Asymptomatic Low Ankle-Brachial Index in Vascular Surgery Patients: A Predictor of Perioperative Myocardial Damage

W.-J. Flu a, J.-P. van Kuijk a, M.T. Voûte b, R. Kuiper a, H.J.M. Verhagen b, J.J. Bax c, D. Poldermans b,*

a Department of Anesthesiology, Erasmus Medical Center, Rotterdam, The Netherlands
b Department of Vascular Surgery, Erasmus Medical Center, Rotterdam, The Netherlands
c Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

Submitted 17 July 2009; accepted 6 September 2009
Available online 7 October 2009

Abstract
Objectives: This study evaluated the prognostic value of asymptomatic low ankle-brachial index (ABI) to predict perioperative myocardial damage, incremental to conventional cardiac risk factors imbedded in cardiac risk indices (Revised Cardiac index and Adapted Lee index).

Materials and methods: Preoperative ABI measurements were performed in 627 consecutive vascular surgery patients (carotid artery or abdominal aortic aneurysm repair). An ABI < 0.90 was considered abnormal. Patients with ABI > 1.40 or (a history of) intermittent claudication were excluded. Serial troponin-T measurements were performed routinely before and after surgery. The main study endpoint was perioperative myocardial damage, the composite of myocardial ischaemia and infarction. Multivariate regression analyses, adjusted for conventional risk factors, evaluated the relation between asymptomatic low ABI and perioperative myocardial damage.

Results: In total, 148 (23%) patients had asymptomatic low ABI (mean 0.73, standard deviation ± 0.13). Perioperative myocardial damage was recorded in 107 (18%) patients. Multivariate regression analyses demonstrated that asymptomatic low ABI was associated with an increased risk of perioperative myocardial damage (odds ratio (OR): 2.4, 95% CI: 1.4–4.2)

Conclusions: This study demonstrated that asymptomatic low ABI has a prognostic value to predict perioperative myocardial damage in vascular surgery patients, incremental to risk factors imbedded in conventional cardiac risk indices.

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complications reflects the high prevalence of underlying ischaemic heart disease. Adequate preoperative evaluation is inevitable in vascular surgery patients to (1) identify patients at increased cardiac risk, (2) initiate risk-reduction therapy and (3) select optimal surgical and anaesthesia techniques.

In conventional preoperative cardiac risk indices (Revised Cardiac Risk index and Adapted Lee index), age, heart failure, ischaemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus and high-risk surgery have been identified as independent predictors of perioperative cardiovascular events.

Peripheral arterial disease (PAD) is associated with an increased risk of cardiovascular mortality and morbidity. The ankle-brachial index (ABI) is a simple non-invasive test to screen patients with suspected PAD. In the non-surgical setting, a resting low ABI (ABI < 0.90) has been associated with a two- to fourfold increased risk of cardiovascular mortality or severe cardiovascular events compared with normal ABI. Low ABI has demonstrated to improve risk prediction for cardiovascular mortality and major non-fatal myocardial infarction (non-surgical setting), even beyond risk prediction properties using cardiac risk scores. However, the predictive value of asymptomatic low ABI for perioperative myocardial damage has not been studied yet. The current study evaluated if asymptomatic low ABI has a predictive value for perioperative myocardial damage, independent from conventional risk factors imbedded in conventional cardiac risk indices.

Material and Methods

Study population

The original study population consisted of 1113 consecutive patients undergoing vascular surgery during the period 2002–2009. The study was performed at the Erasmus Medical Center in Rotterdam, a tertiary hospital in the Netherlands. After exclusion of (1) lower-extremity arterial or abdominal aortic stenosis repair patients, (2) patients with (a history of or current) intermittent claudication assessed with the Edinburgh questionnaire and (3) patients with asymptomatic ABI > 1.40; a total 627 patients were included (Fig. 1). The study was approved by the hospital’s ethics committee and performed with the informed consent of all patients.

Baseline characteristics

Prior to surgery, a detailed history was obtained from every patient. Clinical data included age, sex, ischaemic heart

Figure 1 Overview of the selected patient population. ABI = ankle-brachial index.
disease (defined as a history of myocardial infarction, coronary revascularisation or the presence of pathologic Q-waves on preoperative electrocardiogram), cerebrovascular disease (defined as a history of ischaemic or haemorrhagic stroke), renal dysfunction (serum creatinine $>2.0 \text{ mg/dL}^{-1}$), diabetes mellitus (fasting blood glucose $\geq 6.1 \text{ mmol/L}^{-1}$ or requirement of anti-diabetic medication), hypertension (blood pressure $\geq 140/90 \text{ mmHg}$ in nondiabetics and $\geq 130/80 \text{ mmHg}$ in diabetics or requirement of antihypertensive medication), hypercholesterolemia (history of hypercholesterolemia or low-density lipoprotein (LDL) cholesterol $>3.5 \text{ mmol/L}^{-1}$), chronic obstructive pulmonary disease (history of chronic obstructive pulmonary disease or according to the Global Initiative on Obstructive Lung Diseases classification) and smoking status. The use of the prescription medications was captured and included beta-blockers, statins, angiotensin-converting enzyme inhibitors, aspirin and oral anticoagulants. Preoperatively, transthoracic echocardiography was performed in all patients using a hand-held Acuson Cypress Ultrasound System (7V3c transducer) manufacturers address 1220 Charleston Road, Mountain View, CA 94043. Standard parasternal and apical two- and four-chamber views were obtained during rest with the patient in the left lateral decubitus position, as recommended.

Ankle-brachial index

The ABI at rest was measured in each patient by trained technicians, using a Doppler ultrasonic instrument with an 8-MHz vascular probe (Imexdop CT+ Vascular Doppler; Nicolet Vascular, Madison, WI, USA). The ABI in the right and left leg was calculated by dividing the right and the left ankle pressures by the brachial pressure. The higher of the two brachial blood pressures was used if a discrepancy in systolic blood pressure was present. Further, the higher of the dorsalis pedis and posterior tibial artery pressures was used if a discrepancy in systolic blood pressure between the two arteries was measured. Asymptomatic low ABI was defined as an ABI $< 0.90$ with an inter- and intra-observer agreement of 97% and 98%, as shown previously.

Study outcomes

The main study endpoints were perioperative myocardial damage (defined as non-fatal myocardial ischaemia or infarction up to 30 days after surgery) and long-term mortality. Serial electrocardiograms and troponin-T measurements were obtained from all patients prior to surgery, postoperatively on days 1, 3 and 7 and before discharge. Myocardial ischaemia was present in patients with normal preoperative and elevated ($>0.03 \text{ ng/ml}^{-1}$) troponin-T levels postoperatively. Elevated troponin-T levels in combination with electrocardiographic changes (new-onset ST–T changes and pathological Q-waves) or symptoms of angina pectoris defined myocardial infarction. Patients with elevated troponin-T levels prior to surgery were not included in the study. Long-term mortality was assessed by approaching the municipal civil registries. Median follow-up was 2 years (interquartile range (IQR) 1–3).

Statistical analysis

Dichotomous data are described as numbers and percentages. Continuous variables are described as mean $\pm$ standard deviation (SD). Continuous data were compared using ANOVA and categorical data were compared using a chi-square test. Cox regression analyses were performed to evaluate the relationship between asymptomatic low ABI and the study endpoint, perioperative myocardial damage and long-term mortality. Cumulative long-term survival was determined using the Kaplan–Meier method. Multivariate regression analyses were adjusted for sex, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease, current smoking and risk factors imbedded in conventional cardiac risk indices (age, ischaemic heart disease, symptomatic heart failure, cerebrovascular disease, renal dysfunction, diabetes mellitus and high-risk surgery).

We report both the crude and the adjusted odds ratio (OR) and hazard ratios (HRs) with their 95% confidence intervals (95% CIs). For all tests, a $P$-value $<0.05$ (two-sided) was considered significant. All analyses were performed using SPSS Inc., Chicago, IL, USA.

Results

Prevalence of PAD and baseline characteristics

The initial study population consisted of 690 patients. In total, 54 patients with (a history of) intermittent claudication and nine patients with an asymptomatic ABI $> 1.40$ were excluded from the analyses. Therefore, 627 patients, without (a history of) intermittent claudication, undergoing carotid artery stenosis (N = 241) or abdominal aortic aneurysm (N = 386) repair were included in the study. In total, 148 (23%) patients had asymptomatic low ABI (mean 0.73, SD $\pm$ 0.13). The distribution of asymptomatic low ABI values is demonstrated in Fig. 2. In addition, baseline characteristics stratified to ABI are shown in Table 1. The majority of patients were males (82%) and the mean age was 70 (SD $\pm$ 8.6) years. Asymptomatic low ABI was associated with ischaemic heart disease, renal dysfunction, smoking and a left ventricular ejection fraction $<40%$.

Perioperative myocardial damage

The study endpoint, perioperative myocardial damage, was reached in 107 (17%) patients, as shown in Table 2. Of these patients, 76 (71%) had myocardial ischaemia and 31 (29%) had myocardial infarction. Symptoms of angina pectoris were reported in only six (6%) patients. As demonstrated in Table 2, the prevalence of perioperative myocardial damage was the highest in patients undergoing AAA repair of open surgery. In addition, 32% (47/148) of patients with
asymptomatic low ABI had perioperative myocardial damage compared with 13% (60/479) of patients with normal ABI.

Multivariate analyses showed that risk factors imbedded in the Revised Cardiac index and Adapted Lee index (combined risk factors) were predictive for perioperative myocardial damage, as shown in Table 3A, Model 1. When including ABI in the model (Table 3A, Model 2 + 3), asymptomatic low ABI was independently associated with an increased risk of perioperative myocardial damage with an OR of 2.4 (95% CI: 1.4–4.2). The risk for developing myocardial damage was higher in patients with asymptomatic ABI < 0.70 (OR: 2.6, 95% CI: 1.4–5.1) compared with patients with asymptomatic ABI 0.70–0.89 (OR: 2.3, 95% CI: 1.3–4.4). In addition, patients with low ABI and (a history of) intermittent claudication had the highest risk for developing perioperative myocardial damage (OR: 2.8, 95% CI: 1.2–6.4).

Multivariate sub-analyses performed in patients undergoing AAA repair, and patients undergoing carotid repair separately, demonstrated that asymptomatic low ABI was associated with an increased risk for myocardial damage in both groups with ORs of 1.9 (95% CI: 1.1–3.6) and 5.3 (95% CI: 2.4–19.8), respectively.

**Long-term mortality**

In total, 111 (18%) patients died during follow-up (Table 2) and the prevalence of long-term mortality was the highest in patients undergoing AAA repair. Of the patients who died, 36% (40/111) had perioperative myocardial damage and 39% (43/111) patients had asymptomatic low ABI. Cumulative 6-year survival (log rank p < 0.01) is shown in Fig. 3. Survival rates in patients with normal ABI and asymptomatic low ABI were (1) 87 ± 2% and 72 ± 5% during a 2-year follow-up, (2) 76 ± 3% and 59 ± 6% during a 4-year follow-up and (3) 60 ± 6% and 48 ± 9% during a 6-year follow-up, respectively.

Multivariate analyses showed that the combined risk factors were predictive for long-term mortality, as shown in Table 3B, Model 1. When including ABI in the model (Table 3B, Model 2 + 3), asymptomatic low ABI was independently associated with an increased risk of long-term mortality with a HR of 1.9 (95% CI: 1.2–2.8). The risk of long-term mortality was higher in patients with asymptomatic ABI < 0.70 (HR: 2.4, 95% CI: 1.5–3.8) compared with patients with asymptomatic ABI 0.70–0.89 (HR: 1.6, 95% CI: 1.1–2.6). In addition, patients with low ABI and (a history of) intermittent claudication had the highest risk of long-term mortality (HR: 3.0, 95% CI: 1.2–3.4).

Multivariate sub-analyses performed in patients undergoing AAA repair, and patients undergoing carotid repair separately, demonstrated that asymptomatic low ABI was associated with an increased risk for long-term mortality in both groups with HRs of 1.8 (95% CI: 1.2–3.0) and 2.3 (95% CI: 1.7–7.9), respectively.

**Discussion**

The current study demonstrated that asymptomatic low ABI was present in around one out of four patients undergoing carotid artery stenosis or abdominal aortic aneurysm repair. To our knowledge, this study is the first to
demonstrate that asymptomatic low ABI has prognostic value to predict perioperative myocardial damage in vascular surgery patients, incremental to risk factors imbedded in conventional cardiac risk indices.

Ischaemic heart disease, cerebrovascular disease and PAD result from atherosclerotic arterial disease. Atherosclerosis is a systemic inflammatory disease of the vasculature and a response to injury, lipid peroxidation and inflammation. The process of atherosclerosis is known to affect multiple sections of the arterial tree simultaneously. Large international registries, such as the REACH registry, have shown a high prevalence of multiple-affected vascular beds in patients with PAD (around 20%) indicating that these patients often have concomitant ischaemic heart or cerebrovascular disease. The ABI is a non-invasive and reliable indicator for the atherosclerotic status of the lower leg vasculature. Multiple studies have demonstrated that the majority of patients with PAD, defined as ABI < 0.90, are asymptomatic. Patients with asymptomatic PAD have an increased risk for cardiovascular disease, equal to patients with intermittent claudication. The high prevalence of asymptomatic PAD suggests that ABI should be systematically measured in high-risk hospitalised patients to ensure that appropriate secondary prevention programmes are initiated. In our patient population, three out of four patients with low ABI did not have (a history of) intermittent claudication.

The current study is the first to demonstrate that, after adjusting for risk factors imbedded in conventional cardiac risk indices, asymptomatic low ABI was associated with an increased risk of perioperative myocardial damage in vascular surgery patients. The prevalence of myocardial damage after vascular surgery is shown in Table 2 and Table 3A.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Ankle-brachial index and post operative outcome.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>All N = 627</td>
</tr>
<tr>
<td>Perioperative myocardial damage</td>
<td>All procedures</td>
</tr>
<tr>
<td></td>
<td>AAA open procedures</td>
</tr>
<tr>
<td></td>
<td>endovascular procedures</td>
</tr>
<tr>
<td></td>
<td>Carotid open procedures</td>
</tr>
<tr>
<td></td>
<td>endovascular procedures</td>
</tr>
<tr>
<td>Long-term mortality</td>
<td>All procedures</td>
</tr>
<tr>
<td></td>
<td>AAA open procedures</td>
</tr>
<tr>
<td></td>
<td>endovascular procedures</td>
</tr>
<tr>
<td></td>
<td>Carotid open procedures</td>
</tr>
<tr>
<td></td>
<td>endovascular procedures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3A</th>
<th>Multivariate association between ankle-brachial index and perioperative myocardial damage.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>Model 1a</td>
</tr>
<tr>
<td>Myocardial damage</td>
<td>Odds ratio [95% CI]</td>
</tr>
<tr>
<td>Combined Risk Factors</td>
<td></td>
</tr>
<tr>
<td>Age (&gt;70 years)</td>
<td>1.6 [2.1–5.2]</td>
</tr>
<tr>
<td>Symptomatic heart failure</td>
<td>3.2 [1.7–5.5]</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>2.4 [1.3–4.6]</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1.4 [1.9–6.1]</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>1.7 [1.8–7.7]</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.2 [1.1–3.0]</td>
</tr>
<tr>
<td>High-risk surgery</td>
<td>7.3 [3.6–14.6]</td>
</tr>
</tbody>
</table>

| ABI | |
| 0.90 | |
| <0.90 asymptomatic | |
| <0.90 intermittent claudication | |

95% CI = 95% confidence interval, ABI = ankle-brachial index.

a Model 1: Predictive value of Combined Risk Factors derived from the RCR and Adapted Lee Risk Indices: multivariate analysis adjusted for: gender, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease and current smoking.

b Model 2: Predictive value of low ABI: multivariate analyses adjusted for Combined Risk Factors, gender, left ventricular ejection fraction <40%, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease and current smoking.

c Model 3: Predictive value of low ABI: multivariate analyses adjusted as in model 2 and for medication use (beta-blockers, statines, aspirin, oral anticoagulants and angiotensin-converting enzyme inhibitors).
ischaemia has been evaluated in the non-surgical setting that focussed on patients with symptomatic PAD and without clinical ischaemic heart disease. In a study conducted by Raby et al., the prevalence of myocardial ischaemia detected with Holter monitoring was around 18% and was demonstrated to be an independent predictor of 2-year prognosis.\textsuperscript{25}

The ABI collaboration group demonstrated that low ABI has the potential to improve risk prediction for major non-fatal myocardial infarction, beyond the Framingham Risk Score.\textsuperscript{11} Recently, Mostaza et al. evaluated silent myocardial ischaemia, detected with exercise stress tests, in 85 patients with asymptomatic low ABI. Although the sample size in this study was limited, the authors found that a positive exercise test was present in 16% of patients with asymptomatic low ABI, compared with 3.5% in control patients.\textsuperscript{26} As the authors themselves state, the real prevalence of ischaemic heart disease in these patients remains unknown, because no additional tests were performed in patients with a positive exercise test. To our knowledge, the impact of asymptomatic low ABI on perioperative myocardial damage in vascular surgery patients has not been studied yet. The current study demonstrated that the risk of patients with asymptomatic low ABI to develop perioperative myocardial damage was more than twice as high compared with patients with normal ABI. In line with previous studies, endovascular surgery was associated with a reduced incidence of perioperative myocardial damage, possibly explained by reduced myocardial stress during endovascular procedures.\textsuperscript{27,28}

Perioperative myocardial damage is most often silent and the great majority of these patients (95%) remain untreated, which might contribute to an increased risk of long-term cardiovascular mortality.\textsuperscript{25,27,29–31}

Multiple studies have demonstrated that low ABI has the potential to improve prediction of long-term mortality over and above conventional risk factors.\textsuperscript{9,11} In line with these studies, we found that after adjusting for conventional risk factors, imbedded in conventional cardiac risk indices, asymptomatic low ABI was associated with increased risk of long-term mortality after vascular surgery.

Our results indicate that preoperative counselling of vascular surgery patients undergoing carotid stenosis or aortic aneurysm repair should include systematic screening

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**Table 3B  Multivariate association between ankle-brachial index and long-term mortality.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Model 1\textsuperscript{a}</th>
<th>Model 2\textsuperscript{b}</th>
<th>Model 3\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term mortality</td>
<td>Hazard ratio [95% CI]</td>
<td>Hazard ratio [95% CI]</td>
<td>Hazard ratio [95% CI]</td>
</tr>
<tr>
<td>Combined risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (&gt;70 years)</td>
<td>3.2 1.3–4.2</td>
<td>3.0 1.2–4.3</td>
<td>3.0 1.2–4.2</td>
</tr>
<tr>
<td>Symptomatic heart failure</td>
<td>2.6 1.6–3.4</td>
<td>2.5 1.6–4.0</td>
<td>2.3 1.4–3.7</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>2.0 1.2–4.9</td>
<td>1.8 1.1–5.2</td>
<td>1.7 1.1–5.4</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1.2 1.1–3.2</td>
<td>1.3 1.2–3.8</td>
<td>1.3 1.1–3.9</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>2.3 1.6–4.0</td>
<td>1.9 1.1–3.7</td>
<td>1.9 1.1–3.9</td>
</tr>
<tr>
<td>Diabetes mellitus, insulin dep.</td>
<td>1.2 1.2–3.5</td>
<td>1.7 1.4–3.7</td>
<td>1.7 1.4–3.8</td>
</tr>
<tr>
<td>High-risk surgery</td>
<td>2.9 1.6–3.4</td>
<td>2.0 1.2–3.8</td>
<td>1.9 1.1–3.7</td>
</tr>
<tr>
<td>ABI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥0.90</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>&lt;0.90 asymptomatic</td>
<td>–</td>
<td>2.0 1.3–3.0</td>
<td>1.9 1.2–2.8</td>
</tr>
<tr>
<td>&lt;0.90 intermittent claudication</td>
<td>–</td>
<td>3.1 1.2–3.6</td>
<td>3.0 1.2–3.4</td>
</tr>
</tbody>
</table>

95% CI = 95% confidence interval, ABI = ankle-brachial index.

\textsuperscript{a} Model 1: Predictive value of Combined Risk Factors derived from the RCR and Adapted Lee Risk Indices: multivariate analysis adjusted for: gender, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease and current smoking.

\textsuperscript{b} Model 2: Predictive value of low ABI: multivariate analyses adjusted for Combined Risk Factors, gender, left ventricular ejection fraction <40%, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease and current smoking.

\textsuperscript{c} Model 3: Predictive value of low ABI: multivariate analyses adjusted as in model 2 and for medication use (beta-blockers, statines, aspirin, oral anticoagulants and angiotensin-converting enzym inhibitors).
for asymptomatic lower-extremity PAD by measuring the ABI. A recent study conducted by Hoeks et al. has observed a care gap between guideline recommendations and clinical practice in PAD patients. Standard screening for asymptomatic PAD could reduce this observed care gap by initiating recommended medical treatment with (1) statins, (2) antiplatelet therapy to reduce the risk of adverse cardiovascular ischaemic events and (3) angiotensin-converting enzyme inhibition, which may be considered for cardiovascular risk reduction. The presence of asymptomatic lower-extremity PAD creates the need for optimal lifestyle modification and screening for additional risk factors. Our results indicate that asymptomatic lower-extremity PAD is associated with an increased risk for systolic left ventricular dysfunction and ischaemic heart disease. Standard cardiac evaluation during preoperative counselling should therefore be considered in asymptomatic lower-extremity PAD patients. Asymptomatic systolic left ventricular dysfunction with an ejection fraction <40% should be treated with an angiotensin-converting enzyme inhibitor or, in case of intolerance, an angiotensin-receptor blocker. In patients with a history of ischaemic heart disease, beta-blockers treatment should be initiated as well. Patients with asymptomatic lower-extremity PAD are at increased risk for perioperative myocardial damage. Perioperative monitoring with cardiac biomarkers, such as troponin-T, could be justified since the majority of perioperative myocardial damage is silent and patients therefore remain untreated. Available evidence suggests that beta-blockers reduce perioperative ischaemia and the latest American College of Cardiology/American Heart Association (ACC/AHA) guidelines on perioperative care provide a (Class IIa, Level of evidence B) recommendation to initiate beta-blocker treatment in patients with one or more cardiovascular risk factors.

Potential limitations of these data merit consideration. First, the study population consisted of patients referred to a tertiary referral center and may not fully represent a general population scheduled for elective vascular surgery. Second, we did not address non-fatal cardiovascular events during long-term follow-up. Third, we included both open and endovascular surgical procedures. The number of endovascular procedures has increased in the past 3 years, which has influenced the median follow-up period.

In conclusion, the current study demonstrated that asymptomatic low ABI has prognostic value to predict perioperative myocardial damage in vascular surgery patients, incremental to conventional risk factors imbedded in the RCR and Adapted Lee Risk indices. These data suggest that ABI measurements should be systematically performed in patients scheduled for carotid artery stenosis or abdominal aortic aneurysm repair to ensure that appropriate perioperative treatment is initiated.

Conflict of Interest

Willem-Jan Flu has no conflicts of interest to disclose.
Jan-Peter van Kuijk has no conflicts of interest to disclose.
Michiel T Voûte has no conflicts of interest to disclose.
Ruud Kuiper has no conflicts of interest to disclose.

Hence JM Verhagen has no conflicts of interest to disclose.
Jeroen J Bax has no conflicts of interest to disclose.
Don Poldermans has no conflicts of interest to disclose.

Funding

Willem-Jan Flu, Jan-Peter van Kuijk and Michiel Voûte are supported by an unrestricted grant from “lijk en leven” Foundation, Rotterdam, The Netherlands.

Acknowledgements

All authors contributed to the study conception and design, revision of the manuscript and approved the final version. In addition, Willem-Jan Flu and Jan-Peter van Kuijk were responsible for the statistical analysis and Hence JM Verhagen, Jeroen J Bax and Don Poldermans contributed to the interpretation of the analysis. Willem-Jan Flu, Jan-Peter van Kuijk and Don Poldermans were responsible for writing of the manuscript. Willem-Jan Flu, Jan-Peter van Kuijk, Michiel Voûte and Ruud Kuiper took part in the data acquisition and Don Poldermans supervised the study and was responsible for the funding source.

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