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Dihydropiridine calcium-channel blockers and perioperative mortality in aortic aneurysm surgery†

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Background. Dihydropiridine calcium-channel blockers are often used as an alternative to beta-blockers for the treatment of hypertension in patients undergoing aortic aneurysm surgery. We studied the relation between dihydropiridine calcium-channel blocker use and perioperative mortality in patients undergoing aortic aneurysm surgery.

Methods. We studied 1000 patients [mean (range) age, 69 (22–95) yr; males 810] who underwent acute or elective abdominal or thoracoabdominal aortic aneurysm surgery between January 1999 and April 2007, at Semmelweis Medical University (Budapest, Hungary). Patients were evaluated for clinical risk factors, chronic medication use, and surgical characteristics. Propensity score analysis was used to adjust for the potential bias in dihydropiridine calcium-channel blocker use. Multivariable logistic regression analyses were applied to study the association between the likelihood of dihydropiridine calcium-channel blocker use and mortality occurring within 30 days of surgery.

Results. Perioperative mortality occurred in 85 (8.5%) patients. Thirty-day mortality was significantly higher in dihydropiridine calcium-channel blocker users compared with non-users, 14.0% *vs* 6.0%; crude odds ratio (OR) 2.6, 95% confidence interval (CI): 1.6–4.0, $P<0.0001$. Even after correcting for other baseline covariates and propensity for these agents dihydropiridine calcium-channel blocker use was associated with increased 30-day mortality, OR (95% CI) 2.5(1.3–4.6), $P=0.003$.

Conclusions. Dihydropiridine calcium-channel blocker use in patients with acute or elective aortic aneurysm surgery is independently associated with an increased incidence of perioperative mortality.

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Perioperative cardiac mortality and morbidity are the most frequently occurring adverse events in patients undergoing major vascular surgery including aortic aneurysm surgery.[1] This is related to the high prevalence of ischaemic heart disease, which is also one of the most common forms of target-organ damage associated with hypertension. Patients with aortic aneurysms often have hypertension and stable coronary artery disease for which the initial treatment may be a beta-blocker.[2] Beta-blockers may also be of value for the prevention of perioperative cardiac mortality in patients undergoing aortic aneurysm repair.[3] However, many of these patients either have absolute or relative contraindications to beta-blockade (cardiac conduction disorders, severe reactive airway disease, severe peripheral vascular disease, brittle diabetes mellitus) or are intolerant to beta-blocker use, which often

†This article is accompanied by Editorial 1

leads physicians to avoid prescribing beta-blockers and consider alternative drugs such as calcium-channel blockers.[2] Calcium-channel blockers are effective drugs for the treatment of hypertension and stable coronary artery disease[2 4] but their efficacy in the reduction of perioperative cardiac mortality in non-cardiac surgery has been controversial. Earlier studies were inconclusive mainly as the result of small number of patients and different groups of calcium-channel blockers studied, and/or lack of appropriate risk-adjustment techniques used.[5–8] Recently, a meta-analysis of 11 studies in total of 1007 patients showed that calcium-channel blockers significantly reduced ischaemia, supraventricular arrhythmias, and combined endpoint defined as death, myocardial infarction or congestive heart failure in the setting of non-cardiac surgery.[9] However, these benefits were mainly attributable to diltiazem, a non-dihydropiridine calcium-channel blocker, whereas the efficacy of dihydropiridine calcium-channel blockers in the reduction of cardiac complications was not studied. Therefore, the aim of the present study was to investigate the association between chronic dihydropiridine calcium-channel blocker use and 30-day mortality in patients undergoing aortic aneurysm surgery.

Methods

Study population

According to research governance protocols at our institution there is no requirement for written informed consent for observational studies of the type reported here. Between January 1, 1999 and April 30, 2007, a total of 25 692 patients >18 yr of age underwent non-cardiac arterial or venous surgical procedures at the Department of Cardiovascular Surgery, Semmelweis University in Budapest, Hungary. Each surgical technique performed was classified by treating physicians according to a standardized national coding system that was developed in co-operation with the Hungarian National Health Service. The patient's name, gender, type of surgery, and the name of the operating surgeon were uploaded to an electronic database maintained by the Medical Information Unit of the Department; via this database 1000 consecutive patients were identified who underwent open aortic aneurysm surgery. A research nurse (K.S.V.) collected a standard set of perioperative data for these patients using data from medical files, surgical reports, anaesthetic and postoperative charts, discharge letters and records of the outpatient clinic visit. These data were recorded using a standard electronic data collection form. Quality of data collection was ascertained by two of the investigators (M.D.K., J.G.) using regular checks of database and included checks for completeness of the collected data, and cross-check for inconsistencies or missing information between the collected database and medical records.

Definition of clinical risk factors and perioperative outcome

Potential clinical determinants of perioperative mortality examined in this study included advanced age (>70 yr), gender, current stable or prior angina pectoris, prior myocardial infarction on the basis of medical history or a finding of pathologic Q waves on the electrocardiography, compensated congestive heart failure or a history of heart failure, renal dysfunction (serum creatinine >180 μmol litre^{-1}), current oral or insulin treatment for diabetes mellitus, a history of prior cerebrovascular accident including transient ischaemic attack, chronic pulmonary disease (forced expiratory volume in 1 s ⩽75% of normal adjusted for age and gender) and smoking.[10 11] Ischaemic heart disease was defined as a history of current stable or chronic angina pectoris or history of myocardial infarction. Extracardiac arteriopathy was defined as any one or more of the following: claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the limb arteries or carotids. For the purposes of this study hypertension was routinely defined as history of treated hypertension, and on long-term anti-hypertensive therapy. If a patient during the preoperative visit was found with elevated blood pressure then the diagnosis of hypertension was made if blood pressure was 140/90 mm Hg or higher after three separate measurements at least 1 week apart. In addition, the database was reviewed for American Society of Anesthesiologists scoring,[12] aortic aneurysm size, type, and timing of aortic aneurysm surgery.

On the day of surgery, anaesthesia was induced by fentanyl, atracurium, and propofol, and maintained by sevoflurane with supplemental bolus doses of fentanyl. Radial artery, central venous and, if indicated on clinical grounds, pulmonary artery catheters were inserted for haemodynamic monitoring and blood sampling. Patients with abdominal aortic surgery had tracheal intubation and patients with thoracoabdominal aortic aneurysm surgery had endobronchial tube inserted. The lungs were ventilated (volume- or pressure-controlled) depending on the nature of procedure, using an oxygen–air mixture with an inspiratory oxygen concentration of 40%. A PEEP of 5 cm H_2O was applied. If no intraoperative complications occurred patients were extubated immediately otherwise delayed extubation was performed. All patients were admitted to our Intensive Therapy Unit for postoperative management.

The outcome was all-cause mortality within 30 days of surgery. The cause of perioperative death was retrieved from hospital records or autopsy results.

Chronic medication use

According to routine procedure at the Department of Cardiovascular Surgery, elective patients visited the outpatient clinic at least 1–3 months before the planned operation, and all patients were screened for medication use in conjunction with their medical history. During the

preoperative visit additional cardiac medications including beta-blockers, calcium-channel blockers or statins were prescribed at the discretion of the attending physicians. Patients continued taking their cardiac medication on the day of surgery, and oral medication use was resumed on an average 3 days after surgery. Based on institutional guidelines aspirin use was not discontinued before the operation. Chronic medication use was considered to be medication use documented at least 1–3 months before hospital admission for surgery. In case of patients admitted for emergency operation, previous medical history and chronic cardiac medication use was ascertained based on discharge letters from the patient's general practitioner or discharge letters documenting previous hospital admissions.

Statistical analysis

Continuous variables were described as mean values and standard deviations, and categorical variables as percentages. Differences between patient subgroups were evaluated using *t*-tests or χ^2 tests. As the decision to administer dihydropiridine calcium-channel blockers was not randomized, adjustments were made for clinical characteristics that may have influenced the decision to use dihydropiridine calcium-channel blockers. A propensity score was constructed using multivariable logistic regression to identify baseline clinical characteristics that were significantly associated with the use of dihydropiridine calcium-channel blockers.

The association of dihydropiridine calcium-channel blocker use with 30-day mortality was assessed through multivariable logistic regression. Univariable associations with $P \leq 0.25$ were considered in the initial construction of the mortality model, and the final model was then selected according to backward deletion of the least significant predictors. The propensity score of dihydropiridine calcium-channel blocker use was then introduced to the final model. The discriminatory power of the model was quantified by the c-index, which corresponds to the area under the receiver operating characteristic curve; ranging from 0.5 (not predictive at all) to 1.0 (optimal performance). The model fit was further assessed by the Hosmer–Lemeshow goodness-of-fit test.[13] Odds ratios (OR) and corresponding 95% confidence intervals (CI) are reported. All analyses were performed using SPSS statistical software (SPSS Inc., Chicago, IL, USA, version 12.0).

Table 1 Characteristics of the population (all data are presented as number (percentage) or mean [range for age and standard deviation otherwise] unless otherwise indicated; for definition of risk factors see 'Methods' section)

Characteristics	Patients who used dihydropiridines *n*=314 (%)	Patients who did not use dihydropiridines *n*=686 (%)	*P*-value
Patient characteristics			
Age (yr)	69.9 [29–90]	68.7 [22–95]	0.07
Age≥70 yr	162 (51.6)	329 (48.0)	0.30
Male sex	245 (78.0)	565 (82.4)	0.12
Body mass index (kg m^{-2})	26.0 [4.2]	26.2 [4.0]	0.48
Current smoker	122 (39.0)	277 (40.4)	0.68
Medical history			
Ischaemic heart disease	101 (32.2)	214 (31.2)	0.77
Congestive heart failure	17 (5.4)	30 (4.4)	0.52
Diabetes mellitus	42 (13.4)	92 (13.4)	1.0
Prior cerebrovascular accident	55 (17.5)	76 (11.1)	0.006
Renal insufficiency	29 (9.2)	36 (5.2)	0.03
Pulmonary disease	89 (28.3)	149 (21.7)	0.03
Hypertension	308 (98.1)	603 (87.9)	<0.0001
Prior coronary bypass surgery	18 (5.7)	62 (9.0)	0.08
Prior percutaneous transluminal coronary angioplasty	10 (3.2)	17 (2.5)	0.53
Extracardiac arteriopathy	120 (38.2)	210 (30.6)	0.02
Chronic cardiac medication			
ACE inhibitors	173 (55.1)	366 (53.4)	0.63
Aspirin	39 (12.4)	94 (13.7)	0.62
Beta-blockers	154 (49.0)	320 (46.6)	0.50
Diuretics	101 (32.2)	172 (25.1)	0.02
Nitrates	90 (28.7)	192 (28.0)	0.82
Statins	76 (24.2)	162 (23.6)	0.87
Surgical characteristics			
ASA score			0.05
II	82 (26.1)	211 (30.8)	
III	195 (62.1)	417 (60.8)	
IV+V	37 (11.8)	58 (8.4)	
Emergency surgery	44 (14.0)	75 (11.0)	0.17
Thoracoabdominal aortic aneurysm	48 (15.3)	81 (11.8)	0.013
Aortic aneurysm diameter (cm)	6.4 [1.6]	6.4 [1.7]	0.54
Preoperative haemoglobin concentration (g dl^{-1})	13.4 [2.2]	13.6 [2.2]	0.26
Duration of surgery (min)	158 [55]	151 [55]	0.08
Packed red blood transfusion, unit			0.003
Not given	84 (26.8)	258 (37.7)	
1 to 2	140 (44.6)	264 (38.5)	
3 or more	90 (28.6)	164 (23.8)	

Results

Patient characteristics

Baseline characteristics of the 1000 consecutive patients are presented in Table 1. The mean (range) age of the cohort was 69 (22–95) yr, and 810 (81%) of the patients were men. A history of ischaemic heart disease was present in 31.5% of patients, and 4.7% had a history of congestive heart failure. Thirteen per cent of patients had a history of cerebrovascular disease; 13.4%, diabetes mellitus; and 6.5%, chronic renal disease. The greatest percentages of patients underwent an elective procedure (88.1%), and had abdominal aortic aneurysm surgery (88.1%). There were 314 (31.4%) patients treated with dihydropiridine calcium-channel blockers, and 75 (7.5%) patients were non-dihydropiridine calcium-channel blocker users.

Patients treated with dihydropiridine calcium-channel blockers had a higher prevalence of prior cerebrovascular events, chronic renal insufficiency, chronic obstructive

pulmonary disease, hypertension, extracardiac arteriopathy (any one or more of the following: claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the limb arteries or carotids), and chronic diuretic use. There was no difference in the prevalence of chronic cardiac medication use, American Society of Anesthesiology score or in surgical characteristics but dihydropiridine calcium-channel blocker users more often received intraoperative blood transfusion (Table 1). In 314 patients who were dihydropiridine calcium-channel blocker users the most frequently prescribed calcium-channel blockers were amlodipine (64.3%), nifedipine (29.6%), and felodipine (6%), respectively. There was no statistically significant difference in the incidence of perioperative mortality between patients who were nifedipine users compared with patients who were using amlodipine or felodipine (17.1% *vs* 12.3%, P=0.24).

To account for the effect of study year, the 9 yr study period was divided for two periods between 1999–2002 and 2003–2007. This was done to account for any likely differences in treatment changes such as more widespread use of beta-blockers and statins for the prevention of perioperative cardiac complications.[1] The prevalence of type of surgery and clinical risk factors and the incidence of perioperative mortality did not show significant differences between the two periods.

Perioperative death occurred in 85 (8.5%) patients. Among these, there were 35 (41%) cardiac deaths (death attributable to myocardial infarction, congestive heart failure, or ventricular arrhythmia in the absence of any other precipitating factor, or if death was sudden and unexpected). Death was attributed to stroke in seven patients (8%), respiratory failure (Pa_{O_2}<8 kPa, P_{CO_2}>6.7 kPa, necessity for mechanical ventilation, reintubation and mechanical ventilation >24 h, and presence of alveolar consolidation on chest X-ray) in six patients (7%) and renal failure (sudden three-fold or more increase in serum creatinine or creatinine >355 μmol litre^{-1} or urine output below 0.3 ml kg^{-1} for 24 h with subsequent need for renal replacement therapy) in nine patients (11%). In the remaining 28 (33%) patients the causes of death were bleeding, intestinal necrosis, multiorgan failure or sepsis. Autopsy was performed in 46 (54%) patients. In patients who died and underwent post-mortem examination the cause of death was more often classified as cardiac death (56%) than in patients who died but did not undergo autopsy (21%).

Propensity for dihydropiridine calcium-channel blocker use

The univariable analyses for propensity score showed that significant characteristics (P≤0.05) associated with dihydropiridine calcium-channel blocker use were history of prior cerebrovascular accident, hypertension, chronic obstructive pulmonary disease, chronic renal dysfunction, peripheral vascular disease, ASA category of IV or higher, and chronic diuretic use (Table 2). When multivariable analysis was performed the propensity score for dihydropiridine calcium-channel blocker use showed that patients with histories of prior cerebrovascular accident, history of hypertension, and chronic obstructive pulmonary disease were more likely to be prescribed dihydropiridine calcium-channel blockers. The propensity score for dihydropiridine calcium-channel blocker use had moderate discriminatory power and good fit (c-index, 0.60; overall goodness-of-fit Hosmer–Lemeshow test; χ^2=0.12, P=0.94).

Table 2 Significant univariable and multivariable predictors for the prescription of dihydropiridine calcium-channel blockers

Variables	Univariable analysis		Multivariable analysis	
	Odds ratios (95% CI)	*P*-value	Odds ratios (95% CI)	*P*-value
Cerebrovascular event	1.7 (1.2–2.5)	0.005	1.7 (1.2–2.5)	0.01
Hypertension	7.1 (3.1–16.4)	<0.0001	7.0 (3.0–16.1)	<0.0001
Chronic obstructive pulmonary disease	1.4 (1.1–1.9)	0.02	1.5 (1.1–2.0)	0.02
Chronic renal dysfunction	1.8 (1.1–3.1)	0.02		
Extracardiac arteriopathy	1.4 (1.1–1.8)	0.02		
Diuretic use	1.4 (1.1–1.9)	0.02		
ASA score				
II	1.0			
III	1.2 (0.9–1.6)	0.24		
IV+V	1.6 (1.0–2.7)	0.04		

Association of dihydropiridine calcium-channel blocker use with perioperative mortality

Univariable associations of baseline characteristics and 30-day mortality are shown in Table 3. We also studied the association between dihydropiridine calcium-channel blocker and beta-blocker use in relation to perioperative mortality. Among 366 patients not taking either of these medications the incidence of perioperative mortality was significantly lower (6.8%) compared with the incidence of perioperative mortality (20%) in 160 patients using only dihydropiridine calcium-channel blockers, crude OR (95% CI) 3.41 (1.95–5.97). However, there was no significant difference in the incidence of mortality between patients using beta-blockers only (5%) compared with the incidence of mortality (7.8%) in patients using a combination of beta-blockers and dihydropiridine calcium-channel blockers, crude OR (95% CI) 1.61 (0.74–3.48). There was no evidence of a differential effect of dihydropiridine calcium-channel blocker use in these subgroups of patients (P-value for interaction=0.12).

History of ischaemic heart disease, congestive heart failure, chronic renal dysfunction, chronic obstructive pulmonary disease, emergency surgery, thoracoabdominal aortic aneurysm surgery, a larger aortic aneurysm

Table 3 Univariable and multivariable predictors of perioperative mortality of the 1000 patients (*for definition of risk factors see 'Methods' section; †history of current stable or chronic angina pectoris or history of myocardial infarction)

Variables*	Univariable analysis		Multivariable analysis		Multivariable analysis propensity adjusted	
	Odds ratios (95% CI)	*P*-value	Odds ratios (95% CI)	*P*-value	Odds ratios (95% CI)	*P*-value
Age >70 yr	1.7 (1.1–2.7)	0.02				
Males	0.8 (0.5–1.4)	0.41				
Current smoker	1.1 (0.7–1.7)	0.80				
Ischaemic heart disease†	2.4 (1.5–3.8)	<0.0001	2.6 (1.4–4.7)	0.003	2.5 (1.4–4.7)	0.003
Congestive heart failure	6.6 (3.4–12.7)	<0.0001	3.1 (1.2–8.5)	0.03	3.1 (1.1–8.7)	0.03
Cerebrovascular event	1.6 (0.9–2.8)	0.10				
Diabetes mellitus	1.4 (0.8–2.6)	0.23				
Chronic renal dysfunction	4.5 (2.5–8.3)	<0.0001	3.8 (1.6–9.0)	0.002	3.7 (1.5–8.7)	0.003
Chronic obstructive pulmonary disease	3.4 (2.2–5.3)	<0.0001	1.9 (1.1–3.5)	0.03	1.7 (0.9–3.4)	0.13
Hypertension	2.1 (0.7–5.8)	0.20				
Percutaneous coronary intervention	1.4 (0.4–4.6)	0.60				
Coronary artery bypass surgery	0.3 (0.1–1.1)	0.06				
Extracardiac arteriopathy	1.0 (0.6–1.6)	0.90				
ACE-inhibitors	0.8 (0.5–1.3)	0.4				
Aspirin	0.8 (0.4–1.5)	0.44				
Beta-blockers	0.5 (0.3–0.8)	0.006	0.5 (0.3–0.9)	0.03	0.5 (0.3–0.9)	0.03
Dihydropiridine calcium-channel blockers	2.6 (1.6–4.0)	<0.0001	2.6 (1.4–4.7)	0.002	2.5 (1.3–4.6)	0.003
Non-dihydropiridine calcium-channel blockers	0.8 (0.3–1.9)	0.56				
Diuretics	0.9 (0.5–1.4)	0.58				
Nitrates	1.0 (0.6–1.6)	0.9				
Statins	0.1 (0.0–0.3)	<0.0001	0.3 (0.1–0.9)	0.04	0.3 (0.1–0.98)	0.04
ASA score						
II	1.0					
III	2.1 (1.1–4.3)	0.03				
IV+V	14.4 (6.7–30.8)	<0.0001				
Period of operation, 2003–2007 *vs* 1999–2002	1.1 (0.7–1.7)	0.71				
Emergency surgery	21.3 (12.8–35.3)	<0.0001	8.3 (4.4–15.8)	<0.0001	8.3 (4.4–15.7)	<0.0001
Thoracoabdominal aortic aneurysm	5.8 (3.6–9.3)	<0.0001	3.2 (1.6–6.1)	0.001	3.2 (1.6–6.1)	0.001
Aortic aneurysm diameter 1 cm increase	1.3 (1.2–1.4)	<0.0001	1.2 (1.0–1.4)	0.04	1.2 (1.0–1.4)	0.03
Increment in preoperative haemoglobin level by 1 g dl^{-1}	0.7 (0.6–0.7)	<0.0001				
Increment in duration of surgery by 30 min	1.2 (1.1–1.3)	0.002				
Intraoperative packed red blood cell transfusions, unit						
Not given	1.0		1.0		1.0	
1 to 2	6.2 (1.8–21.0)	0.003	4.0 (1.1–14.2)	0.03	4.0 (1.1–14.0)	0.04
3 or more	35.7 (11.1–115.4)	<0.0001	7.0 (2.0–25.0)	0.002	6.8 (1.9–24.3)	0.003

diameter, and intraoperative blood transfusion were significantly associated with an increased risk of perioperative mortality (Table 3). Additionally, dihydropiridine calcium-channel blocker users were at almost three-fold risk of perioperative mortality. Beta-blocker and statin use, however, independently were associated with a reduced risk of perioperative mortality. When propensity score was added, the association between dihydropiridine calcium-channel blocker use and the perioperative mortality was little changed (Table 3). The combination of clinical and surgical characteristics, beta-blocker and statin use, and dihydropiridine calcium-channel blocker use resulted in a mortality model with excellent discriminatory power and good fit (c-index, 0.92; overall goodness-of-fit Hosmer–Lemeshow test; χ^2=5.0, P=0.76).

Discussion

Our data suggest that dihydropiridine calcium-channel blocker use in patient undergoing acute or elective aortic aneurysm surgery is associated with a significantly increased risk of perioperative mortality. This association remained statistically significant after adjustment of clinical risk factors and surgical characteristics associated with perioperative mortality was made.

Several studies have shown that cardiac complications are the leading cause of perioperative mortality in patients undergoing aortic aneurysm surgery.[10 11] Among these, perioperative myocardial infarction, which is predominantly silent, non-Q-wave, and preceded by prolonged myocardial ischaemia[14] is the most frequently occurring complication. Prolonged myocardial ischaemia in the perioperative setting may arise either from increased myocardial oxygen demand or reduced supply. Periods of tachycardia and hypertension resulting from surgical stress, postoperative pain, or the use of sympathomimetic drugs can all increase myocardial oxygen demand. In contrast, decreased supply may be the result of hypotension, vasospasm, anaemia, hypoxia or coronary artery plaque rupture. Dihydropiridine calcium-channel blockers, which are often prescribed in these patients as an alternative

treatment for hypertension, chronic angina pectoris and for stable coronary artery disease may partially also improve this imbalance through negative inotropic, negative chronotropic, afterload reducing and coronary and peripheral vasodilator properties. However, their negative inotropic and most importantly their negative chronotropic effect are rarely if ever seen in treated patients. As the most frequent underlying mechanism of prolonged perioperative myocardial ischaemia is high frequency tachycardia,[15–17] the lack of negative chronotropic effect of dihydropiridine calcium-channel blockers may well explain the observed association between their use and the increased risk of perioperative mortality in the present study. In that respect, beta-blockers titrated to achieve tight heart rate control,[17 18] could be effective measures for preventing perioperative cardiac complications in high-risk patients.[19 20] Nevertheless, many high-risk patients either have contraindications to beta-blockers or may be intolerant to them, which in the present study was also reflected by the fact that dihydropiridine calcium-channel blocker users had a higher prevalence of chronic obstructive pulmonary disease, hypertension, and extracardiac arteriopathy. Diltiazem, a non-dihydropiridine calcium-channel blocker with similar cardiovascular characteristics as beta-blockers, could be considered in these patients for the treatment of hypertension, stable coronary artery disease, and for the prevention of perioperative cardiac complications. It has been shown that diltiazem use in patients undergoing non-cardiac surgery is associated with reduced myocardial ischaemia, supraventricular arrhythmias, myocardial infarction, and mortality without any significantly increased risk of perioperative hypotension or bradycardia.[9]

As with some previous studies an association between beta-blocker use[20 21] and reduced perioperative mortality was observed. Interestingly, when the differential beneficial effect of beta-blocker use on dihydropiridine calcium-channel blocker use in relation to outcome was studied the results showed significantly reduced risk of perioperative mortality. Thus, in this study, beta-blocker use was independently associated with a reduced incidence of perioperative mortality even in the presence of dihydropiridine calcium-channel blockers. Beta-blockers apart from their direct haemodynamic effect such as reduction in heart rate and contractility may also indirectly influence the determinants of shear stress and reduce inflammation through decreases in sympathetic tone.[22] These properties of beta-blockers may counterbalance the effect of dihydropiridine calcium-channel blockers with a subsequent reduction in perioperative cardiac complications.

To date, there are few studies that have evaluated the efficacy of perioperative calcium-channel blocker use,[23–25] and only few of these investigated dihydropiridine calcium-channel blockers for the prevention of perioperative cardiac complications in patients undergoing non-cardiac surgery including vascular surgery.[7 8] The findings of du Toit *et al*.[7] in a small group of 50 patients undergoing total hip replacement showed that although statistically not significant, patients randomized to nifedipine use had a higher incidence of perioperative myocardial ischaemia compared with patients randomized to placebo [8 (31%) *vs* 4 (17%)]. In a retrospective study of 450 patients with either arterial hypertension or coronary artery disease undergoing non-cardiac surgery including vascular surgery, Sear *et al*.[5 6] noted an increased incidence of silent myocardial ischaemia in patients receiving chronic calcium-channel blockers. However, in a subsequent Case–Control study in which no differentiation was made between non-dihydropiridine and dihydropiridine calcium-channel blockers the same investigators found no significant association between calcium-channel blocker use and perioperative cardiovascular mortality in patients undergoing elective and emergency non-cardiac surgery.[6]

Several limitations should be kept in mind when interpreting these results. The design of the present study may limit the strength of the inferences made. As this study was observational and the decision to use dihydropiridine calcium-channel blockers was non-randomized, there is a limitation in the ability to establish causal relationship. Although we used contemporary statistical methods to adjust for potential confounders, the possibility that unmeasured confounders may affect the unfavourable effect of dihydropiridine calcium-channel blocker use, and perioperative mortality may exist. Additionally, as in every retrospective observational study, dihydropiridine calcium-channel blocker use might have been missed in some patients, as not all patients systematically received dihydropiridine calcium-channel blockers based on elevated blood pressure or a history of coronary artery disease. If this had been the case, however, the unfavourable effect of dihydropiridine calcium-channel blocker use would have been underestimated in the present study and its adverse effect would be even stronger. Interestingly, in our study we also observed that dihydropiridine calcium-channel blocker users more frequently required red blood cell transfusions than non-users. Given the retrospective nature of our study, data on several perioperative variables associated with perioperative blood loss and transfusion were not systematically collected so we were not able to further elaborate on this issue. Nevertheless, it should be noted that there are some previous studies that showed association between calcium-channel blocker use and clinically significant bleeding complications.[26 27] Finally, given the retrospective nature of our study we used all-cause mortality rather than cardiovascular mortality as an endpoint which could have resulted in a spurious association between dihydropiridine calcium-channel blocker use and outcome. Nonetheless, there is a strong relation between perioperative cardiac and non-cardiac complications and subsequent mortality in patients undergoing non-cardiac surgery including vascular surgery;[28] almost half of the

patients who experience cardiac morbidity develop other types of non-cardiac complications and mortality. Therefore, the estimation of the risk of all-cause mortality such as in our study could provide a more appropriate interpretation and estimation of the risk of all-cause mortality.[29]

This study revealed that dihydropiridine calcium-channel blocker use in patients who underwent acute or elective aortic aneurysm surgery is associated with an increased incidence of perioperative mortality irrespective of clinical risk factors, surgical characteristics, and chronic cardioprotective medication use. It seems likely, therefore that dihydropiridine calcium-channel blocker use should not be considered for patients undergoing aortic aneurysm surgery.

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References

1 Fleisher LA, Beckman JA, Brown KA, *et al*. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 guidelines on perioperative cardiovascular evaluation for noncardiac surgery): developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *Circulation* 2007; **116**: e418–99

2 Chobanian AV, Bakris GL, Black HR, *et al*. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560–72

3 Kertai MD, Boersma E, Westerhout CM, *et al*. A combination of statins and beta-blockers is independently associated with a reduction in the incidence of perioperative mortality and nonfatal myocardial infarction in patients undergoing abdominal aortic aneurysm surgery. *Eur J Vasc and Endovasc Surg* 2004; **28**: 343–52

4 The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA* 2002; **288**: 2981–97

5 Sear JW, Foex P, Howell SJ. Effect of chronic intercurrent medication with beta-adrenoceptor blockade or calcium channel entry blockade on postoperative silent myocardial ischaemia. *Br J Anaesth* 2000; **84**: 311–5

6 Sear JW, Howell SJ, Sear YM, *et al*. Intercurrent drug therapy and perioperative cardiovascular mortality in elective and urgent/emergency surgical patients. *Br J Anaesth* 2001; **86**: 506–12

7 du Toit HJ, Weich HF, Weymar HW, Przybojewski JZ. Effects of nifedipine on the peri-operative ECG, as determined by continuous Holter monitoring. A double-blind study. *S Afr Med J* 1986; **69**: 427–31

8 Retamal O, Coriat P, Pamela F, *et al*. [Prevention of hypertensive attacks after carotid surgery. The value of nifedipine and diltiazem]. *Ann Fr Anesth Reanim* 1986; **5**: 278–86

9 Wijeysundera DN, Beattie WS. Calcium channel blockers for reducing cardiac morbidity after noncardiac surgery: a meta-analysis. *Anesth Analg* 2003; **97**: 634–41

10 Lee TH, Marcantonio ER, Mangione CM, *et al*. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999; **100**: 1043–9

11 Kertai MD, Boersma E, Klein J, *et al*. Optimizing the prediction of perioperative mortality in vascular surgery by using a customized probability model. *Arch Intern Med* 2005; **165**: 898–904

12 New classification of physical status. *Anesthesiology* 1963; **24**: 111

13 Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York, NY: John Wiley & Sons, Ltd, 1989

14 Mangano DT. Perioperative cardiac morbidity. *Anesthesiology* 1990; **72**: 153–84

15 Landesberg G, Mosseri M, Zahger D, *et al*. Myocardial infarction after vascular surgery: the role of prolonged, stress-induced, ST depression-type ischemia. *J Am Coll Cardiol* 2001; **37**: 1839–45

16 Mangano DT, Hollenberg M, Fegert G, *et al*. Perioperative myocardial ischemia in patients undergoing noncardiac surgery–I: Incidence and severity during the 4 day perioperative period. The Study of Perioperative Ischemia (SPI) Research Group. *J Am Coll Cardiol* 1991; **17**: 843–50

17 Raby KE, Brull SJ, Timimi F, *et al*. The effect of heart rate control on myocardial ischemia among high-risk patients after vascular surgery. *Anesth Analg* 1999; **88**: 477–82

18 Feringa HHH, Bax JJ, Boersma E, *et al*. High-dose beta-blockers and tight heart rate control reduce myocardial ischemia and Troponin T release in vascular surgery patients. *Circulation* 2006; **114**: 1344–49

19 Poldermans D, Bax JJ, Schouten O, *et al*. Should major vascular surgery be delayed because of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight heart rate control? *J Am Coll Cardiol* 2006; **48**: 964–9

20 Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. *N Engl J Med* 1996; **335**: 1713–20

21 Poldermans D, Boersma E, Bax JJ, *et al*. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med* 1999; **341**: 1789–94

22 Ohtsuka T, Hamada M, Hiasa G, *et al*. Effect of beta-blockers on circulating levels of inflammatory and anti-inflammatory cytokines in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2001; **37**: 412–7

23 Godet G, Coriat P, Baron JF, *et al*. Prevention of intraoperative myocardial ischemia during noncardiac surgery with intravenous diltiazem: a randomized trial versus placebo. *Anesthesiology* 1987; **66**: 241–5

24 Amar D, Roistacher N, Burt ME, *et al*. Effects of diltiazem versus digoxin on dysrhythmias and cardiac function after pneumonectomy. *Ann Thorac Surg* 1997; **63**: 1374–81

25 Van MW, Tits G, Demuynck K, *et al*. Verapamil as prophylactic treatment for atrial fibrillation after lung operations. *Ann Thorac Surg* 1996; **61**: 1083–5

26 Becker RC, Caputo R, Ball S, Corrao JM, Baker S, Gore JM. Haemorrhagic potential of combined diltiazem and recombinant tissue-type plasminogen activator administration. *Am Heart J* 1993; **126**: 11–4

27 Wagenknecht LE, Furberg CD, Hammon JW, Legault C, Troost BT. Surgical bleeding: unexpected effect of a calcium antagonist. *Br Med J* 1995; **310**: 776–7

28 Fleischmann KE, Goldman L, Young B, Lee TH. Association between cardiac and noncardiac complications in patients undergoing noncardiac surgery: outcomes and effects on length of stay. *Am J Med* 2003; **115**: 515–20

29 Lauer MS, Blackstone EH, Young JB, Topol EJ. Cause of death in clinical research: time for a reassessment? *J Am Coll Cardiol* 1999; **34**: 618–20