MEDICAL & TECHNICAL CONSIDERATIONS IN VASCULAR SURGERY

Michiel Th. Voûte

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CONTENTS

PREFACE

Evidence based medicine has led to a high demand for researchers to continuously improve health care. The current expectations of an applicant for surgical training have led to a large flock of researchers, all with future surgical training positions in mind.

After successfully writing a thesis or dissertation one acquires the title of *Doctor of Philosophy (PhD)*, from the Ancient Greek *Philosophia* which means “love of wisdom”. This doctorate degree is the highest academic degree that one can acquire at a Dutch university.

Are all surgical trainees, in possession of a doctorate, madly in love with acquiring wisdom? Do all of them aspire to an academic career? Is this highest academic degree still a unique achievement, a rarity which deserved the utmost respect?

The first marathon was run in 490 B.C. by a single soldier. Today, over half a million people finish a marathon each year in the U.S. alone. That doesn’t mean that each runner does not put in the hours of preparation, make the extensive effort and perform at his best up to the finish line.

I never ran a marathon. I did however, write this thesis.

Thank you for reading.

INTRODUCTION

It is estimated that in the year 2020 more than a million non-cardiac, vascular surgery procedures will be performed annually in Europe. The same applies for the US. With this growing application of high-risk procedures, it is important to continuously strive for improved patient safety and surgical outcome.

Regarding patient safety, it is key to recognize a change in patient populations and patient selections. Due to anesthetic and medical improvements as well as surgical innovation, the vascular surgery population is increasing in age, tends to have more co-morbidity and more often uses multiple prescription drugs. In other words, it is a fragile population, undergoing high-risk surgery.

Cardiovascular adverse events are responsible for a major proportion of morbidity and mortality in patients undergoing vascular surgery, with an estimated incidence of more than 5% of ischemic complications, and up to 10% new-onset arrhythmias in major vascular surgery. In the first part of this thesis, certain patient safety issues, secondary prevention and future perspectives are discussed, regarding these cardiovascular complications.

Medical considerations

In Chapter 1, a comprehensive outline is provided of the optimal medical management, in regard to the fine balance between bleeding and thrombotic complications in any surgical procedure. A number of drugs are discussed that can help reduce cardiac ischemic complications, such as statins and beta-blockers.
The pros and cons of statin use in high-risk surgery is further elaborated in Chapter 2. Specifically, the clinical applications of the extended release fluvastatin is evaluated.
Chapter 3 is a literature review on the safety of beta-blockade in surgery patients. The aphorism to ‘start low and go slow’ is presented as a guide to safely introduce beta-blockade in the perioperative period.

In an effort to find new prevention strategies against cardiovascular disease, the relationship between patients' vitamin D status and the severity of arterial disease is reported in Chapter 4.

Having only looked into ischemic complications so far, Chapter 5 presents a pilot study with an insertable cardiac monitor, to reveal the true incidence of new-onset cardiac arrhythmias in vascular surgery patients, atrial fibrillation (AF) in particular. New-onset AF after vascular surgery has a reported incidence of 4-13%, is a known major risk factor for postoperative stroke, myocardial infarction and pulmonary embolism, and it can be treated if diagnosed. Traditional monitoring methods are intermittent, and may possibly fail to detect a proportion of patients at high risk for thromboembolic complications. Can we improve detection, and therefore patient safety and outcome?

Technical considerations

Since the introduction of endovascular techniques, carotid artery disease is often treated with angioplasty and stenting. Literature suggests that the radial force of a carotid stent is related to the clinical outcome, in terms of short term emboli and long-term patency. In Chapter 6 a comparison is made of the radial force of four widely-used carotid stents, by testing them in a purpose-built measuring device at the Technical University in Delft, The Netherlands.

Another application of endovascular surgery is the endovascular repair of abdominal aortic aneurysms (EVAR), first introduced by Dr. Juan Parodi in 1991. New technology brings new complications and clinical entities. The post-implantation syndrome is one of these entities. Why and how often does this flu-like syndrome occur after EVAR? Chapter 7 explores the difference in incidence, depending on the type of graft material that was implanted.

Another complication after EVAR, unknown with open aneurysm repair, is the occurrence of endoleaks. In open repair, branching arteries from the aneurysm are inevitably ligated after clamping the aorta and opening the aneurysm sac, to reduce blood loss and improve sight. In EVAR procedures, the aneurysm sac is not opened, and

side-branches such as lumbar arteries are left untouched. Retrograde flow in these lumbar arteries can therefore reach the excluded sac, a phenomenon called a type II endoleak, and cause expansion of the aneurysm. Hypothetically, this could lead to a reduced seal of the graft and threaten patient safety and surgical outcome.

Between 1999 and 2005, a series of patients underwent a laparoscopic procedure, in which side-branches were clipped and the aneurysm sac was fenestrated, to reduce pressure. The aim was to stop sac growth. Chapter 8 presents long-term follow-up of this somewhat experimental approach.

The importance of a type II endoleak has often been subject of discussion in scientific literature. Conflicting data on the natural history of type II endoleak have been published. There is no consensus on the threshold for treatment of type II endoleak and controversy exists about the optimal treatment modality. Chapter 9 discusses the current evidence behind treating type II endoleak and investigates the need for treatment. Perhaps, in retrospect, there was never any need to perform additional surgery on the patients discussed in the previous chapter?

Medical

Considerations

Blood thinners
Statins
Beta-blockers
Vitamin D status
New-onset arrhythmias
Carotid stent characteristics
Aortic stentgraft composition
Laparoscopic sac fenestration after EVAR
Need we intervene for type II endoleaks?

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ABSTRACT

This paper provides a comprehensive outline of the optimal perioperative medical management, concerning cardiac risk in any surgical population, based on recent guidelines. Special attention is paid to the fine balance between bleeding complications and thrombotic complications, as well as medical therapy to reduce the risk of an oxygen supply-demand mismatch in the perioperative period.

The authors emphasize that knowledge of, and adherence to current guidelines is essential for optimal care and safety of surgical patients.

MANUSCRIPT

INTRODUCTION

Undergoing surgery imposes certain risks on the patient, such as impaired wound healing, bleeding complications, perforations, nerve damage and infection. These are all well-known points of attention when planning a surgical procedure. Apart from these apparent risks directly related to the target area of the surgical procedure, there are other surgery-related factors contributing to the outcome, which tend to be overlooked by the treating physicians. Of all contributors to poor postoperative outcome, cardiac complications are the most important, including myocardial infarction (MI), congestive heart failure (CHF), stroke and arrhythmias. An estimated 10-40% of postoperative mortality is attributed to myocardial infarction. With over 230 million surgical procedures being performed worldwide each year, the perioperative period is also a golden hour to initiate secondary prevention. Identification of risk factors for perioperative cardiac adverse events and risk stratification of surgery patients are the pillars for reducing cardiovascular complication rates.

The overall theme for perioperative care is to find the balance between risk reduction strategies, with a potential delay of the index surgical procedures, and its impact on the operation. For instance, how to handle the controversy between hemorrhagic control and prevention of thrombosis related complications, such as MI and stroke. Patients with antiplatelet therapy represent a surgical challenge, in terms of bleeding risk, while withdrawal can increases the risk of coronary thrombosis. In this paper we aim to provide a comprehensive overview of the optimal medical management around the time of surgery, shedding light on all key issues.

PATHOFYSIOLOGY OF SURGICAL RISKS

Surgery causes physiological changes, affecting multiple organs apart from the primary target of the procedure. These changes can increase myocardial oxygen demand and reduce supply because of thrombosis, both leading to (fatal) myocardial ischemia. The most important contributors to these pathophysiological pathways will be outlined briefly.

Stress and the oxygen mismatch

In the perioperative period, surgical stress induces a catecholamine surge, prompted by incisional tissue injury and mediated by neuroendocrine factors. The surgical stress causes an increase in heart rate and myocardial contractility, leading to an increased myocardial oxygen demand. Subsequently, an oxygen supply-demand mismatch can occur in patients with coronary artery disease. Another pathway of stress causing perioperative ischemia is plaque rupture. The stress-induced, increased mechanical activity of the heart can lead to shear stress on coronary plaques, increasing plaque instability and subsequent rupture or emboli. Plaque rupture and emboli decrease the oxygen supply, increasing the oxygen mismatch, and the risk for myocardial infarction.

Inflammation and the oxygen mismatch

Apart from focal damage, surgery induces an generalized inflammatory response, with an increase of circulating C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). This response is further increased by the use of general anesthesia. The progression of atherosclerosis can be propelled by increased IL-6 and other inflammatory cytokines, leading to the genesis of more lesions and growth of existing atherosclerotic plaques. Increased levels of inflammation have also been linked to coronary plaque vulnerability and rupture.[1] In short, the surgical inflammatory response can lead to a narrowing of the coronary lumina, and possible plaque rupture, both decreasing the oxygen supply to the myocardium.

Laparoscopy and thrombosis

Laparoscopic procedures cause minimal incisional tissue damage, but have another pathway leading to an increased cardiac risk. The increase in intra-abdominal pressure – due to the pneumoperitoneum that is used – reduces the venous return and therefore decreases cardiac output, and increased systemic vascular resistance. The decreased flow velocity that follows increases the risk of thrombus formation and growth. Taken this into account, minimally invasive surgery patients should be regarded as equal to open surgery patients, in terms of cardiac risk stratification.

Hypercoagulability and thrombosis

Another consequence of surgery is a change in the balance of prothrom-botic versus fibrinolytic factors. Platelet activation and aggregation, elevation of coagu-lation factors (e.g. fibrinogen) on one side, and a decrease in fibrinolysis on the other can result in a state of hyper-coagulability, increasing the risk of coronary artery thrombosis. This process predisposes for myocardial ischemia and heart failure during and after the surgical procedure.

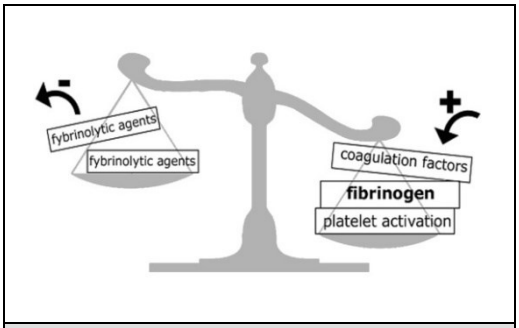

Figure 1. The changes in the balance of prothrombotic versus fibrinolytic factors, due to surgery

PREOPERATIVE RISK ASSESSMENT

An adequate risk assessment can serve multiple purposes. The predicted risk guides the preoperative workup, such as initiation of risk reduction strategies, and helps decide the selection of the best surgical and anesthesiological techniques. Preoperatively, both the risk of the surgical procedure as the cardiac risk of the individual patient should be taken into account. A distinction is made between surgical procedures with a high, an intermediate and a low cardiovascular risk. Based on estimates from Boersma et al., high risk surgery has an estimated 30-day postoperative cardiac event rate of >5%, intermediate risk surgery a 1-5% event rate and low risk surgery <1%.[2] The risk of cardiac complications should be assessed for each individual patient. Useful risk factors

were identified by Lee et al. in prospectively gathered data of 2893 patients, undergoing a variety of surgical procedures.[3] Lee's risk index includes ischemic heart disease (e.g. angina pectoris or myocardial infarction), heart failure, stroke, diabetes, renal dysfunction and surgical risk. With equal contributions of each risk factor, the incidence of cardiac complications increases with each added risk factor. In their paper, Lee et al. found that in patients with 0, 1, 2 and ≥ 3 risk factors, the incidence of cardiac complications was 0.4%, 0.9%, 7% and 11% respectively. The predicted perioperative cardiac risk guides the initiation or continuation of medical therapies.

ANTIPLATELET MANAGEMENT AND THROMBOSIS

Advances in interventional cardiology, radiology and endovascular surgery have resulted in an increasing number of patients receiving antiplatelet therapy. Recommendations for antiplatelet therapy include treatment regiments in patients with, among others, atrial fibrillation (AF), coronary artery disease (CAD), acute coronary syndrome (ACS), cerebrovascular disease and chronic peripheral arterial disease, as well as patients that have been treated with bare-metal stents (BMS), drug-eluting stents (DES), endovascular prostheses or via carotid endarterectomy (CEA).[4] According to existing guidelines, duration of antiplatelet therapy can vary from 6 weeks (e.g. after BMS placement) to a lifelong continuation for some indications.[5] Guidelines even recommend dual antiplatelet therapy (i.e. aspirin and clopidogrel) for patients with non-ST-segment elevation ACS. High-risk patients with recurrent ischemia, ST-segment depression, troponin release and diabetes may also receive a Gp IIb/IIIa receptor inhibitor, on top of aspirin and clopidogrel, as triple therapy.

Surgeons must beware of the balance between bleeding risk, when performing surgery under antiplatelet therapy, and the risk for thrombotic complications when discontinuing the antiplatelet agents. Perioperative withdrawal from single antiplatelet therapy precedes 10% of cardiovascular events, according to a meta-analysis by Burger et al.[6] Collet et al. found that in patients treated with antiplatelets for having received a DES or BMS, interruption of antiplatelet therapy led to death in up 25 to 50 per cent.[7] Furthermore, surgery-related inflammatory response and hypercoagulability may be especially hazardous in these thrombogenic patients. Therefore, it is essential to have an understanding on how to manage a patient with current antiplatelet therapy, when considering a surgical procedure.

Aspirin

The most widely prescribed antiplatelet agent is acetylsalicylic acid, or aspirin. Aspirin is an antithrombotic agent that acetylates part of cyclooxigenase (COX) 1. This inhibits the release of thromboxane A_2, which acts as a stimulator of platelet activation. Since platelets are unable to generate new COX 1, the affected platelets are impaired for the duration of their life.

Surgeons tend to instruct patients to stop taking aspirin no less than a week before surgery, concerned of bleeding complications. For example, a 1.5 fold increase in the risk of bleeding complications was reported in a meta-analysis by Burger et al., without an increase in the severity of hemorrhagic complications. However, in patients at risk

for or with ischemic heart disease, perioperative aspirin withdrawal was associated with a 3 fold higher risk for major adverse cardiac events.[8] There are no specific guidelines on treatment of major bleeding in surgical patients under current aspirin treatment, but discontinuation of aspirin and platelet transfusions are possible resorts in case of emergency.

Before planning surgery, the procedural bleeding risk and the individual risk of ischemic events should be carefully weighed. In most cases, including minor and endoscopic surgery, continuing aspirin perioperatively is safe and advisable. Except for prostatectomy and intra-cranial surgery, low-dose aspirin is not associated with an increased severity of bleeding nor perioperative mortality because of bleeding complications. If a planned surgical procedure is expected to have very difficult haemostatic control, withdrawal from aspirin therapy 7 days prior to surgery can be considered. Not much guidance is available on preoperative aspirin withdrawal, nor on restarting aspirin postoperatively. Future publication of the ASPIRIN trial (Antiplatelet Strategies in the Perioperative Period in Patients at Risk of Ischemic Events) may provide definitive guidelines for patients taking aspirin in the perioperative period.[4]

Clopidogrel

Thienopyridines, of which clopidogrel is the most prescribed agent, have a different acting site on platelets, and therefore can be prescribed as double therapy besides aspirin, or as solitary prevention in patients with high thromboembolic risk (e.g. after coronary DES placement). The use of clopidogrel has been implemented in guidelines after percutaneous coronary interventions (PCIs) and (non)ST-segment elevation myocardial infarction (STEMI).[5] These indications illustrate the strong necessity of antiplatelet therapy, at the risk of (stent)thrombosis and cardiac ischemia. Meta-analysis showed that patients who prematurely discontinue clopidogrel treatment after coronary stent insertion are ten times more likely to die or be readmitted during the next year.[6] In comparison with aspirin, this new generation antiplatelet agent is more powerful, and has been called “a surgeon’s headache”, due to its capacity to cause bleeding.

If a patient under clopidogrel therapy is planned for an operation, surgeons tend to discontinue the clopidogrel treatment. However, consulting a cardiologist is warranted considering the high thrombotic risk of clopidogrel withdrawal. In a report by Wilson et al., early (<6 weeks after coronary stenting) surgery with premature clopidogrel withdrawal was associated with an incidence of death, MI or stent thrombosis of 4.8%, compared to no acute events in patients who underwent surgery >6 weeks after coronary stent placement.[9]

Collet and Montalescot designed an algorithm for patients receiving dual antiplatelet therapy after DES insertion, undergoing surgery.[7] In this approach, bleeding risk and stent thrombosis risk should be assessed by the surgeon, an anesthesiologist and a cardiologist. If there is a great risk for both bleeding and stent thrombosis, surgery should be postponed until the clopidogrel therapy is ended, as was supported by a review from Thachil et al.[10] If delay is inadmissible, clopidogrel should be

discontinued 5 days before surgery and aspirin should be continued. If the bleeding risk is small and there is a major risk of stent thrombosis, surgery should be performed under dual antiplatelet therapy.
If surgery is performed in a patient with current clopidogrel therapy and a severe bleeding occurs, the drug should then be discontinued in agreement with a cardiologist. To reverse the effect of clopidogrel in severe bleeding cases, platelet transfusions can be considered, as well as administration of antifibrinolytic agents or recombinant factor VIIa, although these recourses remain subject of further investigation.

Prasugrel
Prasugrel is a potent novel thienopyridine antiplatelet agent and has been shown in preclinical and clinical studies to achieve faster onset, higher levels of platelet inhibition, and less response variability than clopidogrel. This antiplatelet profile reflects more efficient generation of the active metabolite of prasugrel. As a consequence, the TRITON-TIMI 38 trial found that prasugrel was superior to clopidogrel as measured by the composite endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke in patients with ACS undergoing PCI, but was associated with a minor increase in the risk of bleeding. Future studies may address the additional perioperative bleeding risk of prasugrel, and the thrombotic risk of perioperative withdrawal, in (non)cardiac surgery.

Gp IIb/IIIa inhibitors
The third major class of antiplatelet agents is inhibitors of the Gp IIb/IIIa receptor, which plays a key role in the linking of activated platelets and the formation of platelet thrombi. These agents (i.e. abciximab, cilostazol) have been tested in patients admitted with an acute coronary syndrome (ACS), patients undergoing thrombolytic therapy for acute myocardial infarction and patients undergoing percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).[4] Triple therapy has been reported to improve cardiac outcome and survival in patients with acute STEMI undergoing PCI.[11] Further studies and guidelines on the usefulness of Gp IIb/IIIa inhibitors in patients undergoing non-cardiac surgery have yet to be published.

BOX 1: Antiplatelet therapy and surgery

- Alterations in antiplatelet therapy can best be deliberated between surgeon, anaesthesist and cardiologist to ensure optimal balance between chance of bleeding and risk of ischemia
- Aspirin should be continued in surgery patients, unless there is a severe bleeding risk
- Clopidogrel should be discontinued before surgery
- However, if clinically admissible, delaying surgery until clopidogrel can be terminated safely is warranted
- If severe bleeding occurs in a surgical patients under clopidogrel treatment, discontinue clopidogrel in agreement with a cardiologist
- To counter the antiplatelet effect of clopidogrel, consider platelet transfusions
- More evidence is needed for guidelines on triple antiplatelet therapy around the time of non-cardiac surgery

ANTICOAGULANT MANAGEMENT AND THROMBOSIS

In patients treated with oral vitamin K antagonists (VKA), more commonly known as coumarins (e.g. warfarin, acenocoumarol, phenprocoumon), there is an increased risk of bleeding complications when performing non-cardiac surgery. In surgical procedures with an increased bleeding risk, anticoagulation should be discontinued. However, since these patients benefit from anticoagulant therapy, temporary cessation of these drugs can lead to thrombo-embolic events. There is a need for bridging therapy, consisting of low molecular weight heparin (LMWH) or unfractionated heparin (UFH). Thromboembolic risk is especially considered high 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, among other conditions.[12] For bridging therapy, current guidelines prescribe discontinuation of VKA no less than 5 days before surgery, due to the long lasting biological availability of these agents. There are differences between agents in pharmacogenetics. Phenprocoumon for instance has a longer lasting effect, and a more steady INR throughout treatment, than acenocoumarol. Therefore, guidelines on anticoagulant withdrawal and INR control are generally helpful, but INR control in the individual patient is nevertheless warranted.

BOX 2: Anticoagulants and bridging therapy

Low bleeding risk

- Continue anticoagulant therapy with INR in therapeutic range

Low thromboembolic risk, high bleeding risk

- Discontinue anticoagulants 5 days before surgery
- Start LMWH prophylaxis *once daily* or UFH intravenously 1 day after acenocoumarol interruption, and 2 days after warfarin interruption. Administer the last dose of LMWH at least 12 hours before the procedure or give UFH intravenously up to 4 hours to surgery.
- Resume LMWH or UFH at preprocedure dose 1 to 2 days (at least 12 hours) after the procedure according to hemostatic sufficiency. Resume VKA 1 to 2 days after surgery 150% of pre-procedure dose for 2 consecutive days according to hemostatic adequacy.
- Low molecular weight heparin or UFH is continued until the INR returned to therapeutic levels.

High thromboembolic risk, high bleeding risk

- Discontinue anticoagulants 5 days before procedure.
- Start therapeutic LMWH *twice daily* or UFH intravenously 1 day after acenocoumarol interruption, and 2 days after warfarin interruption. Administer the last dose of LMWH at least 12 hours before the procedure or give UFH intravenously up to 4 hours to surgery.
- Resume LMWH or UFH at preprocedure dose 1 to 2 days (at least 12 hours) after the procedure according to hemostatic adequacy. Resume VKA 1 to 2 days after surgery 150% of pre-procedure dosefor 2 consecutive days according to hemostatic sufficiency.
- Low molecular weight heparin or UFH is continued until the INR returned to therapeutic levels.

One day before surgery the INR should have decreased to below 2.0, so that it can be expected to reach a level <1.5 on the day of surgery. Generally, if the international normalized ratio (INR) is <1.5, any type of surgery can be performed safely.[10] Otherwise, an oral dose of 1-2 mg of vitamin K1 can be administered 24 hours before surgery, or considerations should be given to postponing the procedure.

The recommended daily dose of bridging LMWH is 70 anti-Xa U/kg, and should be administered subcutaneously. In high risk patients two daily doses should be administered. Box 2 provides a timeline for discontinuation of VKA, bridging therapy and postoperative restarting of heparin and VKA. As anticoagulation is restarted, extra attention should be paid to possible bleeding complications.

MEDICAL MANAGEMENT AND OXYGEN MISMATCH

Risk reduction in the surgery patient population can be achieved by coronary revascularisation and medication. The focus for intervention is on plaque stabilization and prevention of the oxygen supply/demand mismatch. Some perioperative medication (i.e. beta-blockers, statins) has been widely studied, and a good guideline on their treatment regiments has been published in Education in Heart by Schouten et al.[13] An update on the latest recommendations and developments on these agents will be discussed briefly in the following paragraphs.

Beta-blockers

The use of β-adrenoreceptor antagonists, or beta-blockers, is primarily aimed at reducing the heart rate, counteracting the effect of the catecholamine surge and reducing the oxygen supply-demand mismatch prevents myocardial ischemia to occur. A recent meta-analysis of 12306 patients underlined the effect of beta-blockade in high-risk surgery patients on all-cause mortality (63% decreased risk) and non-fatal myocardial infarction (44% decreased risk). In intermediate surgical-risk patients, 30% reduction of the risk of non-fatal MI was found, at the expense of an increased risk of all-cause mortality, non-fatal stroke and hypotension.[14] This was challenged by a recent RCT in intermediate surgical-risk patients, which showed improved perioperative outcome, without an increased rate of these complications.[15]

The introduction of esmolol, an ultra-short acting beta-blocker, has provided a new tool to better mitigate heart rate but prevent hypotension. A recent meta-analysis including 1765 patients showed a decrease of myocardial ischemia in noncardiac surgery, without an increase in the rate of hypotension or bradycardia.[16] In future guidelines, perhaps esmolol will take a prominent place in perioperative medical management. Dosage and timing of beta-blocker therapy have great influence on the treatment effect. According to guidelines, medical treatment should commence 30 days prior to surgery, with a low starting dose of 2.5 mg bisoprolol or 50 mg metoprolol succinate. Subsequently, dose can be titrated to the preferred range of resting heart rate, which is around 60-70 bpm.[12] Peri- and postoperatively, intravenous beta-blockade is warranted when oral administration is not possible.

BOX 3. Cardioprotective measures: Beta-blockers
• Beta-blockers are recommended in patients with ischemic heart disease or myocardial ischemia on preoperative stress testing • Beta-blockers are highly recommended in high-risk surgery patients • Beta-blockers are recommended in intermediate risk surgery patients • Beta-blockers should be administered 30 days prior to surgery • Beta-blockers should be titrated to heart rate 60-70 bpm • Short acting beta-blockers could decrease hypotension and bradycardia rates

Statins

In the process of cholesterol synthesis, the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) plays a crucial role. HMGR inhibitors, better known as statins, directly influence this process. Generally prescribed to patients as primary or secondary prevention of cardiac ischemia, statins are renowned for their lipid lowering effect. Additionally, statins have so-called pleiotropic effects, adding to their cardio-protective value. These include decreasing lipid oxidation, inflammation, matrix metalloproteinase and cell death, and increasing tissue inhibitor of metalloproteinase and collagen. It is these effects that may prevent plaque instability and subsequent rupture around the time of surgery.

Several reports on the effects of perioperative statin showed improved cardiac outcome, especially in high-risk surgery patients. Meta-analysis of 18 studies including a total of 799632 patients showed a 30% to 42% reduction of perioperative rates of death or ACS in patients taking statins.[17] However, large prospective studies had not been performed at the time. In the recently published DECREASE III trial by Schouten et al., an RCT including 497 vascular surgery patients, fluvastatin use (80 mg extended release) was associated with 10.8% myocardial ischemia, compared to 19.0% in the placebo group.[18]

Lacking evidence in intermediate and low risk surgery, perioperative statin therapy is not recommended for these types of surgery. However, discontinuation of statins may be harmful, independent of surgery. Therefore, perioperative statin continuation is recommended regardless of the type of surgery. Lacking intravenous substitutes, the use of statins with a prolonged half-life (e.g. atorvastatin or fluvastatin extended release) is preferable, to bridge the immediate postoperative period in which oral statin administration is impaired.[12]

BOX 4. Cardioprotective measures: Statins
• Perioperative continuation of current statin therapy is recommended • Statins should be started 30 days prior to high-risk surgery • Statins with prolonged half-life are preferable • Statins should be restarted as soon as possible, following postoperative withdrawal

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors can be prescribed in patients with left ventricular (LV) systolic dysfunction (e.g. postmyocardial infarction) as well as for hypertensive patients. ACE-inhibitors have several effects on endothelial function and atherosclerosis, adding to the treatment effect in especially high risk patients. Regarding surgical patients, current studies do not support perioperative ACE-inhibitor therapy to have added cardioprotective value.[19] However, if a patient is receiving ACE-inhibitor therapy preoperatively for LV dysfunction instead of hypertension, this should not be discontinued. If LV dysfunction is discovered preoperatively, it is preferable to start ACE-inhibitor and beta-blocker therapy, and therefore temporarily postpone surgery.[20] Considering the type of surgery, starting perioperative ACE-inhibitor therapy for LV systolic dysfunction in stable patients is more strongly advised in high risk surgery than intermediate risk surgery.[12]

BOX 5. Cardioprotective measures: ACE-inhibitors

- Withdrawal from ACE-inhibitors for hypertension can be considered before non-cardiac surgery
- ACE-inhibitor therapy in stable patients with LV systolic dysfunction should be continued during non-cardiac surgery
- Upon discovery of LV systolic dysfunction, ACE-inhibitors should be started before high risk surgery
- Upon discovery of LV systolic dysfunction, starting ACE-inhibitors can be considered before intermediate risk surgery

SUMMARY

Due to technical advancement and improved life expectancy, the surgical patient population is increasing in age and level of comorbidities. In an effort to decrease postoperative cardiac complications and death, optimal medical management is essential. Undergoing surgery has an accelerating effect on coronary atherosclerosis, increases inflammation and induces a state of hypercoagulability in patients. Therefore, cardioprotective measures should be taken, especially in patients with a high risk of cardiac complications after surgery. Furthermore, an increasing number of patients scheduled for surgery is treated with antiplatelet and/or anticoagulant therapy. These agents require strict management around the time of surgery, due to their ability to cause hemorrhage on one hand and the increased cardiac risks of withdrawal on the other hand.

As planning for surgery begins, cardioprotective measures are best initiated. Optimally, 30 days before surgery both beta-blockade and statin therapy are recommended to start. Especially in high cardiac risk patients, these medications have proven to be beneficial in the perioperative period and on long-term follow-up. Additionally, the use of antiplatelet therapy should be assessed. A cardiologist and an anesthesiologist should be consulted if the planned procedure has such high bleeding risk, that

withdrawal from antiplatelet therapy is considered by the surgeon. Antiplatelet withdrawal – especially clopidogrel – is often hazardous to the patient, and surgery should therefore be postponed until clopidogrel therapy has ended, if possible.

Patients with current anticoagulant treatment should discontinue their therapy 5 days before most types of surgery. This will reduce the risk of bleeding during surgery, but it will increase the risk for thrombosis. In general, low molecular weight heparin (LMWH) will be used as bridging therapy to reduce the perioperative thrombotic risk. LMWH therapy should commence one day after acenocoumarol or two days after warfarin, and be continued until 12 hours prior to surgery. One or two days, and certainly no less than 12 hours after surgery, LMWH bridging therapy can be continued. One or two days after surgery, anticoagulant therapy should be restarted at 150% of the preoperative daily dose for two days, and then continued at the preoperative daily dose. Heparin is discontinued when the INR reaches the therapeutic range.

This paper provides a comprehensive outline of the optimal perioperative medical management, concerning cardiac risk in any surgical population, based on recent guidelines. We emphasize that knowledge of, and adherence to current guidelines is essential for optimal care and safety of surgical patients.

The advices about the perioperative use of statins and beta-blockers in this and the two following chapters are in line with the recent new guideline of the American Heart Association.[21] The indication for triple therapy described in Box 1 of this chapter has been narrowed based on a high bleeding risk.[22] The individual perioperative strategy for triple therapy should be based on a multidisciplinary decision. Nonetheless, there is an unchanged need for a high level of evidence to strengthen our perioperative strategies related to triple therapy. The novel factor Xa inhibitors (so-called ‘xabans’) are discussed in the new guideline on perioperative management of patients undergoing noncardiac surgery.[21]

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Blood thinners

Statins

Beta-blockers

Vitamin D status

New-onset arrhythmias

Carotid stent characteristics

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Laparoscopic sac fenestration after EVAR

Need we intervene for type II endoleaks?

2

Published as:

"Safety of fluvastatin in patients undergoing high-risk noncardiac surgery"

Expert Opinion on Drug Safety 2010;9:793-800

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ABSTRACT

Importance of the field
In patients undergoing vascular surgery there is a high incidence of adverse cardiac events, due to sudden coronary plaque rupture. The non-lipid lowering, or pleiotropic effects of statins can help reduce adverse cardiovascular events, associated with vascular surgery.

Areas covered in this review
The evidence for perioperative use of fluvastatin, as well as other statins, in high-risk surgery patients is summarized in this review. Data on pharmacokinetics and metabolism is presented, together with considerations on possible drug interactions in the perioperative period.

What the reader will gain
The reader will gain a comprehensive understanding of the existing safety and efficacy data for fluvastatin and other statins in the perioperative period. The practical considerations of perioperative fluvastatin therapy will be presented, including potential side-effects and management of the early non-oral phase immediately postoperative. Finally, advice on when to initiate therapy and safety recommendations are offered.

Take home message
In patients scheduled for high-risk vascular surgery, fluvastatin improves postoperative outcome, reducing the incidence of myocardial damage by almost 50% in the first 30 days following vascular surgery. In comparison with placebo, fluvastatin was not associated with a rise in liver enzymes or creatine kinase levels. To bridge the non-oral phase, an extended-release formula is recommended.

MANUSCRIPT

INTRODUCTION

Statins are renowned for their ability to reduce low-density lipoprotein (LDL) cholesterol in patients at with hypercholesterolemia.[1-3]Apart from their lipid-modifying properties, other treatment effects of statins, so called pleiotropic effects, have been investigated over the last decade, including anti-inflammatory effects and cardiac risk reduction, among others.[4-6] Fluvastatin (Lescol®, Novartis Pharmaceuticals, Switzerland) was first tested in humans in 1986 and was approved for clinical use in the USA since December 1993.[7-8] In this review, we summarize the pharmacology of fluvastatin, evaluate the efficacy and safety in patients undergoing high-risk surgery and comment on possible future developments.

PHARMACOLOGY

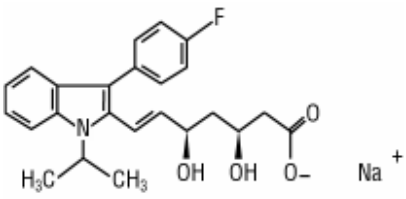
Pharmacodynamic properties

Fluvastatin sodium is a white to pale yellow, hygroscopic powder. It is soluble in water, ethanol and methanol. Fluvastatin, like all statins, is an inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, an enzyme that is rate-controlling in the mevalonate pathway. Mevalonate is a precursor of sterols, including cholesterol. Inhibition of this enzyme leads to a decrease in cholesterol levels in serum, as well as hepatic cells. This leads to an increase in receptors for low-density lipoprotein (LDL), which clear LDL from the bloodstream, adding to the lipid-lowering effect of fluvastatin.

Additionally, statins has been described to have non-lipid lowering effects, or pleiotropic effects. These effects contribute to the reduction of macrovascular risk that is seen in treated patients. Fluvastatin has been described to improve endothelial function, reducing the expression of adhesion molecules in the peripheral and coronary circulation.9 Also, by inhibiting the secretion of metallo-proteases by macrophages, fluvastatin may stabilize atherosclerotic lesions, reducing the risk of plaque rupture. Finally, effects on clotting, fybrinolysis and platelet aggregation can prevent extensive thrombus formation on fissured or ruptured plaques.[9]

Pharmacokinetic properties of fluvastatin

When administered orally, fluvastatin absorption takes place primarily in the small intestine. About 90% of an oral dose is absorbed. Peak concentrations in plasma are reached on average at 0.5 – 1.5 hour in healthy, fasting individuals. Administration with food reduces the rate but not the extent of the absorption. A 50% lower maximum concentration is however reached when taken with food, after twice as much time, when compared to administration 4 hours after a meal. Fluvastatin endures a substantial first-pass effect in the liver after absorption, with a wide variety in non-hepatic bioavailability of ~ 24% on average (range 9-50%) after a 10mg single dose. Liver metabolism of fluvastatin is saturable, so that the systemic bioavailabilty increases in a non-linear manner after single or multiple doses above 20 mg.

BOX 1. Drug summary.	
Drug name	Fluvastatin
Phase	Launched
Approved indication	Hypercholesterolemia, mixed dyslipidemia Heterozygous familial hypercholesterolemia in pediatric patients Secondary prevention of coronary events Atherosclerosis
Pharmacology description	HMG-CoA reductase inhibitor*
Route of administration	Oral
Chemical structure	 $C_{24}H_{25}FNO_4 \cdot Na$ Mol. wt. 433.46
Pivotal trial(s)	LIPS, LCAS†; ALERT, DECREASE-III§

*HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A, † Key studies supporting approved indications, § Other large-scale key studies

Acronyms: LIPS, Lescol Intervention Prevention Study; LCAS, Lipoprotein and Coronary Atherosclerosis Study; ALERT, Assessment of LEscol in Renal Transplantation; DECREASE, Dutch Echographic Cardiac Risk Evaluation Applying Stress Echo study group

Subject to multiple larger doses, the systemic non-hepatic bioavailability can increase to 45-65% in humans.[10-12]

Pharmacokinetic properties of fluvastatin extended release

The main development rationale for fluvastatin XL was to provide an extended release formulation that allows for once daily dosing of 80 mg of fluvastatin while maintaining low plasma levels. A hydrophilic cellulose matrix, containing the drug, was designed to swell when in contact with intestinal fluids, allowing the drug to diffuse out.[11] The time to peak plasma concentrations was 3-6 hours with fluvastatin XL, within the dose range of 80-320 mg. Steady state concentrations were observed within 7 days with regular daily doses.[13]

Metabolism and excretion

Fluvastatin is rapidly metabolized by several cytochrome (CYP) P450 isoenzymes, mainly CYP2C9 (75% of metabolism), primarily via hydroxylation. This process lead to forming of three main metabolites, 5-hydroxy fluvastatin, 6-hydroxy fluvastatin and des-isopropyl-fluvastatin. Ex vivo, the 5- and 6-hydroxy metabolites have an inhibitory

effect on HMG-CoA (88% and 45% of unmetabolised fluvastatin, respectively), but in vivo there is no clinical relevance to these metabolites due to rapid elimination from the circulation. Fluvastatin is excreted primarily in bile, and leaves the body in feces. Over 90% of fluvastatin is found in feces as metabolites, and less than 2% present as unchanged drug. Only 5% of radiolabeled fluvastatin is recovered in urine.[10-12]

CLINICAL APPLICATION OF FLUVASTATIN IN HIGH-RISK SURGERY

Clinical efficacy in trials

In a report by Boersma et al. surgical procedures were categorized into low, intermediate and high perioperative cardiac risk.14 In later guidelines from the European Society of Cardiology (ESC), high-risk surgery was defined as aortic and peripheral vascular surgery, because there is a high probability that the atherosclerotic process is also present in the coronary arteries. Endovascular procedures are considered to be of intermediate cardiac risk, based on data from several randomized trials with open or endovascular aneurysm repair, as is carotid artery endarterectomy.[3]

Few reports have been published on the use of statins in the perioperative period to reduce the risk for a cardiac event after vascular surgery. Only one paper to date has prospectively investigated the effect of fluvastatin on perioperative cardiac events in high-risk surgery patients. The DECREASE-III trial was a large, placebo-controlled trial that assesses the effect of fluvastatin on the 30-day postoperative outcome in vascular surgery patients.[15] In the DECREASE-III trial, 497 patients (372 male) were enrolled at a median of 37 days prior to vascular surgery. Double-blinded randomization took place between fluvastatin (n=250) and placebo (n=247). No adverse cardiac outcome was reached before surgery. In the first 30 days postoperative, evidence of myocardial ischemia was seen in 27 patients (10.8%) in the fluvastatin group, and 47 patients (19.0%) in the placebo group (P=.016). The secondary endpoint of death from cardiac causes or non-fatal myocardial infarction was reached in 12 patients (4.8%) on fluvastatin and 25 patients (10.1%) on placebo (P=.039). The number needed to treat (NNT) to prevent one occurrence of myocardial ischemia in the first 30 days after vascular surgery was 12; the NNT to prevent one nonfatal MI was 36; and the NNT to prevent one cardiovascular death was 42.[15-16]

SAFETY EVALUATION

Side-effects of fluvastatin treatment

Fluvastatin is generally well tolerated in treated patients. Combining all clinical trials, Lawrence et al. found only 1% of patients to withdraw from fluvastatin therapy due to adverse events, attributed to the study medication.11 Most common are complaints of headache, abdominal symptoms and muscle problems. Statin therapy in general has been reported to lead to myalgia, myositis and myopathy. Although often transient, hepatic abnormalities are also well-known side-effects of statin therapy. Liver function tests should be taken previous to statin administration and regularly thereafter. If a patient has active liver disease or persistent abnormal liver function tests, statin

prescription for continous lipid-lowering purposes is contraindicated.[11] No advice is available on statins as prophylaxis for cardiac events in the perioperative period, in patients with liver disease.

Side-effects of fluvastatin in comparison with other statins seem mild. In a pooled analysis by Novartis Pharmaceuticals in 2002, the proportion of the 8951 patients on fluvastatin (20 or 40 mg) or fluvastatin XL (80 mg) that had a CK level more than five times the upper limit of normal was comparable to placebo-treated patients.[17] A large observational study by Bruckert et al. reported on muscular symptoms in general practice with high-dose statin therapy.[18] The rate of muscular symptoms was 5.1% with fluvastatin, compared to 10.9-18.2 % for other statins. However, all these side-effects were recorded when fluvastatin was prescribed in general practice, not surgery patients.

In the high-risk surgery patients from DECREASE-III, general anesthesia prevented monitoring for muscular complaints, but creatine kinase (CK) levels were measured as part of the safety endpoints. In patients treated with fluvastatin, the median CK level was 141 U/L, compared to 113 U/L for placebo (P=.24), and the proportion of patients that had CK levels > 10 times the upper limit of normal (ULN) was 4.0% in the fluvastatin group versus 3.2% in the placebo group (P=.81). Hepatic toxicity was observed without significant differences between groups. The median levels of alanine aminotransferase (ALT) were 24 U/L for the fluvastatin group and 23 U/L for placebo group (P=.43), and only 3.2% of patients had ALT levels > 3 x ULN in the fluvastatin group, compared to 5.3% for placebo (P=.27).[15]

Safety in special populations

The safety of fluvastatin use in the general population has been subject to research on several occasions. There have been reports on a low incidence of adverse reactions in children and adolescents with familial heterozygous hypercholesterolemia.[19] Animal studies have reported an association of high-dose fluvastatin (12 and 24 mg/kg) with a higher rate of stillbirths and maternal mortality, while a low-dose (2 mg/kg) therapy had no effects on the dam nor the foetus.[20] No data with fluvastatin in pregnant women are available, but statin use should be discontinued in women who become pregnant, and in nursing mothers statin use is strongly discouraged.[21]

With regard to high-risk surgery patients, advanced age and renal insufficiency are common. Age was found not to be of influence on the plasma concentrations for the general population.[10,22] However, the treatment response measured by LDL-level changes was slightly higher in patients ≥65 years of age, than in patients aged under 65 (30% versus 27%). Subject to the large role of the liver in the metabolism of fluvastatin, renal dysfunction is of no large influence on fluvastatin pharmacokinetics.

Drug interactions

When prescribing statins, the possibility of drug interactions is important to consider. This may inhibit normal metabolism, leading to increased plasma levels, or increase normal metabolism, via enzyme induction, leading to a decreased treatment effect.

Statin toxicity has been reported to cause myalgia or rhabdomyalysis and statin inhibition can lead to under-treatment of dislipidemia and subsequent increased cardiovascular risk.

As mentioned, the metabolism of fluvastatin takes place via the CYP P450 system. Where other statins are metabolized primarily by the CYP3A4 isoenzyme (atorvastatin, lovastatin and simvastatin) or not by the liver at all (pravastatin), fluvastatin is the only statin that is predominantly metabolized by the CYP2C9 isoenzyme (75%), and to a much lesser extent by CYP3A4 (~20%). There are several known interactions between statins and other drugs that are metabolised by, or are of influence on CYP3A4. Drugs that inhibit this isoenzyme are antigungals, erythromycin and other macrolides, histamine-2 blockers, cyclosporin, calcium channel blockers and grapefruit juice. All these agents lead to an increase in plasma concentration of statins, and the use of pravastatin or fluvastatin may be preferable, since these are not primarily metabolized by CYP3A4. Rifampicin, Phenobarbital, carbamazepine and phenytoin are examples of drugs that induce both CYP3A4 and CYP2C9, and therefore lead to increased metabolism of hepatically-metabolized statins.[23] The lipid-lowering effect of statins, including fluvastatin, can be reduced by concomitant use of these drugs.

Warfarin is metabolized by CYP3A4 and CYP2C9, and there have been few reports that patients on fluvastatin/warfarin are potentially at risk for bleeding complications. Careful monitoring of the INR is advised in patients on warfarin, following the start of or any change in statin use (except pravastatin).[24-25]

Interactions with anesthetic agents

Commonly used agents for general anesthesia may have interactions with statin therapy. Midazolam, a commonly used benzodiazepine, is metabolized in part by the same CYP P450 isoenzyme as most statins, CYP3A4. In theory this could lead to interactions and alterations on the efficacy of either drug or both. However, a recent report showed that statins had no influence on midazolam pharmacokinetics in healthy subjects, dismissing this theory.[26] Among hypnotic agents, propofol is a widespread example, generally used for narcotic induction. It is metabolized primarily by direct glucuronidation in the liver.[27] However, one report suggests that propofol can influence midazolam metabolism by inhibition of CYP3A4. In theory, an interaction between propofol and statins could also be expected based on this report. Finally, narcotic analgesics are used for general anesthesia patients. Fentanyl was introduced in the 1960s, and has been in use ever since. CYP3A4 is the major catalyst in fentanyl metabolism in humans.[28] An interaction with other drugs, metabolized by the same isoenzyme, is hypothesized, but not reported. Alfentanil, a derivate of fentanyl, was investigated in surgery patients with atorvastatin therapy.[29] There was no sign of altered pharmacokinetics of alfentanil.

Safety considerations of statin withdrawal

Caution in prescribing statin to surgery patients is warranted, in light of the mentioned safety evaluations, but statin withdrawal should be given equal consideration. In the first days directly following surgery, oral medication is often inhibited. Since the

pleiotropic effects of statins are often underappreciated, postoperative statin withdrawal is common.[16]

Unfortunately, statin withdrawal can cause a rebound effect, diminishing the treatment benefit of statin administration. Discontinuation of short-acting statins was associated with an increase in inflammatory markers and oxidative stress, and an increase in cardiac events has been observed following acute withdrawal of statins during periods of instability, compared to continuation of statin therapy.[30] In vascular surgery patients, an increased incidence of cardiovascular events was reported, related to statin withdrawal after surgery. In that report, fluvastatin XL was considered a usefull long-acting agent, with a lower rate of adverse cardiac events after withdrawal, than other agents.[31] In guidelines from the European Society of Cardiology the use of a long-acting statin is advised to prevent the withdrawal effect.[3]

USE OF OTHER STATINS IN HIGH-RISK SURGERY

Apart from DECREASE-III, there have only been four other reports on statin use in patients undergoing vascular surgery.[32-35] Two additional reports discuss the benefit of statin therapy during major noncardiac surgery, including both vascular and nonvascular, or in intermediate risk surgery, excluding vascular surgery entirely.[36-37] From the four reports on statin use during the perioperative period in vascular surgery patients, three were based on retrospective data acquisition, and only one was a prospectively randomized trial.

Poldermans et al. performed a retrospective case-controlled study in 2816 major vascular surgery patients.[32] Cases were all 160 (5.8%) patients who died during perioperative hospital stay, and for each case 2 controls were selected (n=320) from all survivors, stratified according to year and type of surgery. Information on perioperative statin use, cardiac risk factors and other medication was gathered for all subjects. There were significantly fewer statin users among those that died (8%) than among those that survived (25%, P<.001).[32]

Kertai et al. studied 570 patients who underwent abdominal aortic aneurysm (AAA) surgery.[34] Information on advanced age, medical history, results of dobutamine stress echography, and statin and beta-blocker therapy were collected. They found the incidence of the combined endpoint of perioperative mortality and MI to be significantly lower in statin users than nonusers (3.7% vs. 11.0%). Even after correcting for other covariates, statin therapy was beneficial to AAA-surgery patients (OR: 0.24, 95% confidence interval: 0.10-0.70, P=.01). Beta-blockers were also beneficial to the study population, and a combination of both drugs resulted in the highest relative reduction of the composite endpoint.[34]

The StaRRS study was a retrospective study in 1163 hospitalizations for noncardiac vascular surgery.[35] Patient characteristics, medical history and medication were collected, and perioperative complications, including death, MI, ischemia, congestive heart failure and ventricular tachyarrhythmias were scored.

Complications occurred in 9.9% of statin users, and in 16.5% in nonusers (P=.001). Even after correcting for other covariates, statins were associated with a reduction in risk of complications (OR=0.52, P=.001).[35]

Durazzo et al. conducted the first prospective, placebo-controlled, double-blind randomized trial on the effect of statins on cardiovascular event following vascular surgery.[33] They randomized one hundred patients for atorvastatin (n=50) or placebo, on average 30 days before vascular surgery. The combined primary endpoint consisted of death from cardiac cause, nonfatal myocardial infarction, unstable angina and stroke. During the 6-month follow-up period, the incidence of the primary endpoint was 26.0% in the placebo group, compared to 8.0% with atorvastatin. The event-free survival, as a function of time, was significantly higher in patients treated with atorvastatin (P=.018, according to Kaplan-Meier method).[33]

Comparison of the efficacy and safety of fluvastatin and other statins in high-risk surgery patients is inhibited by the lack of comparative studies, and the limited amount of prospectively randomized placebo-controlled trials. Only one prospective RCT was performed using fluvastatin, and one atorvastatin. The rate of cardiac death or non-fatal MI in DECREASE-III was 4.8%, whereas in the data from Durazzo et al. atorvastatin seemed to be associated with an incidence of 8.0% for the same endpoints.[15, 33] However, there were differences in patients characteristics, distribution of target vessels and years of surgery. More importantly, the incidence of cardiac events in the placebo group was substantially higher in the study by Durazzo et al. (20.0%), compared to DECREASE-III (10.1%).

USE OF FLUVASTATIN IN INTERMEDIATE-RISK SURGERY

Besides high-risk surgery, the treatment effect of fluvastatin has also been investigated in intermediate-risk surgery patients. DECREASE-IV was a multicenter RCT among 1066 patients undergoing elective nonvascular surgery.[37] In this trial, a trend was observed of reduced cardiac events with fluvastatin therapy in the perioperative period in nonvascular surgery patients. This was not statistically significant, possibly due to under enrollment of the study.[37] However, a recent follow-up study of DECREASE-IV showed that perioperative fluvastatin therapy had a so-called “legacy-effect” in these nonvascular surgery patients. Perioperative fluvastatin, discontinued 30 days after surgery, was associated with a reduction in the incidence of myocardial infarction at long-term follow-up of over thirty months. This suggests that the pleiotropic effects of statin therapy can help reduce the atherosclerotic burden at postoperative hospital discharge. Untreated patients are predisposed to a higher risk of cardiovascular events, compared to patients who did receive perioperative fluvastatin as cardioprotection.

CONCLUSIONS

The use of fluvastatin as lipid-lowering therapy in the general, non-surgical population has been reported in several studies, and was evaluated in a previous Expert Opinion by Lawrence and Reckless.[11] Fluvastatin was described to be effective at lowering total

and LDL cholesterol, and to be safe and well-tolerated. Furthermore, drug interactions are low in comparison with other hepatically metabolized statins.

The use of statins in patients undergoing high-risk surgery is aimed at reducing the incidence of perioperative cardiovascular adverse events. Of the few reports on this subject, fluvastatin was the agent of choice in the largest, prospectively randomized, placebo-controlled trial to date. Compared to placebo, fluvastatin is associated with a significant reduction of myocardial ischemia, myocardial infarction and cardiac death. In terms of safety, no significant adverse reaction was seen on CK-levels or liver enzymes levels, compared to placebo. Fluvastatin seems to be a safe and effective agent, suitable for perioperative treatment in patients undergoing vascular surgery.

EXPERT OPINION

Although currently no statin has a particular approved indication for perioperative cardiac prevention, statin are often considered in vascular surgery patients. Not only because of the high incidence of dyslipidemia in this population, but also because of the pleiotropic effects of statin therapy.
Fluvastatin is effective in reducing cardiovascular adverse events in the perioperative period in high-risk surgery patients. Considering the low proportion of patients with side-effects and the extended release formulation, no other available statin is preferential to fluvastatin XL. Unfortunately, no large RCTs have been performed with other statins to provide us with comparable data. For now, the DECREASE-III trial advocates fluvastatin XL administration prior to high-risk surgery. For adequate implementation of fluvastatin prescription in patients scheduled for surgery, some questions remain.

Is development of a non-oral form of administration warranted?
Surgery patients often have a limited intake immediately after surgery. To bridge these first days, a non-oral form of fluvastatin might be helpful. However, since the acting site of fluvastatin is primarily the liver, where it is metabolized, an intravenous solution may not be optimal. The passage of enteral fluvastatin through the liver is essential to its therapeutic effect. Suppositories may provide a solution, although uptake in the rectum is still not equal to the proximal intestinal tract.

Are there racial differences in the efficacy of fluvastatin?
Although no specific information on fluvastatin is available, racial differences have been reported in the efficacy of lipid-lowering therapy, with evidence that African-Americans are less likely to reach LDL-level goals with statin therapy.[38-39] However, for cardiac events in the perioperative period, no reports on race as a factor have been published. The racial differences in pleiotropic effects of perioperative fluvastatin use for the prevention of perioperative cardiac events are therefore unknown. Since the lipid profile plays an important role in atherosclerotic advancement, only large future studies may reveal that statin therapy is less effective in the prevention of perioperative cardiac events in certain races.

What is the best timing for perioperative statin therapy?

There are some studies of cell cultures and the influence of statins on inflammatory response markers. These show that only 4 hours after simultaneous administration with interleukin (IL)-6, a reduction of C-reactive protein (CRP) release in human hepatic cells was established by statins.[5] An in vitro study found that fluvastatin inhibited IL-6 expression in human vascular smooth muscle cells, even after only 4 hours.40 The effect substantiated after 8 hours, leading to nearly 50% reduction of IL-6 after 24 hours. In other words, in vitro it seems that fluvastatin has pleiotropic effects after 4-24 hours.

What can be expected for the future?

In DECREASE-III, fluvastatin has proven to reduce cardiovascular events immediately after vascular surgery.[15] The mentioned follow-up study from DECREASE-IV showed additional effects of perioperative fluvastatin at long-term follow-up in intermediate-risk surgery patients. Future studies may reveal a similar legacy effect of perioperative fluvastatin therapy in high-risk surgery patients.

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Blood thinners
Statins
Beta-blockers
Vitamin D status
New-onset arrhythmias
Carotid stent characteristics
Aortic stentgraft composition
Laparoscopic sac fenestration after EVAR
Need we intervene for type II endoleaks?

3

Published as:
"Safety of perioperative beta-blocker use: how do β-blockers compare in terms of side effects?"
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ABSTRACT

Introduction
In the perioperative setting, there is still a high incidence of adverse cardiac events, due to sudden coronary plaque rupture or oxygen supply-demand imbalance. β-blockers play an important role in preventing these cardiac events. Discussion however remains on side-effects accompanying this therapy.

Areas covered
The evidence for perioperative use of β-blockers is summarized in this review, in terms of risk reduction, perioperative safety and current clinical use. Furthermore, data on pharmacokinetics, -dynamics and -genetics is presented.

Expert Opinion
In perioperative care, β-blockers are recommended and can be given safely when started early in a low dose, titrated to heart rate. In the future, there could be a place for added perioperative short-acting β-blockers to further optimize heart rate control.

MANUSCRIPT

INTRODUCTION

β-blockers are well established drugs for the treatment and prevention of heart failure (HF), cardiac arrhythmias, hypertension (HT) and coronary artery disease (CAD) [1-5]. In recent years β-blocker use in the perioperative setting has become common and has been advocated by both European and US guidelines [6,7]. Their implementation is based upon several RCT's demonstrating a positive effect on reducing cardiac death and non-fatal myocardial infarction (MI) [e.g. 8-15]. This is very recently underscribed by a retrospective study from Wallace et al., in which patients were divided into four groups, based on the pattern of perioperative β-blocker use (None, Addition, Withdrawal and Continuous). The Addition group and the Continuous group were both associated with a reduction in 30 day and 1 year mortality. In contrast withdrawal was associated with an increase in 30 day and 1 year mortality [16]. Perioperative cardiac events can be caused by multiple mechanisms. Due to the stress of surgery, a catecholamine surge takes place, which will increase heart rate and myocardial contractility. In patients with fixed coronary plaques, this can lead to an oxygen supply-demand imbalance, leading to infarction. In patients with unstable plaques the perioperative inflammatory response, as well as sheer stress caused by an increased heart rate, can cause rupture of these plaques, followed by thrombus formation and subsequent acute coronary thrombosis, leading to ischemia and infarction [17]. Perioperative ischemia and infarction have shown to be risk factors for increased cardiac mortality in the perioperative period as well as in long term follow-up. This has also been described for heart failure and arrhythmias [18,19]. Based on the pharmacological properties of β-blockers, they could play a prominent role in the treatment and prevention of these risk factors.

Discussion still remains on the safety of the perioperative use of β-blockers, especially regarding stroke, hypotension and bradycardia, particularly triggered by the results of the large POISE study [14]. In this review, after shortly summarizing the pharmacology of β-blockers, the efficacy and safety of β-blockers in patients undergoing non-cardiac surgery will be evaluated and a treatment recommendation based on current literature and our own experience will be provided.

PHARMACOLOGY

β-Adrenergic antagonists (β-blockers) block β-adrenergic receptors, of which 3 types have been differentiated. β_1-receptors are predominantly located in cardiac tissue, in addition to cells of the juxtaglomerular apparatus (renin release). β_2-receptors are also present in the heart but can mainly be found in the smooth muscle of the peripheral blood vessels and bronchi and are involved in metabolic effects such as lipolysis, glycogenolysis, gluconeogenesis, insulin release. Both receptors will lead to increased heart rate and contractility of the myocardium when they are stimulated [20]. β_3-adrenoceptor mRNAs have been detected in the ventricles and atria of the heart, in the

Box 1. Guidelines on perioperative patient management regarding β-blocker use.

ACCF/AHA guideline November 2009 [7]	ESC guideline August 2009 [6]
Class I β-blockers should be continued in patients undergoing surgery who are receiving β-blockers for treatment of conditions with ACCF/AHA Class I guideline indications for the drugs. (Level of Evidence: C)	*Class I* β-blockers are recommended in patients who have known IHD or myocardial ischemia according to pre-operative stress testing* (Level of Evidence: B) β-blockers are recommended in patients scheduled for high-risk surgery* (Level of Evidence: B) Continuation of β-blockers is recommended in patients previously treated with β-blockers because of IHD, arrhythmias, or hypertension (Level of Evidence: C)
Class IIa β-blockers titrated to heart rate and blood pressure are probably recommended for patients undergoing vascular surgery who are at high cardiac risk owing to coronary artery disease or the finding of cardiac ischemia on preoperative testing. (Level of Evidence:B) β-blockers titrated to heart rate and blood pressure are reasonable for patients in whom preoperative assessment for vascular surgery identifies high cardiac risk, as defined by the presence of more than 1 clinical risk factor* (Level of Evidence: C) β-blockers titrated to heart rate and blood pressure are reasonable for patients in whom preoperative assessment identifies coronary artery disease or high cardiac risk, as defined by the presence of more than 1 clinical risk factor*, who are undergoing intermediate-risk surgery. (Level of Evidence: B)	*Class IIa* β-blockers should be considered for patients scheduled for intermediate-risk surgery* (Level of Evidence: B) Continuation in patients previously treated with β-blockers because of chronic heart failure with systolic dysfunction should be considered (Level of Evidence: C)
Class IIb The usefulness of β-blockers is uncertain for patients who are undergoing either intermediate-risk procedures or vascular surgery in whom preoperative assessment identifies a single clinical risk factor in the absence of coronary artery disease* (Level of Evidence:C) The usefulness of β-blockers is uncertain in patients undergoing vascular surgery with no clinical risk factors* who are not currently taking β-blockers. (Level of Evidence: B)	*Class IIb* β-blockers may be considered in patients scheduled for low-risk surgery with risk factor(s) (Level of Evidence: B)
Class III β-blockers should not be given to patients undergoing surgery who have absolute contraindications to β-blockade. (Level of Evidence: C) Routine administration of high-dose β-blockers in the absence of dose titration is not useful and may be harmful to patients not currently taking β-blockers who are undergoing noncardiac surgery. (Level of Evidence: B)	*Class III* Perioperative high-dose β-blockers without titration are not recommended (Level of Evidence: A) β-blockers are not recommended in patients scheduled for low-risk surgery without risk factors (Level of Evidence: B)
*Clinical risk factors include history of ischemic heart disease, history of compensated or prior heart failure, history of cerebrovascular disease, diabetes mellitus, and renal insufficiency (defined in the Revised Cardiac Risk Index as a preoperative serum creatinine of greater than 2 mg/dL). Data from [7]	* 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. IHD, ischemic heart disease. Data from [6]

brain, stomach, small and large intestines, gall and urinary bladders, prostate and myometrium [21]. Stimulation of these receptors in the ventricles decrease cardiac contractility, as has been shown by giving isoprenaline in the presence of nadolol, a β_1 and β_2-receptor antagonist [22]. This indicates that β_3-receptors might act as a safety valve during intense adrenergic stimulation, as further demonstrated by their overexpression in hypertension and heart failure. [23]. Results concerning atrial β_3-receptor stimulation are still conflicting [21].

Table 1. Receptor involvement and effect by organ system

Organ	Receptor-subtype	Physiological effect
Heart	β1 >> β2 β3	Heart rate, contractility, conduction velocity and automacity ↑ contractility↓
Gastrointestinal tract	β1, β2	Smooth muscle tone ↓
Bronchial tract	β2	Smooth muscle tone ↓ (bronchodialtion)
Uterus	β2	Smooth muscle tone ↓ (relaxation)
Blood vessel	β2 β3	Smooth muscle tone ↓ (vasodilation) vasodilation
Kidney	β1	Renin release ↑
Fat tissue	β2 > β1 (2:1), (β3)	Lipolysis ↑
Pancreas (β-cells)	β2, (β3)	Insulin release ↑
Liver	β2	Glycogenolysis ↑, Gluconeogenesis ↑
Skeletal muscle	β2	Glycogenolysis ↑, K+ uptake ↑, Tremor ↑
Thyroid gland	β2	T4 → T3 ↑ (conversion)

β-blockers prevent catecholamines from binding to the β-adrenergic receptor, hereby blocking their positive chronotropic and inotropic actions, which gives a decrease in heart rate (HR) and myocardial contractility, resulting in a lower cardiac output [20]. The effect on HR is especially visible during periods of dominant sympathetic control, such as exercise and stress. Further aspects of β-blockers consist of anti-ischemic, anti-arrhythmic and anti-renin/angiotension properties. They prolong coronary diastolic filling time, inhibit catecholamine induced cardiac necrosis [24] and suppress the induction of stress induced proinflammatory cytokines [25]. Some β-antagonists partially activate the β-adrenergic receptor. This phenomenon is known as Intrinsic Sympathetic Activity (ISA). It is thought that β-blockers with intrinsic activity have less influence on resting HR, therefore giving fewer bradycardias [26]. However, the clinical relevance has shown to be rather controversial. Because of this, β-blockers with ISA do not play a role any longer in clinical use [27].

β-antagonists can be classified in multiple ways, by generation, selectivity, or by elimination. There are 3 generations of β-blockers. First generation agents are non-selective (eg propranolol). Second generation agents are β_1-selective (atenolol, metoprolol, betaxolol, bisoprolol) and third generation β-blockers have additional properties, such as vasodilation (carvedilol, nebivolol). β_1-selectivity depends on the β-

blocker concentration at the receptor and is therefore relative. β_2-blocking will give rise to peripheral vasoconstriction, by unopposed α-stimulation and to bronchoconstriction. Elimination can be either by hepatic metabolism, renal excretion (unchanged substance) or both [20]. Those drugs that are eliminated via the hepatic route are mostly lipid soluble, have a low bioavailability due to a high first pass effect and require more frequent administration, due to a short half life. In contrast, drugs that undergo renal metabolism are water soluble, also have a low variable bioavailability but have longer half lives [26]. Like in all orally administered drugs, the effective dose is dependent on the extent of absorption, half life and bioavailability. Dosing interval depends mostly on half life and absorption through the gastrointestinal tract, especially in extended release agents.

The four most described β-blockers in perioperative care are 1) atenolol, 2) metoprolol, 3) bisoprolol and 4) esmolol. All four agents are β_1-selective. However, the degree of β_1-selectivity is different between these agents [20]. While the β_1-selectivity of bisoprolol extends beyond the therapeutic dose range, this is not the case with atenolol and metoprolol which may also block some β_2-receptors. At a dose of 100mg or more, metoprolol will also have an effect on β_2-receptors [26]. For bisoprolol this happens at 20mg, where the range of used perioperative dose is 2.5 – 10mg [26]. Schnabel et al. concluded that atenolol, metoprolol and bisoprolol also bind to the β_3-receptors [28]. Taken this into account, bisoprolol remains the most selective agent. The effect of these β-blockers on β_3-receptors is still unclear. It has been demonstrated that Nebivolol (a β_1-selective agent) has an agonistic effect on β_3-receptors [29]. For the β-blockers used in perioperative care, this still has to be assessed.
Metoprolol comes in a short- and long-acting oral form (tartrate and succinate respectively) and is available for intravenous (iv) injection. The tartrate form has a half life of 3-4 hours. For succinate, this is a factor 2-4 longer. As a consequence, dosage should be adjusted accordingly. Bisoprolol comes in an oral form only and has a half life of 10-12 hours, which is comparable to metoprolol succinate. Atenolol is available for iv and oral administration, has a half life of 5-8 hours and should therefore be dosed twice daily. Esmolol can only be administered intravenously and has a very short half life of 9 minutes.

A different aspect of β-blockers that has been given more and more attention lies in the field of pharmacogenetics. The hepatic elimination of some β-blockers depends on the catalytic activity of the hepatic cytochrome P450 isozyme CYP2D6 (carvedilol, nebivolol and metoprolol) [30]. A poor metabolizer (PM) phenotype results if all inherited alleles are non-functional (or null- *0) alleles. It has been demonstrated that in patients with these phenotypes metoprolol concentrations are 3-10 times higher. This phenomenon is seen shortly after drug administration, as well as during chronic use [30-32]. Bisoprolol has a relatively constant β-adrenergic inhibition independent of CYP2D6 genotype. Because of this difference in CYP2D6 dependency, there may be a greater variety in β-blocker plasma concentrations in the trials using metoprolol, compared to those which use bisoprolol.

RISK REDUCTION

Among patients undergoing noncardiac surgery, complications of underlying (a)symptomatic coronary artery disease are the major cause of perioperative mortality [33]. Mangano described that a myocardial infarction or cardiac death was seen in 2.5% of all patients over the age of 40, undergoing noncardiac surgery. Within vascular surgery patients this was 6.2% [34]. He furthermore estimated that in 2001 a hundred million patients would undergo surgery around the world, of which one third would be over the age of 65 or have more than 2 cardiac risk factors. An estimated 10% of these patients would suffer a perioperative MI. Because of these findings there have been many trials investigating the effectiveness of perioperative β-blocker use to reduce the oxygen demand of-, and the stress on the myocardium, and thus prevent perioperative myocardial ischemia. Of the randomized controlled trials (RCTs) that we reviewed, 7 show a reduction in perioperative myocardial ischemia and/or MI after β-blocker use [8,9,11-15], and 4 do not [35-38]. These RCT's differ substantially in their methods, as described in Table 2.

In 1988 Stone et al. randomized 128 hypertensive patients (blood pressure 160/90 mmHg – 200/100 mmHg) to either a single small oral dose of a beta-blocker (labetolol 100mg, atenolol 50mg, or oxprenolol 20mg) or standard care [8]. 11 of the 39 untreated patients had intraoperative ischemia, where in the patients who were treated with a β-blocker only 2 out of 89 suffered ischemia ($p<0.001$). All episodes of ischemia were related to a preceding episode of tachycardia, but not to an increase in blood pressure.

In 1996 Mangano et al. performed a randomized, double-blind, placebo-controlled trial to compare the effect of atenolol with that of a placebo on overall survival and cardiovascular morbidity in patients with or at risk for coronary artery disease (CAD) who were undergoing noncardiac surgery [9]. Patients were considered at risk for CAD if they had at least two of the following cardiac risk factors: age ≥65 years, hypertension, current smoking, a serum cholesterol concentration ≥240 mg per deciliter (6.2 mmol per liter), and diabetes mellitus. 200 patients were randomly assigned to receive either atenolol or placebo. In the placebo group 12 patients had a cardiac event (defined as a combined variable of myocardial infarction, unstable angina or congestive heart failure requiring hospital admission and clinical diagnosis and treatment, myocardial revascularization [coronary-artery bypass graft surgery or percutaneous transluminal coronary angioplasty], and death), six months after surgery. Within the group of patients who were treated with atenolol, no events were observed ($p<0.001$). Holter registration was performed from the day of surgery to 7 days postoperatively. These recordings showed no difference in ischemia pre- and during surgery. In the postoperative period however, there was a 50% lower incidence of ischemia in the atenolol group in the first 48 hours post surgery ($p=0.03$). For the first 7 days this was 40% ($p=0.008$) [10].

Zaugg et al. randomly assigned 63 patients to 1 of 3 groups: group I, no atenolol; group II, pre- and postoperative atenolol; group III, intraoperative atenolol [11]. The study

period ranged from directly preoperative to 72 hours postoperative. 17 out of 59 (29%) patients had a troponin I (cTnI) release. Perioperative release of cTnI was detected in 8 of 19, 4 of 20, and 5 of 20 patients in groups I, II, and III, respectively. Peak levels of cTnI occurred intraoperatively in 6 patients (two from each group) and postoperatively in 11 patients (group I: 6; group II: 2; group III: 3). Postoperative cTnI release was significantly related to increased postoperative HR (68 ± 14 vs. 78 ± 15 bpm, p=0.002). The percentage of patients with a postoperative tachycardia was higher in patients in group I, compared to those in groups II and III. These findings suggest a protective effect of β-blockers on myocardial damage.

In 1999 Raby et al. included 26 patients with preoperative ischemia at 24 hour Holter monitoring, scheduled for aortic aneurysm repair, infrainguinal arterial bypass, or carotid endarterectomy [12]. They identified the lowest HR at which ischemia occurred (ischemic threshold) and set the target heart rate at a heart rate 20% below the ischemic threshold or an absolute minimum of 60 bpm. Patients were then randomized to receive either IV esmolol, starting at 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$, or to placebo. The study period included the first 48 postoperative hours. During this period patients were monitored by a Holter recording. Patients receiving esmolol had 33% postoperative ischemia, whereas in the placebo group this was 73% ($p<0.05$). Of the 15 patients receiving esmolol, 9 patients had a mean HR below the ischemic threshold, and all these subjects were without postoperative ischemia. In both groups one cardiac event occurred. Both had a mean HR well above their ischemic threshold. Heart rate control was the only multivariate predictor of postoperative ischemia ($p <0.01$). The authors concluded that postoperative ischemia depended more on a tight heart rate control, rather than on β-blocker therapy. Furthermore, they concluded that the type of β-blocker was also less important than heart rate control.

Also in 1999, Poldermans et al. performed a randomized controlled trial (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography [DECREASE] -I) [13]. 112 high risk patients, selected by stress echocardiography, were randomized to receive bisoprolol and standard care (n=59) or standard care alone (n=53). In the standard care group 9 patients (17%) had a nonfatal MI within 30 days postoperative, as compared to none in the bisoprolol group.

The PeriOperative Ischemic Evaluation trial (POISE), which was published in 2008, reported a protective effect of perioperative metoprolol succinate with regard to myocardial infarctions 30 days after surgery (HR 0.73, 95%CI 0.60 – 0.89; p=0.0017) [14]. In this study noncardiac surgery patients were randomly assigned to extended release metoprolol succinate or placebo. 152 of 4174 (3.6%) patients receiving metoprolol had a non-fatal myocardial infarction as compared to 215 of 4177 (5.1%) in the placebo group.

Dunkelgrun et al. showed in 2009 that for intermediate risk patients undergoing noncardiac and nonvascular surgery, bisoprolol was associated with a significant reduction in 30-day non-fatal MI [15]. They randomized a total of 1066 patients to 4 groups (bisoprolol, fluvastatine, both or neither). In the bisoprolol group (n=264) there was an incidence of 1.9% for perioperative MI. In the double control group (n=268) this was 6.7% (p = 0.01).

Table 2. Study designs of included trials

Study	Beta-blocker	Starting Dose	Continuous Dose	Treatment start	Treatment end	Minimum HR *	Minimum RR *	Cardiac risk groups†	Surgery type risk groups‡
Stone [8]	Labe-tolol Atenolol Ox-prenolol	L 100mg A 50mg O 20mg	NA	Single oral dose 2hrs before induction				Inter & High	Inter & High
Mangano [9]	Atenolol	10mg iv	10mg iv or 1dd 100mg oral	30 min preop	7 days postop	< 55 bpm	SBP <100 mmHg	Inter & High	All
Zaugg [11]	Atenolol	5-10mg iv or 5mg/5 min	5-10mg iv or NA	30 min preop or intraop only	72 hrs postop or directly postop	< 55 bpm	SBP <100 mmHg	Inter & High	Inter
Raby [12]	Esmolol	100-300 microgr/kg/min	100-300 microgr/kg/min	directly postop	48 hours postop			Inter & High	Inter & High
DECREASE I [13]	Biso-prolol	5-10mg	5-10mg	1 week preop	30 days postop	< 50 bpm	SBP <100 mmHg	High	High
POISE [14]	Meto-prolol Succ.	100mg	200mg	2-4 hours preop	30 days postop	< 50 bpm	SBP <100 mmHg	Inter & High	Inter & High
DECREASE IV [15]	Biso-prolol	2.5mg – 5mg	2.5mg – 5mg	1 month preop	1 month postop	< 50 bpm	SBP <100 mmHg	Inter	Low & Inter
POBBLE [33]	Meto-prolol Tart.	4mg iv	2dd 25-50mg	5-10 min preop	7 days postop	< 50 bpm	SBP <100 mmHg	Inter	High
MaVS [34]	Meto-prolol Tart.	25-100mg	15mg iv/6 hours or 2dd 25-100mg	2 hours preop	5 days postop	< 50 bpm (awake), <45 bpm (asleep)	SBP <100 mmHg	All	High
BBSA [35]	Biso-prolol	5-10mg	5-10mg	3 hours preop	10 days postop	< 50 bpm	SBP <100 mmHg	Low & Inter (3,6% High)	Inter
DIPOM [36]	Meto-prolol Succ.	100mg	100mg	2 hours preop	8 days postop	< 55 bpm	SBP <100 mmHg	Inter & High	All

* When HR or RR was below the indicated minimum value, medication was withheld.
† Risk groups as defined by the Lee index (Low = 0; Intermediate = 1-2; High = ≥3) [7]
‡ Surgical risk group as described by Boersma et al. [6]

The 4 RCT's that do not report a beneficial effect of perioperative β-blocker therapy are the PeriOperative β-Blocker trial (POBBLE) [35] the Metoprolol after Vascular Surgery (MaVS) study [36], the Beta Blocker in Spinal Anaesthesia (BBSA) study [37] and the DIabetes POstoperative Mortality and morbidity (DIPOM) trial [38].

The POBBLE trial showed that 18 (42%) of 43 patients in the placebo group and 16 (32%) of 50 patients in the metoprolol group, had significant myocardial ischemia in the first month after surgery (P = 0.36) [35]. In the MaVS trial 496 patients were randomized to receive metoprolol or placebo [36]. 19 out of 246 patients in the metoprolol group had a perioperative MI within 30 days after surgery, as compared to 21 out of 250 patients in the control group (p=0.87).

Similar findings were reported from the BBSA study. This trial randomized between bisoprolol and placebo [37]. In the treatment group the incidence of perioperative MI was 1.8% (2 out of 110). In the placebo group the incidence was 0.9% (1 out of 109) (p=0.90).

Juul et al. reported the results of 921 diabetic patients from the DIPOM trial [38]. Patients were randomized to either metoprolol or placebo. 30 days after surgery, 27 patients in the metoprolol group and 21 patients in the placebo group (6% and 5% respectively), reached the primary endpoint (a combined endpoint of all cause mortality, acute MI, unstable angina, or congestive heart failure discovered or aggravated during admission to the hospital). 6 months after surgery this was 21% in the metoprolol and 20% in the placebo group (p=0.66).

The limitations of these trials might partially explain why these differed in their findings as compared to the previously mentioned studies. POBBLE included 103 patients over a period of nearly 3 years and was discontinued because of poor recruitment and lack of funding. The BBSA trial was underpowered and included patients had varying cardiac risk profiles. Furthermore, the authors from the DIPOM trial concluded that they included only patients with diabetes and might not have included enough patients. However, an absolute risk reduction of 7% with a power of 80% was possible to detect.
Bangalore et al. performed a meta-analysis [39] in which they included 12306 patients from 33 randomized trials. They found that β-blocker therapy was associated with a 35% decreased risk of non-fatal myocardial infarction (numbers needed to treat (NNT) 63) and a 64% decreased risk of myocardial ischemia (NNT 16) at 30 days postoperative. Trials were classified on bias-risk. Trials were analyzed for sequence generation of allocation, allocation concealment and masking of participants, personnel, and outcome assessors. When a trial was considered to have a low quality on any of these 3 components, it was classified as high or unclear risk for bias. When analyzing only the low-risk bias trials, there still was a 28% decreased risk of non-fatal MI (NNT 80) and a 59% decreased risk of myocardial ischemia (NNT 23). Figure 1 describes the OR's for a composite endpoint of ischemia, non-fatal MI and cardiac death for the previous mentioned studies.

Decreasing myocardial oxygen consumption is one way of preventing perioperative cardiac death by using β-blockers. Additional cardioprotective factors are redistribution of coronary blood flow to the subendocardium and increasing the threshold for ventricular fibrillation. Analyzing the previously mentioned RCT's for perioperative death, either all cause or cardiac origin, the results are mainly in line with what was found for ischemia. Except in the POISE trial, where an increased total mortality was found in the treatment group (HR 1.33, 95%CI 1.03 – 1.74; p=0.0317) [14]. The amount of cardiovascular death did not differ significantly (HR 1.30, 95%CI 0.92 – 1.83; p=0.14). Only sepsis or infection was significantly different between groups as a cause of death. Both were more common among the patients allocated to metoprolol. Clinically significant hypotension had the largest population attributable risk (PAR) for death (37.3%, 29 – 45) and had an adjusted odds ratio (OR) of 4.97 (95% CI 3.62 – 6.81). Furthermore, suffering an intra- or postoperative stroke had an OR of 18.97 (95% CI

9.93 – 36.3). Patients in the metoprolol group more often suffered a stroke than did patients in the placebo group. This was also related to clinically significant hypotension ([OR 2. 14, 95%CI 1.15 – 3.96] [PAR 14.7%, 95%CI 5.2 – 35.4]).

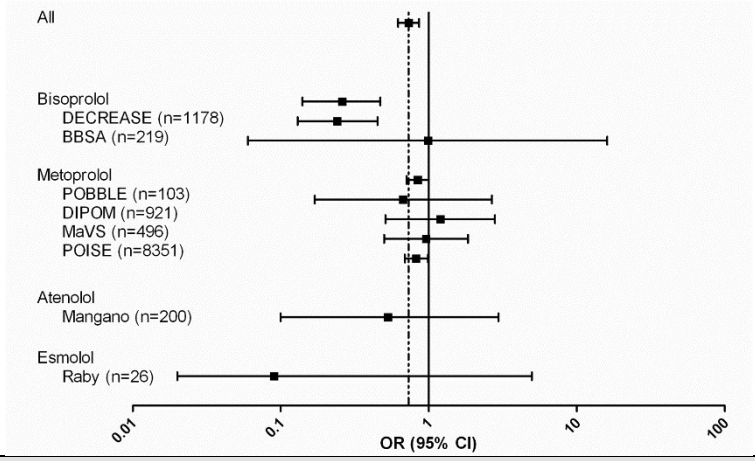

Figure 1. Odds ratios (OR) of randomized β-blocker trials for perioperative stroke.

BBSA = Beta Blocker in Spinal Anesthesia; CI = confidence interval; DECREASE = Dutch Echocardiographic Risk Evaluation Applying Stress Echocardiography; DIPOM = DIabetes Postoperative Mortality and morbidity; MaVS = Metoprolol after Vascular Surgery; POBBLE = Perioperative Beta-BLockadE; POISE = PeriOperative Ischemic Evaluation trial.

Also provided are the weighted means for all studies using bisoprolol and for all studies using metoprolol.

Mangano et al. reported a significant reduction in all cause mortality during 2 year follow-up [9]. In the placebo group 21 patients out of a 101 died (20%), of which 12 were of cardiac causes. For the atenolol group this was 9 out of 99 (9%) (4 of cardiac causes). Thus, overall mortality was 55 percent lower in the atenolol group (p=0.019) and mortality from cardiac causes was 65 percent lower (p=0.033). The first six to eight months were mostly responsible for the effect of atenolol therapy on cardiac outcomes (1 death from noncardiac causes in the atenolol group vs. 10 in the placebo group, 7 of which were from cardiac causes; p=0.001). It has to be noted that in a multivariate analysis, diabetes was the only statistical significant predictor of death. Furthermore, results might have been influenced by preoperative β-blocker withdrawal in the control group. However the 2 year results did not indicate this. There were 12 cardiac deaths in the 2 years after surgery in the control group. From the 8 patients using β-blockers preoperatively, 1 patient died (12%), as compared to 11 deaths out of 91 patients not using β-blockers (12%).

In the DECREASE-I trial 9 patients in the standard-care group (17 percent) died of cardiac causes during the perioperative period, as compared to two patients (3.4 percent) in the bisoprolol group (p=0.02) [13]. This resulted in 34% of patients receiving standard care alone and 3.4% of patients receiving standard care and bisoprolol reaching the combined endpoint of cardiac death and nonfatal MI (p<0.001).

Dunkelgrun et al. showed a similar result in the DECREASE IV study [15]. 5 patients died in the control group, where no patients from the bisoprolol group died. In the study of Raby et al. no patients died [12]. In the 4 trials that did not show a difference with regard to ischemia (POBBLE, MaVS, BBSA and DIPOM) [35-38], there also was no difference in mortality. Bangalore reported a 28% increased risk of all-cause mortality (number needed to harm (NNH) 164), while there was no difference in cardiovascular mortality between the treatment and the placebo group. This result was mainly driven by the results from the POISE trial [39].

SAFETY EVALUATION

Historically β-blockers were thought to worsen symptoms of respiratory dysfunction, heart failure, impotence and intermittent claudication. In this section, these aspects and other side effects of β-blockade will be discussed, and summarized in Table 3.

Respiratory effects

Chronic obstructive pulmonary disease (COPD) has shown to be an independent cardiovascular risk factor. In 1998 Gottlieb et al. retrospectively investigated the records of 201.752 patients with MI [40]. 22.1% of COPD patients and 17.7% of asthma patients received a β-blocker. These patients had a 40% reduction in mortality compared to patients with pulmonary disease who did not use a β-blocker. Side effects however, were not reported.

Van Gestel et al. evaluated 3371 patients undergoing major vascular surgery, of which 1205 patients had a history of COPD. 462 (37%) received β-blocker therapy. β-Blocker use was associated independently with lower 30-day (OR 0.37; 95% CI 0.19–0.72) and long-term mortality in patients with COPD (HR 0.73; 95% CI 0.60–0.88) [41]. It was concluded that in carefully selected patients with COPD, the use of cardioselective β-blockers appears to be safe and associated with reduced mortality.

Salpeter et al. performed a meta-analysis to asses the effect of β-blockers on respiratory function in patients with reactive airway disease [42]. Nineteen single dose treatment studies (with a total of 204 patients) and 10 continued dose studies (with a total of 141 patients) were included. The β-blockers used were atenolol, metoprolol, bisoprolol and practolol. FEV-1 was reduced with 7.46% (CI 5.59 - 9.32%) after a single dose and was not reduced after continued treatment (which ranged from 3 days to 4 weeks). For both single dose and continuous treatment, no increase in respiratory symptoms was seen. The authors concluded that, based on these trials, cardioselective β-blockers should not be withheld from patients with mild to moderate airway disease in conditions for which a clear benefit has been demonstrated. Salpeter et al. found that the same held true for patients with COPD [43]. No significant change in FEV-1 or patient symptoms was seen after β-blocker use, be it either single dose or continuous therapy, even in patients with severe COPD.

Table 3. Take home messages concerning side effects.

Side effect	Take home message
Respiratory	- β-blockers minimally reduce FEV-1, but don't increase respiratory symptoms in asthma and COPD patients [40-43].
Bradycardia	- β-blockers commonly cause bradycardia. However, only a small part requires treatment [37,44].
Hypotension and stroke	- In a high dose, given shortly preoperative, β-blockers significantly increase the incidence of hypotension and stroke. This effect disappears when administration is started early, in a low dose and titrated to heart rate [14,47,48].
Heart failure	- (A)symptomatic heart failure is a predictor for worse perioperative cardiovascular outcome. β-blockers have become a cornerstone of heart failure therapy [18,49-52].
Intermittent claudication	- β-blockers do not increase symptoms of intermittent claudication [53].
Impotence	- Erectile dysfunction seems to be caused by the underlying disease and psychological factors [54-56].
Withdrawal	- β-blocker withdrawal shortly preoperative has shown to cause a hypersensitivity reaction, and is related to worse perioperative cardiovascular outcome. Therefore, β-blockers should be continued in patients already using them [16,57-64].

Bradycardia

Since β-blockers suppress sympathetic activity and thereby cause a decrease in heart rate, bradycardia is a common side-effect [44]. Bangalore et al. described a high risk of perioperative bradycardia (OR 3.13, 95% CI 2.51–3.92, p<0.0001; I^2=29.5; NNH 8), but the risk of bradycardia requiring treatment was markedly lower (NNH 22) [37].

Hypotension and Stroke

Controversy about perioperative β-blocker use is mainly based on a reported increase in the amount of strokes in the POISE trial [14]. It reported an incidence of stroke of 1.0% in the metoprolol group and of 0.5% in the placebo group (HR 2.17, 95%CI 1.26 – 3.74, p=0.0053) and that clinically significant hypotension had the largest intraoperative or postoperative risk for stroke (adjusted OR 2.14, 95%CI 1.15 – 3.96. Population attributable risk 14.7%, 95%CI 5.2 – 35.4). This high incidence of stroke was not found in the other previously described RCT's. The difference might be explained by important differences in the treatment protocols, i.e. differences in the use of the BB, such as different dosage, titration of the dose according to HR or not, route of administration and time of onset and duration of β-blocker therapy (Table 3). In POISE, the following treatment protocol was used: 100mg metoprolol succinate was given two to 4 hours preoperatively and 0 to 6 hours postoperatively. 12 hours after the first postoperative dose, patients received a dose of 200mg metroprolol succinate, if permitted by heart rate and blood pressure, which was then continued daily for 30 days post surgery. This protocol could have led to a maximum dose of 400mg in the first 24

hours, which is 100% of the maximum recommended daily dose as stated by the Food and Drug Administration's Center for Drug Evaluation and Research database (6,670 mg/kg/day for an average adult of 60 kg) [45].

At high metoprolol doses, additional β_2-receptor blockade will ensue, due to the decreased β_1-selectivity, which might cause cerebral ischemia by blocking β_2-receptor mediated cerebral vasodilation, as described by Badget et al. [46]. As a comparison, for heart failure the recommended daily starting dose of metoprolol succinate is 12.5-25mg, usually increased at 2-4 weekly intervals [3] and for hypertension the starting dose is 25-50mg [1]. Van Lier et al. described the total incidence of postoperative stroke in the DECREASE I, II and IV trials, which was 0.46% (18 of 3,884) [47]. For patients on perioperative β-blocker therapy, the incidence was 0.5% (OR 1.16, 95% CI 0.4 to 3.4). They concluded that a low-dose bisoprolol regimen, started at least 30 days before surgery, had no association between β-blocker use and postoperative stroke. Figure 2 shows the OR's for perioperative stroke in the previously mentioned studies.

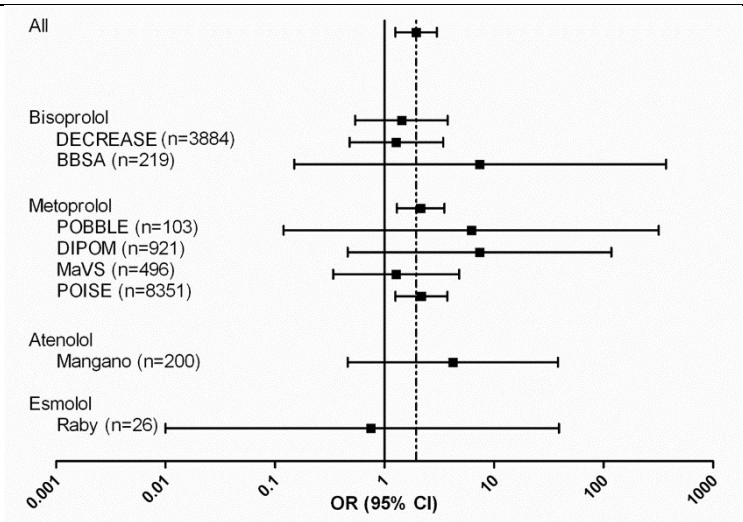

Figure2. Odds ratios (OR) of randomized β-blocker trials for perioperative myocardial infarction (MI) and cardiac death.

BBSA = Beta Blocker in Spinal Anesthesia; CI = confidence interval; DECREASE = Dutch Echocardiographic Risk Evaluation Applying Stress Echocardiography; DIPOM = Diabetes Postoperative Mortality and morbidity; MaVS = Metoprolol after Vascular Surgery; POBBLE = Perioperative Beta-BLockadE; POISE = PeriOperative Ischemic Evaluation trial. Also provided are the weighted means for all studies using bisoprolol and for all studies using metoprolol.

A case control study among 186,779 patients who underwent noncardiac surgery, carotid artery and intracerebral surgery excluded, showed an incidence of perioperative stroke of 0.02% [48]. All of the 34 cases of strokes were matched with 2 controls, which were stratified according to calendar year, type of surgery, and age. A similar use of β-blockers was found in both groups (29% vs. 29% p=1.0). In the subgroups of patients

who used cardiovascular therapy (blockers, statins, angiotensin-converting enzyme inhibitors, calcium channel blockers, angiotensin-II antagonists, nitrates, aspirin, dipyridamole, and clopidogrel) or had a presence of cardiac risk factors, comparable results were found. None of the cases had used β-blockers shorter than one month preoperatively. The percentage of the maximum recommended therapeutic dose was also similar in the cases and controls (median 25% vs. 25%, p=0.239).

These findings implicate that an early started, low dose long acting β-blocker regimen, titrated according to heart rate will have no increased risk for perioperative stroke, where a regimen started shortly preoperatively in a high dose, does have an increased risk.

Heart Failure

Flu et al. demonstrated that asymptomatic heart failure is predictive for 30-day and long-term cardiovascular outcome in open vascular surgery. Therefore, they advocated preoperative echocardiographic screening, next to inquiring for heart failure symptoms, as part of the standard preoperative work-up [18]. A recently published review concludes that adequate treatment of CHF is of great importance in the reduction of perioperative morbidity and mortality. Furthermore, it states that bisoprolol reduces all-cause mortality in patients with CHF undergoing major noncardiac surgery [49]. It was once thought that β-blockers would worsen outcome in patients with heart failure, because of the negative inotropic effect, which could cause decompensation in these patients. However, multiple studies have shown that in this population β-blockers give a reduction of all-cause mortality and significantly reduce HF hospitalizations and worsening of HF [50]. The benefit of β-blockers on mortality in heart failure patients is for ischemic as well as for non-ischemic heart failure through all stages of the disease [50-52].

Worsening of Intermittent Claudication

It was thought β-blockade would worsen complaints of patients with peripheral arterial disease, because of a blockade of peripheral β_2-receptors by non-selective or less beta$_1$-selective β-blockers thus inhibiting the vasodilation these receptors normally are mediating. Blocking of these peripheral β_2-receptors leads to peripheral vasoconstriction, due to unopposed vasoconstriction mediated by α_1-receptors and therefore less perfusion of the lower limbs. A recent Cochrane Review demonstrated that there is currently no evidence supporting this hypothesis. It reviewed 6 RCT's with a total of 119 patients and concluded that none of the trials showed a statistically significant worsening effect of beta blockers [53].

Impotence

Animal studies suggested that β-blockers, especially lipophilic, may increase the latency to initial erection and ejaculation, and may reduce the number of erectile reflexes [54].
Recently Cocco performed a randomized controlled trial in which hypertensive patients received Metoprolol Succinate, and were randomized into 3 groups [55]. Group 1 was informed that the drug was Metoprolol and that it might induce Erectile Dysfunction (ED). Group 2 was told that they received Metoprolol, but the possible ED was not

mentioned. Group 3 was told neither. After 60 days the incidence of ED was 32%, 13% and 8% in Group 1, 2 and 3 respectively ($p<0.01$). The second phase of the study was that Metoprolol was continued and patients would be randomized to Tadalafil or placebo to treat ED. The results were similar. Therefore, they concluded that ED was mostly psychological and not so much due to β-blockade.

ED is common in patients with vascular disease. Both diseases share the same risk factors (age, hypertension, hypercholesterolemia, diabetes, and smoking) [56]. Patients tend to blame their ED on drug use, but a large part of this condition seems to be caused by the underlying disease and psychological factors.

Withdrawal

Next to side effects, withdrawal of currently used medication shortly before surgery or in the immediate postoperative period, also influences the perioperative safety of β-blocker use. It might contribute to adverse myocardial outcome, because of a rebound effect, resulting in increased heart rate, blood pressure and plasma noradrenalin concentrations [57-61]. Redelmeier et al. demonstrated that longer acting β-blockers (such as atenolol) have a better perioperative cardiac protective action than short acting drugs (metoprolol), probably as a result of acute withdrawal effects from missed doses of short-acting β-blockers [62]. In concordance with these findings, Shammash et al. showed that postoperative β-blocker withdrawal was associated with an increase in total mortality (50% after withdrawal vs. 1.5% with continuation, OR 65.0, $p<0.001$), cardiovascular mortality (29% after withdrawal vs. 0% with continuation, $p=0.005$) and postoperative myocardial infarction (OR 17.7, $p=0.003$) [63]. Furthermore, the study of Hoeks et al. also demonstrated an increase in 1-year mortality after β-blocker withdrawal compared with non-users (HR 2.7, 95%CI 1.2 to 5.9) [64]. This was recently underscribed by Wallace et al. as discussed previously [16].

CLINICAL APPLICATIONS

Current recommendations on the perioperative use of BBs from the ACCF/AHA [7] and from the ESC [6] are described in Box 1. Both advocate a target heart rate of 60-70 bpm or 60-80 bpm for the ESC and ACCF/AHA respectively. To achieve this, initiation of β-blocker therapy is recommended between 30 days and 1 week before surgery at a daily dose of 2.5mg of bisoprolol or 50mg of metoprolol succinate. Furthermore, it is recommended that the dose be adjusted before surgery to achieve the target heart rate. The ESC advocates a systolic blood pressure >100mmHg, where the ACCF/AHA only mentions “no hypertension”. The optimal heart rate range remains the same throughout the entire perioperative period, using iv administration when oral administration is not possible. Post-operative tachycardia should result in the first instance in treating the underlying cause, for example hypovolaemia, pain, blood loss, or infection, rather than increasing the β-blocker dose [6,7]. This regimen will have the best chance of attaining an optimal perioperative heart rate with a low risk of perioperative complications.

There are some differences between both guidelines [65]. These are mainly on the number of risk-factors needed, before β-blockers are mandatory. The ACCF/AHA seems

to be somewhat more conservative. However, both guidelines recommend perioperative β-blocker use in high- and intermediate risk surgery.

Although both guidelines recommend the perioperative use of β-blockers, guideline adherence is far from complete. Sidiqui et al. described 336 cases of cholecystectomy, for which criteria for β-blocker use were met in 146 patients [66]. Of these patients 70% were not receiving a β-blocker and of that group, β-blocker therapy was only started in 8% preoperatively [66]. In accordance to these findings, Hoeks et al. showed that the use of recommended medication in 711 patients with peripheral arterial disease (PAD) was lower than expected based on the current guidelines [67]. At baseline 48% of patients were on β-blocker therapy. After 3 year follow-up this increased slightly to 54%. In patients with PAD and ischemic heart disease (IHD), β-blocker use was higher (68% at baseline and 68% 3 years after surgery).

CONCLUSIONS

Historically there has been a reluctance to use β-blockers in a perioperative setting, especially in patients with peripheral arterial disease, because of the hypothetical side effects and worsening of outcome. In the last decade it has become apparent that β-blockers reduce the risk of perioperative myocardial ischemia, myocardial infarction and cardiac mortality. When started at least one week prior to surgery, given in a low dose and titrated to heart rate, the benefits of β-blocker therapy still remain and side effects can be kept to a minimum. Both US and European guidelines have therefore incorporated perioperative β-blocker use into their recommendations.

EXPERT OPINION

β-blockers have earned their place in the perioperative treatment of intermediate and high risk patients. An optimal balance between the reduction of cardiac events and the frequency of major side effects still has to be found. Cucherat performed a meta-regression of 17 randomized trials to asses the relationship between HR reduction and mortality after MI. He concluded that a drop of 10 bpm in HR reduces the relative risk for cardiac death by 30% [68]. Feringa et al. showed that a higher dosed β-blocker leads to a lower heart rate and thereby to a lower incidence of myocardial ischemia, Troponin T release and mortality [69]. On the other hand, the results from POISE and the ClOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) demonstrated that a high dose β-blocker regime can also lead to more adverse events such as bradycardia, hypotension, cardiogenic shock and stroke [14,70]. In COMMIT 45852 patients with an acute MI, existing shorter than 24 hours, were randomly assigned to metoprolol or placebo. Metoprolol was administered intravenously up to 15mg directly after inclusion. 15 min after these intravenous doses, a 50 mg metoprolol or placebo tablet was to be given, and repeated every 6 h during days 0–1. From day 2 onwards, a 200 mg controlled-release metoprolol or placebo tablet was to be given once daily for up to 4 weeks. They observed a decrease of 5 patients with a reinfarction and 5 patients having ventricular fibrillation. However they also observed a rise of 11 patients developing cardiogenic shock. This was mostly seen in hemodynamically unstable patients. Both this dosing scheme as the one used in POISE are markedly higher than the ones used in those trials where no increase in major adverse events was observed.

The perioperative period is known to be a period of fluctuating heart rate, due to stress and a catecholamine surge, but also due to other factors such as hypovolemia. These different causes of tachycardia need a different treatment approach. Where β-blocker therapy is well suited to treat the extra catecholamine release, it is not indicated in case of a hypovolemia. Therefore, it is preferred not to have a β-receptor blocking effect which is too strong during surgery.

As shown by Raby et al., Esmolol (a short-acting β-blocker with a half-life of 9 minutes) can be well titrated and thereby achieve a heart rate within the preferred range [12]. A combination of a timely started, low dose long-acting β_1-selective β-blocker and a perioperative short-acting, easily titratable β-blocker might lead to a better heart rate control, without the extra risk of adverse events as seen in a high dose long-acting β-blocker regimen. With such a regimen, treating physicians will be better able to diagnose and treat the different causes of tachycardia, wile the chance of hypotension and bradycardia is reduced. A perioperative target heart rate of 60-70 bpm is advocated. To achieve this, initiation of β-blocker therapy is recommended between 30 days and 1 week before surgery. The starting dose should be low (2.5 mg bisoprolol or 50mg metoprolol succinate) and titrated to heart rate. Especially shortly postoperative, there is a rise in heart rate as shown by Raby et al. [12]. Using a short-acting β-blocker in this period, titrated to heart rate, might improve outcome with respect to cardiac events.

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Blood thinners
Statins
Beta-blockers

4

Vitamin D status

New-onset arrhythmias
Carotid stent characteristics
Aortic stentgraft composition
Laparoscopic sac fenestration after EVAR
Need we intervene for type II endoleaks?

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ABSTRACT

Objectives
The aim of this study was to assess the vitamin D status in patients with occlusive or aneurysmatic arterial disease in relation to clinical cardiovascular risk profiles and markers of atherosclerotic disease.

Methods
We included 490 patients with symptomatic peripheral arterial disease (PAD, n=254) or aortic aneurysm (n=236). Cardiovascular risk factors and comorbidities, carotid intima-media thickness (CIMT), ankle-brachial index (ABI), serum high-sensitive C-reactive protein (hs-CRP), and vitamin D were assessed. Patients were categorized into severely (≤25nmol/L) or moderately vitamin D deficient (26-50nmol/L), vitamin D insufficient (51-75nmol/L), or vitamin D sufficient (>75nmol/L).

Results
Overall, 45% of patients suffered from moderate or severe vitamin D deficiency. The prevalence of vitamin D deficiency was similar in patients with PAD and those with an aortic aneurysm. Low levels of vitamin D were associated with comorbid congestive heart failure and cerebrovascular disease. Adjusting for clinical cardiovascular risk factors, multivariable regression analyses showed that vitamin D deficiency was associated with high CIMT (P=0.001), low ABI (P<0.001) and elevated hs-CRP (P=0.025).

Conclusions
The current study shows a strong association between low vitamin D status and arterial disease, independent of traditional cardiovascular risk factors and irrespective of the type of vascular disease, i.e. occlusive or aneurysmatic disease.

MANUSCRIPT

INTRODUCTION

Several large epidemiological studies have concluded that vitamin D deficiency is associated with excess mortality.[1,2] It is becoming increasingly clear that vitamin D has a much broader range of actions in the human body in addition to its well-known effects on calcium homeostasis and bone metabolism. There is accumulating evidence that vitamin D deficiency has important extraskeletal effects, including the cardiovascular system.[3,4] Several clinical studies have reported a high prevalence of vitamin D deficiency in patients with peripheral arterial disease[5], coronary artery disease[6], and stroke[7], as well as the association of vitamin D deficiency with cardiovascular mortality.[2,8,9] Furthermore, low vitamin D status is related to major cardiovascular risk factors, such as hypertension, obesity, and diabetes mellitus.[4,10,11]

The aforementioned studies suggest that vitamin D deficiency promotes atherosclerosis.[4,12] However, it is not known whether this is a direct effect of vitamin D on the arterial wall, and/or the result of a vitamin D deficiency-associated increase in established cardiovascular risk factors. It is also unclear whether the severity of arterial disease is related to the severity of vitamin D deficiency. Furthermore, it is not known whether patients with aneurysmatic arterial disease also display vitamin D deficiency.

To answer these questions, we assessed the vitamin D status in a large population of patients with occlusive or aneurysmatic arterial disease, and related this to clinical cardiovascular risk profiles as well as to markers for the severity of arterial disease.

MATERIALS AND METHODS

Study population

The study population consisted of patients with peripheral arterial disease (PAD) or aortic aneurysmatic disease treated between 2004 and 2011 in the Erasmus University Medical Center in Rotterdam, the Netherlands. Patients with PAD were defined as having symptomatic atherosclerotic lower extremity arterial disease with an ankle-brachial index (ABI) of ≤0.9. Patients with aortic aneurysms were defined as having an aortic diameter >30 mm. Common carotid artery intima-media thickness (CIMT), ankle-brachial index, and high-sensitive C-reactive protein (hs-CRP) were routinely measured in all vascular surgery patients. Patients with routinely measured serum vitamin D levels at the vascular outpatient clinic were included, whereas patients using vitamin D supplementation were excluded from this study. The study complies with the Declaration of Helsinki and was approved by the Institutional Review Board.

Baseline characteristics

A detailed history was obtained from every patient, including traditional risk factors; age, sex, hypertension (defined as a blood pressure ≥140/90 mmHg in non-diabetics, ≥130/80 mmHg in diabetics or use of antihypertensive medication),

hypercholesterolemia (defined as a low-density lipoprotein [LDL] cholesterol ≥3.5 mmol/L or use of lipid lowering medication), chronic obstructive pulmonary disease (COPD; defined as a history of COPD or stage ≥1 according to the GOLD classification), diabetes mellitus (defined as a fasting plasma glucose ≥7.0 mmol/L, non-fasting glucose ≥11.1 mmol/L or use of anti-diabetic medication) and smoking status. Furthermore, the atherosclerotic and cardiac risk factors as embedded in the Revised Cardiac Risk (RCR) index were obtained.[13] The RCR index includes congestive heart failure (defined as a history of congestive heart failure), ischaemic heart disease (defined as a history of myocardial infarction, coronary revascularisation or the presence pathologic Q-waves on the electrocardiogram), cerebrovascular disease (defined as a history of ischaemic/haemorrhagic stroke or transient ischaemic attack), renal failure (defined as a serum creatinine ≥2.0 mg/dL) and insulin dependent diabetes mellitus. The use of prescription medications was recorded and included statins, beta-blockers, renin-angiotensin system (RAAS) inhibitors and diuretics.

Atherosclerotic markers

The severity of atherosclerotic disease was assessed by measurements of the CIMT, ABI and hs-CRP. The CIMT was measured using the guidelines from the 'Mannheim Carotid Intima-Media Thickness Consensus'.[14,15] Several measurements from the left and the right common carotid artery were made. The highest CIMT value was used for analysis, while measurements of plaques (defined as a focal structure encroaching into the arterial lumen of at least 0.5mm)[14] were excluded from analysis. The ABI was measured at rest using a portable counter-top Doppler 8-MHz vascular probe (Imexdop CT+ Vascular Doppler; Nicolet Vascular, Madison, WI, USA). The ABI was calculated by dividing the higher of the right and left systolic ankle pressures (posterior tibial or dorsal pedal artery) by the highest systolic brachial blood pressure according to the TASC guidelines.[16] Serum hs-CRP was measured using immunochemistry (Beckman Coulter, Woerden, the Netherlands).

Vitamin D measurements

Serum vitamin D was measured in fresh blood samples using a 25-hydroxyvitamin D radioimmunoassay (Diasorin Inc, Stillwater, MN, USA). Within-run coefficient of variation (CV) was 8.6-12.5% and total imprecision CV was 8.2–11.0%. Patients were categorized into 4 groups based on commonly used cut-off values:[17-19] severely (≤25 nmol/L) or moderately (26-50 nmol/L) vitamin D deficient, vitamin D insufficient (51-75 nmol/L), or vitamin D sufficient (>75 nmol/L). To convert nanomolar to nanogram per millilitre one should divide by 2.496.

Statistical analysis

Dichotomous data are described as counts and percentages. Continuous variables are described as mean±standard deviation (SD), or median and interquartile ranges [IQR] in case of non-Gaussian distribution. Categorical data were compared using chi-square tests. Continuous variables were compared using ANOVA, or using Kruskal-Wallis tests as appropriate. Linear univariable and multivariable regression analyses were performed in separate models using CIMT, ABI, or the natural logarithm of hs-CRP as dependent variable.

Table 1. Baseline characteristics according to vitamin D status

	Total population	Vitamin D status				P for trend
		Severely deficient	Moderately deficient	Insufficient	Sufficient	
		≤25 nmol/L	26-50 nmol/L	51-75 nmol/L	>75 nmol/L	
	n=490	n=62	n=160	n=138	n=130	
Vitamin D level (nmol/L), mean(±SD)	57±93	17±6	39±7	62±7	96±19	-
Baseline characteristics						
Male gender (%)	355(72.4)	42(67.7)	114(71.3)	111(80.4)	88(67.7)	0.083
Age (years±SD)	66.8±10.7	64.±11.6	66.9±11.2	67.8±9.6	66.7±10.6	0.212
Body mass index (kg/m2), mean(±SD)	26.4±4.4	26.1±5.3	26.4±4.6	26.8±4.2	26.0±4.0	0.495
eGFR (ml/min/1,73m2), mean(±SD)	78.32±26.29	86.07±30.75	75.18±28.74	78.46±23.48	78.35±22.97	0.053
Diagnosis						
Peripheral arterial disease (%)	254(51.8)	39(62.9)	81(50.6)	72(52.1)	62(47.6)	0.258
Thoracic and/or abdominal aneurysm (%)	236(48.2)	23(37.1)	79(49.4)	66(47.8)	68(52.3)	
Cardiovascular diseases						
Congestive heart failure (%)	40(8.1)	12(19.3)	16(10.0)	6(4.3)	6(4.6)	0.001
Ischemic heart disease (%)	185(37.7)	27(43.5)	69(43.1)	50(36.2)	39(30.0)	0.112
Cerebrovascular disease (%)	85(17.3)	13(20.9)	35(21.8)	27(19.5)	10(7.6)	0.009
Cardiovascular risk factors						
Kidney disease (≥2.0mg/dl)	46(9.1)	4(6.4)	22(13.7)	11(7.9)	9(6.9)	0.103
Diabetes mellitus (%)	100(20.4)	20(32.2)	32(20.0)	25(18.1)	23(17.6)	0.103
Hypertension (%)	329(67.1)	41(66.1)	105(65.6)	103(74.6)	80(61.5)	0.152
Hypercholesterolemia (%)	455(92.8)	58(93.5)	152(95.0)	126(91.3)	119(91.5)	0.573
Smoking – current (%)	209(42.6)	36(58.0)	71(44.3)	62(44.9)	40(30.7)	0.014
Smoking – ever (%)	379(77.3)	54(87.0)	120(75.0)	110(79.7)	95(73.0)	0.129
Chronic obstructive pulmonary disease (%)	171(34.8)	22(35.4)	59(36.8)	43(31.1)	47(36.1)	0.691
Revised Cardiac Risk (RCR) index						
RCR score, mean(±SD)	1.16±1.01	1.45±1.14	1.27±1.10	1.11±0.84	0.93±0.97	0.004
0-1 risk factors (%)	333(67.9)	36(58.0)	100(62.5)	98(71.1)	99(76.1)	0.001
2 risk factors (%)	105(21.4)	14(22.5)	38(23.7)	33(23.9)	20(15.3)	
≥3 risk factors (%)	52(10.6)	12(19.3)	22(13.7)	7(5.0)	11(8.4)	
Medication						
Statins (%)	411(83.8)	54(87.0)	139(81.2)	112(81.1)	106(81.5)	0.548
Beta-blockers (%)	383(78.1)	50(80.6)	124(77.5)	110(79.7)	99(76.1)	0.903
Renin-angiotensin system inhibitors (%)	235(47.9)	32(51.6)	78(48.7)	71(51.4)	54(41.5)	0.384
Diuretics (%)	122(24.8)	14(22.5)	44(27.5)	37(26.8)	27(20.7)	0.536
Antiplatelets (%)	327(66.7)	49(79.0)	99(61.8)	92(66.6)	87(66.9)	0.124

25-hydroxyvitamin D per 10 nmol/L was used as independent variable and adjustments were made for age, gender, congestive heart failure, ischemic heart disease,cerebrovascular disease, renal function by estimated glomerular filtration rate (eGFR), diabetes mellitus, chronic obstructive pulmonary disease, hypertension, and smoking. To address the seasonal fluctuation of vitamin D levels, further adjustments were made for calendar season of vitamin D measurement. For all tests, a P-value <0.05 (two-sided) was considered significant. All analyses were performed using PASW version 17.0 statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 490 patients were included in the study. 254 patients (51.8%) were diagnosed with peripheral arterial disease (PAD) of the lower extremities and 236 patients (48.2%) were diagnosed with a thoracic and/or abdominal aortic aneurysm. The mean age of the population was 67±11 years and the average value of vitamin D concentration was 57±93 nmol/L, as presented in Table 1. A total of 62 patients (12.7%) were severely vitamin D deficient, 160 patients (32.7%) were moderately deficient, 138 patients (28.2%) were vitamin D insufficient, and 130 patients (26.5%) had sufficient vitamin D levels. There were no differences between patients with PAD and those with an aortic aneurysm with regard to the frequencies of vitamin D deficiency (P=0.258, Figure 1), or the mean vitamin D
concentration (57±31 and 59.2±27 nmol/L, P=0.390). Mean ABI in the patients with aneurysmatic disease was 0.88 and 47% of these patients had an ABI ≤0.9. No significant differences in vitamin D concentration were found between AAA patients with normal ABI or low ABI (mean 63 nmol/L vs. 55 nmol/L, P=0.066).

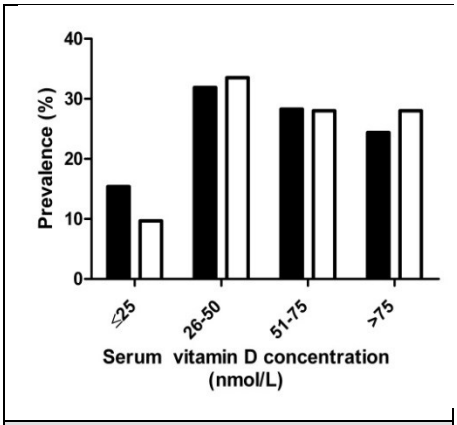

Figure 1. Prevalence of vitamin D deficiency according to type of arterial disease.
Black bars show peripheral arterial disease.
White bars show aneurysmatic disease.

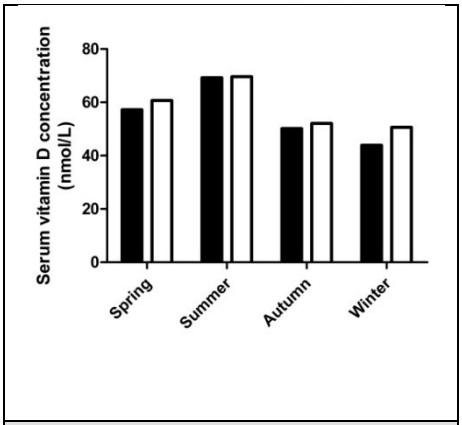

Figure 2. Seasonal variation in vitamin D deficiency according to type of arterial disease.
Black bars show peripheral arterial disease.
White bars show aneurysmatic disease.

Also, although seasonal variation in vitamin D deficiency was observed in the overall population, no differences between patients with PAD and aneurysms were observed, as presented in Figure 2.

Cardiovascular risk factors

Patient groups with decreasing vitamin D levels had an increasing prevalence of congestive heart failure (P=0.001), cerebrovascular disease (P=0.009) and were more frequent current smokers (P=0.014), as presented in Table 1. Overall high risk cardiovascular profiles were significantly associated with lower vitamin D levels, as illustrated by a stepwise increase in RCR scores for groups with increasing vitamin D deficiency (P=0.004).

Atherosclerotic markers

The mean (±SD) CIMT in all patients was 0.97±0.31 mm and a stepwise decrease was observed from 1.06±0.37 mm in patients with severe vitamin D deficiency to 0.90±0.27 in patients with sufficient vitamin D levels (P=0.007), as presented in Table 2. The mean ABI was 0.70±0.26 and increased stepwise in each group from 0.56±0.28 in patients with severe vitamin D deficiency to 0.77±0.24 in patients with sufficient vitamin D levels (P<0.001). Furthermore, median hs-CRP in all groups was 4.3 mg/L [IQR: 2.2-7.8 mg/L]. High concentrations of hs-CRP were especially observed in patients with severe vitamin D deficiency with a median of 7.5 mg/L [2.5-12.7 mg/L] (P=0.040).

Table 2. Atherosclerotic markers according to vitamin D status

Athero-sclerotic markers	Total population	Vitamin D status				P for trend
		Severely deficient ≤25 nmol/L	Moderately deficient 26-50 nmol/L	Insufficient 51-75 nmol/L	Sufficient >75 nmol/L	
CIMT (mm)	0.97±0.31	1.06±0.37	1.01±0.34	0.94±0.27	0.90±0.27	0.007
ABI	0.70±0.26	0.56±0.28	0.68±0.25	0.72±0.26	0.77±0.24	<0.001
hs-CRP (mg/L)	4.3[2.2-7.8]	7.5[2.5-12.7]	4.0[2.3-7.9]	3.8[1.9-6.8]	4.8[2.2-7.8]	0.040

CIMT and ABI are presented as mean±SD, hs-CRP as median and interquartile range.
Abbreviations: CIMT; common carotid intima-media thickness, ABI; ankle-brachial index, hs-CRP; high-sensitive C-reactive protein.

Multivariable linear regression analyses were performed to determine the association between vitamin D concentration and CIMT, ABI and hs-CRP independently of clinical risk factors. Significant associations for vitamin D concentration per 10 nmol/L were observed for CIMT (beta -0.017 mm, 95%CI: -0.027:-0.007, P=0.001), ABI (beta 0.017, 95%CI: 0.008:0.026, P<0.001) and hs-CRP (beta -0.046 mg/L, 95%CI: -0.085:-0.006, P=0.025) (Table 3).

Table 3. Multivariable linear regression models for associations between vitamin D and atherosclerotic markers

Markers	n		Beta for vitamin D[#]	95% CI for Beta	P-value
CIMT	439	Unadjusted	-0.019	-0.029 : -0.009	<0.001
		Adjusted[*]	-0.017	-0.027 : -0.007	0.001
ABI	365	Unadjusted	0.017	0.008 : 0.026	<0.001
		Adjusted[*]	0.017	0.008 : 0.026	<0.001
hs-CRP	391	Unadjusted	-0.044	-0.082 : -0.005	0.027
		Adjusted[*]	-0.046	-0.085 : -0.006	0.025

[*]adjusted for: age, gender, congestive heart failure, ischaemic heart disease, cerebrovascular disease, renal function using eGFR, diabetes mellitus, chronic obstructive pulmonary disease, hypertension, smoking and calendar season of 25-hydroxyvitamin D measurement.
[#] Vitamin D per 10 nmol/L.

DISCUSSION

The current study shows a strong association between low vitamin D status and the severity of arterial disease, independent of traditional cardiovascular risk factors and irrespective of the type of vascular disease, i.e. occlusive or aneurysmatic disease.
Vitamin D_3 is synthesized in the skin from cholesterol under the action of ultraviolet B light.[3] Furthermore, vitamin D can be ingested as cholecalciferol (vitamin D_3) or ergocalciferol (vitamin D_2). Vitamin D is subsequently converted to 25-hydroxyvitamin D (calcidiol) in the liver or stored in adipose tissue. In the kidneys, 25-hydroxyvitamin D is converted to 1,25-dihydroxyvitamin D (calcitriol), which is the biologically active form of vitamin D.[3] The blood concentration of 25-hydroxyvitamin D reflects the dietary intake of vitamin D_2 or D_3 and the amount of vitamin D_3 produced in the skin, and is considered the best indicator of vitamin D storage.[17] Since there is still some debate on the best classification of vitamin D status,[17-20] we used a currently proposed vitamin D classification including clinical relevant cut-off values to describe vitamin D status in our patient cohort.
The observed prevalence of vitamin D deficiency (i.e. ≤50 nmol/L) of 45% in patients with arterial disease is comparable to previous reports on vitamin D levels in patients with peripheral arterial disease.[21-24] Since vitamin D deficiency has been identified as an independent risk factor for mortality,[1,2] the question arises if and how vitamin D deficiency is related to the occurrence of cardiovascular events. In line with previous reports,[7,25] we found that vitamin D deficiency is associated with the occurrence of congestive heart failure and cerebrovascular disease in univariable analyses. In addition, as compared to patients with sufficient vitamin D levels, patients with severe vitamin D deficiency had a significantly higher RCR index, a well known predictor of postoperative cardiovascular events in patients undergoing non-cardiac surgery.[13]

Next, we attempted to identify how vitamin D deficiency is related to the severity of arterial disease. We observed a strong association between vitamin D deficiency and the atherosclerotic markers of CIMT and ABI. The CIMT and ABI provide information about the progression of atherosclerosis. In previous reports, Flu et al. showed the prognostic value of CIMT and ABI, independent of the RCR index.[26,27] Targher et al. observed a similar association between vitamin D deficiency and CIMT in patients with diabetes mellitus,[28] and Reis et al. reported a significant association between vitamin D deficiency and the internal, rather than the common, carotid intima-media thickness.[29] To our knowledge, only two other studies reported ABI measurements in patients with vitamin D deficiency.[5,30] Although both studies reported mild associations, our study clearly shows the stepwise decrease in ABI per vitamin D deficiency category, and a significant correlation in multivariable linear regression models. Additionally, whereas other studies reported varying results regarding CRP and vitamin D deficiency,[30-32] the current study shows that serum hs-CRP levels are elevated in patients with severe vitamin D deficiency.

In contrast to previous studies, we found that vitamin D deficiency was not related to the classic clinical risk factors for cardiovascular disease, including hypertension, obesity, diabetes, and dyslipidemia. Furthermore, the correlation between low vitamin D status and markers of atherosclerotic severity was independent of these cardiovascular risk factors.

Interestingly, a similar association between vitamin D deficiency and occlusive arterial disease was also observed in patients with aneurysmatic disease. To our knowledge, this relationship between vitamin D status and aneurysm formation has thus far not been reported in humans. Although aortic aneurysms have traditionally been attributed to atherosclerosis, there is increasing epidemiological, biochemical and genetic evidence that aneurysmal arterial disease is different from occlusive atherosclerotic disease, a common denominator being aging of the arterial wall.

Taken together, the data in the current study suggest that the relationship between vitamin D deficiency and arterial disease is mediated by an independent effect of vitamin D deficiency on the arterial wall. Vitamin D receptors are not exclusively detected in the bone and mineral pathway, but have a wide tissue distribution, including vascular smooth muscle cells and vascular endothelial cells.[17] The diverse physiologic actions of vitamin D on the vascular wall include reduction of smooth muscle cell proliferation,[33] reduction of macrophage secretion of pro-inflammatory cytokines IL-6 and TNF-α, and increased secretion of the anti-inflammatory cytokine IL-10, leading to a state of vascular inflammation.[34-36] In an atherosclerotic mouse model it has been demonstrated that oral vitamin D_3 reduces the formation of atherosclerotic plaques by the suppression of proatherogenic T lymphocytes.[37] In addition, low circulating levels of vitamin D have been associated with endothelial dysfunction in humans.[38,39] Furthermore, it has previously been reported that people with vitamin D deficiency have increased vascular calcification, a sign of advanced atherosclerosis,[40,41] as well as increased aortic stiffness.[42] These vitamin

D related effects all promote arterial disease.[4,12] Experimental studies provide increasing evidence that factors regulating mineral ion homeostasis, such as vitamin D, affect the aging process, including vascular aging.[43]

There are several limitations that need to be considered. Due to the nature of this study it remains uncertain whether the association between vitamin D deficiency and arterial disease is causal, or whether vitamin D deficiency is just a bystander. Furthermore, several potentially confounding factors could have influenced our analyses, the most important ones being race, diet, and sunlight exposure. Since our study population consisted mostly of Caucasians, race was not a factor in our analyses. Moreover, as lower vitamin D levels are observed in non-Caucasian populations, the true prevalence of vitamin D deficiency in PAD patients may actually have been underestimated. The influence of low dietary intake, thereby not only reducing vitamin D but also other nutrients, was not taken into account in this study. However, low vitamin D in the European population is mainly caused by low sunlight exposure rather than diet.[17,44] Therefore, in the multivariable models we corrected for the season of vitamin D measurement to minimize confounding by seasonal variations in sunlight exposure.

CONCLUSION

In conclusion, this study demonstrates that low vitamin D status is an indicator for the severity of arterial disease, independent of traditional cardiovascular risk factors and irrespective of the type of vascular disease, i.e. occlusive or aneurysmatic disease. It might be hypothesized that primary and secondary preventive strategies to reduce vascular disease should focus on vitamin D status, in addition to blood pressure reduction, lipid and glucose control, weight loss, and lifestyle changes. A beneficial effect of vitamin D supplementation on blood pressure reduction has been demonstrated in several clinical trials.[45,46] Although improving vitamin D status might be a promising public health strategy to reduce cardiovascular disease and improve survival,[47,48] there is still much debate about the requirement levels of vitamin D in relation to extra-skeletal outcomes.[20] Further large-scale, randomized clinical trials are needed to test the effects of vitamin D on cardiovascular disease and to further elucidate the biology of vitamin D on the arterial wall.

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Blood thinners
Statins
Beta-blockers
Vitamin D status

5

New-onset arrhythmias

Carotid stent characteristics
Aortic stentgraft composition
Laparoscopic sac fenestration after EVAR
Need we intervene for type II endoleaks?

Submitted as:
"The incidence of new-onset perioperative arrhythmias in major vascular surgery may be much higher than expected"

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ABSTRACT

Introduction

Cardiovascular complications, such as ischemic and/or arrhythmic events, are a major cause for morbidity and mortality after vascular surgery. The most frequent perioperative arrhythmia is new-onset atrial fibrillation (AF), with a reported incidence of 4-13%. AF is a known major risk factor for postoperative stroke, myocardial infarction and pulmonary embolism. Some of these complications may be preventable such as AF, and can be treated if diagnosed. Current standard Holter recording or periodical electrocardiography (ECG) cannot always identify these paroxysmal arrhythmias. An insertable cardiac monitor (ICM; Reveal XT, Medtronic) continuously monitors for a prolonged period of time, and has clinically proven its use in the detection of paroxysmal arrhythmias. The primary objective of the current study was to detect the true incidence of new-onset cardiac arrhythmias in patients undergoing major vascular surgery using an ICM, and to compare the results with a 72-hour Holter monitoring.

Material/Methods

After informed consent, patients undergoing major vascular surgery received a 72-hour Holter and an ICM prior to elective surgery. After 72 hours the Holter was removed and the data collected, while the ICM data was retrieved electronically from the implanted device. One month after surgery the ICM was removed after a final read-out of the data. Collected data was reviewed independently by a senior cardiologist and an independent core lab, scoring AF, sustained ventricular tachycardia, or ventricular flutter. Fisher's exact test was used to compare Reveal and Holter outcomes. Inter-rater agreement was reviewed by Cohen's kappa.

Results

A total of 43 patients were monitored successfully with both devices. Implantation of the Reveal took approximately 20 minutes under local anesthesia. One patient was diagnosed chronic AF, despite normal ECG recording at the outpatient clinic. Of the remaining 42 patients, 5 patients (11.9%) developed arrhythmias according to Reveal, and only 1 (2.4%) on Holter monitoring in the first 72-hours after surgery. Up to one month postoperatively, new-onset arrhythmias were detected in 11 patients (26.2%) with ICM, comprising paroxysmal AF in 10 cases (90.9%). Sustained VT was detected in one case (2.4%). Inter-rater agreement was 94.9%, with a 0.88 kappa.

Conclusions

The true incidence of paroxysmal AF after major vascular surgery seems to be much higher than estimated with standard practice Holter monitoring, leaving most cases currently undetected and untreated. An insertable cardiac monitor, evaluating rhythm disturbances continuously for weeks or months before and after surgery, detects patients at risk for thromboembolic complications reliably, opening a new treatment window for these patients. Future research should be aimed at the optimal treatment strategy for this patient category.

MANUSCRIPT

INTRODUCTION

Vascular surgery is associated with a high risk of cardiovascular complications, such as cardiac ischemia, stroke and cardiac arrhythmias.[1] Cardiac arrhythmias most often occur during surgery or within the first few postoperative days.[2, 3] Fluid challenges, vagal triggering, cardiac stress and medication are all among the possible contributing factors.[4, 5]

The most frequent perioperative arrhythmia is atrial fibrillation (AF).[6] New-onset AF in vascular surgery has a reported incidence of 4-13%[7-10], and is a known major risk factor for postoperative stroke, myocardial infarction, congestive heart failure and pulmonary embolism.[11, 12] Furthermore, perioperative arrhythmias are directly associated with morbidity, long-term mortality and increased length of hospital stay and health costs.[13-15]

The majority of perioperative arrhythmias is asymptomatic, transient and unpredictable.[16, 17] This causes arrhythmias to be frequently missed and, hence, undertreated. Using traditional detection strategies - such as serial ECG, in-hospital telemetry or even Holter monitoring - the true incidence of perioperative arrhythmias are possibly underestimated.[18, 19] Longer continuous cardiac monitoring could have an advantage over Holter monitoring and significantly increase the number of detected arrhythmias.[20] The use of an insertable cardiac monitor (ICM) has been validated to detect paroxysmal AF, and proven effective in out-patients.[21] Revealing the true incidence of perioperative arrhythmias and raising awareness may open a new treatment window for patients undergoing major vascular surgery, potentially improving outcome.

The primary objective of the current study was to estimate the true incidence of new-onset cardiac arrhythmias in major vascular surgery patients by making use of an ICM, and to compare it to the present gold standard, the 72-hour Holter device.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Elective AAA repair or open surgical lower extremity revascularization • Willingness to wear a 72-hour Holter and receive an ICM perioperatively • Written informed consent • Aged 18 years and over	• An implanted pacemaker or implantable cardioverter defibrillator • Physiological of ECG abnormalities that preclude assessment of cardiac arrhythmias • A history of cardiac arrhythmia • Legal incompetence • Pregnancy

METHODS

This study was a non-randomized, open-label, single-center prospective pilot study. The study was conducted from 2008 to 2012 at the department of Vascular Surgery, Erasmus Medical Center, Rotterdam, the Netherlands.

Subject enrollment

All patients without a history of arrhythmias scheduled for elective aortic abdominal aneurysm repair or open surgical lower extremity revascularization at the Erasmus Medical Centre were approached to participate in this study. Inclusion and exclusion criteria are presented in Table 1. The study was compliant with the international standard for clinical investigation of medical devices in human subjects, ISO 14155, and the Declaration of Helsinki. The study protocol was approved by the institutional Medical Ethics Committee (MEC-2008-130).

Baseline characteristics of the patients, including medical history and possible risk factors for the development of new-onset arrhythmias were prospectively registered. These included advanced age, a history of congestive heart failure (CHF), hypertension (defined as systolic blood pressure over 140mmHg or diastolic blood pressure over 90mmHg or the use of antihypertensive drugs), renal insufficiency (serum creatinin >2 mg/dl) and preoperative low serum potassium levels.[3] Furthermore, the CHA_2DS_2-VASc score was documented. The CHA_2DS_2-VASc score is the main prediction model for stroke in patients with (persistent of paroxysmal) AF, and includes hypertension, age over 65, diabetes and vascular disease, among other risk factors.[22]

Cardiac rhythm monitoring

All patients were monitored in the perioperative period using two devices, a 72-hour surface ECG recording system (12-lead DR180 Digital Holter Recorder; NorthEast Monitoring Inc., Maynard, MA, USA), and an ICM (Reveal® XT; Medtronic, Minneapolis, MN, USA), as illustrated in Figure 1. Reveal® is a single-use device containing two electrodes on the body of the device for continuous (i.e., looping) recording of the patient's subcutaneous ECG. The Holter was applied the day before surgery and ran for up to 72 hours. The ICM was inserted approximately one month prior to surgery and removed one month after surgery.

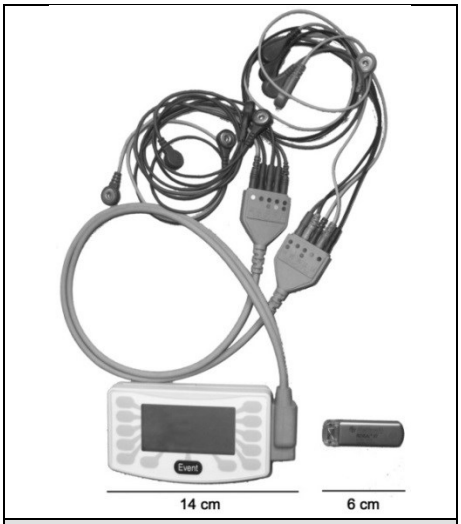


Figure 1. Devices used to detect perioperative arrhythmias
Holter monitor on the left, the ICM on the right.

Intermediate reports from the ICM were collected one day prior to surgery, 2 to 3 days after surgery and after one month. All Holter and ICM application and data collection was subject to the elective planning of the surgical procedures.

Study endpoints

The primary endpoint was any episode of new-onset arrhythmia, comprising AF or sustained ventricular tachycardia (VT), detected either by Holter or ICM. Definitions of the reported episodes of arrhythmia for this study are defined in Table 2. Secondary endpoints for the study were long-term survival and length of hospital stay. Possible adverse events in this study included ICM device rejection phenomena that participants could encounter, including local tissue reaction, device migration, infection and erosion through the skin.

Data analysis of all ICM and Holter recordings was performed by an independent senior cardiologist. An independent core lab (Cardialysis, Rotterdam, The Netherlands), blinded for the results, analyzed a sample of twenty ICM and twenty Holter recordings to verify the outcome.

Statistics

Baseline characteristics of participants are presented as medians with the interquartile range for continuous variables and categorical data are presented as counts and percentages. Use of monitoring, arrhythmia detection, risk factors, length of hospital stay and survival were compared between patients with and without new-onset arrhythmias. Considering the small number of patients in this pilot study, non-parametric tests were used to compare these two groups, e.g. Kruskal-Wallis tests for continuous data and Fisher's exact test tests for categorical data. Differences in mortality between patients with and without a detected event were calculated by a log-rank test, taking into account the length of follow-up after surgery. Agreement between the independent cardiologist and the core lab was verified using Cohen's Kappa. All statistical analyses were performed on a windows-based computer, using SPSS version 21 (IBM Corporation, Armonk, NY, USA).

Table 2. Definitions of reported arrhythmias

Type of arrhythmia	Definition
Atrial fibrillation (AF)	An episode of at least 30 seconds in which the RR intervals follow no repetitive pattern, but can be labeled as 'irregularly irregular'. Also no distinct P waves can be detected. Defined as paroxysmal AF (PAF) when episodes recur at least once, and last for no more than 7 days.
Sustained ventricular tachycardia (VT)	A sequence of ventricular beats, with a frequency higher than 100 beats per minute (bpm). Sustained implies a duration of more than 30 seconds.

RESULTS

Study population

A total of forty-nine patients had an ICM device implanted, of which one subsequently did not undergo surgery due to health issues. One patient suffered from surgical site infection, therefore the ICM was removed prior to surgery with no further clinical consequences. This resulted in an ICM implantation adverse event rate of 2.0% (1/49). Of the 47 remaining cases, Holter lead wires were disconnected in four patients upon arrival at the OR or at the ICU postoperatively, as they were judged to interfere with clinical ECG monitoring by tending physicians. No postoperative Holter data was recovered for these patients. All patients without postoperative data from either Holter or ICM monitoring were excluded from the analysis. Finally, one case was diagnosed with chronic AF on both ICM and Holter monitoring, despite normal ECG recordings at the outpatient clinic. Exclusion of this case resulted in 42 patients in the final analysis (Figure 2).

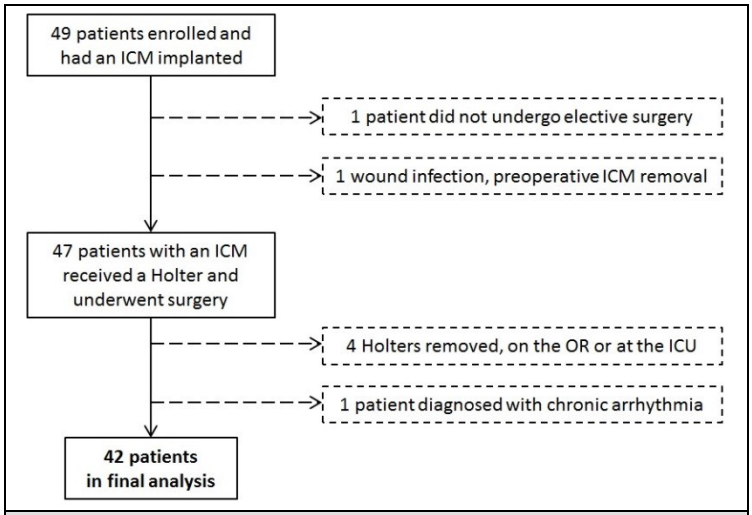


Figure 2. Study enrollment and drop-outs prior to final analysis
OR denotes operating room, ICU intensive care unit

The majority of subjects was male (85.7) and median age was 69 (interquartile range 61.7-74.8). A total of 14 patients (33.3%) underwent open aortic surgery, while 18 (42.9%) underwent endovascular aneurysm repair (EVAR) of an infrarenal aneurysm, and 10 patients (23.8%) underwent lower extremity revascularization. Medical history of the study population, as illustrated in Table 3, was comparable to any general vascular surgery population.

Table 3. Baseline characteristics

Variable	Total (n=42)
General statistics	
Male gender, n (%)	36 (85.7)
Age, years	69.0 (61.7 – 74.8)
Open abdominal aortic surgery, n (%)	14 (33.3)
Endovascular aneurysm repair, n (%)	18 (42.9)
Lower extremity revascularization, n (%)	10 (23.8)
Medical history	
Ischemic heart disease, n (%)	18 (42.9)
CHF, n (%)	3 (7.1)
Stroke, n (%)	4 (9.5)
Renal insufficiency, n (%)	8 (19.0)
Hypertension, n (%)	33 (18.6)
High cholesterol, n (%)	36 (85.7)
Diabetes, n (%)	8 (19.0)
COPD Gold 3-4, n (%)	3 (7.1)
BMI	26.3 (23.0 – 29.4)
Serum potassium (mmol/l)	4.5 (4.3 – 4.8)
Rhythm registration	
Holter recording, days	3 (3-3)
ICM recording, days	30 (30-30)

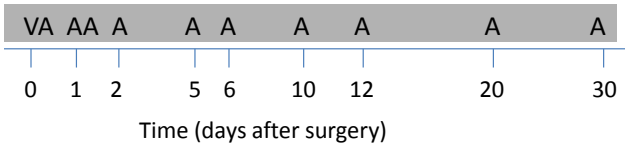
Note: CHF denotes congestive heart failure, COPD chronic obstructive pulmonary disease, ICM insertable cardiac monitor, BMI body mass index. Continuous values are presented as median and interquartile range.

New-onset arrhythmia detection

The total reported incidence of new-onset arrhythmias in the study was 11 (26.2%) with ICM monitoring, yet only 1 (2.4%) with Holter monitoring (Table 4). The median time of arrhythmia detection was 5 days (IQR 1-12) after surgery. The one arrhythmia both devices identified was an episode of sustained VT just hours after surgery, which lasted for well over a minute. This was accompanied by a lack of cardiac output, for which CPR was administered briefly, before restoration of sinus rhythm and cardiac output.

Table 4. New-onset arrhythmia detection of Holter and ICM over time

Device	Timeline of arrhythmia detection	Events, n (%)
Holter	V	1 (2.4)
ICM	VA AA A A A A A A A	11 (26.2)



A denotes atrial fibrillation, V sustained VT. Grey boxes display the intended length of recording by each device.

An additional 10 cases, all with paroxysmal AF, were identified only by the ICM, of which 6 occurred outside the 72-hour window of Holter monitoring.

There was an inter-observer agreement between the core-lab and the independent cardiologist regarding arrhythmia detection in nearly ninety-five percent of observations (Kappa: 0.88, p<0.001). The median CHA_2DS_2-VASc score of 10 patients with new-onset AF was 4.0 (IQR 2.5-4.25), with 8 out of 2 cases (80.0%) gathering a score of ≥2 on this risk index. Of these 8, three cases died shortly after surgery, respectively due to graft infection and shock (n=1), respiratory failure (n=1) and a myocardial infarction (n=1). Upon discharge of the remaining five cases, 3 received oral anticoagulants and 2 were only treated with aspirin.

Secondary endpoints

Possible risk factors associated with new-onset arrhythmias were not found to be significantly increased in the patients that suffered an event, compared to the control group (Table 5). A significant increase in length of hospital stay was associated with perioperative arrhythmias (median 18.0 days) in comparison with patients that had an event-free discharge (median 4.0 days; P=0.002). Also, a higher 3-year mortality rate was associated with perioperative arrhythmias during long-term follow-up (54.5% versus 6.5%, P=0.01).

Table 5. Comparison between patients with and without new-onset arrhythmia on ICM monitoring

Variable	New-onset arrhythmia (n=11)	No arrhythmia (n=31)	P value
General statistics			
Age, years	65.5 (62.6 – 74.7)	69.3 (61.7 – 74.9)	0.81
CHF, n (%)	1 (9.1)	2 (6.5)	1.0
Renal insufficiency, n (%)	4 (36.4)	4 (12.9)	0.17
Hypertension, n (%)	9 (81.8)	24 (77.4)	1.0
Serum potassium (mmol/l)	4.5 (4.4 – 4.7)	4.5 (4.2 – 4.8)	0.92
Secondary outcome			
Length of hospital stay, days	18.0 (6.0-37.0)	4.0 (2.0-7.0)	0.002
Survival, years	2.4 (0.1-4.3)	3.2 (2.3-4.0)	0.32
3-year mortality, n (%)	6 (54.5)	2 (6.5)	0.01

Continuous values are presented as median and interquartile range.

DISCUSSION

In this pilot study, the percentages of AF and sustained VT registered with Holter (2.4%) are similar to the historical estimate. However, the reported incidence of new-onset AF was over twenty-five percent using an ICM. The possibilities of an ICM to monitor continuously for a longer period was of direct influence on the number of arrhythmias detected in the perioperative period, as suggested in other studies.[24, 25] This could be of advantage to current methods, e.g. routine intermittent 12-lead ECGs or continuous surface electrocardiography during no more than a few days of ICU stay.[26-29]

Outside the field of vascular surgery, the increased diagnostic yield of the ICM for arrhythmia detection was already embraced earlier; for instance in neurology, among patients suffering from cryptogenic stroke.[30] In over two hundred patients randomized to receive an ICM, the detected incidence of AF was more than six times greater than in an equal sized group that was randomized to receive standard follow-up after cryptogenic stroke.[31] In cardiology, ICM implantation helped to identify almost twice as many patients with recurrent AF after trans-catheter ablation, when compared to regular follow-up and periodical 12-lead ECG screening.[32].

The large difference in arrhythmias detection in the current study is explained by the prolonged duration of ICM monitoring versus Holter monitoring, in part at least. However, even in the first 48-hours after surgery – the time-frame of postoperative Holter monitoring – the ICM registered three times more arrhythmias than the Holter. A possible explanation could be that body sweat, external manipulation and battery failure cause a Holter to detach, record interference, or terminate, impairing proper rhythm analysis.[33] Although this may be a weakness of the study, it is even more so an indication of the weakness of 12-lead surface cardiac monitoring. There are other, wireless alternatives that are not invasive, which also proved useful in arrhythmia detection in the first 14 days after implantation.[34]

Apart from a much higher reported incidence, the current study also suggest that patients suffering from paroxysmal AF not only have a longer hospital stay, but also have a shorter life expectancy. After identifying patients with new-onset AF, it is key to imbed a proper treatment strategy in clinical practice. This should include referral to a cardiologist to consider medical treatment of AF, as well as risk management for late thromboembolic adverse events.[35]

According to the 2010 Guidelines from the European Society of Cardiology on the treatment of (persistent or paroxysmal) AF, harboring one of these risk factors already merits treatment with aspirin, but preferably oral anticoagulant therapy (OAC).[35] When harboring two risk factors, e.g. a vascular surgery patient with hypertension or advanced age, it is strictly advised to start OAC upon detection of AF. The patients with new-onset arrhythmia in our study had a score of ≥2 in the large majority of cases, but not all received anticoagulant therapy at the time. Currently, no specific clinical data is

available on the health benefits of starting OAC in vascular surgery patients with at least one more CHA_2DS_2-VASc risk factor, suffering from a brief episode of paroxysmal AF. Future research is needed to develop a comprehensive treatment guideline for this particular patient population.

This is the first study to report the use of the ICM in vascular surgery patients without a history of cardiac arrhythmias. Results show that the incidence of new-onset paroxysmal AF is higher than generally believed. However, being able to identify these cases depends on their willingness to undergo ICM implantation prior to a vascular procedure. In the process of enrollment for this study, only a small proportion of patients were willing to undergo implantation of the ICM. This was the main factor in the slow enrollment of this pilot study, and could reduce future perspectives for this type of monitoring. With the recent introduction of an even smaller ICM, the Reveal LINQ™, the threshold for patients to undergo implantation of such a device will be lower, since implantation is easier and causes less morbidity.[36]

Eventhough this is a pilot study in which only a “proof of concept” was studied, it still has limitations such as the relatively small number of patients included. Second, slow enrollment could have introduced a selection bias. However, gold-standard Holter monitoring led to a similar incidence of new-onset arrhythmia as current literature, and baseline characteristics showed our population was exemplary for the general surgery population. Third, it remains unclear what the clinical significance is for paroxysmal AF, detected by an ICM. Although this pilot was not powered for it, detected arrhythmias (in post-analysis) were related to a longer hospital stay and a higher long-term mortality.

CONCLUSION

The true incidence of paroxysmal AF after major vascular surgery seems to be much higher than estimated with standard practice Holter monitoring, leaving most cases currently undetected. An insertable cardiac monitor, evaluating rhythm disturbances continuously for weeks or months after surgery, detects patients at risk for thromboembolic complications reliably, opening a new treatment window for these patients. Future research should be aimed at the optimal treatment strategy for this patient category.

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Technical Considerations

Blood thinners
Statins
Beta-blockers
Vitamin D status
New-onset arrhythmias

6

Carotid stent characteristics

Aortic stentgraft composition
Laparoscopic sac fenestration after EVAR
Need we intervene for type II endoleaks?

Published as:
"Radial force measurements in carotid stents: influence of stent design and length of the lesion"
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ABSTRACT

Purpose
To assess the differences in radial force of carotid stents, and to evaluate if the length of the lesion is influential to the measurements.

Materials and methods
Similar sized, tapered stents (length 30mm) of different make and models were used. The tapered nitinol Acculink®, Protégé® and Cristallo Ideale® carotid artery stents, and the straight, braided elgiloy carotid Wallstent® were compared. A measurement device was developed, consisting of three film loops along the stent body, connected to aluminium rods armed with copper strain gauges. Five stents of each type were deployed within a 3mm stenosis, in a long (26mm) and in a short (8mm) stenosis simulation.

Results
In the short stenosis simulation, the greatest radial force was seen in the Protégé, reaching 3.14±0.45 Newton, followed by the Cristallo Ideale (1.73±0.51 N), the Acculink (1.16±0.21 N) and the Wallstent (0.84±0.10 N)($P<0.001$). In the long stenosis simulation, peak radial force again was highest in the Protégé (1.67±0.37 N), but second was the Acculink (0.95±0.12 N) and third, the Wallstent (0.80±0.06 N). The Cristallo Ideale, in large contrast with a short stenosis, produced the least radial force (0.44±0.13 N) in a long stenosis simulation ($P= 0.001$).

Conclusions
Radial forces exerted by carotid stents vary significantly between various stent designs. Differences between stent types are dependent of the length of the stenosis. An understanding of radial force is necessary for a well-considered choice of stent type in the individual patient.

MANUSCRIPT

INTRODUCTION

Carotid angioplasty and stenting (CAS) is a frequent treatment modality for carotid artery stenosis.[1,2] The most important complication of CAS is stroke, due to emboli or hemodynamic depression (HD).[3-9] According to literature, several properties of the carotid stent and the delivery system play an important role in the final outcome.[10] The main concerns for procedural efficacy are trackability in straight or tortuous arteries, scaffolding of hard or soft plaques and achieving optimal patency. These individual stent properties have been investigated on many occasions, for better understanding and possible improvement of the technique.
Trackability was evaluated by comparing strut behaviour of open versus closed cell designs in a curved vessel model.[11] Additionally, the force needed for bending and the torsion angle were reported in another effort to compare trackability between open and closed stents.[12] Scaffolding properties and free cell area have been assumed to play a role in the embolic complications rate.[12] While open cell designs were observed to have a higher rate of emboli in one study, another study reported conflicting results, leaving room for debate.[13,14] Regarding achieved patency rates after CAS, there are numerous studies on the safety and efficacy with different types of carotid stents.[15,16] The difficulty in analyzing results from all these reports, is that plaque constitution is often not taken into account. Therefore, the results may be influenced by patient-related factors. In theory, patency rates are primarily ascribed to the radial force of carotid stents.
In this study, we aim to measure the radial force in three frequently used nitinol self-expanding stents and in one type of braided elgiloy stents, in both a short and a long stenosis. This can provide information for comparison, and support future decision-making in the choice of stent type in the individual patient.

METHODS

Stent types

In this comparative study we tested the nitinol Acculink® (Guidant Corporation, Santa Clara, CA, USA), Protégé® (EV3, Plymouth, MN, USA) and Cristallo Ideale® (Invatec, Frauenfeld, Switzerland) carotid artery stents, and the braided elgiloy carotid Wallstent® (Boston Scientific, Natick, MA, USA). Stents of all four types were distributed freely and without terms of agreement. The stent designs are shown in figure 1. The Acculink stent has an open cell design, with connecting struts aligned throughout the length of the stent. The Protégé stent has a cell design with many connecting struts at alternating locations on the stent, but is still regarded an open cell design. The Cristallo Ideale has few connecting struts on either end of the stent, but has a middle section where all struts are connected. This combination of open and closed cell design is called hybrid. The Wallstent has a closed cell design over the entire length of the stent. Another difference in design is that the Acculink and Cristallo Ideale have a gradual tapered shape over the length of the stent, while the Protégé has a bottleneck shape in

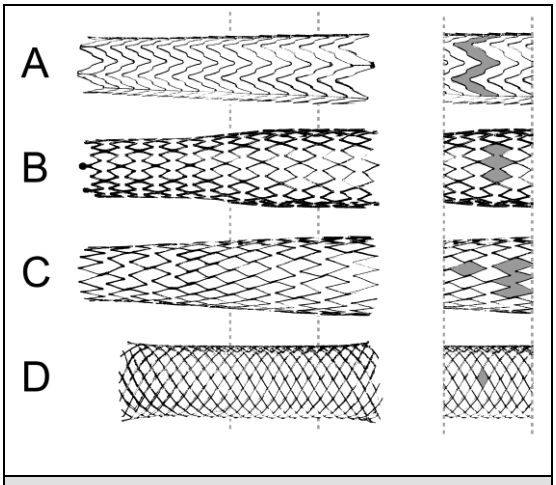

Figure 1. Stent shape and strut design of all four types.
(A) Acculink (B) Protégé (C) Cristallo Ideale (D) Wallstent. To the left, a full length picture of the stent shape, visualizing the differences in strut designs. Dotted lines limit the section that was re-printed to display free cell area on the right, marked in grey.

the middle section. The Wallstent is not tapered, but has a straight tube-like design, as can be seen on the left of figure 1.

For comparison purposes we chose to use stents of similar dimensions for all four types. The stent size according to manufacturer's data was 6-8x30mm for Protégé and Acculink stents, 6-9x30mm for Cristallo Ideale stents and 7x30mm for the Wallstent.

Measuring device

A testing method was used, similar to one previously reported by Duda et al.[17] The device is shown in figure 2. Basic elements of the device are three film sheets that are fixed on one end, looped around the distal, middle or proximal section of the stent and connected to aluminium rods on the other end. By changing the distance to the aluminium rods from the set-up, the diameter of the film loops could be adjusted. The films are made of biaxially-oriented polyethylene terephthalate, or BOPET, with a width of each film loop of 8mm. The radial (or expansive) force of the stent is translated to pulling strength of the film on the aluminium rods. Copper strain gauges, forming a half Wheatstone bridge, on either side of the rods measure the strain in the aluminium. Pre-tests with calibrated weights were executed to allow for conversion from measured currents to radial forces in Newtons.

Radial force measurement

Testing was performed in a heated booth, at a constant temperature of 36°C. We tested five stents of every type, from different batches. Due to the obvious differences in stent design, blinding was not possible. Each stent was deployed inside the loops at a diameter of 3mm, the most common diameter of endovascular balloons used in our clinic for predilatation. This is a short procedure prior to carotid stenting, where a high-grade stenosis is widened slightly by balloon-dilatation, so that the delivery device of the carotid stent can safely pass the lesion. Generally, 3mm is a standard diameter through which most delivery devices can pass. The diameter of the loops was enlarged to full expansion on all three sections, gradually deploying the stent inside the device to

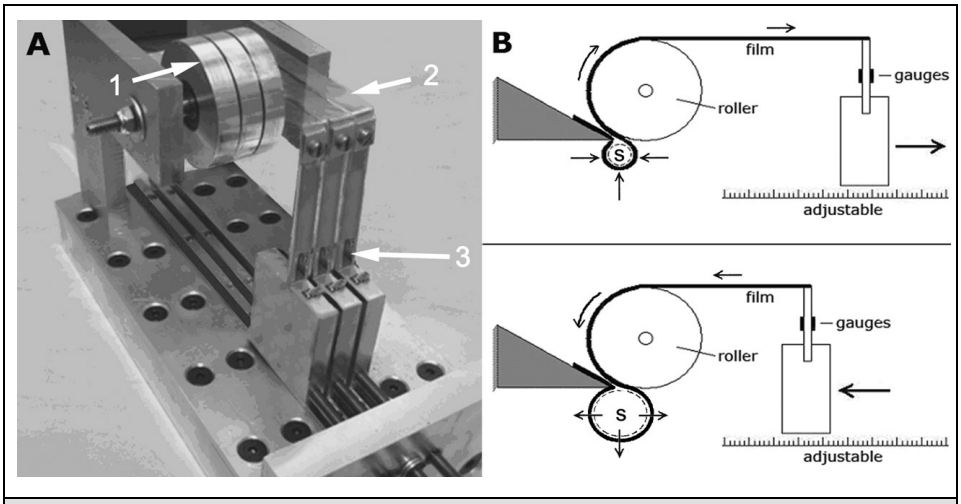

Figure 2. Measuring device.
(A) Photo of measuring device with three separate rollers (1), film loops (2) and strain gauges (3).
(B) schematic lateral view of the measuring device. By adjusting the position of the gauges the diameter of the stent (s) could be reduced (top) or enlarged (bottom). Radial force of stent is translated to the gauges by film.

prevent displacement of the stent due to shortening. Once satisfied with stent placement inside the three loops, with the middle section of the stent located inside the middle film loop, simulations started.
For a long (26mm) stenosis, just shorter than the manufacturer's data on stent length, the diameter of all three loops was adjusted to 3mm and then gradually and simultaneously increased with increments of a 1mm, up to full expansion. The sum of radial force within all three loops was measured and tabulated. For a short (8mm) stenosis, located in the center of the stent position, only the middle loop was narrowed. Subsequently, radial force was only measured in the middle loop during the simulation of a short stenosis. For steady fixation, both outer loops were adjusted to fit the fully expanded ends of the stent, tapered in all but the Wallstent. A short stenosis was then simulated by adjusting the middle loop to a diameter of 3mm, as illustrated in figure 3. The diameter of the loop was then increased with increments of 1mm, up to full deployment. Measurements of the radial force were performed on each interval. We repeated this procedure 3 times for each stent, treating all measurements as individual results.

Statistics
Results were analysed using non-parametric tests. To compare all stent types at different diameters, the Kruskal-Wallis test was used. Peak radial force differences between stent types were then separately analyzed, using the Mann-Whitney test. Statistical differences with a p-value below 0.05 were considered significant. All analyses were performed using the Statistical Package for Social Sciences (version 15; SPSS Inc., Chicago, IL, USA).

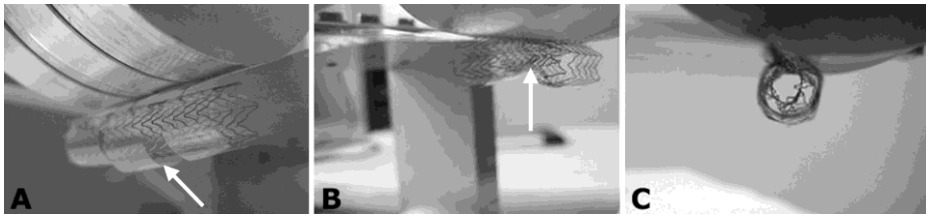

Figure 3. Stent positioning in measuring device.
(A) Acculink stent placed inside three film loops, middle loop oversized (arrow).
(B) Middle loop stenosed to 3mm (arrow), outer loops at 6mm and 8mm, respectively.
(C) luminal view of stent inside stenosis.

RESULTS

Stent placement within the device was successful in all cases. No stents showed failure or manufacturing flaws. The radial force of the stents was measured at diameters ranging from 3-6 mm and compared for all four stent types (Table 1). In the short stenosis simulation, the greatest radial force was seen in the Protégé, reaching 3.14±0.45 Newton, followed by the Cristallo Ideale (1.73±0.51 N), the Acculink (1.16±0.21 N) and the Wallstent (0.84±0.10 N)(P<0.001). At increasing stent diameters the radial force stepwise decreased in all four stent types. Although the radial force in the Protégé decreased most rapidly, its residual radial force remained higher than all other stent types up to a diameter of 5mm. With all stent diameters at 6mm, the residual radial force in the acculink was the highest of the four types.

Table 1. Radial forces in a short and long stenosis at different diameters.

Radial force, N	Protégé	Cristallo	Acculink	Wallstent	p-value
Short stenosis (8mm)					
Ø 3.0 mm	3.10±0.45	1.73±0.51	1.16±0.21	0.84±0.10	<0.001
Ø 4.0 mm	0.95±0.13	0.50±0.08	0.40±0.05	0.29±0.03	<0.001
Ø 5.0 mm	0.34±0.10	0.28±0.10	0.26±0.04	0.15±0.02	<0.001
Ø 6.0 mm	0.06±0.04	0.12±0.04	0.16±0.04	-	<0.001
Long stenosis (26mm)					
Ø 3.0 mm	1.67±0.37	0.44±0.13	0.95±0.12	0.80±0.06	0.001
Ø 4.0 mm	0.82±0.36	0.26±0.11	0.74±0.13	0.55±0.09	0.013
Ø 5.0 mm	0.39±0.25	0.18±0.08	0.63±0.11	0.28±0.12	0.019
Ø 6.0 mm	0.10±0.11	0.10±0.07	0.51±0.10	-	0.011

Continuous data are represented as means (in Newtons) ± standard deviation
P-values are calculated with the Kruskal-Wallis test
Ø: outer diameter

In the long stenosis simulation, peak radial force again was highest in the Protégé (1.67±0.37 N), but second was the Acculink (0.95±0.12 N) and third, the Wallstent (0.80±0.06 N). The Cristallo Ideale, in large contrast with a short stenosis, produced the least radial force (0.44±0.13 N) in the long stenosis simulation (P = 0.001). Differences between all four stent types were highly significant at all diameters, both in a short (8mm) and a long (26mm) stenosis, according to Kruskal-Wallis statistics.

Separate analyses of the radial force differences between each two stent types were then performed. Differences between any two stents were found to be significant, according to Mann-Whitney U statistics (Figure 4).

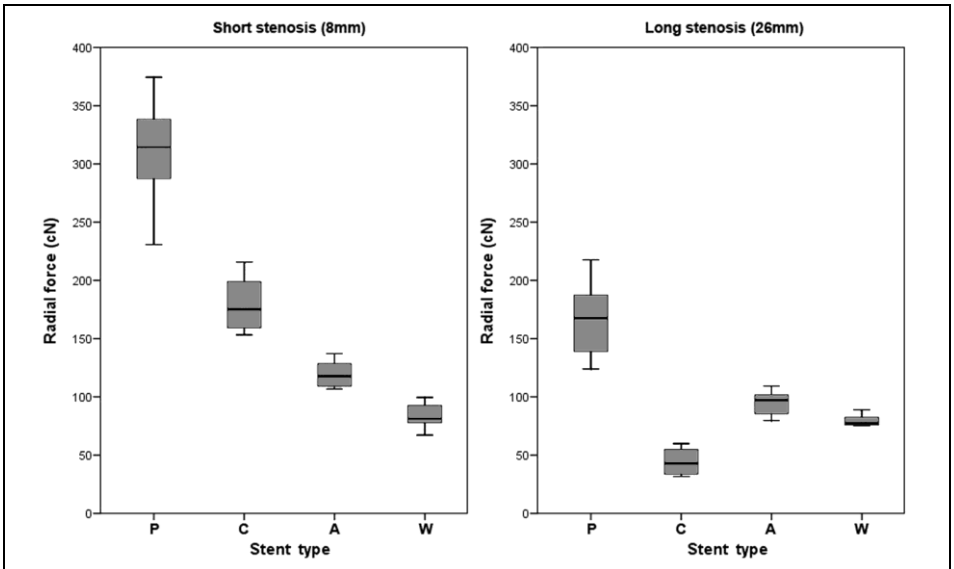

Figure 4. Peak radial force of all stent types in two stenosis simulations.
Boxes display the mean and interquartile range, whiskers indicate the range.
(P) Protégé, (C) Cristallo Ideale (A) Acculink, (W) Wallstent.

DISCUSSION

In the current study, a method was presented for comparative radial force measurements in different types of carotid stents, in both a short and a long stenosis. Significant differences were observed between stent types, and also a clear influence of lesion length was noticeable on the total radial force, exerted by the stents.

Radial force measurements have been previously reported using a dual plate compression test.[18] However, this is more a measurement of force during deformity rather than reduced lumen diameters. A stenosis results in a restriction of the luminal volume. However, during plate compression, the diameter is reduced in the vertical direction, but expands in the horizontal direction, much like a balloon that is

compressed. The volume is not altered, and the reactive force of the stent during plate compression is quite different from a test where the actual luminal volume is reduced. A circular compression, loop-strap or hoop strength test was used in previous reports on carotid stents, biliary stents and stents used in stenosed native aortic valves.[12,19,20]

In the current report, we set out to compare the radial force of three different nitinol stents and the elgiloy Wallstent. Our results clearly show that all tested nitinol stents produce a higher radial force than the elgiloy Wallstent. The Protégé generated a radial force far greater than all others, in both a short and a long stenosis simulation. The hybrid design Cristallo Ideale produces a large radial force in a short stenosis, compared to the Acculink and the Wallstent, but loses the majority of its expansive capacity in a longer stenosis. It produces less radial force than any other stent type measured in a long stenosis in the current study. This dependency of lesion length in the Cristallo Ideale is probably related to the hybrid design of the stent. The middle section (closed cell) and the outer sections (open cell) are of different compostion, which may cause a discrepancy in the performance in a stenosis that is limited to the middle section and a full length stenosis. Another interesting finding was the great difference between two open cell design stents. Of the three nitinol stents we tested, the open cell Protégé exerted the highest radial force, and the open cell Acculink the lowest. In clinical literature, results with open or closed cell designs are often clustered as a group. Our results show that this is erroneous, and clinical results with one stent should never be generalized for all others from the same – open or closed cell – group.

In the individual stent selection, radial force should be taken into account. Reading into Bosiers et al., one could argue that a high degree of scaffolding - e.g. in a closed cell design - is most important when the plaque is soft, or atheromatous, and a stent with a large free cell area can not sufficiently support this tissue to keep the lumen patent.[13] We propose that in a more calcified plaque support at only a few sites - e.g. an open cell design - may possibly suffice in scaffolding the plaque, but a larger radial force would be necessary to achieve patency in such a hardened plaque.

There are certain limitations to this study. First, we only included five stents of each type in our tests; second, stent placement inside the device was performed manually, leaving room for human error; third, friction between the film loops and the stent might be of influence on the results. However, friction between the vessel wall, plaque and different stent designs will also occur in vivo. Given the comparative purpose of this study, not correcting the results for possible friction was therefore considered acceptable. Considering the use of high quality materials, such as the non-expansive BOPET film and validated copper strain gauges, this study is regarded as easily reproducible, in spite of the above mentioned limitations. Finally, the stenosis model in this study was straight and static. In vivo, carotid stents would experience vessel curvature, vascular smooth muscle actions and a much more dynamic situation. Although this makes extrapolation to a clinical setting difficult, the reported results are clear and undiluted by any of these confounders.

CONCLUSIONS

Radial forces exerted by carotid stents vary significantly between various stent designs. Clinical results of CAS may be dependent of a number of stent specific factors, including the radial force exerted upon the arterial lesion and the carotid wall. Future studies should investigate the relationship between plaque constitution, radial force and patency rates.

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Blood thinners
Statins
Beta-blockers
Vitamin D status
New-onset arrhythmias
Carotid stent characteristics

7

Aortic stentgraft composition

Laparoscopic sac fenestration after EVAR
Need we intervene for type II endoleaks?

Published as:
"Stentgraft composition plays a material role in the post-implantation syndrome"
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ABSTRACT

Objective
In patients undergoing EVAR the post-implantation syndrome (PIS), comprising fever and inflammation, occurs frequently. The cause of PIS is unclear, but graft composition and acute thrombus formation may play a role. The objective of this study was to evaluate these possible causes of the inflammatory response after endovascular aneurysm repair (EVAR).

Methods
One-hundred and forty-nine patients undergoing elective EVAR were included. Implanted stentgrafts differed mainly in the type of fabric used; either woven polyester (n=82) or expanded polytetrafluorethylene (ePTFE, n=67). Tympanic temperature and CRP were assessed daily during hospitalization. PIS was defined as the composite of a body temperature of ≥38 degrees Celcius coinciding with C-reactive protein (CRP) >10 mg/L. Besides graft composition, the size of the grafts and the volume of new-onset thrombus were calculated using dedicated software and results were correlated to PIS.

Results
Implantation of grafts made of polyester was associated with higher postoperative temperature (P<0.001), CRP levels (P<0.001) and incidence of PIS (56.1% versus 17.9%; P<0.001), compared to ePFTE. Following multivariate analysis, woven polyester stentgrafts were independently associated with an increased risk of PIS (Hazard ratio 5.6, 95%CI 1.6-19.4, P=0.007). Demographics, amount of graft material implanted or new-onset thrombus had no association with PIS.

Conclusions
The composition of stentgrafts may play a material role in the incidence of post-implantation syndrome in patients undergoing endovascular aneurysm repair. Implantation of stentgrafts based on woven polyester was independently associated with a stronger inflammatory response.

MANUSCRIPT

INTRODUCTION

In patients undergoing endovascular aneurysm repair (EVAR) for an abdominal aortic aneurysm (AAA), an acute phase inflammatory response may occur shortly after implantation.[1-4] This so-called post-implantation syndrome (PIS) is defined as fever coinciding with a rise in inflammatory markers.[5-9] PIS is thought to be transient and harmless, but its true significance is unknown and no clear guidelines exist for management.]10] Importantly, the cause of the inflammatory response remains unclear. Proposed mechanisms are related to the introduction of the different components of the stentgraft[11,12] or the amount of mural thrombus within the aneurysm.[13]

Initial results of endovascular repair with the woven polyester Talent Abdominal Stent Graft (Medtronic Inc., Minneapolis, MN, USA) showed a high incidence of fever and a systemic inflammatory response as the most common serious complication.[14] Based on clinical experience, PIS seems to be even more frequent since the recent introduction of the woven polyester Endurant Abdominal Stent Graft (Medtronic). It is not uncommon for patients to suffer from fatigue and elevated body temperatures, sometimes for weeks after the procedure.

For optimal management of patients with post-implantation fever and rise in inflammatory markers, and to contribute to future stent-graft design, a better understanding of the cause of PIS is necessary. This retrospective study investigates the role of graft material on the post-implantation syndrome by comparing two types of graft material, woven polyester and ePTFE. Besides the type of material, the quantity of implanted graft and the association of new-onset thrombus with the inflammatory response are investigated.

METHODS

Study population

The study population was derived from a cohort of consecutive patients undergoing an EVAR procedure between 2004 and 2010 at the Erasmus University Medical Center, Rotterdam, The Netherlands. Exclusion criteria were the concurrent use of different graft materials on the same patient, hybrid procedures combining endovascular with open surgical treatment, urgent EVAR and recent surgery or major trauma within 30 days of the procedure. Patients with missing data on temperature or C-reactive protein (CRP) were also excluded, as were patients who suffered a postoperative complication that had an effect on inflammatory markers, including urinary tract infections, pneumonia and haematomas (Figure 1).

Baseline characteristics comprised of gender, age and all traditional cardiac risk factors from the Revised Cardiac Risk (RCR) index[15], as well as the incidence of chronic obstructive pulmonary disease (COPD), smoking and hypercholesterolemia. Additionally, the use of medication with known anti-inflammatory or anti-pyretic effects such as aspirin, statins and beta-blockers, was recorded.

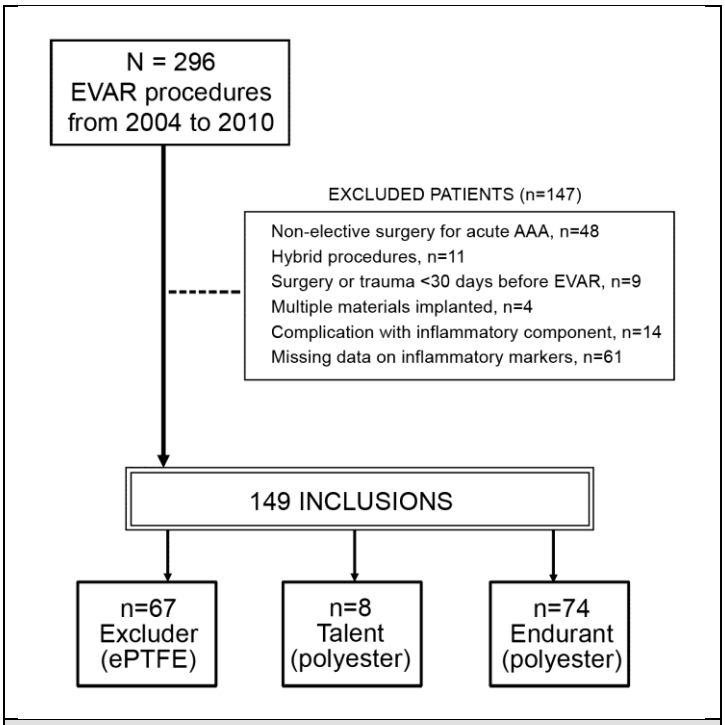

Figure1. Flowchart of patient inclusion

According to hospital protocol, all patients underwent an endovascular procedure with prophylactic antibiotics in the form of 1 gram of cefazolin 30 minutes prior to incision, and 5000 units of heparin prior to introduction of the stent graft deployment system. Additionally, low-molecular weight heparin was administered in all surgical patients during hospital admission (2500 IU dalteparin daily in all patients, 5000 IU daily in those with a body weight over 80 kg). Type of anesthesia was selected at the discretion of the surgical team. The study was conducted according to the guidelines provided by the Institutional Review Board.

Definition of endpoints

The primary endpoint of the study was the occurrence of PIS shortly after EVAR. PIS was defined as fever coinciding with an elevated serum CRP level. Fever was defined as a tympanic temperature of ≥38.0 degrees Celsius (˚C), and the upper level of normal for CRP was 10 mg/L in our institutional laboratory. Tympanic temperature and serum CRP levels were assessed each morning, starting one day prior to EVAR. Subsequent measurements were performed on the day of EVAR, and then daily up to 4 days following implantation. As mentioned, patients suffering from non-graft-related complications associated with inflammation were excluded from the study, including patients with reported postoperative wound infections, pneumonia and infections of the urinary tract.

Endograft composition

To evaluate the role of the graft component of endovascular aortic devices on the occurrence of PIS, enrolled patients were divided into two groups: in the first group the graft composition was expanded polytetrafluoroethylene (ePTFE), in the second group both devices were composed of a woven polyester graft. The first group comprised patients exclusively treated with the low-permeability Excluder AAA Endoprosthesis (W.L. Gore & Associates, Flagstaff, AZ, USA). The second group was composed of patients treated with the Talent Abdominal Stent Graft or the Endurant Abdominal Stent Graft (both Medtronic). All used stentgrafts were bifurcated, modular devices with a nitinol exoskeleton. An important difference between the two groups was that the low-permeability Excluder was available since late 2004, while the majority of woven polyester grafts were Endurant, which was first used in our hospital in 2008.

Other EVAR-related causes of PIS

Additional to the type of graft material, the total quantity of implanted material may be of importance, as it may be possible that a certain type of graft is simply larger or more extensions are used. As a marker for size, the volume inside each graft was measured on contrast-enhanced computed tomographic angiography (CTA) using dedicated post-analysis software with central lumen line reconstructions (3mensio Vascular software, 3mensio Medical Imaging BV, Bilthoven, The Netherlands). Volume measurements were done semi-automatically, according to a standard protocol as described earlier.[16,17]

Finally, the amount of new-onset thrombus – filling the excluded aneurysm sac immediately after EVAR – was measured using the same dedicated software by calculating luminal volume prior to EVAR and comparing this with the postoperative volume measurements (Figure 2). The difference between the two measurements represents the excluded sac volume, discarding any chronic mural thrombus already present before the procedure. For both these measurements, CTA prior to and/or after EVAR are a necessity, thus excluding patients without available CTAs from these sub-analyses.

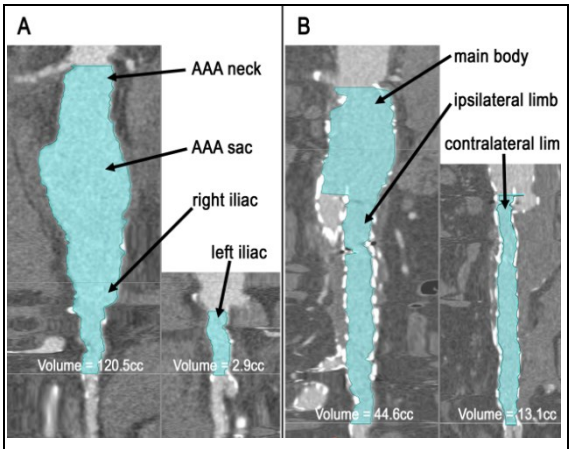

Figure 2. Luminal volume calculations before and after EVAR
An example of segmented aorto-iliac luminal volume measurements before (Panel A) and after (Panel B) endovascular repair using dedicated software. The difference in luminal volume is used as a quantitative measure for new-onset thrombus after EVAR.

Statistical analysis

All baseline characteristics and medication use were tabulated, as well as temperatures and CRP levels. Continuous variables were presented as means±SD or, in case of a non-Gaussian distribution, as medians and interquartile range [IQR], and compared with Student's T-test or Mann-Whitney U statistics, respectively. Dichotomous variables were presented as counts and percentages, and compared between groups using Pearson's chi-square statistics. The maximum body temperature and CRP level from the first four days after the procedure was compared to the day prior to surgery. The changes in body temperature were compared for the two types of graft material using Student's T-test, and changes in CRP were compared by Mann-Whitney U statistics. To test the association of graft size and new-onset thrombus with the postoperative rise in temperature and CRP, Pearson's and Spearman's correlation coefficients were calculated in the total population and within each group of graft material. Accounting for the historical difference between groups, we calculated the conditional probability of receiving a woven polyester graft based on baseline characteristics using propensity score analysis.

Propensity scores were generated using logistic regression with graft material as the dependent variable. Variables included to generate the propensity scores were all those presented as group descriptive in Table 1, complemented by the type of anaesthesia. To evaluate the association of graft material with PIS, a propensity adjusted binary logistic regression analysis was performed, further correcting for statin use, type of anesthesia, new-onset thrombus and graft size. Hazard ratios and 95% confidence intervals (CIs) were presented. All statistical tests were 2-sided, and considered statistically significant when the P-value was <.05. All analyses were performed using PASW statistics 17 for Windows (SPSS Inc., Chicago, Illinois).

RESULTS

A total of 8 Talent, 74 Endurant and 67 Excluder stentgrafts were included in the study. This amounts to a study population of 149 patients, divided in woven polyester (n=82) and ePTFE (n=67) grafts. Patients were predominantly male (87.9%) and had a mean age of 72.6±7.5 years at the time of surgery. In terms of baseline characteristics, traditional cardiac risk factors were equally distributed among groups (Table I). The preoperative AAA diameter was 59.8±11.5 mm, without significant difference between the two groups.

When compared to the ePTFE group, patients in the woven polyester group had a higher BMI (26.6±4.8 versus 25.1±3.2, P=0.026) and were more frequently medicated with statins (79.3% versus 64.2%, P=0.040) Also, A higher proportion patients in the woven polyester group received general anesthesia (73.2% versus 35.8%, P<0.001). Besides general anesthesia (n=84), other types of anesthesia used were spinal (n=33), local (n=24) or a combination (n=8).

Table 1. Baseline characteristics, medication use and risk profile by graft material

Baseline characteristics	Woven polyester (n=82)	ePTFE (n=67)	P-value
AAA diameter, mean (mm) ± SD	58.4 ± 11.0	61.1 ± 11.9	.22
Age, mean (years) ± SD	72.8 ± 7.2	72.4 ± 7.9	.75
Male gender, n (%)	71 (86.6)	60 (89.6)	.58
Ischemic heart disease, n (%)	32 (39.0)	34 (50.7)	.15
Diabetes mellitus, n (%)	14 (17.1)	10 (14.9)	.72
Renal dysfunction, n (%)	15 (18.3)	9 (13.4)	.42
Cerebrovascular disease, n (%)	7 (8.5)	10 (14.9)	.22
CHF, n (%)	5 (6.1)	8 (11.9)	.21
COPD, n (%)	5 (6.1)	19 (28.4)	<.001
Hypercholesterolemia, n (%)	23 (28.0)	21 (31.3)	.66
Body mass index, mean (kg/m^2) ± SD	26.6 ± 4.8	25.1 ± 3.2	.026
Creatinine, mean (umol/L) ± SD	102.1 ± 38.4	97.3 ± 32.2	.42
Smoking, n (%)	20 (24.4)	26 (38.8)	.058
Medication use			
Aspirin, n (%)	49 (59.8)	34 (50.7)	.27
Statin, n (%)	65 (79.3)	43 (64.2)	.040
Beta-blocker, n (%)	71 (86.6)	59 (88.1)	.79

ePTFE denotes expanded polytetrafluoroethylene, SD standard deviation,
CHF congestive heart failure and COPD chronic obstructive pulmonary disease

Table 2. Inflammatory markers before and after surgery by graft material

	Woven polyester (n=82)	ePTFE (n=67)	P-value
Temperature (°C)			
Prior to surgery, mean ± SD	36.6 ± 0.4	36.7 ± 0.5	.15
Post-operative, mean ± SD	38.2 ± 0.7	37.6 ± 0.7	<.001
Difference, mean ± SD	1.6 ± 0.7	0.9 ± 0.8	<.001
C-reactive protein (mg/L)			
Prior to surgery, median [IQR]	5.0 [2.0 – 8.0]	3.2 [2.0 – 8.0]	.30
Post-operative, median [IQR]	164.0 [87.0 – 201.0]	49.0 [20.0 – 104.0]	<.001
Difference, median [IQR]	154.8 [82.6 – 198.5]	38.0 [13.7 – 94.0]	<.001

Postoperative values presented are the maximum for days 1 to 4 after the procedure

Graft type and PIS

The mean length of stay was 4.4 days (SD 4.7 days). The incidence of PIS was 46 (56.1%) for the woven polyester group, compared to 12 (17.9%) in the ePTFE group (P<.001). PIS occurred almost exclusively in the first three days after woven polyester implantation and the first two days after ePTFE implantation.

Broken down to individual inflammatory markers, a similar trend was observed. On the morning prior to surgery, temperatures were not significantly different between the woven polyester and ePTFE groups (36.6±0.6°C versus 36.7±0.5 °C, P=.15), nor were CRP levels (5.0 [2.0-8.0] versus 3.2 [2.0-8.0], P=.30) (Table 2).

In the four days after EVAR, both body temperature and CRP levels rose significantly higher in the woven polyester group, compared to the ePTFE group (Figure 3). When calculating the maximum rise in body temperature and CRP compared to baseline for both groups, patients that received a woven polyester graft suffered a higher rise in body temperature (+1.6 versus +0.9 °C, P<.001) and CRP levels (+154.8 versus +38.0 mg/L, P<.001) compared to patients that received an ePTFE graft (Table 2).

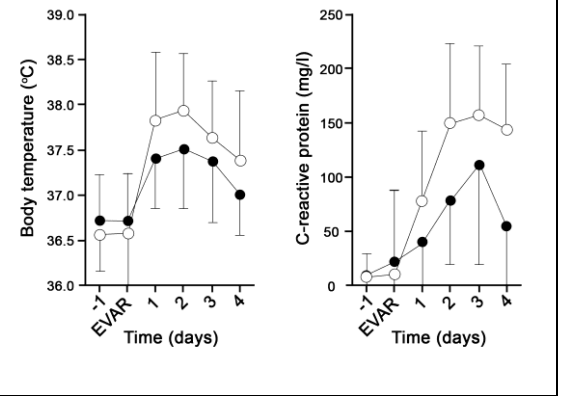

Figure 3. Day by day inflammatory response after stentgraft implantation

Graphs display the mean±SD for body temperature and serum C-reactive protein in relation to implantation of a stentgraft made of woven polyester (open circles) or ePTFE (closed circles).

Subanalyses of graft size and new-onset thrombus

A total of 72 patients from the woven polyester group (87.8%) and 64 from the ePTFE group (95.5%) had available imaging for in-graft volume measurements. The mean in-graft volume of the implanted grafts was 44.6±13.7 cc. The woven polyester group had a larger in-graft volume than the ePTFE group (50.8±13.3 cc versus 37.7±10.6 cc, P<.001). In general, this marker for graft size showed a statistical correlation to the postoperative rise in temperature (Pearson's rho 0.29, P=.001) and CRP (Spearman's rho 0.26, P=.003). However, after stratifying for type of material, these correlations were no longer significant.

A total of 63 patients from the woven polyester group (76.8%) and 46 from the ePTFE group (68.7%) had available imaging for new-onset thrombus measurements. The mean volume of new-onset thrombus was 51.3±45.8 ml, without significant differences between woven polyester and ePTFE groups (50.8±45.1 ml versus 51.7±46.6 ml, P=.91). Subsequent analyses showed no significant correlation between new-onset thrombus and the rise in temperature (P=.08) or CRP (P=.17).

Multivariable risk model for PIS

As mentioned, several possible confounders of the inflammatory status of the patients were found to be significantly different between groups. Therefore, differences in baseline characteristics were addressed in a propensity score analysis. The association of graft material with PIS was evaluated in a propensity adjusted model, additionally corrected for differences in statin use, graft size and new-onset thrombus. In this analysis the use of woven polyester remained the only significant factor associated with an increased risk of developing post-implantation syndrome (hazard ratio 5.58, 95% confidence interval 1.60-19.42, P=.007)(Figure 4).

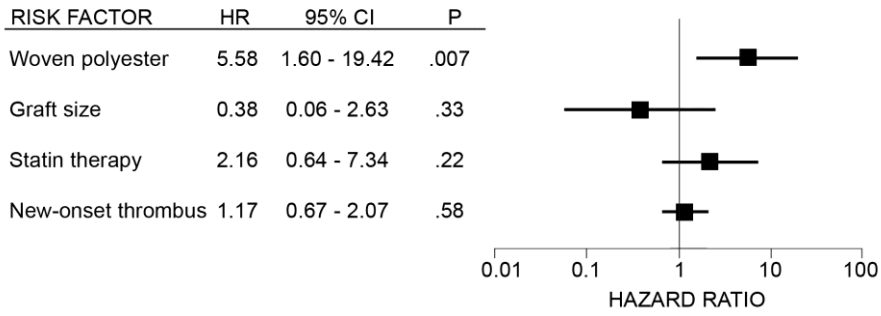

Figure 4. Multivariable associations with PIS

Hazard ratios for individual variables in the propensity adjusted multivariable analysis, illustrating that graft composition was independently associated with post-implantation syndrome.

HR denotes hazard ratio, CI denotes confidence interval. The natural logarithms of graft size and new-onset thrombus were used.

DISCUSSION

With the growing application of EVAR and resolution of many significant issues related to this treatment option, particular details and previously overlooked problems are becoming more evident for physicians and warrant further analysis. PIS is a clear entity that affects a significant number of patients, but the mechanisms behind this phenomenon have been scarcely investigated. The current study shows that the graft type plays a primordial role in the development of an acute phase inflammatory response after EVAR. The implantation of stentgrafts that include woven polyester in their composition is associated with significant changes in body temperature and serum CRP, compared to those that are made of ePTFE.

The current results suggest that ePTFE has less pro-inflammatory properties than woven polyester following endovascular implantation in humans. This is supported by an in vitro study by Swartbol et al., comparing the response of human white blood cells in vitro upon incubation with vascular grafts of ePTFE or woven polyester.[18] The authors

found that woven polyester triggered a significantly larger release of pro-inflammatory markers than ePTFE.
The differences in the incidence of fever between patients who receive stentgrafts of woven polyester or ePTFE are previously described in small numbers.[12] Gerasmidis et al. described a total of 22 consecutive EVAR patients that received a woven polyester graft (n=12) or ePTFE (n=10), and compared the incidence of fever and the post-procedural changes in several biomarkers. Although the study lacked the power to observe large difference in laboratory measurements, fever was observed more frequently in the woven polyester group (3/12 patients versus 1/10).

Another suggested origin for PIS is the excluded aneurysm sac filling with new-onset thrombus, a process that may involve various pro-inflammatory cytokines.[13] The current study is the first to address this hypothesis in a quantitative manner, using dedicated software to calculate the excluded volume after EVAR. Data was not available for every patient in this study, and the amount of graft material was estimated using true, post-implantation graft volumes. Although both these limitations may have influenced the results, the measured volumes of excluded sac content in this study showed no correlation to PIS.

There are other differences between stentgrafts, unrelated to graft material, which may also influence the proposed foreign body reaction. All stentgrafts in this study have an exoskeleton made of nitinol, a nickel-titanium alloy. Unlike the others, the Excluder features an additional outer layer of ePTFE covering the alloy, while in the Endurant and Talent the metal and fabric are adjoined by stitches.[19-21] In addition, these two latter feature a bare top stent, further increasing the amount of nitinol directly exposed to the circulation. Apart from quantity, the precise balance between nickel and titanium or even the cutting and polishing may differ between manufacturers, potentially affecting the antigenic properties of the nitinol.

Since the introduction of nitinol for medical application, it has been widely used in coronary and peripheral arterial "bare-metal" stents.[22] No inflammatory response is reported in these applications, despite frequent treatment of multiple and lengthy lesions, requiring large quantities of the material. Furthermore, the chemical production of nitinol prevents breakdown and special coating reduces nickel exposure.[23] It is therefore unlikely that differences in the application of nitinol between stentgrafts may influence the post-implantation syndrome. We cannot, however, completely exclude this factor using our data. The stitching used in Talent and Endurant devices can also not be ruled out as a possible confounder for the inflammatory response after implantation.

The hypothesis that endothelial damage, due to active fixation from the top stent, plays a role may be dismissed by the current study. Evidently, if endothelial aggression due to penetration of foreign material such as hooks or barbs was key, the inflammatory response would be independent of graft type, since both the Excluder and the Edurant have active proximal fixation.

A final difference between stentgrafts that could have played a confounding role in the incidence of PIS is the different delivery devices they come with. It is quite conceivable that a different method of graft delivery might affect either the rate of embolism, or the duration of lower extremity ischemia, both of which stimulate an inflammatory response. Although we cannot provide data to refute these arguments, it seems unlikely that the delivery system, with its differences but also with many similarities, could explain the observed difference.

Certain limitations related to our study warrant consideration. Firstly, a proportion of eligible patients had missing information on inflammatory markers, excluding them from this study. Although this is regrettable, such a limitation is inevitable in a retrospective study. To assess if a selection bias occurred, a comparison of baseline characteristics was performed between included patients and excluded patients. Demographics were not significantly different in any parameter, rejecting the possibility of selection bias in that regard. Coincidently, this study was not a randomized trial. The choice of graft was not random, but based on individual parameters. This could have caused a selection bias, although factors that influence the choice of graft generally focus on anatomical suitability, and information on the inflammatory response was not available at the time. Additionally, due to chronological differences between groups, baseline differences were observed in possible co-factors such as smoking, but also the use of statins and general anesthesia. These differences mostly reflect the introduction of guidelines on perioperative treatment and subsequent improvement of risk reduction strategies, since most woven polyester grafts were implanted in recent years.[24] Especially, statin therapy has been known to attenuate perioperative inflammation, if administered prior to surgery.[25-28] However, as statin therapy was more frequent in the woven polyester group it could therefore be expected to have attenuated rather than exaggerated the inflammatory response in this group, compared to ePTFE. To address historical differences and non-randomized nature of the study, we performed a propensity adjusted analysis with the addition of statin use as separate covariate, which identified the use of woven polyester as a independent predictor of PIS, compared to ePTFE. Another limitation is that PIS was only measured during hospital stay. Theoretically, PIS could have occurred in patients that were discharged rapidly (i.e. in the first 2-3 days), but patients are generally discharged when inflammation is decreasing and body temperatures are normal. It is therefore not expected that we missed many PIS cases. Lastly, for the CTA-based subanalyses data was missing, due to patient dependent imaging protocols. However, the available data still represents the largest cohort ever published on the subject, and possible selection bias was not associated with the inflammatory endpoints of the study.

CONCLUSIONS

The type of fabric used in manufacturing endovascular stent grafts may play a material role in the development of post-implantation syndrome, measured by an increase in post-procedural body temperature and serum C-reactive protein. According to our findings, implantation of ePTFE-based endografts results in a less pronounced inflammatory response, in comparison to those based on woven polyester.

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Blood thinners
Statins
Beta-blockers
Vitamin D status
New-onset arrhythmias
Carotid stent characteristics
Aortic stentgraft composition

8

Laparoscopic sac fenestration after EVAR

Need we intervene for type II endoleaks?

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ABSTRACT

Objectives:
Sac growth after endovascular aneurysm repair (EVAR) is an important finding, which may influence prognosis. In case of a type II endoleak or endotension, clipping of side-branches and subsequent sac fenestration has been presented as a therapeutic alternative. The long-term clinical efficacy of this procedure is unknown.

Methods:
The study included eight patients who underwent laparoscopic aortic collateral clipping and sac fenestration for enlarging aneurysms following EVAR. Secondary interventions and clinical outcome were retrieved from hospital records. Sac behavior was evaluated measuring volumes on periodical CTA imaging using dedicated software.

Results:
Follow-up had a median length of 6.6 (range 0.6-8.6) years. During this time, only three patients successfully achieved durable aneurysm shrinkage (n=2) or stability (n=1). The remaining patients suffered persistent (n=2) or recurrent sac growth (n=3), all regarded as failure of fenestration. A total of six additional interventions were performed, comprising open conversion (n=2), relining (n=1) and implantation of iliac extensions (n=3). All additional interventions were successful at arresting further sac growth during the remainder of follow-up.

Conclusions:
Despite being a less invasive alternative to conversion and open repair, the long-term outcome of sac fenestration is unpredictable and additional major procedures were often necessary to arrest sac growth.

MANUSCRIPT

INTRODUCTION

Endovascular aneurysm repair (EVAR) of abdominal aortic aneurysm (AAA) has developed since 1991 [1] and is now frequently the preferred method of treatment. The ultimate goal of EVAR is to prevent death from aneurysm rupture by excluding the aneurysm sac from the circulation, thereby relieving it from pressure. After EVAR, most aneurysms will stabilize or shrink in diameter. Some aneurysms, however, will continue to expand.[2-4]

Continued sac expansion after EVAR can have several explanations, but endoleaks and graft porosity (endotension) are frequently cited as culprits. In the case of sac growth, most physicians propose additional treatment to prevent the aneurysm from rupturing or to prevent aortic dilatation near the proximal or distal sealing zones, giving rise to possible migration and/or type I endoleaks. When an endoleak is associated with growth, a secondary endovascular procedure or conversion to open repair is usually performed. When no endoleak is found, the solution is more challenging, as the cause of continued aneurysm expansion is frequently unclear.

Previously, laparoscopic fenestration of the aneurysm sac was suggested as treatment for patients with an enlarging aneurysm sac after EVAR, with clipping of aortic sac collaterals.[5] Although the early results were promising, long-term durability of this treatment remains unknown. The aim of the current study was to evaluate the long-term effects of this treatment on sac behavior, to provide guidance in future decision making.

METHODS

Patient selection

From June 1999 to October 2005, a total of 143 AAA patients underwent an EVAR procedure in our hospital. During follow-up, sac growth was observed in 34 patients (23.8%). Type II endoleaks were detected in 21 cases (14.7%). These were either observed or treated with percutaneous interventions, such as coil-embolisation, glue injections and endoscopic clipping of lumbar arteries, depending on sac behavior. In case of a growing aneurysm sac where no endoleak was detected or when an endovascular approach of type II endoleak was technically unsuccessful or failed to arrest growth, an alternative approach was proposed. Laparoscopic fenestration of the aneurysm sac was then performed, which was preceded by clipping of patent Inferior Mesenteric Artery (AMI) and lumbar arteries. In order to evaluate the effect of fenestration on sac behavior, all patients who underwent this procedure were included. The sole exclusion criterion for this study was the lack of a minimum two post-fenestration imaging studies, as that would make observations on sac behavior impossible. The study was conducted in agreement with the Institutional Medical Ethics Committee guidelines.

Fenestration procedure

The technical details of this intervention were described previously.[5] In summary, all visible lumbar arteries were clipped endoscopically through a retroperitoneal approach, and a patent AMI was clipped laparoscopically. Cleared from all patent side- branches, the aneurysm was then fenestrated. During this phase of the operation, the operators could check for residual back-bleeding and suture any remaining type II endoleaks. Also, the sac contents were removed at this time and an omentum slip was inserted whenever technically possible in the sac to prevent immediate closure of the fenestration, reduce exposure of the bare endograft to the small intestines and possibly facilitate resorption of hygroma in the early stages after fenestration.

In one case, the procedure was converted to open suturing of all patent side-branches and fenestration of the sac. The primary operator during all procedures was the same, experienced vascular surgeon (J.H.), who was assisted by an experienced laparoscopic surgeon.

Efficacy of fenestration

At the time of these procedures, sac growth was a phenomenon that was aggressively treated. Therefore, the preferential outcome of this treatment at the time was to achieve sac stability or shrinkage. Primary endpoint of the current study is therefore persistent or recurrent sac growth, which is considered failure of treatment. Aneurysm related death and additional vascular interventions were recorded as secondary endpoints. Information on survival and the cause of death was retrieved from hospital records.

Analysis of sac behavior

Measurement of the aneurysm sac was performed on computer tomography angiography (CTA) images. The first CTA, within 48h after the fenestration, was considered the baseline for future follow-up. CTAs were then performed approximately every six or twelve months, according to institutional protocol. All hospital records were reviewed for additional interventions and rationale behind treatment decisions. Sac behavior was scored by two complementary methods.[6,7] First, the single largest diameter of the aneurysm sac was measured. Second, the total sac volume was quantified on each CTA and plotted in time-related curves, regarding the first measurement after fenestration as baseline. All measurements were performed on a workstation with dedicated software (3Mensio Vascular v4.2; 3Mensio Medical Imaging B.V., Bilthoven, The Netherlands) and using center-lumen line (CCL) reconstruction. Volume measurements were obtained according to a standardized and previously validated protocol.[8] Sac growth was defined as >5% increase in volume compared to baseline or in a 12 month interval. All data was subsequently analyzed using the Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Study population

In the presented time window, a total of 9 patients with a growing aneurysm after EVAR underwent aneurysm sac fenestration. One patient died of non-Hodgkin lymphoma three months after the procedure, having received only one CTA after the procedure, and was therefore excluded from the current study. From the remaining 8 patients (7 men) one patient suffered from a common iliac artery aneurysm rather than an AAA, but was similarly treated by EVAR and later fenestration for continued growth. In one patient, the endoscopic procedure was converted to an open fenestration procedure, as described.[5] At the time of fenestration, the 8 patients had a median age of 65.2 (range 55.1-74.3) years. Patient baseline characteristics are detailed in Table 1. There was no perioperative mortality.

Table 1. Descriptive statistics for the study population

Baseline characteristics	All patients (n=8)
Age in years, median (range)	65.2 (55.1-74.3)
Female gender, n (%)	1 (12.5)
Ischemic heart disease, n (%)	2 (25)
Diabetes mellitus, n (%)	1 (12.5)
History of stroke, n (%)	0
Congestive heart failure, n (%)	1 (12.5)
Renal dysfunction, n (%)	1 (12.5)
Cardiac arrhythmias, n (%)	1 (12.5)
Hypertension, n (%)	4 (50)
History of smoking, n (%)	3 (37.5)
COPD, n (%)	0

COPD denotes chronic obstructive pulmonary disease

Procedural details

Four patients were treated with an Excluder AAA Endoprosthesis (W.L. Gore and associates, Flagstaff, AZ, USA), one of which was the low permeability design introduced in 2004 (Table 2). The remaining implanted grafts were three Zenith AAA Endovascular Grafts (Cook Medical, Bloomington, IN, USA) and one Ancure Graft (Guidant, Menlo Park, CA, USA). Fenestration took place at a median of 1.7 (range 0.5-5.8) years after EVAR. Pre-fenestration sac diameters measured on CTA had a median of 73.2mm (range 56.5-91.0mm). The indication for fenestration was persistent or recurrent sac growth for all cases. In 50% a type-II EL could be detected as the possible culprit (Table 2). Attempts to treat these first with glue injections and coil embolizations had been unsuccessful. Upon reviewing the imaging studies in preparation of the procedures, no intense inflammatory component was observed nor was this noticed during the operation. During the procedures, the operators concurred in having achieved proper exposure and the ability to clip all side-branches. As confirmation, in only one case residual back-bleeding was observed upon opening the aneurysm sac, which was sutured from within. An omentum slip to leave in the fenestration was available in 5 out of 8 patients.

Table 2. Details on EVAR follow-up prior to fenestration

Case	Implanted graft type	Time since EVAR (years)	Sac diameter (mm)	Detected endoleak
1	Excluder OD	1.6	74.7	none
2	Excluder OD	0.7	68.0	Type II
3	Zenith	1.7	83.5	none
4	Zenith	2.6	69.9	Type II
5	Ancure	5.8	71.6	Type II
6	Zenith	2.4	56.5	none
7	Excluder OD	1.6	84.3	none
8	Excluder LP	0.5	91.0	Type II

EVAR denotes endovascular aneurysm repair, OD original design and LP = low permeability design

Aneurysm sac behavior

Follow-up had a median length of 6.6 (range 0.6-8.6) years. During this time, only three patients experienced durable aneurysm sac shrinkage (n=2) or stability (n=1) and were considered a success. In these three cases where sac growth was successfully arrested, two cases suffered progression of disease leading to dilatation of a common iliac artery (Case #2 and #5). Although this prompted the endovascular extension of one of the distal sealing zones (Table 3), this was not regarded as failure of fenestration.

The remaining five cases suffered persistent sac growth (n=2) or recurrent growth after initial shrinkage (n=3), all regarded as failure of fenestration. The two cases with persistent sac growth comprised one patient with a persistent type II endoleak despite clipping and fenestration, who was converted after 6 months (Case #4), and another patient without detectable endoleaks but an original design Excluder in situ (Case #7). This patient was presumed to suffer from endotension, but refused additional treatment until over 5 years after fenestration, when relining of the endograft finally arrested sac growth.

The three cases with recurrent sac growth included one patient that showed shrinkage during the first 7 years, but on the latest CTA suddenly had growth of the aneurysm sac (Case #3) suggesting re-pressurization, and one patient with a persistent type II endoleak who showed shrinkage at first but recurrent growth within 15 months, spurring conversion (Case #8). In the final case, primary indication for EVAR was a combination of a large iliac aneurysm and a small abdominal aortic aneurysm (Case #6). Sac shrinkage was observed in the first two years after fenestration, but eventually volume and diameter increased again until, finally, contrast was observed in the iliac aneurysm sac, resulting in an extension of the distal dealing zone.

Table 3. Details on fenestration follow-up and outcomes

Case	Baseline volume	Midterm volume	Latest volume	Follow-up (years)	Sac growth	Status endoleak	Additional intervention
1	152	81	81	8.6	No	n/a	None
2	97	97	96	8.6	No	Treated	Iliac extension
3	263	244	289	8.0	Yes	n/a	None
4	239	239	263	0.6	Yes	Persistent	Conversion
5	239	164	151	6.3	No	Persistent	Iliac extension
6	47	37	43	7.0	Yes	n/a	Iliac extension
7	188	387	254	6.0	Yes	n/a	Relining
8	432	381	431	1.3	Yes	Persistent	Conversion

Volumes are abdominal aneurysm sac volumes in ml.
Sac growth was defined as >5% volume change compared to baseline or in a 12 month interval.

No technical aspects of the procedures or observation made during surgery could be identified as playing part in the success rate of fenestrations. As mentioned earlier, no (untreated) back-bleeding was observed during the fenestration that could eventually predispose a patient to a residual or recurrent type II endoleak. Furthermore, the impossibility to mobilize an omentum slip for insertion in the fenestration was no predictor for outcome (arresting growth in two, conversion in one).

In summary, six patients underwent additional interventions after fenestration. Two patients were converted to open repair, both suffering from persisting type II endoleaks and early sac (re-)growth. One patient was relined for persistent sac growth, in the presence of an original design Excluder endoprosthesis. Additionally, three patients underwent implantation of iliac extensions, one of which suffered from recurrent iliac sac growth and the other two from common iliac artery dilatation due to progression of disease. All secondary interventions after fenestration were successful at arresting further sac growth during the remaining duration of follow-up.

DISCUSSION

EVAR has become the preferred method of treatment in many AAA patients, especially when the aortic anatomy is favorable. Despite the early survival advantage, EVAR is associated with greater aneurysm-related complications and therefore most agree on the need for life-long follow-up with imaging studies in order to evaluate migration, stent integrity, endoleaks and aneurysm size.[9-11] Post-implantation growth has received particular attention because it is observed with relative frequency and suggests continued pressurization of the aneurysm sac, and therefore failure of treatment (despite relative rarity in clinical consequences).[12] After EVAR, the majority of patients have either a gradual decline or stabilization of their aneurysm dimensions over the years.[13]

When growth occurs, however, a plausible explanation should be sought and treatment promptly offered. While it may be the accepted standard of care that patients with type I or III endoleaks require rapid intervention, opinions vary over the implications of type II endoleaks, especially in cases where the diameter of the aneurysm stabilizes or only grows slowly.[14,15] Within the last decade, studies report that selective surveillance of a type II endoleak is a safe course.[16] Controversially, Jones et al. reported that persistent type II endoleak increases the risk for rupture and the need for conversion,[17] while data from the EUROSTAR registry suggested that it actually seems to protect the patient against rupture.[14] When the current patients were diagnosed with a growing aneurysm after EVAR, endotension and type II endoleaks were aggressively treated. In 2002, Veith et al. reported on a summit with twenty-seven interested leaders who reached concensus that growing aneurysms without detection of endoleaks should be treated surgically or by repeated EVAR procedure.[17] Concerning type II endoleaks, Steinmetz et al. reported that if no sac growth is seen no additional intervention is necessary.[15] However, general opinion among the leaders previously mentioned was that persistent type II endoleaks required treatment, either with coil/glue embolization[18] or laparoscopic clipping.[19]
With that historical backdrop, a series of 9 patients with growing aneurysms without detectable endoleaks or with persistent type II endoleaks were treated by laparoscopic clipping of side branches and aneurysm sac fenestration. Although the short-term results were promising[5], the current study is the first to show that long-term results are sub-optimal in a large proportion of patients, raising doubt over the applicability of this previously described technique. The ultimate goal of the clipping and fenestration procedure was to halt sac growth. Durable aneurysm sac stability was only achieved in three patients, two of which underwent additional procedures for progression of the disease in the common iliac arteries. Out of the other five cases, two were converted to open repair, one was relined, one was extended at the distal sealing zone and one was diagnosed with recurrent sac growth on the latest scan. In general, the two-step procedure was not particularly successful in achieving its goal of durable sac stability.

The first step in the procedure was to clip all lumbars and other possible side-branches to treat or prevent type II endoleaks. Noticeably, out of four cases presenting with a type II endoleak prior to fenestration in our study, the endoleak persisted in three, despite the subjectively good view on lumbar arteries during this procedure. The only successful elimination of a type II endoleak was achieved in the one patient that was converted, and therefore clipping of collaterals and sac fenestration was performed as an open procedure, reducing the endoscopic success rate of clipping to nil. Interestingly, an open aneurysm sac with a subsequently demonstrable endoleak had no clinical consequences in our series. Although minimally invasive clipping of lumbar side-branches has been frequently performed, right-sided lumbar arteries are technically difficult to expose and clip.[20] In some cases, endoscopic clipping may be unsuccessful, resulting in residual type II endoleaks.[21] This could have contributed to the failure of arresting type II endoleaks durably, in the current study. An alternative approach is primary fenestration and subsequent sewing of back-bleeding lumbars from within the sac.[22,23]

In the current study, fenestration was performed after clipping of the side-branches, allowing for visual control by scanning for residual back-bleeding, as previously described by Dion et al. in 2001.[24] Only in one case back-bleeding was still observed, and this was sutured from within the sac. Although sac contents were thoroughly evacuated after fenestration, the residual type II endoleaks could have been masked by mural thrombus or other debris, missed at the time of surgery. This illustrates that laparoscopic fenestration is a demanding procedure and, even in the hands of experienced vascular and laparoscopic surgeons can lead to underexposure of the inside of the sac, and thus incomplete removal of thrombus and assessment of back-bleeding side-branches.

The most logical indication for fenestration would therefore be endotension as a result of increased graft porosity. Transudate of fluid through the graft fabric is well described, particularly after implantation of the original Excluder endograft (W.L. Gore and associates, Flagstaff, AZ, USA).[18] Releasing the hygroma would theoretically result in arrested growth and prolonged success. This idea has also been defended by others, both with open[19] or with percutaneous sac fenestration. In our series, two patients implanted with the Original Design Excluder continued to exhibit growth without detectable endoleaks prior to fenestration. After fenestration, sac stability was observed in one, but sac growth persisted in the other, who later underwent successful relining with a low-permeability graft. This sac growth could be explained by healing of the fenestration, resulting in the recurrence of hygroma, allowing re-pressurization. Goodney et al. and Kougias et al. have published on their experience with relining, with similar good results at short-term.[21,21] This alternative solution, although promising, still lacks long-term data, but is generally accepted as first line treatment in case of a growing sac with an original Excluder endograft in situ, or when graft integrity is thought compromised at a specific location.[22,23] Importantly, standard CTA is not the most sensitive technique for type-II endoleak visualization, and definite diagnosis of endotension of often only possible after opening the aneurysm sac and visualizing no bleeding aortic collaterals.[25] Therefore, it is theoretical to reserve this technique for endotension cases.

The current report is limited by its observational design and by the small number of patients. Also, the indication for treatment was individualized and no strict criteria were observed, with potential selection bias. For the purpose of demonstrating the safety and efficacy of the technique, however, these limitations - albeit important - can be accepted in order to prevent others to subject their patients to this ineffective treatment as well.

CONCLUSIONS

In conclusion, the results after fenestration are quite variable and, more importantly, largely unpredictable. Sac growth was observed after fenestration in five out of eight cases, spurring additional interventions in the majority. Therefore, we cannot recommend fenestration as primary treatment for sac growth. Other techniques may hold more promise when minimally invasive interventions fail, risk of rupture is considered high and the patient is too frail for aortic cross-clamping and endograft explantation.

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Need we intervene for type II endoleaks?

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ABSTRACT

Endoleaks are the most common problem following endovascular aneurysm repair. The importance of a type II endoleak has often been subject of discussion in scientific literature. Conflicting data on the natural history of type II endoleak have been published. There is no consensus on the threshold for treatment of type II endoleak and controversy exists about the optimal treatment modality. This paper discusses the evidence behind treating type II endoleak and investigates the need for treatment.

MANUSCRIPT

INTRODUCTION

Since first performed in 1987 by Volodos,[1] and first reported by Parodi in 1991,[2] endovascular aneurysm repair (EVAR) has developed into a viable alternative to conventional open surgical repair of abdominal aortic aneurysms (AAA) with advantages regarding perioperative morbidity and mortality.[3,4] Mid- and long-term results have demonstrated the durability of EVAR and equal survival compared to conventional open repair.[5-9] However, long-term follow-up has also revealed a significant amount of endograft-related complications, leading to re-interventions performed after EVAR.[7-9] Endoleaks are a common problem after EVAR; they account for 60% of endograft-related complications and are associated with up to half of all re-interventions.[5,10-12] Endoleak is defined as the persistence of blood flow outside the graft and within the aneurysm sac.[13,14] This persistent flow could prevent aneurysm sac thrombosis, resulting in a potential risk for continuous sac expansion and even rupture.

Endoleaks are categorized in four types according to their cause: type I, as a result of inadequate sealing of the graft proximally and/or distally; type II, by retrograde flow into the aneurysm sac via patent collaterals; type III, due to inadequate sealing of graft joints or graft fabric rupture; and type IV, caused by graft fabric porosity. There is little debate regarding the treatment of type I and III endoleaks, as these signify incomplete exclusion of the aneurysm sac from systemic arterial pressure and therefore ineffective aneurysm repair. In contrast, type II endoleaks are regarded as “low pressure” endoleaks and conflicting data on their natural history and association with adverse long-term outcome have led to controversy on the (need for) treatment of type II endoleaks, which is the focus of this paper.

Type II endoleak

Type II endoleaks are the most common endoleaks after EVAR. The reported incidence of any type II endoleak after EVAR varies from 9% to 29% in literature, depending on type and timing of imaging.[5,10,15-23] Type II endoleaks are related to retrograde flow into the aneurysm sac via collateral aortic branches, most commonly via lumbar arteries or the inferior mesenteric artery (IMA). A variety of demographic and anatomic factors associated with type II endoleaks have been reported. Demographic variables associated with a higher prevalence of type II endoleaks include older age, absence of peripheral arterial disease, and anticoagulation therapy.[21,24,25] Anatomic features frequently associated with type II endoleaks are longer infrarenal neck, larger AAA diameter, lower thrombus load in aneurysm sac, patent IMA, and larger number of patent lumbar arteries.[10,16,19,22,24-26] In contrast, protective factors for development of type II endoleaks are tobacco use, presence of COPD and renal insufficiency.[10,16,20,25]

Natural History

The natural history of type II endoleaks has been subject of research over the last decade. While type I and III endoleaks are grouped together as “high-pressure” leaks (and therefore need prompt treatment), a type II endoleak is generally regarded a “low-pressure” leak. From a physiological point of view, type II endoleaks could not remain patent if only supplied by a single vessel, because end arteries with no outflow inevitably thrombose. Indeed, the majority of type II endoleaks will spontaneously resolve. Approximately half of type II endoleaks, which are present on the completion angiogram of the EVAR, will thrombose spontaneously in the immediate postoperative course.[27,28] Subsequently, the majority of type II endoleaks, diagnosed on the first postoperative CT scan, will seal spontaneously. These type II endoleaks are described as “transient” type II endoleaks.” Persistent” type II endoleaks are endoleaks, which remain present after six months post-EVAR and are reported in only 20% to 39% of patients with a previously diagnosed type II endoleak.[10,17,21,26,29] One has to realize that the presence of type II endoleak on imaging during follow-up after EVAR is highly dependent on operator, imaging modality and techniques used, which is subject of another review in this issue.[30] “Persistent” type II endoleaks may still seal spontaneously over time, as two recent Kaplan-Meier analyses reported a projected 35% rate of spontaneous resolution of “persistent” type II endoleak and 75% rate of spontaneous resolution of all type II endoleaks after five years follow-up.[20,22] Increase in aneurysm sac size has been reported in 5% to 50% of patients with a “persistent” type II endoleak.[17,20-22,26,29]

In summary, extrapolating from a conservatively estimated incidence of 20% of type II endoleaks on the first postoperative CT scan, at one year follow-up 4% of EVAR patients will have a “persistent” type II endoleak. Subsequently, the estimated incidence of a “persistent” type II endoleak with increasing sac size is 0.1% to 2% of all EVAR patients.[28]

“Transient” type II endoleaks are not associated with growing aneurysm sac size or other adverse outcomes.[10,31] “Persistent” type II endoleaks, however, have been suggested as potential predictors of adverse events during follow-up. On this topic, conflicting reports have been published. The majority of authors have not reported any major complications, conversion, rupture or death from type II endoleaks, regardless of sac growth.[17,20,29] In contrast, some papers have associated type II endoleaks with sac expansion and late conversion.[21-24] Type II endoleak has also been associated with rupture, but anecdotally.[21] In a recent systematic review of literature, only 14 described cases of rupture from a type II endoleak were found in nine studies. These studies represented a cohort of 2627 type II endoleaks, suggesting an incidence of rupture from a type II endoleak of 0.5% (14 of 2627 patients), which is the same as reported from the data from the EUROSTAR registry (1 in 191 patients).[16,29] This is, of course, assuming that the type II endoleak is the true cause of rupture in all cases, which was not reported undisputedly and may not correspond to reality. Both the EUROSTAR data as a systematic review have confirmed that rupture and open conversion rates were no different in patients with type II endoleak when compared to patients without type II endoleak.[16,28,32] In summary, only a small proportion of type II endoleaks may have a prognostic influence, and current evidence does not

support the view that presence of a “persistent” endoleak will alter the clinical course of patients after EVAR if left untreated.

PRE-/ OR INTRAOPERATIVE TYPE II ENDOLEAK MANAGEMENT

Identification of patients at risk for developing type II endoleak has been the stimulus for some to adopt a prophylactic strategy of branch vessel management.[33] After preoperative IMA coil embolization a decrease in rate of type II endoleak from 48% to 17% has been reported.[34] However, others have not been able to duplicate these results.[10] A combination of preoperative IMA coil embolization and intrasac thrombin injection led to a non- statistically significant decrease in incidence from 26% to 14%.[35] Finally, intraoperative sac fibrin glue injection was shown to reduce the incidence of type II endoleak to 2-5%.[36,37] Although these figures seem promising, the patient populations were small, non-randomized and often non-controlled, and had limited follow-up. More importantly, results from these studies do not seem to differ from the natural history of untreated type II endoleaks and suggest that prophylactic embolization exposes the majority of EVAR patients to unnecessary risk, aside from increasing the overall cost and complexity of the procedure.

POSTOPERATIVE TYPE II ENDOLEAK MANAGEMENT

There is currently no consensus on the management of type II endoleak. Some authors have propagated a conservative approach to all type II endoleaks.[29] Others have supported an aggressive approach with intervention in all cases.[38] However, the majority of authors have suggested a selective approach in cases of type II endoleak persistence or in cases of type II endoleak in combination with sac growth.[20] Current clinical practice guidelines recommend a conservative approach for type II endoleak without sac growth and recommend intervention if the type II endoleak is associated with sac growth.[39]

Techniques

The most common technique of postoperative endoleak management is transarterial embolization of branch vessels using coils, glue or thrombin. Transarterial embolization of the IMA or lumbar arteries has been associated with encouraging initial technical success, defined as occlusion of the target artery.[40-42] However, during follow-up this technique has been shown to be less effective; failure and recurrence can occur in up to 80%.[15,41,43] Modification of the technique by embolizing both the feeding and draining arteries as the aneurysm sac itself is thought to be more effective, although comparative studies are missing.[43-45] Transarterial embolization is not without risks, as cases of aortoenteric fistula, transient paraplegia and colonic necrosis have been described.[44,46-48] In a recent review of nine years of experience in treatment of type II endoleak the success rate of transarterial embolization, defined as resolution of endoleak, was only 38%, while 27% of patients required blood transfusion, 10% had cardiac complications, and 14% had infectious complications.[49]

An alternative to the transarterial approach is translumbar embolization of the aneurysm sac.[50,51] A retrospective comparison between the modified transarterial embolization and translumbar embolization demonstrated equally success rates, with a major complication rate of 3.2%.[44] Translumbar embolization can also be performed via a translumbar transcaval or an ultrasound-guided transabdominal approach.[52-54]
In a recent study the use of Onyx glue (ev3 Inc, Irvine, California) significantly improved endoleak resolution rates from 38% to 91%.[55] It's important to realize that both coil and glue embolization result in significant scatter on subsequent imaging techniques, and makes further reliable evaluation of the presence of endoleaks difficult or even impossible. (Figure 1)
Alternatively, transcatheter transcaval embolization of the aneurysm has been described, reporting clinical success, defined as absence of type II endoleak after one-year follow-up in 66-83% of patients.[56,57]

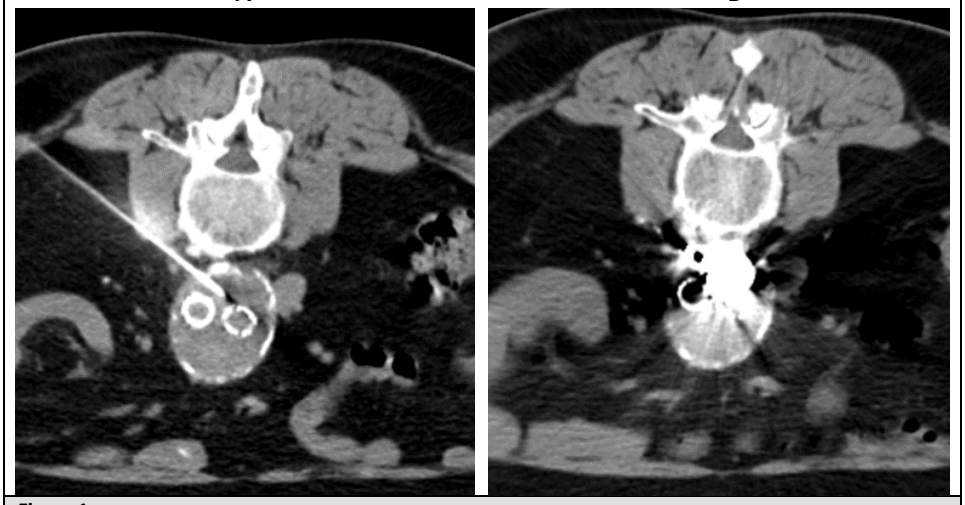

Figure 1.
Panel A: Translumbar CT-guided embolization of aneurysm sac using Onyx for type II endoleak.
Panel B: Follow-up CT-angiogram in the same patient demonstrates significant scattering, which impairs visualization of persistent or newly developed endoleak, as well as sac changes.

Several cases of technically successful laparoscopic retroperitoneal ligation of lumbar arteries or IMA have been reported, including a totally robotic ligation.[58-62] In current practice, laparoscopic ligation is often reserved for failures of endovascular techniques.[49] However, there are very limited data on the effectiveness of laparoscopic ligation. A recent study with long-term follow-up of laparoscopic ligation and sac fenestration reported recurrent aneurysm sac growth in 62% of patients. (Figure 2)[61]
Ultimately, open surgery with endograft removal or sacotomy followed by removal of thrombus from the aneurysm sac and ligation of IMA and lumbar arteries, is a final treatment of type II endoleak, when all above described techniques have failed. This

approach, also known as late conversion, is associated with a considerable morbidity and 10% perioperative mortality.[63]

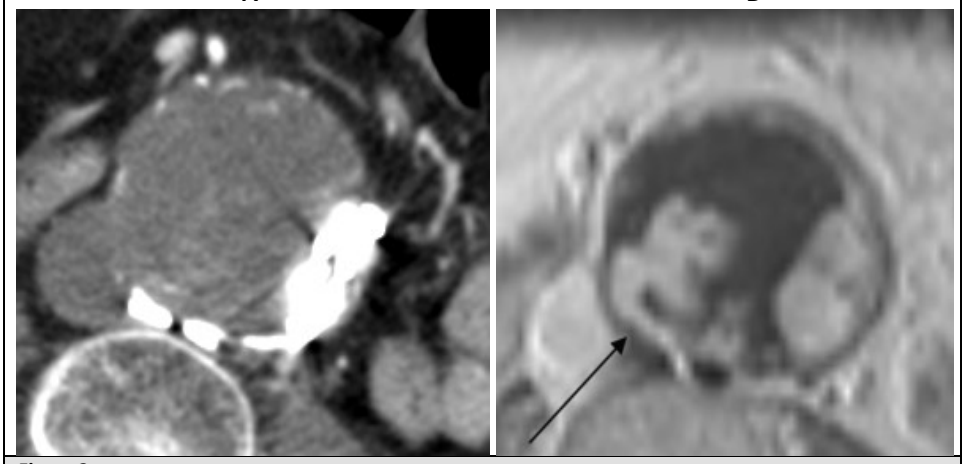

Figure 2.
Panel A: Post-operative CT-angiography after successful laparoscopic clipping of lumbar artery causing type II endoleak. No more type II endoleak is visualized.
Panel B: Follow-up MR-angiography in the same patient reveals persistent flow in aneurysm sac despite previous laparoscopic clipping, most likely because not all patent lumbar arteries were visualized and clipped and there were more patent lumbar arteries than anticipated.

IS THERE A NEED FOR TREATMENT OF TYPE II ENDOLEAK?

Firstly, the current available literature suggests the natural history of type II endoleak to be benign. The majority of type II endoleaks resolves spontaneously and the majority of persistent type II endoleaks does not lead to aneurysm sac expansion.[11,28,64] Moreover, rupture has not been unequivocally associated with isolated type II endoleak.[10,11,16,17,20,24,28,29,31,49,55,65] Conflicting data on the association between type II endoleak and adverse outcomes after EVAR could partly be explained by the fact that in several studies on natural history and treatment of type II endoleak, a significant proportion of patients, ranging from 21% to 36%, appeared to have a type I or III endoleak.[10,65,66] In these studies adverse outcomes may well have been caused by co-existing high-pressure (type I or III) endoleaks. Also, in the EUROSTAR registry (2463 patients), of all patients without discernible endoleak 7% developed an increase in aneurysm size two years after EVAR.[16] Finally, in a recent landmark review of over 10.000 EVAR patients the overall incidence of any endoleak was 31%. Of these patients 21% developed sac size enlargement, which was only 6% of total patients. However, in the total cohort the overall rate of sac size enlargement after five years follow-up was as high as 41%.[67] Both studies suggest therefore, that the presence of a type II endoleak may actually be a confounder.

Secondly, the results of treatment of type II endoleaks are disappointing. Success rates are inhomogeneously described: often only initial technical success is reported, while just a minority of papers mention type II endoleak resolution (immediate and over time) or, most importantly, freedom from sac growth. The latter, of course, is the only relevant successful outcome measure for the treatment of a type II endoleak. Small series of treatment of type II endoleaks have described inhomogeneous success rates of 20% to 100%.[34,40-42,51,56,68] However, the majority of these reports are anecdotal, non-controlled and non-randomized, have very different definitions for success and lack long-term follow up. More recent and larger series with a substantial follow-up report disappointingly low success rates, ranging from 22% arrest of sac growth to 38% resolution of endoleak, at a cost of a significant amount of reinterventions and risk for complications.[10,49,55,65,69] In a rough estimate using the above success rate of around 25%, the percentage of patients that would benefit (i.e. freedom of sac size growth) from treatment of type II endoleak would only be 25% of 4% (incidence of "persistent" endoleak), which is 1% of all patients after EVAR. Thus, the results of postoperative type II endoleak treatment seem to be no different from the natural history of a type II endoleak.

Finally, a recent meta-analysis has reviewed the available evidence to support any threshold for intervention on type II endoleak.[11] Only studies, which specifically reported sac outcome and specified a threshold for intervention, and with data on more than 100 EVAR, were included.[29,38,45,56,70-74] In total 231 patients were analyzed, 56 were treated at an aggressive threshold, 104 at a selective threshold, and 71 at a conservative threshold. The majority of type II endoleaks (194/231, 84%) demonstrated stable or shrinking sacs during follow-up regardless of treatment strategy and no ruptures were recorded. Meta-regression demonstrated no evidence that an aggressive or selective strategy reduced sac expansion, compared to using a conservative approach.

What to do with a patient with a persistent type II endoleak and aneurysm sac expansion?

In case a type II endoleak does not appear to behave benign (i.e. growing sac size), it should be regarded as a "sentinel" endoleak leading the clinician to an exhaustive search for all possible causes of inadequate exclusion of the aneurysm. Other causes of increasing sac size, such as type I endoleaks, type III endoleaks (including positional or intermittent endoleaks) should be treated or excluded. Focusing our attention on a type II endoleak associated with expansion may divert attention to the true (and occult) cause for growth. Balancing the benefit – risk ratio, a patient with type II endoleak and growing sac size, in absence of a type I or III endoleak and with a confirmed adequate distal and proximal seal of the endograft, may be treated conservatively, as long as closely followed. If either the patient of the physician is uncomfortable with this strategy, the only truly effective and definitive treatment remaining today is conversion to open repair, diminishing all reasons for sac growth after EVAR (of which type II endoleak is only one), at the price of high mortality and morbidity.

CONCLUSIONS

The importance and natural history of a type II endoleak following EVAR has often been subject of discussion in scientific literature. There is neither consensus nor evidence on the threshold for treatment of type II endoleak, but the strategy to reserve treatment for patients with a persistent type II endoleak and growing sac size, which reflects only around 1% of all EVAR patients, seems to have gained the most support between vascular surgeons. Controversy exists about the optimal treatment modality, while outcome is ill defined, effectiveness is disappointing, and (serious) complications resulting from treatment should not be neglected. Consequently, a high demand exists for a systematic review on this subject.

In our opinion, a type II endoleak should be regarded as a “sentinel” endoleak that demands a vigorous search for other (high-pressure) causes of aneurysm sac growth, which consequently require expeditious treatment. However, in absence of high-pressure endoleaks and with adequate seal of the endograft, a patient with isolated type II endoleak and growing sac size may be managed conservatively with close observation (provided informed consent) as rupture is unlikely to occur.

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Appendices

SUMMARY AND CONCLUSIONS

Medical considerations in vascular surgery

For optimal patient outcome after surgery, it is critical to accurately assess the preoperative cardiac risk of the individual patient. Undergoing surgery predisposes a patient to an increased risk of cardiac adverse events, caused by a variety of factors. One of these is the occurrence of thrombotic complications in patients at a higher risk of thrombosis, for instance after a myocardial infarction, stroke, coronary stent implantation or carotid surgery. The most important issue addressed in **Chapter 1** is the individual approach required to prepare a patient with an increased risk of thrombotic complications for surgery. Surgeons tend to discontinue aspirin and, especially, stronger antiplatelet agents, due to a fear of bleeding complications during surgery, thereby denying patients the optimal protection from thrombotic complications. Careful deliberation between a cardiologist and a surgeon should result in the best possible timing and preparation for surgery in patients receiving antiplatelet therapy. Furthermore, a timeline for discontinuation of anticoagulant agents and initiation of bridging therapy with low weight molecular heparin is provided, based on recent literature.

Additional to reducing the risk of thrombotic complications, several other pathways to perioperative myocardial damage are targeted by a wide variety of drugs. Some of these have effectively reduced the incidence of perioperative myocardial ischemia and cardiac death. For example, statin therapy is proven to be beneficial to patients, undergoing high-risk surgery. **Chapter 2** is a literature review on the safety of fluvastatin, a low-density lipoprotein cholesterol lowering drug, if prescribed in high-risk surgery patients. As reported, fluvastatin use is safe in patients undergoing high-risk surgery and, in fact, reduces the risk of perioperative myocardial ischemia. This protective effect is partly due to the non-lipid lowering effects, or pleiotropic effects, of statin therapy. These include a reduction of inflammatory markers, thereby promoting coronary plaque stability, thus reducing the risk of plaque rupture and myocardial malperfusion. Initiating statin therapy prior to high-risk surgery seems warranted, and statin discontinuation is discouraged. Therefore, statins with an extended release are preferred, to bridge the postoperative phase during which patients cannot take oral medication.

Complementary to plaque stability, attenuation of a surgery-induced stress response is important, to reduce the risk of a perioperative mismatch between myocardial oxygen demand and supply. This is best acquired by beta-blocker therapy, as frequently reported in literature. Historically there has been a reluctance to use β-blockers in a perioperative setting, especially in patients with peripheral arterial disease, because of the hypothetical side effects and worsening of outcome. In the last decade it has become apparent that β-blockers reduce the risk of perioperative myocardial ischemia, myocardial infarction and cardiac mortality, as discussed in **Chapter 3**. When started at

least one week prior to surgery, given in a low dose and titrated to heart rate, the benefits of β-blocker therapy still remain and side effects can be kept to a minimum.

In a continuous effort to improve cardiovascular outcome in (vascular surgery) patients, research is often directed at new risk markers, biomarkers or unexpected risk factors. This could improve risk stratification and lead to new targets for (secondary) prevention. In this light, serum vitamin D levels are gaining interest. In addition to its well-known effects on calcium homeostasis and bone metabolism, there is accumulating evidence that vitamin D deficiency has important extra-skeletal effects, related to the cardiovascular system. Clinical data suggest that vitamin D deficiency promotes atherosclerosis. However, it is not known whether this is a direct effect of vitamin D on the arterial wall, or the result of a vitamin D deficiency-associated increase in established cardiovascular risk factors, such as hypertension, obesity and diabetes. In **Chapter 4** we assessed the vitamin D status in a large population of patients with occlusive or aneurysmatic arterial disease, and related this to clinical cardiovascular risk factors as well as to direct markers for the severity of arterial disease. We demonstrate that low vitamin D status is an indicator for the severity of arterial disease, independent of traditional cardiovascular risk factors and irrespective of the type of vascular disease, i.e. occlusive or aneurysmatic disease.
Although there is still much debate about the requirement levels of vitamin D to this purpose, it might be hypothesized that primary and secondary preventive strategies to reduce vascular disease should focus on vitamin D status, in addition to blood pressure reduction, lipid and glucose control, weight loss, and lifestyle changes. Future studies could test the effects of vitamin D suppletion on cardiovascular disease and perhaps further elucidate the biology of vitamin D in relation to the arterial wall.

A final major cause for morbidity and mortality after vascular surgery is the occurrence of cardiac arrhythmias. The most frequent perioperative arrhythmia is new-onset atrial fibrillation (AF), a known major risk factor for postoperative stroke, myocardial infarction and pulmonary embolism. Some of these complications may be preventable as AF can be treated if diagnosed. Current standard Holter recording or periodical electrocardiography cannot always identify these (paroxysmal) arrhythmias. As printed in **Chapter 5**, the true incidence of paroxysmal AF after major vascular surgery seems to be much higher (over 25%) than estimated with standard practice Holter monitoring, leaving most cases currently undetected and untreated. An insertable cardiac monitor, evaluating rhythm disturbances continuously for weeks or months after surgery, detects patients at risk for thromboembolic complications reliably, opening a new treatment window for these patients. It is our recommendation that future research is aimed at developing a treatment strategy for this specific patient population.

Technical considerations in vascular surgery

Recent and well-embedded technical advancements in vascular surgery have offered a wide variety of therapeutic options in the individual patient. The introduction of endovascular techniques have expanded the arsenal of treatment modalities for the vascular surgeon. While some of these developments seemed instantly applicable and brilliant at the time, some lessons are learned long after the first patients were treated with these new techniques. The development of the carotid artery stent, for instance, facilitated treatment of carotid artery stenosis in patients with difficult anatomy or severe comorbidities. A multitude of manufacturers launched several carotid stents onto the market, all with different properties. Proper stent selection however, can only be preceded by objective comparison of these properties, which has not been performed on many occasions. In **Chapter 6** an effort is made to compare an underestimated, but critical feature of self-expandable carotid stents: the radial force. The results show that there are significant differences in radial force between different stent types, and that the length of the lesion plays an important role in this. Clinical success of carotid artery stenting may be improved if the proper stent is selected in each individual patient, and radial force is an important property to take into account. In future studies, the influence of radial force on patency rates in different types of lesions should be investigated in the clinical setting.

Another major technical development in vascular surgery is the introduction of endovascular stent grafts to treat aortic aneurysms. Endovascular aneurysm repair (EVAR) has become widely adapted, and this too caused the introduction of a variety of stentgrafts. A major feature in the composition of different devices is the graft material, which most commonly is either woven polyester of a polymer known as ePTFE. As the use of stentgrafts increased, so did the number of reports of flu-like symptoms in patients after implantation. In **Chapter 7** the incidence of the post-implantation syndrome is reported in over one hundred and fifty patients treated by EVAR. About one third of patients developed post-implantation syndrome, comprising fever and inflammation, and a strong association with woven polyester was observed even after multivariable adjustment. Although long-term consequences of post-implantation syndrome remain uncertain, these results may influence the development of future devices.

Another aspect of EVAR is the management of side-branches. With open repair most side branches, such as lumbar arteries, are ligated. In EVAR they are left untreated, allowing for possible back-bleeding or so-called type II endoleaks. A controversial intervention in the case of sac re-growth after EVAR is endoscopic clipping of side-branches and fenestration of the growing aneurysm sac. In **Chapter 8**, long-term follow-up of eight patients that underwent such a procedure is presented. Outcome was largely variable and unpredictable. In some cases, endoleaks persisted or recurred and in some cases recurrent sac growth led to later open surgical repair. Therefore, this procedure does not seem recommendable in the treatment sac growth after endovascular repair.

Ours was not the only endeavour to come up with the optimal treatment strategy for type II endoleaks. Despite many publication with often conflicting data on the natural history of type II endoleak, there is no consensus on the threshold for treatment of type II endoleak and controversy exists about the optimal treatment modality. In the literature, reviewed in **Chapter 9**, the strategy to preserve treatment for patients with a persistent type II endoleak and also a growing aneurysm sac size, seems to be the most supported among vascular surgeons. We make the argument that sac growth should instigate a vigorous search for a more high-pressure endoleak than just a type II endoleak, often resulting in an expeditious treatment of the true cause for sac growth. In absence of such a cause, the surgeon and the patient could reside in a conservative management with close observation, as sac rupture is unlikely to occur.

NEDERLANDSE SAMENVATTING

Medische overwegingen in de vaatchirurgie

Voor een optimale uitkomst na chirurgie is het van essentieel belang om nauwkeurig het preoperatieve cardiale risico in de individuele patiënt in te schatten. Het ondergaan van een operatie stelt de patiënt bloot aan een verhoogd risico op schade aan het hart, veroorzaakt door verschillende factoren.

Een daarvan is het optreden van trombotische complicaties in patiënten met een verhoogd risico op trombose, bijvoorbeeld na een doorgemaakt hartinfarct, een beroerte, een stentplaatsing in een kransslagader of een operatie van de halsslagader. Het belangrijkste van wat behandeld wordt in **Hoofdstuk 1** is de individuele benadering die nodig is om een patiënt met een verhoogd tromboserisico voor te bereiden op chirurgie. Chirurgen hebben de gewoonte om aspirine en, vooral, sterkere plaatjesremmers te staken, uit angst voor bloedingscomplicaties tijdens de operatie, waarmee de patiënt de optimale bescherming van trombotische complicaties wordt ontzegd. Zorgvuldig overleg tussen een cardioloog en de chirurg zou moeten resulteren in de best mogelijke timing en voorbereiding op de operatie in patiënten die plaatjesremmers slikken. Daarnaast wordt een tijdslijn voor het tijdelijk staken van bloedverdunners en het starten van overbruggingstherapie met laaggewicht moleculaire heparine verschaft, gebaseerd op recente literatuur.

Naast het reduceren van trombotische complicaties worden verschillende andere oorzaken van peroperatieve schade van de hartspier behandeld met een breed scala aan medicatie. Sommigen daarvan hebben succesvol de incidentie van peroperatieve hartschade en hartdood verminderd. Zo is bijvoorbeeld het gebruik van cholesterolremmers, statines genaamd, gunstig gebleken voor patiënten die een hoog-risico operatie ondergaan. **Hoofdstuk 2** is een literatuurstudie naar de veiligheid van fluvastatine, een cholesterol verlagend medicijn, indien voorgeschreven bij patiënten voor hoog-risico operaties. Zoals beschreven, is fluvastatine gebruik veilig bij patiënten die een hoog-risico operatie ondergaan, en reduceert het zelfs het risico op peroperatieve hartschade, dankzij de niet-cholesterol gerelateerde effecten, ookwel pleitrope effecten, van deze medicijnen. Statines lijken ontstekingsmediatoren te remmen, waardoor de stabiliteit van verkalkingen in de kransslagaderen wordt bevorderd, en daarmee het risico wordt verlaagd op het losscheuren van deze laesies en op een verslechterde doorbloeding van de hartspier. Het starten van statines in aanloop naar een hoog-risico operatie lijkt aan te raden, en het staken van statines wordt afgeraden. Daarom genieten langwerkende statines de voorkeur, om de periode te overbruggen dat patiënten na een operatie geen orale medicatie kunnen innemen.

Naast stabiliteit van bestaande aderverkalkingen is het afzwakken van de operatie-gerelateerde stress-response belangrijk, om het risico op een discrepantie tussen vraag en aanbod van zuurstof in de hartspier te verlagen. Dit is het best te bereiken met

bètablokker therapie, zoals al vaak in de literatuur beschreven. Historisch gezien was er een aarzeling om bètablokkers te gebruiken rond operaties, vooral in patiënten met perifeer vaatlijden, vanwege hypothetische bijwerkingen en verslechterde uitkomsten. In de laatste tien jaar is steeds meer duidelijk geworden dat bètablokkers het risico verkleinen op peroperatieve hartschade, hartinfarcten en hartdood, zoals besproken wordt in **Hoofdstuk 3**. Wanneer men tenminste een week voor de operatie start, laag doseert en op geleide van de hartslag titreert blijven de voordelen van bètablokkade bestaan, terwijl de bijwerkingen tot een minimum worden beperkt.

In een voortdurende strijd om cardiovasculaire uitkomsten bij (vaatchirurgische) patiënten te verbeteren is onderzoek vaak gericht op nieuwe risicomarkers, biomarkers of onverwachte risicofactoren. Hierdoor zou risicoinschatting kunnen verbeteren en tot nieuwe aanknopingspunten leiden voor (secundaire) preventie. Vanuit dat oogpunt neemt de interesse in de bloedspiegel van vitamine D toe. Naast de welbekende effecten op de calciumhuishouding en botmetabolisme is er opstapelend bewijs dat een vitamine D tekort belangrijke niet-skeletale effecten heeft, gerelateerd aan het hart- en vaatstelsel. Klinische gegevens suggereren dat een vitamine D tekort bijdraagt aan aderverkalking. Het is alleen niet bekend of dit een direct effect is van vitamine D op de vaatwand, of het resultaat van een stijging van risicofactoren die aan vitamine D tekorten gerelateerd zijn, zoals een hoge bloeddruk, overgewicht en suikerziekte. In **Hoofdstuk 4** hebben we de vitamine D status geïnventariseerd in een grote populatie patiënten met vernauwd of verwijd vaatlijden, en dit vervolgens gerelateerd aan bekende klinische risicofactoren en enkele directe tekenen van de ernst van het vaatlijden. We tonen aan dat een laag vitamine D gehalte een indicator is voor de ernst van vaatlijden, onafhankelijk van traditionele risicofactoren, en ongeacht het type vaatlijden, verwijd of vernauwd.

Hoewel er nog veel discussie gaande is over de vereiste bloedspiegel voor vitamine D wat betreft deze toepassing, zou kunnen worden verondersteld dat primaire en secundaire preventie om hart- en vaatziekten terug te dringen zich moeten focussen op de vitamine D status, naast bloeddruk, cholesterol en suiker control, gewichtsverlies en leefstijl veranderingen. Studies in de toekomst zouden de effecten van vitamine D supplementen op hart- en vaatziekten kunnen testen, en misschien de biologie achter vitamine D uitdiepen, in relatie tot de vaatwand.

Een laatste grote oorzaak voor morbiditeit en mortaliteit na vaatchirurgie is het optreden van hartritmestoornissen. De meest frequente peroperatieve hartritmestoornis is nieuw-ontstane boezemfibrilleren (AF), een bekende grote risicofactor voor postoperatieve beroertes, hartinfarcten en longembolieën. Sommige van deze complicaties zouden kunnen worden voorkomen, aangezien AF kan worden behandeld als het wordt gediagnosticeerd. De huidige standaard van Holter opnames of periodieke hartfilmpjes kunnen niet altijd deze (intermitterende) ritmestoornissen identificeren. Zoals in **Hoofdstuk 5** staat gedrukt is de daadwerkelijke incidentie van AF na vaatchirurgie veel hoger (meer dan 25%) dan wordt geschat met de reguliere Holter opnames, waardoor de meeste gevallen onopgespoord en onbehandeld blijven. In implanteerbare hartritmemonitor, die gedurende weken of maanden continue

ritmestoornissen kan evalueren, kan op betrouwbare wijze patiënten identificeren met een verhoogd risico op trombo-embolische complicaties, waardoor nieuwe behandelmogelijkheden voor hen beschikbaar zijn. Wij kunnen aanbevelen dat toekomstig onderzoek zich richt op het ontwikkelen van een behandelstrategie voor deze specifieke patiëntengroep.

Technische overwegingen in de vaatchirurgie

Recente en breed ingevoerde technische ontwikkelingen in de vaatchirurgie hebben een breed scala aan therapeutische opties opgeleverd in de individuele patiënt. De introductie van endovasculaire technieken hebben het arsenaal van behandelwijzen voor de vaatchirurg uitgebreid. Hoewel sommige van deze ontwikkelingen gelijk toepasbaar en een uitkomst leken indertijd, worden sommige lessen pas geleerd, lang nadat de eerste patiënten met deze nieuwe technieken werden behandeld. De ontwikkeling van een stent voor in de halsslagader, bijvoorbeeld, vergemakkelijkte de behandeling van halsslagader stenose in patiënten met een moeilijke anatomie of ernstige co-morbiditeit. Een veelvoud aan fabrikanten hebben diverse stents op de markt gebracht, allen met verschillende eigenschappen. Adequate stent-selectie kan echter alleen maar worden voorafgegaan aan objectieve vergelijking van deze eigenschappen, iets wat niet vaak is gebeurd. In **Hoofdstuk 6** is gepoogd om een onderschatte, maar kritieke eigenschap van zelf-ontplooiende stents te vergelijken: de radiale kracht. De resultaten laten zien dat er significante verschillen bestaan tussen verschillende stenttypes, en dat de lengte van de laesie een belangrijke rol hierin speelt. Het klinisch succes van stenten van de halsslagader zou kunnen worden verbeterd als de juiste stent wordt geselecteerd voor de individuele patiënt, en de radiale kracht is een belangrijke eigenschap om rekening mee te houden. In toekomstige studies zou de invloed van de radiale kracht op de doorgankelijkheid in verschillende typen laesies moeten worden onderzocht in klinisch verband.

Een andere belangrijke technische ontwikkeling in de vaatchirurgie is de introductie van endovasculaire stentgrafts voor de behandeling van het aneurysma van de aorta. Endovasculair aneurysma herstel (EVAR) is wijdverbreid, en hiermee is ook een breed scala van stentgraft geïntroduceerd. Een belangrijke eigenschap in de samenstelling van de verschillende producten is de kunststof prothesewand, welke meest gebruikelijk van gewoven polyester of van een polymeer genaamd ePTFE wordt gemaakt. Terwijl het gebruik van stentgrafts toenam, steeg ook het aantal beschreven griepachtige symptomen in patiënten na implantatie. In **Hoofdstuk 7** wordt de incidentie van het post-implantatie syndroom gerapporteerd in meer dan honderd en vijftig patiënten die middels EVAR zijn behandeld. Ongeveer een derde van de patiënten ontwikkelde het post-implantatie syndroom, een samenstelling van koorts en inflammatie, en een sterke associatie werd waargenomen met geweven polyester, ook na multivariabele correctie. Hoewel de lange termijn consequenties van het post-implantatie syndroom onduidelijk zijn kunnen deze resultaten de ontwikkeling van toekomstige stentgrafts beïnvloeden.

Ena ander aspect van EVAR is de aanpak van zijtakken. Tijdens open chirurgie worden de meeste zijtakken, zoals naar de ruggenwervels, onderbonden. Bij EVAR blijven deze onbehandeld, met de kans op het terug lekken van bloed, de zogenoemde type II *endoleaks*. Een controversiële ingreep in het geval van groei van de aneurysmazak na EVAR is het endoscopisch klemmen van de zijtakken en het openknippen of *fenestreren* van de groeiende aneurysmazak. In **Hoofdstuk 8** wordt de lange termijn follow-up beschreven van acht patiënten die een dergelijke procedure hebben ondergaan.
De uitkomst was zeer wisselend en onvoorspelbaar. Bij een aantal patiënten persisteerde een *endoleak* of keerde het terug, en in een aantal patiënten was hernieuwde groei van de aneurysmazak de aanleiding voor later herstel middels een open buikoperatie. Derhalve lijkt deze procedure niet aan te raden in de behandeling van groei van een aneurysma na een endovasculaire behandeling.

Onze aanpak was niet de enige poging om tot de optimale behandelstrategie te komen voor type II *endoleaks*. Ondanks de vele publicaties, met veelal conflicterende data over de ontstaansgeschiedenis van type II *endoleaks*, is er geen consensus over de drempel voor behandeling van een type II *endoleak* en er bestaat controverse over de optimale behandelwijze. In de literatuur, welke in **Hoofdstuk 9** wordt besproken, lijkt de strategie om behandeling te reserveren voor patiënten die een persisterend type II *endoleak* én ook nog groei van het aneurysma hebben de meeste steun te hebben onder vaatchirurgen. Wij onderbouwen dat groei van een aneurysma zou moeten lijden tot een zorgvuldige zoektocht naar een meer hoge druk *endoleak* dan slechts een type II, wat meestal lijdt tot een spoedige behandeling van de ware oorzaak van de groei. In afwezigheid van een dergelijke verklaring zouden de chirurg en de patiënt kunnen berusten in een afwachtende houding met nauwkeurige observatie, aangezien een ruptuur van het aneurysma onwaarschijnlijk is.

LIST OF PUBLICATIONS

Peer reviewed articles for this thesis

1. **Voûte MT**, Winkel TA, Poldermans D. Optimal medical management around the time of surgery. *Heart. 2010;96:1842-1848.*

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Book chapter

- **Voûte MT**, Akkersdijk GP, Hendriks JM, Vrancken Peeters MPFM, Pattynama PMT, Verhagen HJM. Thrombolysis for acute and chronic arterial occlusion. *Innovative Cardiovascular Procedures, Branchereau A, Jacobs MJHM, ed. 2009*

Oral presentations

- 2014 Vascular Rounds, Rotterdam
- 2011 Vascular Annual Meeting, Chicago (two presentations)
- 2011 Vaatdagen, Noordwijkerhout
- 2010 Stafdag Heelkunde Erasmus MC, Rotterdam *(winner 'Zilveren Kreeft')*
- 2010 Vascular Annual Meeting, Boston
- 2010 Chirurgendagen, Veldhoven (four presentations)
- 2010 Vaatdagen, Noordwijkerhout
- 2009 Stafdag Heelkunde Erasmus MC, Rotterdam
- 2009 European Society of Vascular Surgery Annual Meeting, Oslo
- 2009 Vascular Annual Meeting, Denver
- 2008 Stafdag Heelkunde Erasmus MC, Rotterdam
- 2008 Najaarsvergadering Nederlandse Verenging voor Vaatchirurgie, Zeist

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Canlarım, sizi çok seviyorum!

Erasmus MC
Universitair Medisch Centrum Rotterdam

PhD PORTFOLIO

Summary of PhD training and teaching activities

PhD student:	Michiel Thomas Voûte	PhD Period: 2009-2014
Department:	Vascular Surgery / Anaesthesiology	Promotores:
Research School:	COEUR	H.J.M. Verhagen & R.J. Stolker

1. PhD Training

Courses	**Year**	**ECTS**
- CPO; Good Clinical Practice	2010	1.5
- NIHES; Introduction to Data-analysis	2010	1.0
- COEUR; Cardiovascular pharmacology	2010	1.5
- NIHES; Regression Analysis for Clinicians	2011	1.9
Seminars & Workshops		
- Journal club, Research meetings, Vascular Rounds	2009-2014	5.7
- COEUR PhD Day	2011	0.8
Presentations		
- National lectures	2009-2011	2.8
- International lectures	2009-2011	3.5
Symposia & Meetings		
- National conferences	2009-2011	2.1
- International conferences	2009-2011	7.5

2. Teaching

Supervising	**Year**	**ECTS**
- BSc students at the Technical University Delft	2009	3.0
- First aid for medical student – as examinator	2010	0.5
- MSc Medical students	2010	1.2
Other activities		
- Organization COEUR PhD Day	2011	1.5

CURRICULUM VITAE

Michiel Thomas Voûte is op 4 oktober 1981 geboren te Amsterdam. Nadat hij op veertienjarige leeftijd een vaatoperatie met Professor Frans Moll bijwoonde was hij verkocht aan de vaatchirurgie. Na het behalen van zijn gymnasium diploma studeerde hij Spaanse Taal aan de Universiteit van Barcelona.

In 2000 begon hij met de studie Bouwkunde aan de Technische Universiteit in Delft. Dit leverde hem een rijk studentenleven in Delft op, waar hij ook zijn latere echtgenote leerde kennen. Overigens ontstond de klik pas nadat zij hem de hoofdrol zag vertolken in Oscar Wilde's "An Ideal Husband"…

Al snel stapte hij over naar Geneeskunde aan de Erasmus Universiteit Rotterdam. Tijdens zijn doctoraal onderzoek op de afdeling Vaatchirurgie zette hij een samenwerking op met de vakgroep Biomechanische Wetenschappen aan de TU Delft.

In 2009 behaalde hij zijn artsexamen en startte hij met zijn promotieonderzoek bij de afdelingen Vaatchirurgie (Prof.dr. H.J.M. Verhagen) en Anesthesiologie (Prof.dr. R.J. Stolker), wat resulteerde in dit proefschrift.

In 2012 deed hij klinische ervaring op in het Maasstad Ziekenhuis in Rotterdam, waarna hij op 1 januari 2013 is gestart met zijn opleiding tot chirurg in het IJsselland Ziekenhuis, onder supervisie van dr. I. Dawson en dr. B.P.L. Wijnhoven.

Naast zijn werk besteed Michiel zijn tijd het liefst aan golf en koken (vooral toetjes) en natuurlijk zijn vrouw Demet en hun kinderen. Bovendien werkt hij al jaren aan zijn eerste plaat, welke nog altijd niet op de radio is gedraaid…