mixed Models: Models for Longitudinal and Incomplete Data	2008	1
- NIHES, MSc Epidemiology	2005-2007	70
- COEUR, PhD courses	2006-2009	4.5
<b>Seminars and workshops</b>		
- Consultation Center for Patient Oriented research (CPO)	2007-2008	1.5
- COEUR, Research seminars	2006-2007	1.2
- Journal Club	2006-2010	1
<b>Presentations</b>		
- National conferences	2006-2009	1
- International conferences	2006-2009	4
<b>International conferences</b>		
- European Society of Cardiology Congress, annual	2006-2009	4
- Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke Conference, Washington	2009	1
- American Heart Association Scientific Sessions, Chicago	2006	1

## 2. Teaching

	Year	Workload (ECTS)
<b>Lecturing</b>		
- Epidemiology	2006-2010	1
<b>Supervising practicals and excursions, Tutoring</b>		
- NIHES course 'Classical Methods for Data Analysis'	2006-2010	4
- COEUR 'Cardiovascular research'	2006-2010	4
- MolMed 'Introduction to SPSS'	2009-2010	4
<b>Supervising Master's theses</b>		
- MSc students EUR and University of Tilburg	2008-2010	8

**PUBL**



**ICATIONS**

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