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Timing of Pre-Operative Beta-Blocker Treatment in Vascular Surgery Patients

Influence on Post-Operative Outcome

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Objectives This study evaluated timing of β-blocker initiation before surgery and its relationship with: 1) pre-operative heart rate and high-sensitivity C-reactive-protein (hs-CRP) levels; and 2) post-operative outcome.

Background Perioperative guidelines recommend β-blocker initiation days to weeks before surgery, on the basis of expert opinions.

Methods In 940 vascular surgery patients, pre-operative heart rate and hs-CRP levels were recorded, next to timing of β-blocker initiation before surgery (0 to 1, >1 to 4, >4 weeks). Pre- and post-operative troponin-T measurements and electrocardiograms were performed routinely. End points were 30-day cardiac events (composite of myocardial infarction and cardiac mortality) and long-term mortality. Multivariate regression analyses, adjusted for cardiac risk factors, evaluated the relation between duration of β-blocker treatment and outcome.

Results The β-blockers were initiated 0 to 1, >1 to 4, and >4 weeks before surgery in 158 (17%), 393 (42%), and 389 (41%) patients, respectively. Median heart rate at baseline was 74 (±17) beats/min, 70 (±16) beats/min, and 66 (±15) beats/min ($p < 0.001$; comparing treatment initiation >1 with <1 week pre-operatively), and hs-CRP was 4.9 (±7.5) mg/l, 4.1 (±.6.0) mg/l, and 4.5 (±6.3) mg/l ($p = 0.782$), respectively. Treatment initiated >1 to 4 or >4 weeks before surgery was associated with a lower incidence of 30-day cardiac events (odds ratio: 0.46, 95% confidence interval [CI]: 0.27 to 0.76, odds ratio: 0.48, 95% CI: 0.29 to 0.79) and long-term mortality (hazard ratio: 0.52, 95% CI: 0.21 to 0.67, hazard ratio: 0.50, 95% CI: 0.25 to 0.71) compared with treatment initiated <1 week pre-operatively.

Conclusions Our results indicate that β-blocker treatment initiated >1 week before surgery is associated with lower pre-operative heart rate and improved outcome, compared with treatment initiated <1 week pre-operatively. No reduction of median hs-CRP levels was observed in patients receiving β-blocker treatment >1 week compared with patients in whom treatment was initiated between 0 and 1 week before surgery. (J Am Coll Cardiol 2010; 56:1922–9) © 2010 by the American College of Cardiology Foundation

Beta-blockers are established therapeutic agents for patients with hypertension (1), heart failure (2), and coronary artery disease (3). In the nonsurgical setting, β-blockers are widely used for the prevention and treatment of coronary heart disease and heart failure, both important determinants of perioperative cardiovascular complications. Over the years multiple observational studies and randomized, controlled trials have been performed to evaluate the effect of perioperative β-blocker treatment in patients undergoing noncardiac surgery (4–15). The majority of these studies have demonstrated cardioprotection derived from perioperative β-blocker treatment.

Proposed mechanisms by which β-blockers exert intraoperative cardioprotective effects include heart rate control, reduction of systolic pressure and ventricular contractile force and its anti-arrhythmic properties. For the long-term, β-blockers reduce mechanical stress imposed on coronary plaques preventing plaque rupture (16). Patients receiving β-blockers tend to have lower plasma concentrations of C-reactive protein (CRP) than those not receiving β-blockers, and the anti-inflammatory properties of β-blockers are thought to stabilize coronary plaques (17–19). In addition, β-blockers are known to lessen adverse

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cardiac remodelling in patients with impaired left ventricular function, which is highly prevalent in the vascular surgery population, by inhibiting the sympathetic nervous system and hormone activation (A-type and B-type natriuretic peptides and norepinephrine) (20–22). Potential side effects associated with β-blocker treatment are bradycardia, hypotension, and stroke. Factors that might relate to the effectiveness of β-blocker therapy and the occurrence of side effects are variations in treatment protocols, such as β-blocker type, β-blocker dose, and timing of β-blocker initiation before surgery. However, the duration of β-blocker treatment before surgery and its effect on cardiovascular outcome has not been evaluated yet in a cohort of vascular surgery patients. The present study was conducted to evaluate timing of β-blocker initiation and its influence on pre-operative heart rate, pre-operative high-sensitivity CRP (hs-CRP) levels, and post-operative outcome in vascular surgery patients.

Abbreviations and Acronyms

CI = confidence interval

hs-CRP = high-sensitivity C-reactive protein

MI = myocardial infarction

RAAS = renin-angiotensin-aldosterone system

Methods

Study population. The original study population consisted of 940 vascular surgery patients undergoing (open or endovascular) lower extremity artery, carotid artery, or abdominal aorta repair, receiving pre-operative β-blocker treatment. Open abdominal aortic aneurysm repair and lower extremity revascularization were considered procedures with high cardiac risk. Carotid surgery and endovascular surgery were considered procedures with intermediate-cardiac risk (23). Patients undergoing emergency surgery; randomized for β-blocker treatment in previous randomized, controlled trials; and with pre-operative heart rate <50 beats/min were not included in the present study. The study was performed at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period of 2002 to 2008. The study was approved by the hospital ethics committee and performed with informed consent of all patients.

Baseline characteristics. Before surgery, a detailed history was obtained from every patient. Clinical data included age, sex, ischemic heart disease (defined as a history myocardial infarction [MI], coronary revascularization, or the presence of pathologic Q waves on pre-operative electrocardiogram), heart failure (defined as the presence of heart failure symptoms according the New York Heart Association functional classification or previous hospital admission for decompensated heart failure), and cerebrovascular disease (defined as a history of ischemic or hemorrhagic stroke). In addition, kidney dysfunction (serum creatinine >2.0 mg/dl), diabetes mellitus (fasting blood glucose ≥6.1 mmol/l or requirement of antidiabetic medication), hypertension (blood pressure ≥140/90 mm Hg in nondiabetic patients and ≥130/80 mm Hg in diabetic patients or requirement of antihypertensive medication), hypercholesterolemia (low-density lipoprotein cholesterol >3.5 mmol/l or requirement of lipid-lowering medication), chronic obstructive pulmonary disease (according to the Global Initiative on Obstructive Lung Diseases classification), and smoking status were recorded as well. Peripheral blood samples for hs-CRP in mg/l, measured by a nephelometric assay on a Beckman-Immage analyzer (Beckman-Coulter, Fullerton, California), were routinely performed 1 day before surgery.

Medication use. The use of the prescription medications was captured at baseline and included β-blockers, statins, aspirin, clopidogrel (at the Erasmus Medical Center antiplatelet therapy is continued during surgery per protocol), oral anticoagulants, inhibitors of the renin-angiotensin-aldosterone system (RAAS) (angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, renin inhibitors, aldosterone antagonists), and diuretics. During the first pre-operative visit at the outpatient clinic, pre-operative β-blocker use was established in patients already receiving β-blockers; and in patients not already receiving β-blockers, pre-operative β-blocker treatment was initiated. Pre-operative β-blocker use was subdivided according to initiation time of treatment: 0 to 1, >1 to 4 or >4 weeks before surgery. All patients returned to the outpatient clinic after 1 week; and β-blocker dosage, if needed, was adjusted and titrated as tolerated to obtain a pre-operative heart rate between 60 and 70 beats/min (24). This protocol could not be followed in patients in which β-blocker treatment was initiated <1 week before surgery.

Study outcomes. Main study end points were 30-day cardiovascular events and long-term mortality. The 30-day cardiovascular events were the composite of myocardial damage (defined as myocardial ischemia or infarction), stroke, and mortality up to 30 days after surgery. Serial electrocardiograms and troponin-T measurements were obtained from all patients before surgery; post-operatively on days 1, 3, and 7; and before discharge. Perioperative myocardial ischemia was defined for patients with normal pre-operative and elevated (>0.03 ng/ml) post-operative troponin-T levels. Elevated troponin-T levels in combination with electrocardiographic changes (new onset ST-T changes and pathological Q waves) or with or without symptoms of angina pectoris defined MI (25). Patients with elevated troponin-T levels before surgery were not included in the study. Long-term mortality was assessed by approaching the municipal civil registries. Mean follow-up was 2.2 ± 1.8 years. Secondary end points were pre-operative heart rate (beats/min) and hs-CRP levels (mg/l). Peripheral blood samples for hs-CRP were routinely performed 1 day before surgery. Optimal specificity and sensitivity of hs-CRP to predict post-operative outcome was calculated with receiver-operating characteristic curve analyses, and a cutoff value ≥6.5 mg/l was used in the analyses.

Statistical analysis. Dichotomous data are described as numbers and percentages, and categorical data are compared with the chi-square test. The continuous variable age is described as mean ± SD and compared with analysis of

variance. The continuous variables heart rate and hs-CRP are described as median ± interquartile range and compared with the Mann–Whitney *U* test. The relation between β-blocker use and perioperative myocardial damage was evaluated with logistic regression analyses. In addition, the relation between β-blocker use and long-term follow-up was evaluated with Cox regression analysis. Multivariate analyses were adjusted for demographic data (age and sex), cardiovascular risk factors (ischemic heart disease, cerebrovascular disease, heart failure, kidney dysfunction, diabetes mellitus, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, and smoking status), type of surgery, and medication use (statins, aspirin, and RAAS inhibitors). We report crude and adjusted odds and hazard ratios with their 95% confidence intervals (CIs). For all tests, a p value <0.05 (2-sided) was considered significant. All analyses were performed with SPSS version 15.0 statistical software (SPSS, Inc., Chicago, Illinois).

Results

Baseline characteristics. The baseline study population consisted of 940 patients undergoing carotid artery stenosis (n = 215), abdominal aortic aneurysm (n = 405), and lower extremity artery (n = 153) repair and receiving preoperative β-blocker treatment. A total of 661 (70%) patients received bisoprolol, 186 (20%) received metoprolol succinate, 49 (5%) received atenolol, and 44 (5%) patients received other β-blockers. Clinical parameters stratified by timing between β-blocker initiation and vascular surgery are demonstrated in Table 1. The majority of patients were men (77%), and the mean (SD) age was 67 (10) years. Patients

Table 1 Baseline Characteristics

Baseline Characteristics	Timing of β-Blocker Initiation Before Surgery			p Value*
	0–1 Week (n = 158)	>1–4 Weeks (n = 393)	>4 Weeks (n = 389)	
Demographic data				
Age, yrs (±SD)	68 (11)	67 (10)	67 (10)	0.920
Median HR at day of surgery, beats/min (±IQR)	74 (17)	70 (16)	66 (15)	<0.001
Male	117 (74)	310 (79)	279 (76)	0.437
Medical history				
Ischemic heart disease	56 (35)	142 (36)	208 (54)	<0.01
Heart failure	12 (8)	35 (9)	50 (13)	0.090
Cerebrovascular disease	69 (44)	118 (30)	137 (35)	0.009
Renal dysfunction	28 (18)	55 (14)	87 (22)	0.010
Diabetes mellitus	48 (30)	100 (26)	126 (33)	0.100
Hypertension	101 (64)	236 (60)	290 (75)	<0.01
Hypercholesterolemia	79 (50)	165 (42)	198 (51)	0.032
Smoker, current	75 (58)	167 (43)	157 (40)	0.313
Chronic obstructive pulmonary disease	42 (27)	136 (35)	134 (34)	0.154
Surgery				
Open	91 (58)	260 (66)	247 (63)	0.170
Lower extremity revascularization	29 (18)	92 (23)	110 (28)	0.153
Abdominal aorta repair	29 (18)	110 (28)	95 (24)	0.163
Carotid artery repair	33 (22)	58 (15)	42 (11)	0.973
Endovascular	67 (42)	133 (34)	142 (37)	0.170
Lower extremity revascularization	16 (10)	30 (8)	43 (11)	0.244
Abdominal aorta repair	27 (17)	83 (21)	61 (16)	0.091
Carotid artery repair	24 (15)	20 (5)	38 (10)	0.107
Echocardiography				
Left ventricular ejection fraction <40%	26 (17)	71 (18)	84 (22)	0.312
Laboratory (±IQR)				
Median hs-CRP (mg/l) 1 day before surgery	4.9 (7.5)	4.1 (6.0)	4.5 (6.3)	0.782
Medication				
Statins	118 (75)	289 (74)	296 (76)	0.271
Aspirin	95 (60)	228 (58)	239 (61)	0.187
Clopidogrel	9 (6)	21 (5)	30 (8)	0.371
Oral anticoagulants	25 (16)	57 (15)	71 (18)	0.360
RAAS inhibitors	57 (36)	138 (35)	197 (51)	<0.01
Diuretics	40 (25)	85 (22)	116 (30)	0.030

Values are percentages, unless otherwise indicated. *p value: comparison of groups >1 to 4 weeks and >4 weeks taken together with group 0 to 1 week.

HR = hazard ratio; hs-CRP = high-sensitivity C-reactive protein; IQR = interquartile range; RAAS = renin-angiotensin-aldosterone system.

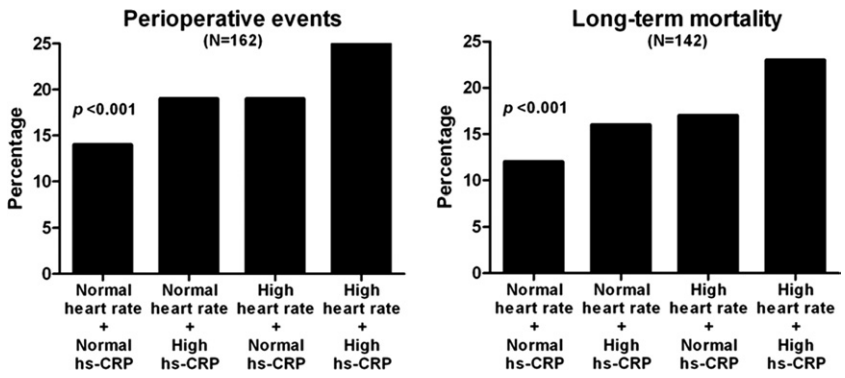

Figure 1 Influence of Pre-Operative Heart Rate and hs-CRP Toward Post-Operative Outcome

hs-CRP = high-sensitivity C-reactive protein.

receiving β-blocker treatment >1 week before surgery more often had a history of ischemic heart disease, kidney dysfunction, and hypertension and more often received RAAS inhibitors and diuretics, compared with patients receiving β-blocker treatment <1 week before surgery.

Pre-operative heart rate, pre-operative hs-CRP, and post-operative outcome. As demonstrated in Table 1, patients receiving β-blocker treatment >1 week before surgery had lower median resting heart rate at day of surgery, compared with patients receiving β-blocker treatment <1 week pre-operatively ($p < 0.001$). No significant difference was observed in median pre-operative hs-CRP levels between these groups ($p = 0.782$). In statin-naive patients ($n = 237$), no significant difference in median pre-operative hs-CRP levels was observed between these groups as well ($p = 0.786$). However, a subanalysis demonstrated that median hs-CRP concentrations were significantly lower in patients receiving statin treatment >1 week before surgery (median hs-CRP = 4.0 mg/l), compared with statin-naive patients (median hs-CRP = 5.7 mg/l; $p = 0.043$).

The influence of median pre-operative heart rate and hs-CRP toward post-operative outcome is demonstrated in Figure 1. An hs-CRP concentration >6.5 mg/l (26 of 139 = 19%) or an increased heart rate >70 beats/min (45 of 243 = 19%) were both associated with an increased incidence of perioperative events (Fig. 1), compared with patients with normal heart rate (60 to 70 beats/min) in combination with an hs-CRP concentration ≤6.5 mg/l (61 of 438 = 14%). Patients with high heart rate (>70 beats/min) in combination with an hs-CRP >6.5 mg/l had the highest incidence of perioperative events (30 of 120 = 25%) with an overall p value <0.001. In addition, an hs-CRP concentration >6.5 mg/l (22 of 139 = 16%) or an increased heart rate >70 beats/min (41 of 243 = 17%) were both associated with an increased incidence of long-term mortality (Fig. 1), compared with patients with normal heart rate (60 to 70 beats/min) in combination with an hs-CRP concentration ≤6.5 mg/l (52 of 438 = 12%). Patients with high heart rate (>70 beats/min) in combination with an hs-CRP >6.5 mg/l had the highest incidence of long-term mortality (27 of 120 = 23%) with an overall p value <0.001.

Initiation of β-blocker treatment and post-operative outcome. During the first 30 days after surgery 150 (16%) patients had troponin-T release, of which 114 (76%) had myocardial ischemia and 36 (24%) had MI. The study end point of 30-day cardiovascular events (composite of myocardial damage, stroke, and 30-day mortality) was reached by 162 patients, as demonstrated in Table 2. In total, 27% (42 of 158) of patients receiving β-blocker treatment <1 week before surgery had a perioperative 30-day cardiovascular event, compared with 15% (120 of 782) of patients who received pre-operative β-blocker treatment >1 week before surgery (Table 3). Multivariate analyses demonstrated that β-blocker treatment initiated >4 and >1 to 4 weeks before surgery were both associated with a reduced incidence of 30-day cardiovascular events with odds ratios of 0.46 (95% CI: 0.27 to 0.48) and 0.48 (95% CI: 0.29 to 0.79) compared with patients in whom β-blocker treatment was initiated <1 week pre-operatively (Table 3). Subanalyses

Table 2 Timing of β-Blocker Initiation Before Surgery and Post-Operative Outcome

Post-Operative Outcome	Timing of β-Blocker Initation Before Surgery			p Value*
	0–1 Week (n = 158)	>1–4 Weeks (n = 393)	>4 Weeks (n = 389)	
30-day outcome				
Troponin-T release	40 (25)	54 (14)	56 (14)	0.032
Mortality	6 (4)	8 (2)	11 (3)	0.495
Stroke	3 (19)	2 (0.5)	2 (0.5)	0.021
Cardiovascular events	42 (27)	58 (15)	62 (16)	<0.001
Long-term outcome				
Mortality	30 (19)	55 (14)	57 (15)	0.039

Values are n (%). *p value: comparison of groups >1 to 4 weeks and >4 weeks taken together with group 0 to 1 week.

Table 3 Association of Time, Between Timing of β-Blocker Initiation and Presence of 30-Day Cardiovascular Events in Vascular Surgery Patients

			Univariate		Multivariate	
30-Day Cardiovascular Events	n	(%)	Odds Ratio	95% CI	Odds Ratio	95% CI
All	162/940					
Timing of β-blocker initiation						
0–1 week pre-operatively	42/158	(27)	1.00		1.00	
>1–4 weeks pre-operatively	58/393	(15)	0.48	0.30–0.78	0.46	0.27–0.76
>4 weeks pre-operatively	62/389	(16)	0.54	0.40–0.88	0.48	0.29–0.79
High-risk procedures	125/469					
Timing of β-blocker initiation						
0–1 week pre-operatively	25/58	(43)	1.00		1.00	
>1–4 weeks pre-operatively	44/204	(22)	0.35	0.18–0.66	0.38	0.19–0.79
>4 weeks pre-operatively	56/207	(27)	0.66	0.36–0.97	0.58	0.29–0.91
Intermediate-risk procedures	37/471					
Timing of β-blocker initiation						
0–1 week pre-operatively	17/100	(17)	1.00		1.00	
>1–4 weeks pre-operatively	14/189	(7)	0.49	0.23–0.97	0.51	0.13–0.79
>4 weeks pre-operatively	6/182	(3)	0.10	0.03–0.34	0.12	0.02–0.25

Multivariate analyses reported in this table are adjusted for age, sex, ischemic heart disease, cerebrovascular disease, heart failure, kidney dysfunction, diabetes mellitus, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, smoking status, and medication use.
CI = confidence interval.

performed in patients undergoing surgery associated with high and intermediate cardiac risk are demonstrated in Table 3.

During long-term follow-up 142 (15%) patients died. Cumulative post-operative survival stratified to β-blocker treatment initiation time is demonstrated in Figure 2 (log-rank $p < 0.01$). Of the patients who died, 33% (47 of 142) had perioperative myocardial damage. In total, 19% (30 of 158) of patients receiving β-blocker treatment <1 week before surgery died, compared with 15% (112 of 782) of patients who received pre-operative β-blocker treatment >1 week before surgery (Table 4). Of the patients who died, 72 patients (51%) had myocardial damage during 30-day follow-up. Multivariate analyses demonstrated that β-blocker treatment initiated >4 and >1 to 4 weeks before surgery was associated with a reduced incidence of long-term mortality with hazard ratios of 0.52 (95% CI: 0.21 to 0.67) and 0.50 (95% CI: 0.25 to 0.71) compared with patients in whom β-blocker treatment was initiated <1 week pre-operatively (Table 4). Subanalyses performed in patients undergoing surgery associated with high and intermediate cardiac risk are demonstrated in Table 4.

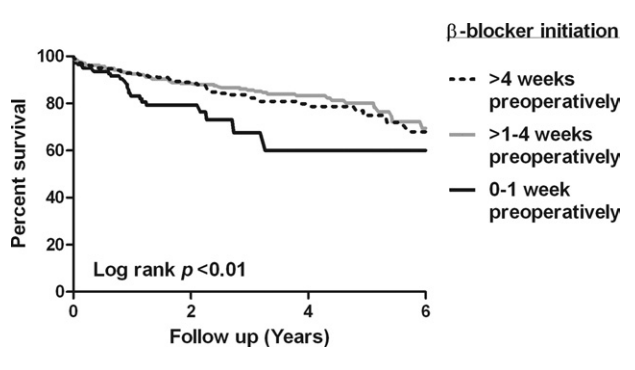

Figure 2 Cumulative Long-Term Survival Stratified to Timing of β-Blocker Initiation

Log-rank p value: comparison of groups >1 to 4 weeks and >4 weeks with group 0 to 1 week.

Discussion

The present study evaluated the influence of timing between β-blocker treatment initiation and vascular surgery outcome. Our results indicate that β-blocker treatment initiated >1 week before surgery is associated with a reduction of pre-operative heart rate compared with treatment initiated <1 week before surgery. Of note, no reduction of hs-CRP levels was observed. Importantly, our results indicate that β-blocker treatment initiated >1 week before surgery is associated with improved post-operative outcome compared with treatment initiated <1 week before surgery, which could be related to adequate heart rate control.

Surgical procedures are associated with tachycardia and increased myocardial contractility leading to an increased oxygen demand (26). Maintaining a balance between the myocardial oxygen demand and supply is key to prevent perioperative cardiac events.

Randomized, controlled trials demonstrated that β-blockers reduce the incidence of adverse cardiac events in patients undergoing intermediate-risk noncardiovascular surgery and in patients undergoing high-risk vascular surgery (10,27). Proposed mechanisms by which β-blockers exert intraoperative cardioprotective effects are: 1) heart rate control with subsequent prolongation of coronary diastolic filling time; and 2) antiarrhythmic properties reducing the risk for tachycardia (17). In addition, β-blockers are known to

Table 4 Association of Time, Between Timing of β-Blocker Initiation and Long-Term Mortality of Vascular Surgery Patients

			Univariate		Multivariate	
Long-Term Mortality	n	(%)	HR	95% CI	HR	95% CI
All	142/940					
Timing of β-blocker initiation						
0–1 week pre-operatively	30/158	(19)	1.00		1.00	
>1–4 weeks pre-operatively	55/393	(14)	0.57	0.32–0.91	0.52	0.21–0.67
>4 weeks pre-operatively	57/389	(15)	0.62	0.35–0.94	0.50	0.25–0.71
High-risk procedures	93/469					
Timing of β-blocker initiation						
0–1 week pre-operatively	17/58	(29)	1.00		1.00	
>1–4 weeks pre-operatively	38/204	(19)	0.31	0.17–0.57	0.37	0.20–0.69
>4 weeks pre-operatively	43/207	(20)	0.47	0.27–0.83	0.46	0.26–0.83
Intermediate-risk procedures	49/471					
Timing of β-blocker initiation						
0–1 week pre-operatively	13/100	(13)	1.00		1.00	
>1–4 weeks pre-operatively	17/189	(9)	0.59	0.27–0.91	0.46	0.21–0.94
>4 weeks pre-operatively	13/182	(7)	0.37	0.16–0.88	0.37	0.15–0.91

Multivariate analyses reported in this table are adjusted for age, sex, ischemic heart disease, cerebrovascular disease, heart failure, kidney dysfunction, diabetes mellitus, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, smoking status, and medication use.
CI = confidence interval; HR = hazard ratio.

reduce systolic pressure and ventricular contractile force (17,19).

In the long-term, β-blockers reduce mechanical stress imposed on coronary plaques preventing plaque rupture (16). In addition, the anti-inflammatory properties of β-blockers are thought to stabilize coronary plaques (17,19). Recently, it is suggested that left ventricular dysfunction is highly present in the vascular surgery population (20). Long-term β-blocker therapy is known to reduce adverse cardiac remodelling in patients with impaired left ventricular function by inhibiting the sympathetic nervous system and hormone activation (A- and B-type natriuretic peptides and norepinephrine) (21,22).

Over the years, multiple randomized, controlled trials evaluated the effectiveness of perioperative β-blocker use and provided conflicting evidence with regard to its benefit (4–15). In 1996, Mangano et al. (9) hypothesized that strict perioperative heart rate control with atenolol might limit the development of perioperative ischemia in high-risk surgery patients. In addition, Raby et al. (11) demonstrated a beneficial effect of heart rate control with the short-acting β-blocker esmolol, immediately after vascular surgery. In the present study, β-blocker treatment >1 week before surgery was associated with lower mean pre-operative heart rate and improved post-operative outcome.

In 2002, Jenkins et al. (18) evaluated the association between β-blockers and plasma CRP levels in patients with symptomatic coronary artery disease. The authors found that patients who were treated with β-blockers had lower plasma concentrations of CRP than those not receiving β-blockers; however, no differences among types or dosages of β-blockers were evident. In our study, all patients received β-blocker treatment, and our results indicate that longer duration of β-blocker therapy is not associated with an additional reduction of hs-CRP levels. No additional reduction of hs-CRP levels was observed in statin-naive patients receiving treatment >1 week before surgery. However, patients receiving statin treatment >1 week before surgery did have mean lower hs-CRP levels before surgery than those not receiving statin treatment, in line with previous studies (28–30). The NAPLES (Novel Approaches for Preventing or Limiting Events)-II trial demonstrated that even a single high (80 mg) loading-dose of atorvastatin reduced the incidence of periprocedural MI in patients undergoing elective percutaneous coronary intervention (29).

In 2008, the POISE (Perioperative Ischemic Evaluation) trial randomized patients to receive either high-dosage metoprolol succinate on the day of surgery or placebo without titration of the dose according to heart rate (5). Although a 30% decrease in nonfatal MI was found in patients treated with high-dose metoprolol succinate, this beneficial effect was accompanied by a 33% increase in total mortality and a 2-fold increased risk in stroke, compared with placebo. Metoprolol is metabolized via the CYP 2D6 pathway and might interact with other drugs, administered intra-operatively and metabolized via the CYP 2D6 pathway as well, underlining the importance for adequate β-blocker dosage (31). Poldermans et al. (10) performed the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography)-I trial and evaluated the effect of low-dose bisoprolol on post-operative outcome after vascular surgery. Bisoprolol treatment was started an average of 37 days before surgery with careful titration according to heart rate to prevent adverse side effects. In contrast to the POISE trial, the incidence of stroke in the DECREASE-I trial was comparable with

placebo, while reducing the incidence of cardiac death and nonfatal MI from 34% in the standard-care group to 3.4% in the bisoprolol-treated group. Interestingly, in all clinical trials that did not demonstrate a difference in post-operative outcome between β-blocker– and placebo-treated groups, β-blocker treatment was initiated <1 week before surgery (4,7,14,15). This could provide an explanation for the conflicting results with regard to the effect of perioperative β-blocker treatment in the published data up to now. In the current study, the stroke rate in patients in whom β-blocker treatment was initiated 0 to 1 week pre-operatively (n = 158) was increased, compared with patients receiving β-blocker treatment >1 week before surgery. In this group, 3 patients or 1.9% suffered a stroke, which is higher compared with the POISE trial; however, this difference is based on very small numbers. In addition, of the patients who received β-blocker treatment >1 week before surgery (n = 782), only 4 patients had a stroke, which is less compared with the group of patients receiving metroprolol succinate in the POISE trial and comparable with the placebo group described in the POISE trial. This result underlines the importance of β-blocker titration >1 week before surgery.

The most recent European Society of Cardiology guidelines, addressing perioperative care, recommend that β-blocker treatment should be initiated between 30 days and at least 1 week before surgery (24). This recommendation is based on an expert opinion with a level of evidence C. In addition, in the 2009 "American College of Cardiology Foundation/American Heart Association Focused Update on Perioperative β-Blockade for Noncardiac Surgery," it is suggested that, when possible and where indicated, β-blockers should be started days to weeks before elective surgery (32). The results from the present study underline the importance of β-blocker initiation >1 week before vascular surgery. One of the reasons we did not observe better survival of patients in whom β-blocker treatment was initiated >4 weeks, compared with patients in whom β-blocker treatment was initiated ≤4 weeks before surgery, is an increased prevalence of ischemic heart disease and renal dysfunction present in this patient group.

With regard to perioperative β-blocker treatment, the following questions could be asked. First, could one give just a slightly higher β-blocker dose to achieve adequate heart rate control and routinely start the treatment <1 week before surgery to reach an improved post-operative outcome as well? As we have learned from the POISE trial, treatment with high β-blocker dosage and without up-titration is accompanied with an increased incidence of side effects (bradycardia, hypotension, and stroke). In the present study, the incidence of stroke was increased in patients receiving β-blocker treatment <1 week before surgery compared with patients receiving β-blocker treatment >1 week before surgery. In patients in whom β-blocker therapy is initiated shortly before surgery, there might be an increased risk of side effects, because treatment is initiated too aggressively and the response to β-blocker therapy cannot be adequately monitored during this short period of time, leading to an overdosing danger (33). In addition, as recently described by Beattie et al. (34), β-blocked patients do not seem to tolerate surgical anemia when compared with patients who are naive to β-blockers. Although one could assume that high β-blocker dosage might prevent compensatory mechanisms evoked by perioperative anemia, such as an increase in heart rate, optimal β-blocker titration in anemic patients remains to be elucidated. A second question to be asked is what to do with β-blocker–naive patients in urgent need for vascular surgery (i.e., should surgery be postponed to obtain first adequate heart rate control). The results of this study have demonstrated that β-blocker initiation >1 week before surgery is not associated with a reduction of hs-CRP concentrations, which might indicate that anti-inflammatory effects are achieved within days. In addition, β-blocker initiation at day of surgery is known to reduce pre-operative heart rate as well (9). Treatment with the ultra-short-acting β-blocker esmolol can be performed safely during the perioperative period, as demonstrated by Raby et al. (11). The short-acting character of esmolol could limit the occurrence of adverse myocardial events in patients undergoing urgent vascular surgery; however, future studies are needed to address this point.

Study limitations. Potential limitations of these data merit consideration. First, the study population consisted of patients referred to a tertiary referral center and might not fully represent a general population scheduled for elective vascular surgery. Second, although more than 900 patients were included in the study, the observational and retrospective nature of the study remains a limitation. Third, nonfatal cardiovascular events during long-term follow-up were not addressed; however, the study focused on the hard end point of long-term mortality. Fourth, data in the current study are not randomized according to initiation time of β-blocker treatment. Although multivariate analyses were adjusted for known confounders, the possibility of uncaptured confounders persists.

Conclusions

The present study provides an indication that β-blocker therapy initiated >1 week before surgery is associated with reduced pre-operative heart rate and improved post-operative outcome, compared with patients in whom β-blocker therapy was initiated <1 week before vascular surgery. In addition, no reduction of median hs-CRP levels was observed in patients receiving β-blocker treatment >1 week compared with patients in whom treatment was initiated between 0 and 1 week before surgery. Therefore, improved post-operative outcome of patients receiving β-blocker treatment >1 week before vascular surgery could be related to adequate heart rate control.

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