Perioperative asymptomatic cardiac damage after endovascular abdominal aneurysm repair is associated with poor long-term outcome

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Background: **Endovascular abdominal aortic aneurysm (AAA) repair (EVAR) is associated with a decreased incidence of perioperative cardiac complications compared with open repair. However, EVAR is not associated with long-term survival benefit. This study assessed the effect of perioperative asymptomatic cardiac damage after EVAR on long-term prognosis.**

Methods: **In 220 patients undergoing elective EVAR, routine sampling for levels of cardiac troponin T and electrocardiography (ECG) were performed on days 1, 3, and 7 during the patient's hospital stay. Elevated cardiac troponin T was defined as serum concentrations ≥0.01 ng/mL. Asymptomatic cardiac damage was defined as cardiac troponin T release without symptoms or ECG changes. The median follow-up was 2.9 years. Survival status was obtained by contacting the Office of Civil Registry.**

Results: **Release of cardiac troponin T (median, 0.08 ng/mL) occurred in 24 of 220 patients, of whom 20 (83%) were asymptomatic and without ECG changes. Patients with asymptomatic cardiac damage had a mortality rate of 85% after 2.9 years vs 51% for patients without perioperative cardiac damage ($P < .001$). Also after adjustment for clinical risk factors and medication use applying multivariate Cox regression analysis, asymptomatic cardiac damage was associated with a 2.3-fold increased risk for death (95% confidence interval, 1.1-5.1). Statin use was associated with a reduced long-term risk for death (hazard ratio, 0.5; 95% confidence interval, 0.3-0.9).**

Conclusion: **Asymptomatic cardiac damage in patients undergoing EVAR is associated with poor long-term outcome. Routine perioperative cardiac screening after EVAR might be warranted. (J Vasc Surg 2009;50:749-54.)**

Endovascular abdominal aneurysm (AAA) repair (EVAR) is associated with fewer perioperative cardiac complications compared with open AAA repair. Although symptomatic and asymptomatic cardiac damage occurs in up to 25% of patients undergoing open AAA repair, the incidence of symptomatic and asymptomatic cardiac damage in EVAR is about 10%, even in those at high cardiac risk.[1-3]

Despite this perioperative cardiac advantage of EVAR, the early benefits of EVAR dissipate ≤2 years, as has been shown in the Dutch Randomised Endovascular Aneurysm Management (DREAM) and Comparison of Endovascular Aneurysm Repair with Open Repair in Patients with Abdominal Aortic Aneurysm (EVAR-1) trials.[4,5] Although aneurysm-related survival in DREAM and EVAR-1 was better in patients treated with endovascular techniques, all-cause mortality was similar in both groups. Cardiac-frail patients are less likely to survive the stress of open repair than the relatively safe endovascular repair. Consequently, several studies have suggested that long-term outcome after successful AAA repair is related primarily to the presence and extent of underlying coronary artery disease and not to treatment modality.[6,7]

If patients are screened rigorously after EVAR, however, a substantial proportion will have asymptomatic cardiac damage as assessed by cardiac tronopin T measurements,[1,2] which is a sensitive and specific marker for myocardial injury.[8] However, the effect of elevations of cardiac troponin T, without clinical evidence of myocardial ischemia and persistent electrocardiographic (ECG) abnormalities, is unknown.

If asymptomatic cardiac troponin T release after endovascular treatment is associated with poor long-term outcome, it might be used to identify those patients who will benefit from aggressive follow-up and medical treatment after EVAR. Therefore, we planned the current study to assess the prognostic value of asymptomatic cardiac troponin T release in patients undergoing EVAR.

METHODS

Patients. The study population consisted of 220 patients undergoing elective EVAR from January 2003 to November 2008. These patients were identified in a prospectively maintained database of all patients undergoing vascular surgery at Erasmus Medical Center, Rotterdam,

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Competition of interest: none.

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The Netherlands. The Medical Ethics Committee of Erasmus Medical Center approved the study.

Before surgery, a detailed cardiac history was obtained, and patients were screened for hypertension (blood pressure >140/90 mm Hg, or medical therapy to control hypertension) and diabetes mellitus (fasting glucose level >7.0 mmol/L, or medication to control diabetes). The presence of coronary artery disease was indicated by a previous myocardial infarction, previous coronary intervention, or present stable angina pectoris. Other cardiovascular risk factors documented were a history of cerebrovascular accident or transient ischemic attack, age >70 years, chronic heart failure, and chronic obstructive pulmonary disease (defined as a forced expiratory volume in 1 second <70% of age and gender predictive value, or medication use). Preoperative serum creatinine values were routinely obtained.

The Modification of Diet in Renal Disease formula [186 × (serum creatinine)–1.154 × (age)–0.203 × (0.742 if female) × (1.212 if African American)] was used to estimate the glomerular filtration rate (eGFR). Patients were categorized as having no renal impairment (eGFR >90 mL/min/1.73 m^2), mild renal impairment (60 to 90 mL/min/1.73 m^2), moderate renal impairment (30 to 60 mL/min/1.73 m^2), and severe renal impairment (<30 mL/min/1.73 m^2).

Additional cardiac stress testing. Preoperative stress testing at our institution is done according to the number of cardiac risk factors identified at preoperative screening. Patients without cardiac risk factors usually do not undergo additional cardiac stress testing. As is shown in the Dutch Echocardiographic Cardiac Risk Evaluation (DECREASE II) trial, patients with one or two factors also do not need additional cardiac stress testing.[9] Patients with three or more risk factors all undergo additional testing. Some patients included in the current study underwent EVAR before the DECREASE II trial was completed; thus, some patients with one or two risk factors also underwent additional cardiac stress testing. Because we did not have stress test results for all patients, we did not perform an analysis between preoperative stress testing and postoperative outcome.

Troponin measurement. Troponin T levels are routinely measured at our institution in patients undergoing major vascular surgery on postoperative days 1, 3, and 7 of the patient's hospital stay, and whenever clinically indicated by ECG changes consistent with myocardial ischemia or infarction. ECGs are routinely recorded preoperatively and on days 1, 3, and 7 of the patient's hospital stay, and at 30 days after surgery. Troponin T levels were measured by using a whole blood rapid test (TropT v2; Roche Diagnostics, Mannheim, Germany). Only patients with asymptomatic cardiac troponin T release (ie, without ischemic symptoms or new ECG abnormalities) were included in the current study.

End point. In January 2009 a follow-up was performed of all patients who survived major vascular surgery for at least 30 days. The primary end point was death from all causes to avoid misclassification among cardiac, arrhythmic, and noncardiac deaths. Information about vital status was requested from the Office of Civil Registry.

Statistical analysis. The Fisher exact test was used to compare dichotomous variables, and the Kruskal-Wallis test was used to compare continuous variables. The Kaplan-Meier method was used to evaluate the prognostic value of asymptomatic troponin release with respect to survival. Differences in survival curves were compared by the log-rank test.

Univariable Cox proportional hazard regression models were used to assess the independent association between troponin release, baseline clinical characteristics, and all-cause mortality. To avoid model over-fitting, we applied a clinical risk model used in the DECREASE studies.[9,10] In this model, 1 point is assigned for the following risk factors: age >70 years, myocardial infarction, angina pectoris, heart failure, diabetes mellitus, renal dysfunction, and history of cerebrovascular accident or transient ischemic attack. Patients with no risk factors are considered at low cardiac risk, those with 1 or 2 risk factors are at intermediate cardiac risk, and those with >3 risk factors are at high cardiac risk. Multivariable regression models were constructed by backward stepwise deletion of the least significant characteristics.

Hazard ratios (HR) and corresponding 95% confidence intervals (CI) are reported; continuous data are reported with the interquartile range (IQR). For all tests, a value of $P < .05$ was considered significant. All analyses were performed using SPSS 15.0 software (SPSS Inc, Chicago, Ill).

RESULTS

Patient characteristics. The study included 220 patients (88% men) undergoing EVAR. Their mean age was 72.9 ± 7.4 years. General anesthesia was used in 102 patients (47%). According to the cardiac risk score, the cardiac risk was low in 14%, intermediate in 60%, and high in 26%. Troponin T release was documented in 24 patients (10.9%) ≤30 days after surgery. Four patients (17%) had symptomatic troponin T release or ECG changes, or both, and 20 (83%) had asymptomatic troponin T release without ECG changes. Baseline differences between patients with and without asymptomatic troponin T release are reported in Table I. Patients who experienced asymptomatic troponin T release were more likely to have preoperative renal dysfunction; 11 of 20 (55%) of patients with postoperative asymptomatic troponin T release had an estimated GFR <60 mL/min/1.73 m^2 compared with 40 of 196 (20%) without postoperative troponin T release ($P < .01$). Postoperatively, 22 patients were admitted to the postanesthesia care unit or intensive care unit (ICU). Only two patients required an ICU stay longer than 1 day.

Long-term prognosis of patients with asymptomatic cardiac damage. The median follow-up was 2.9 years (IQR, 0.9-4.3 years), during which 46 patients (21%) died. Asymptomatic troponin T release was significantly associated with poor long-term survival in patients undergoing EVAR (Fig 1). In univariate analysis, patients with asymptomatic troponin T release had a 3.6-fold increased risk

Table I. Baseline clinical characteristics

Variable *No. (%) or mean ± SD*	*All patients* *(N = 216)*	*Troponin+* *(n = 20)*	*Troponin−* *(n = 196)*	P
Male	190 (88)	18 (90)	172 (88)	.77
Age, y	73 ± 7.4	77 ± 6.6	73 ± 7.4	<.01
Myocardial infarction	74 (34)	6 (30)	68 (35)	.81
Angina	53 (25)	6 (30)	47 (24)	.55
Heart failure	19 (9)	3 (15)	16 (8)	.30
TIA or CVA	30 (14)	5 (25)	25 (13)	.13
Diabetes	26 (12)	2 (10)	24 (12)	.77
Renal dysfunction	23 (11)	5 (25)	18 (9)	.03
Hypertension	122 (57)	10 (50)	112 (57)	.54
COPD	59 (27)	6 (30)	53 (27)	.78
Previous CABG or PCI	40 (19)	1 (5)	39 (20)	.13
β-blocker use	187 (87)	15 (75)	172 (88)	.11
Statins	125 (58)	9 (45)	116 (59)	.22
GFR, mL/min/1.73 m^2[a]				<.01
<30	10 (5)	4 (20)	6 (3)	
>30-60	41 (19)	7 (35)	34 (17)	
>60-90	110 (51)	6 (30)	104 (53)	
>90	55 (26)	3 (15)	52 (27)	

CABG, Coronary artery bypass grafting; *COPD,* chronic obstructive pulmonary disease; *CVA,* cerebrovascular accident; *GFR,* glomerular filtration rate; *PCI,* percutaneous coronary intervention; *SD,* standard deviation; *TIA,* transient ischemic attack.
[a]Estimated using the Modification of Diet in Renal Disease formula.

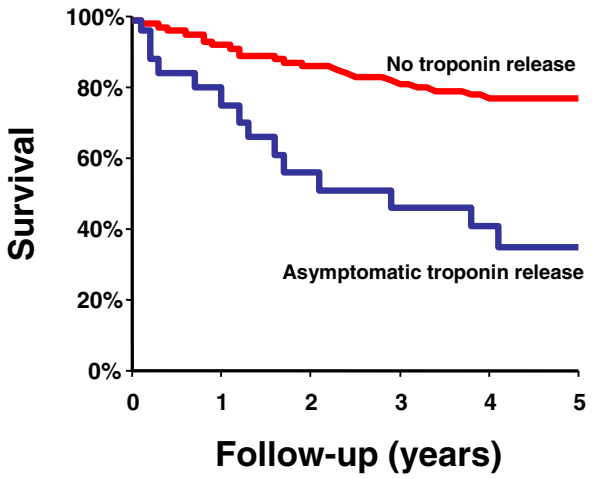

Fig 1. Long-term survival of patients without perioperative troponin release is compared with patients with asymptomatic troponin release.

(95% CI, 1.8-7.2) for death during follow-up. Other variables that were associated with poor long-term outcome included a history of ischemic heart disease (HR, 1.6; 95% CI, 0.9-2.9), heart failure (HR, 2.4; 95% CI, 1.1-5.2), renal failure (HR, 2.3; 95% CI, 1.1-4.8), and age >70 years (HR, 2.1; 95% CI, 1.1-4.3). Importantly, also in multivariate analysis, asymptomatic cardiac troponin release was still associated with a 2.3-fold (95% CI, 1.1-5.1) increased risk for all-cause mortality during a median follow-up of 2.9 years (Table II).

Long-term prognosis of patients with asymptomatic cardiac damage and renal dysfunction. A recurring discussion is whether asymptomatic cardiac troponin T release in patients with renal dysfunction has any clinical relevance. A separate analysis was done of the 51 patients who had an eGFR <60 mL/min/1.73 m^2; of these, 11 had asymptomatic cardiac troponin release that was associated with a 3.0-fold (95% CI, 1.2-7.5) increased risk for long-term mortality (Fig 2). Multivariate analysis also documented a significant 2.8-fold (95% CI, 1.1-7.3) increased risk for death when adjusted for the presence of ischemic heart disease, age >70 years, and congestive heart failure.

Table II. Multivariate Cox regression analysis for all-cause mortality[a]

Variable	*HR*	*95% CI*	P
Peri-op troponin release	2.33	1.07-5.07	.03
Age, per year increase	1.05	1.01-1.10	.02
Ischemic heart disease	1.88	0.99-3.55	.05
GFR[b] <60 mL/min/1.73 m^2	1.81	0.92-3.56	.09
Statin use	0.47	0.25-0.90	.02

CI, Confidence interval; *GFR,* glomerular filtration rate; *HR,* hazard ratio.
[a]Adjusted for age, gender, diabetes, stroke, chronic obstructive pulmonary disease, hypertension.
[b]Estimated using the Modification of Diet in Renal Disease formula.

Effect of statin therapy on long-term outcome. At the time of hospital discharge, 41% of patients were not receiving statin therapy. During follow-up, use of statins at hospital discharge was associated with a decrease in all-cause mortality compared with nonuse (HR, 0.52; 95% CI, 0.29-0.94, Fig 3). After adjustment for clinical baseline characteristics and perioperative troponin release, statin use was also associated with improved outcome (HR, 0.47; 95% CI, 0.25-0.90).

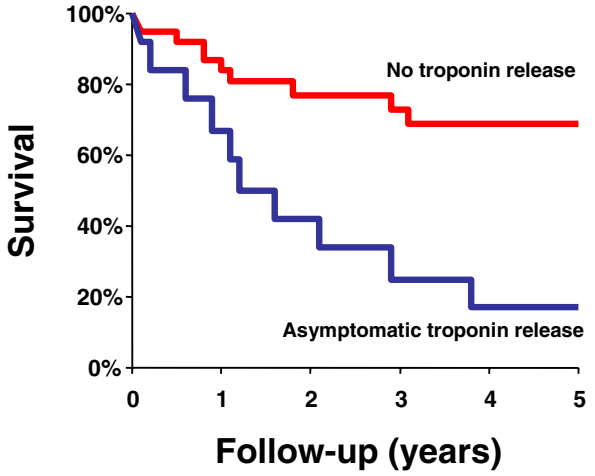

Fig 2. Long-term survival is shown of patients with an estimated glomerular filtration rate <60 mL/min/1.73 m^2 with and without asymptomatic perioperative troponin release.

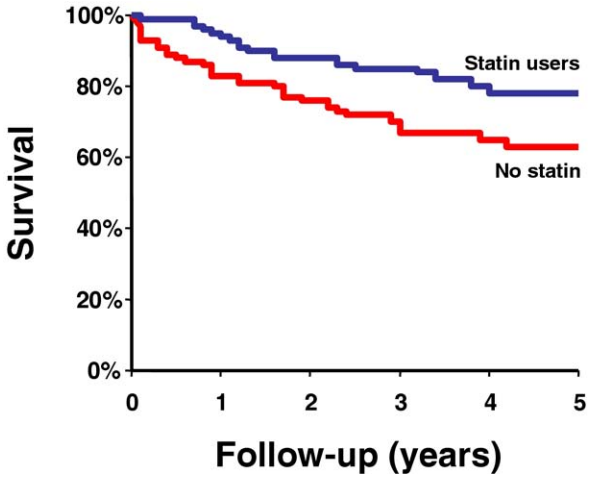

Fig 3. Long-term survival is shown in statin users and nonusers after endovascular abdominal aortic aneurysm repair.

DISCUSSION

The current study shows a strong association between perioperative asymptomatic cardiac troponin T release and poor long-term outcome after EVAR. Despite the relatively low surgical stress of EVAR, approximately 10% of patients sustain asymptomatic myocardial damage that will not be detected without routine postoperative cardiac troponin T measurements.

The perioperative benefits of EVAR are widely accepted, but the long-term benefit of EVAR is less well established. Although previous studies suggest a potential survival benefit free of cardiac events for patients undergoing EVAR, these patients are still considered to be at high risk for cardiac events compared with the general population.

The compromised long-term survival of EVAR patients might be explained by the high prevalence of symptomatic and asymptomatic underlying coronary artery disease. As was already shown 25 years ago by Hertzer et al,[11] only 6% of patients with an AAA have a healthy coronary artery tree, and 36% have severe coronary artery disease. More recent series using functional tests such as dobutamine stress echocardiography confirmed these findings. As has been shown previously, the presence and extent of coronary artery disease seems to have much greater effect on long-term survival of patients with AAA than the choice of treatment.[6]

The finding of cardiac troponin T in approximately 10% of patients undergoing EVAR is in line with previously published work. In a previous smaller study, we found a 10.2% incidence of perioperative myocardial injury after EVAR in 49 unselected patients.[12] Also in 55 EVAR patients at high clinical cardiac risk according to traditional cardiac risk factors, the incidence of perioperative myocardial injury was 13%, which is relatively low.[7] Other authors confirmed these findings. Abraham et al[1] found an incidence of 10% in patients undergoing elective EVAR. It is remarkable that none of these patients had clinical signs of ischemia and would thus have been missed if routine cardiac troponin T measurement had not been performed. These findings agree with the results of the current study, as 77% of patients with troponin release were asymptomatic.

The concealed cardiac damage might also explain the low incidence of ischemic cardiac complications reported in other studies and randomized trials. For example, the DREAM trial showed a 5.3% incidence of cardiac complications in the endovascular group, of which 66% were classified as being not severe.[13] Patients undergoing EVAR are usually hospitalized for only 2 or 3 days postoperatively; thus, it might be argued that the true incidence of myocardial damage is even higher than reported in the current study because troponin levels were only measured during hospitalization.

Cardiac troponin release occurs in almost 100% of patients with an acute coronary syndrome as a consequence of the ischemic cardiac event.[8] Indeed, troponin I and T are cardiac isoforms and solely expressed in cardiac muscles, making them very sensitive markers for myocardial injury. Several other conditions can trigger troponin release, however, including sepsis, systemic inflammatory response syndrome, pulmonary embolism, acute and chronic heart failure, and end-stage renal disease.[8] The cause of troponin release in these conditions is not clarified. A transient leakage of troponin of the cytosolic pool might be an explanation for troponin release into the bloodstream, in particular, in case of pulmonary embolism or after physical exercise.

The current study supports the observations in patients undergoing major open vascular surgery. In a study of 447 patients by Landesberg et al,[14] even minor elevations of cardiac troponin during the first 3 days postoperatively were associated with a twofold increased risk for long-term mortality after major vascular surgery. A study by Kertai et al[15] including 393 patients undergoing open aortic or

infrainguinal vascular surgery confirmed this twofold increased risk for patients with asymptomatic troponin release. A study by de Virgilio et al[16] of patients undergoing EVAR with an asymptomatic rise in creatine kinase-MB fraction or troponin found a clear trend for an increased risk for long-term mortality ($P = .09$). An important note to their study is that it began in 1996, when troponin essays were less sensitive. This is reflected in the 6% incidence of patients with troponin release in their study compared with 11% in our study.

Patients with renal dysfunction who undergo EVAR repair are considered to be at high risk for long-term events. In a study by Azizzadeh et al[17] in 398 patients, a reduced GFR was associated with a significantly increased risk for long-term mortality. The meaning of troponin release in patients with renal dysfunction is a matter of recurrent debate. Patients with end-stage renal disease often have levels of troponin >99th percentile.

In the current study, patients with renal dysfunction more frequently had postoperative asymptomatic troponin release; for these patients, the pattern of troponin release is of particular interest. Patients with renal dysfunction might have elevated troponin levels before the actual cardiac damage occurs; therefore, in the presence of a classic pronounced rise and fall of troponin levels in these patients, they still should be considered as having a cardiac event.[18]

The current study showed that new-onset perioperative troponin release in patients with moderate renal dysfunction (eGFR <60 mL/min/1.73 m^2) is associated with a poor long-term prognosis. Therefore, asymptomatic perioperative troponin release in patients with renal dysfunction should not be considered a relatively harmless condition.

The optimal treatment of patients with asymptomatic troponin release is still ill defined. As with all vascular surgical patients, statins and aspirin should be prescribed.[19,20] In the nonoperative setting, patients with non-ST elevation myocardial infarctions are usually prescribed aggressive antiplatelet therapy, such as clopidogrel.[21] Whether it would also improve long-term outcome in patients with marginally elevated levels of troponin T after EVAR remains to be determined.

The true incidence of myocardial damage may be even higher than reported in the current study because troponin was only measured during hospitalization, and many patients are discharged ≤3 days postoperatively. In fact, in the current study the median length of stay was 3 days; thus, some patients might have had troponin release after postoperative day 3 that was missed.

CONCLUSIONS

Perioperative asymptomatic troponin T release in patients undergoing EVAR is a marker for poor long-term survival, even in those with renal dysfunction. Although only 10% of patients experience asymptomatic troponin T release, 55% of deaths during 2.9 years of follow-up occurred in this group of patients. Stringent follow-up and adherence to secondary prevention guidelines in these patients is of utmost importance.

AUTHOR CONTRIBUTIONS

Conception and design: TW, OS, HV, DP
Analysis and interpretation: TW, OS, JK, JB, DP
Data collection: TW, OS, JK, HV
Writing the article: TW
Critical revision of the article: OS, JK, HV, JB, DP
Final approval of the article: TW, OS, JK, HV, JB, DP
Statistical analysis: TW, OS
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Overall responsibility: DP

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DISCUSSION

Dr W. Moore *(Los Angeles, Calif)*: How do we know that, in fact, that there has been myocardial damage just because you happen to have an asymptomatic troponin release in the absence of EKG changes?

Our cardiologists often describe the so called troponin leak phenomenon, particularly when there may be an episode of hypertension in the perioperative interval. I think your increased incidence of mortality may simply represent a higher risk group in which the troponin leak population occurred. You showed that there was a higher incidence of prior myocardial infarction and other comorbidities in the troponin leak group. Therefore I wonder if the troponin event is simply a marker for the higher risk group rather than a morbid event in of itself?

Dr Schouten: As shown on the slides on pathophysiology of troponin release, there must be a compromised membrane of the cardiomyocytes for troponin to be released into the bloodstream. This implies that there must be cardiac damage one way or the other.

We also did a subgroup analysis for patients who stayed at the ICU for at least two days after surgery, more or less the critically ill patients with episodes of hypotension, and also, in that group of patients, those with troponin release did much worse than patients without troponin release. While the exact pathophysiology is not entirely clear for this group of patients, the main message is that if you have a patient with cardiac troponin release, either it's symptomatic or asymptomatic, they do much worse on the long term. These patients probably will benefit from more aggressive medical therapy and more aggressive follow-up on the long term.

Dr J. Ricotta *(Washington, DC)*: I was actually going to ask you to elaborate on that last question. In your units, do you have a protocol for how you evaluate these patients after you find that they have asymptomatic troponin release. Do you have a standard algorithm for evaluation and management?

Dr Schouten: Currently we are performing another study in this patient population with asymptomatic cardiac troponin T release. It's called the DECREASE VII trial. And what we do in that trial is that we randomize patients who have asymptomatic cardiac troponin release to receive either clopidogrel on top of beta blockers, statins and aspirin, or placebo on top of this medication.

In terms of cardiac stress testing or coronary angiography, it depends on whether or not the patient will get eventually EKG abnormalities. If the patient remains asymptomatic and has no EKG abnormalities, we will not perform any other additional cardiac evaluation or cardiac tests.

Dr P. Goodney *(Lebanon, NH)*: We studied similar questions in our vascular study group in Northern New England. One of the questions we struggled with was a lack of a multivariate finding for beta blockers and statins. I noticed your model similarly didn't include those medical regimens. I thought you might comment on that.

Dr Schouten: At our unit all patients are on beta blockers, so it is impossible to find any benefit or harm of beta blockers in this study. What we have found in this study in terms of medication use—I did not include it in this presentation because of time restraints is that patients who were not on statins, which were approximately 30% of the patients, had a worse outcome than patients on statins. The odds ratio was approximately 0.65. So statins seem to work. But on the other hand, nowadays, all our patients will get statins anyway.

Dr P. Gloviczki *(Rochester, Minn)*: Have you looked at preoperative cardiac variables, cardiac risk factors, and would they predict your elevated troponin release?

Dr Schouten: One of the slides showed a multivariate analysis for predictors of asymptomatic cardiac troponin release, and these risk factors were more or less the same as for more hard endpoints like myocardial infarction and cardiac deaths.

Dr F. Mussa *(New York, NY)*: Along the same line of Dr. Gloviczki's question, did you go back and change your preoperative workup for those patients based on your troponin release? Nowadays, we're doing less extensive workup for patients with stable coronary disease undergoing vascular or endovascular procedures.

Dr Schouten: No, we did not change our preoperative workup based on these study results. Our current preoperative policy is based on earlier DECREASE studies, and in particular DECREASE II: patients with 1 risk factor can undergo surgery quite safely with beta blockers and statins. Also patients with 2 risk factors will benefit from statins and beta blockers and can undergo vascular surgery quite safely.

The problem is with patients who have 3 or more risk factors. In those patients we perform cardiac stress testing, in all patients. But that's not something that we've investigated in this study and it's not something which we will change based on these study results.