

Beta-blockers and statins are individually associated with reduced mortality in patients undergoing noncardiac, nonvascular surgery

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Background Patients undergoing noncardiac, nonvascular surgery are at risk for perioperative mortality owing to underlying (a)symptomatic coronary artery disease. We hypothesized that β -blocker and statin use are associated with reduced perioperative mortality.

Methods We performed a case-control study in 75 581 patients who underwent 108 593 noncardiac, nonvascular surgery at the Erasmus Medical Center between 1991 and 2001. Cases were the 989 patients who died during hospital stay after surgery. From the remaining patients, 1879 matched controls (age, sex, calendar year and type of surgery) were selected. Information was then obtained regarding the use of β -blockers and statins and the presence of cardiac risk factors.

Results The median age of the study population was 63 years; 61% were men. β -blockers were less often used in cases than in controls (6.2 vs. 8.2%; $P=0.05$), as were statins (2.4 vs. 5.5%; $P<0.001$). After adjustment for the propensity of β -blocker use and cardiovascular risk factors, β -blockers were associated with a 59% mortality reduction (odds ratio 0.41; 95% confidence interval 0.28–0.59). Statins were associated with a 60% mortality reduction (adjusted odds ratio 0.40; 95% confidence interval 0.24–0.68). A significant interaction between β -blockers and statins was observed ($P<0.001$). In the presence

of each other, statins and β -blockers were not associated with reduced mortality (adjusted odds ratio 2.0 and 95% confidence interval 0.74–5.7 and adjusted odds ratio 1.3 and 95% confidence interval 0.52–3.2). It should be, however, noted that only nine cases and 29 controls used both agents simultaneously.

Conclusion This case-control study provides evidence that β -blockers and statins are individually associated with a reduction of perioperative mortality in patients undergoing noncardiac, nonvascular surgery. *Coron Artery Dis* 18:67–72 © 2007 Lippincott Williams & Wilkins.

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Introduction

Annually, approximately 4% of the Dutch population is scheduled for noncardiac surgery, with an estimated 1.9% mortality rate [1]. Major cardiac complications are important contributors to perioperative mortality. They are estimated to occur in 1–5% of the noncardiac surgical population, and contribute to 30% of deaths in the perioperative period [1,2]. Perioperative myocardial infarction is the most frequent fatal cardiovascular complication during noncardiac surgery [3].

During surgery, the patient is exposed to a broad spectrum of physiologic changes: an increased sympathetic tone by surgical and anesthesiological stress, hypercoagulability, hypothermia, anemia and pain. This stress response contributes to coronary plaque instability

and possible rupture, which is an important aspect of the pathophysiology of perioperative myocardial infarction [4,5]. Coronary plaque rupture may lead to thrombus formation and subsequent vessel occlusion, resulting in myocardial ischemia. In patients with fixed stenotic coronary lesions, increased heart rate and contractility induce an oxygen supply and demand mismatch, which results in myocardial ischemia and eventually myocardial infarction [5].

Several factors are associated with an increased risk of perioperative myocardial infarction, including advanced age, cardiovascular risk factors and type of surgery [1,6]. Both β -blockers and statins have previously been associated with improved outcome in high-risk major noncardiac surgery [7–12]. The majority of patients,

however, are scheduled for low-risk to intermediate-risk surgical procedures [1]. In this surgical population, data on the effect of perioperative β -blocker and statin use are not available. Our study was designed to evaluate the possible protective effects of both agents in this large noncardiac, nonvascular surgical population.

Methods

Study design

We undertook a retrospective case-control study among the 75 581 patients above the age of 15 years who underwent 108 593 noncardiac surgical procedures between 1 January 1991 and 1 January 2001 in the Erasmus Medical Center, Rotterdam, The Netherlands. The computerized hospital information system was used to identify cases and controls. This system holds demographic and clinical data of all admitted patients, as well as information on the perioperative course.

Selection of cases and controls

Two thousand eight hundred and sixteen patients undergoing vascular surgery and 129 patients with an American Society of Anesthesiologists (ASA) classification V (moribund, not expected to live 24 h irrespective of operation) were excluded. Candidate case individuals were the 1040 patients from the remaining population who died of any cause during surgery or during the hospital stay after surgery within 30 days. It is speculated that β -blockers and statins mainly affect cardiac mortality. Retrospective classification of cardiac death is, however, often inaccurate owing to a lack of autopsy reports in patients. Therefore, we chose all-cause mortality as the end point of our study.

We intended to select two controls for each case from the remaining patients. Cases and controls were matched according to age (within an interval of plus or minus 5 years), sex, calendar year of surgery and type of surgery. Surgical procedures were grouped according to a modified version of the American Heart Association/American College of Cardiology (AHA/ACC) classification as follows: low risk including breast, dental, endocrine, eye, gynecology and reconstructive surgery; low-risk to intermediate-risk including orthopedic and urologic surgery; intermediate-risk to high-risk including abdominal, ear, nose, throat, neurologic, pulmonary and renal transplant [1]. Note that we excluded all vascular procedures; therefore, no patients were classified as high-risk surgery. For 890 cases, two matching controls could be selected. For 99 other cases only one matching control could be selected, whereas for 51 cases no matching controls could be selected. The 51 cases without controls were excluded from the study population, as a result the study population consisted of 989 cases and 1879 matching controls.

Data collection

To study the relationship between β -blocker use, statin therapy and perioperative mortality, the computerized hospital database, patient medical records, nursing reports, surgical reports, anesthetic reports and discharge letters were thoroughly analyzed by our investigators to obtain the following information on cases and controls; type of surgery, year of surgery, age, sex, diabetes, hypertension, family history of coronary artery disease, smoking, history of angina pectoris, myocardial infarction, heart failure, coronary artery bypass grafting, percutaneous coronary intervention, cerebrovascular disease, chronic obstructive pulmonary disease and renal insufficiency, as well as the ASA classification and the perioperative use of aspirin, oral anticoagulant therapy, β -blockers, nitrates, angiotensin-converting enzyme inhibitors, angiotensin 2 antagonists, statins, diuretics, prednisone, insulin and oral antidiabetic medication.

Statistical analysis

Continuous data are presented as median value and corresponding 25th and 75th percentiles; dichotomous data are presented as numbers and percentages. Differences in baseline characteristics between cases and controls were studied by Mann-Whitney tests, χ^2 tests or Fisher's exact tests, as appropriate.

To adjust for selection bias, we developed a propensity score for the likelihood of receiving perioperative β -blocker (statin) therapy. Multivariable logistic regression analysis was applied to identify baseline factors that were associated with such early β -blocker (statin) use. We considered a broad range of patient baseline characteristics, including age, sex, diabetes, hypertension, family history of coronary artery disease, smoking, history of angina pectoris, myocardial infarction, heart failure, coronary artery bypass grafting, percutaneous coronary intervention, cerebrovascular disease and renal insufficiency, as well as the ASA classification and the perioperative use of aspirin, oral anticoagulant therapy, β -blockers (as appropriate), nitrates, angiotensin-converting enzyme inhibitors, angiotensin 2 antagonists, statins (as appropriate), diuretics, prednisone, insulin and oral antidiabetic medication. Potential interactions between these variables were not considered. All variables entered the multivariable stage. In general, for the development of a propensity score, it is recommended to use an extensive model, to ensure that any predictors (true and chance) are accounted for. For practical reasons, however, we decided to develop a somewhat reduced model, and excluded variables with a P -value > 0.5 via a backward deletion procedure. We report adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of the variables that compose the final propensity score. The performance of the propensity score model was studied with respect to discrimination and calibration. Discrimination refers to the ability to distinguish statin users from nonusers; it

was quantified by the C-statistic. Calibration refers to whether the predicted probability of statin use is in agreement with the observed probability; calibration was measured with the Hosmer–Lemeshow goodness-of-fit test.

Univariable and multivariable logistic regression analysis was applied to evaluate the relation between β -blocker (statin) use and perioperative mortality. We adjusted for the propensity of β -blocker (statin) use, the matching factors age, sex, calendar year and type of surgery, as well as for a number of potential confounders, including cardiovascular risk factors, history of cardiovascular or cerebrovascular disease, renal disease and ASA classification. The multivariable models were constructed by backward deletion of the least significant characteristics, while applying the Akaike information criterion (i.e. the applied threshold of significance depended on the degrees of freedom associated with the variable at hand; if degrees of freedom = 1, then $P = 0.157$). We report crude and adjusted ORs and corresponding 95% CIs.

Stratified analyses were performed according to statin (β -blocker) use and the factors that compose the Lee risk index for perioperative cardiovascular events: type of surgery, age, angina pectoris, myocardial infarction, heart failure, cerebrovascular disease (CVA/TIA) and renal insufficiency [6]. To reveal a possible heterogeneity in ORs between subgroups of patients, interaction terms between the stratification characteristic and β -blocker (statin) use were included in the models.

All statistical tests were two-sided, including tests for interaction. P -value < 0.05 was considered significant.

Results

Characteristics of cases and controls

Important differences were present in clinical baseline characteristics between cases and controls (Table 1). In total, 237 patients (24%) died of a definite cardiac cause according to available autopsy reports. The prevalence of cardiovascular risk factors, including diabetes, hypertension, hypercholesterolemia and current smoking was higher in cases than in controls. A history of circulatory disease, pulmonary disease and renal disease was also more often seen in cases than in controls. Finally, the general condition of cases before surgery, as reflected by the ASA classification, was worse when compared with controls.

Propensity of beta-blocker or statin use

The most relevant characteristics that were associated with β -blocker use included hypertension (adjusted OR 4.8 and 95% CI 3.4, 6.9), a history of angina pectoris (OR 4.5 and 95% CI 3.0 and 6.6), ASA classification III or IV (OR 2.9 and 95% CI 1.9, 4.5), the use of oral anticoagulant medication (OR 2.5 and 95% CI 1.6, 4.0) and a

Table 1 Baseline characteristics of cases and controls

	Cases	Controls
No. of patients	989	1879
Type of surgery ^a		
Low risk (%)	8	6
Low–intermediate risk (%)	20	22
Intermediate–high risk (%)	72	72
Age (years)	63.5 (48, 74)	63.3 (47, 74)
Male gender (%)	61	62
Medical risk factors (%)		
Diabetes mellitus	25	9 [‡]
Hypertension	19	14 [‡]
Hypercholesterolemia	16	6 [‡]
Family history of coronary disease	2	1
Current smoking	14	8 [‡]
Angina pectoris	13	7 [‡]
Myocardial infarction	26	8 [‡]
Heart failure	11	2 [‡]
Percutaneous coronary intervention	2	1
Coronary artery bypass grafting	3	3
Peripheral vessel disease	11	5 [‡]
Cerebrovascular disease	7	5*
Chronic obstructive pulmonary disease	13	8 [‡]
Renal insufficiency	34	14 [‡]
ASA classification		‡
I	13	47
II	18	31
III	41	21
IV	28	1

ASA, American Society of Anesthesiologists.

^aAccording to the American Heart Association/American College of Cardiology classification: high-risk = aortic; intermediate-risk = abdominal; ear, nose, throat; neurologic; orthopedic; pulmonary; renal transplant; urologic; vascular, excluding aortic and carotid; low-risk = breast; carotid; dental; endocrine; eye; gynecology; reconstructive. We have demonstrated [10] that within the intermediate-risk group, patients undergoing orthopedic or urologic surgery had significantly lower risk than patients undergoing other types of surgery. Therefore, we labeled orthopedic and urologic procedures as low-intermediate risk, and the remaining procedures as intermediate-high risk. Note that we excluded any vascular surgery, therefore, we don't have any patients in the high-risk category.

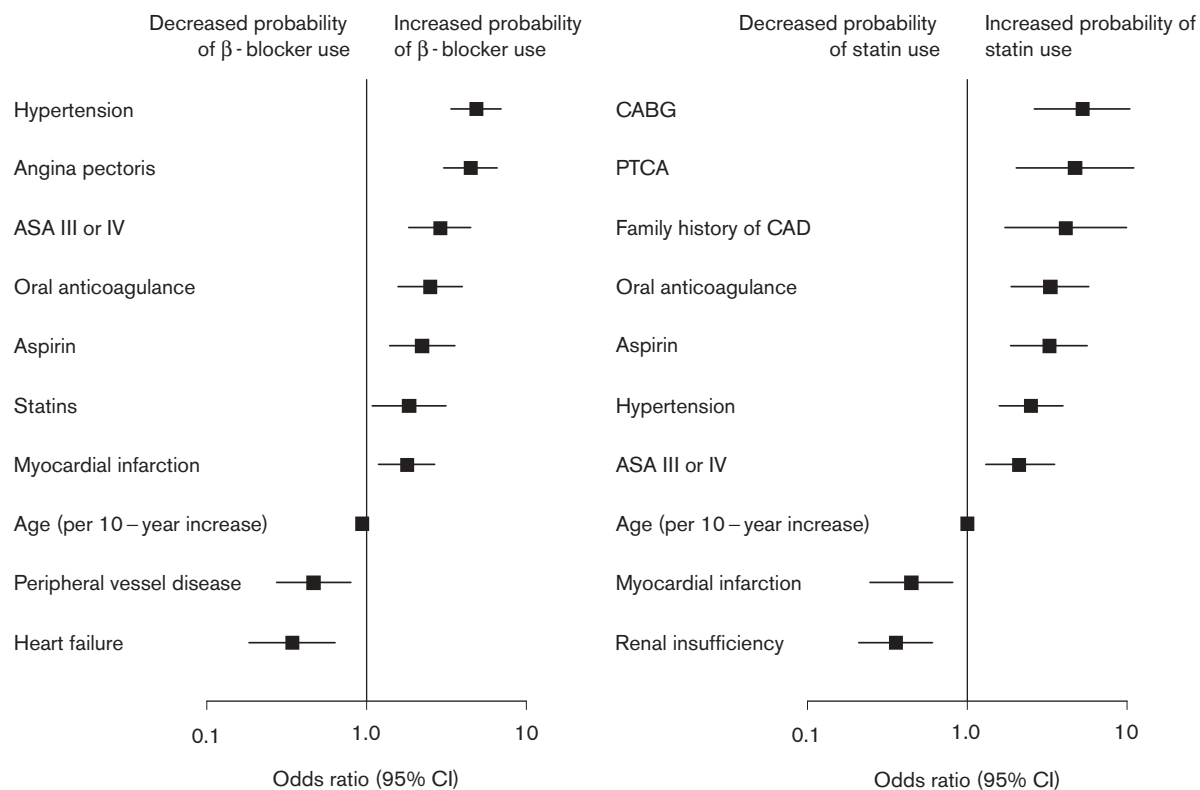
* $P < 0.05$; [‡] $P < 0.01$; [‡] $P < 0.001$.

history of heart failure (OR 0.34 and 95% CI 0.18, 0.64). The most relevant characteristics that were associated with statin use included a history of coronary artery bypass surgery (adjusted OR 5.2 and 95% CI 2.6, 10.4), the use of oral anticoagulant medication (OR 3.3 and 95% CI 1.9, 5.7), the use of aspirin (OR 3.2 and 95% CI 1.9, 5.6), hypertension (OR 2.5 and 95% CI 1.6, 4.0) and renal insufficiency (OR 0.36 and 95% CI 0.21, 0.61). The propensity scores (Fig. 1) were highly predictive of the likelihood of β -blocker (C-statistic 0.90) or statin use (C-statistic 0.85). The Hosmer–Lemeshow test showed a significant value for the β -blocker propensity model (P -value 0.001), indicating that its calibration was not optimal.

Relation between beta-blocker and statin use and perioperative mortality

Data on perioperative β -blocker use were lacking in one case and in four controls. β -blocker use was less common in cases than in controls (61 cases [6.2%] and 153 controls [8.2%]; P -value 0.05). After adjustment for multiple confounders and the propensity of their use, β -blockers

Fig. 1

Propensity scores of the likelihood of β -blocker and statin use in the study population.

were associated with a significant 59% relative reduction in perioperative mortality (adjusted OR 0.41 and 95% CI 0.28 to 0.59). Data on perioperative statin use was missing in two cases and in four controls. Statins were significantly less commonly used by cases than controls [24 cases (2.4%) and 103 controls (5.5%); P -value < 0.001]. After adjustment for multiple confounders and the propensity of their use, statins appeared associated with 60% reduced mortality (adjusted OR 0.40 and 95% CI 0.24 to 0.68) (Fig. 2).

The observed relations between β -blocker and statin use and perioperative mortality were significantly modified by each other (P -value for interaction < 0.001). In the absence of statins, β -blockers were associated with 66% reduced mortality (adjusted OR 0.34 and 95% CI 0.23–0.50), whereas in the presence of statins, β -blockers were not associated with reduced mortality (adjusted OR 2.0 and 95% CI 0.74–5.7). Similarly, in the absence of β -blockers, statins were associated with 73% reduced mortality (adjusted OR 0.27 and 95% CI 0.14–0.51), whereas in the presence of β -blockers, statins were not associated with reduced mortality (adjusted OR 1.3 and 95% CI 0.52–3.2). It should be noted, however, that there were only nine cases and 29 controls who used both agents simultaneously.

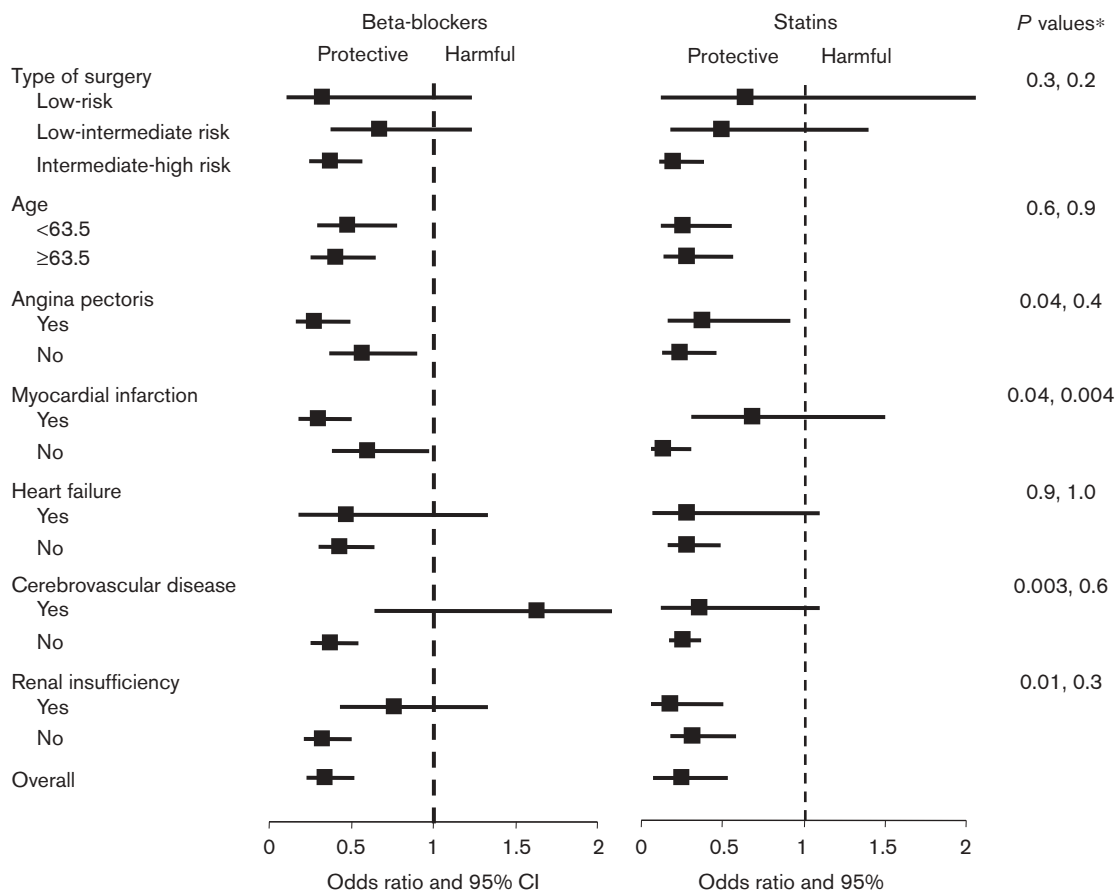
Although there was evidence of heterogeneity in treatment effect in relation to specific patient characteristics, β -blockers and statins were consistently associated with reduced mortality in the specified strata (Fig. 2). Patients with a history of cerebrovascular disease formed the single exception. The mortality reduction associated with β -blocker use was particularly profound in patients with a history of angina pectoris or myocardial infarction, and in patients with normal renal function. Statin use was associated with a larger mortality reduction in patients without a history of myocardial infarction than in those with a history of myocardial infarction.

Discussion

In this case–control study of patients undergoing non-cardiac, nonvascular surgery, β -blockers and statins were individually associated with reduced perioperative mortality. Compared with nonusers, β -blocker users and statin users had a 2.5-fold lower risk of mortality. These results are consistent with case–control studies and randomized clinical trials in patients undergoing major noncardiac, vascular surgery [7–12].

Patients scheduled for low-risk or intermediate-risk surgery represent the majority of the surgical population.

Fig. 2



Odds ratios for perioperative mortality in relation to β -blocker and statin use in selected subgroups of patients. Odds ratios are adjusted for the propensity of β -blocker (statin) use and the following variables that appeared related (P -value < 0.157 ; see Methods section) with perioperative mortality: age, sex, diabetes, family history of coronary disease, current smoking, history of angina pectoris, myocardial infarction, heart failure, peripheral vessel disease, cerebrovascular disease, chronic obstructive pulmonary disease, renal insufficiency and American Society of Anesthesiologists (ASA) classification. * P values for homogeneity of odds ratios in subgroups of patients using β -blockers and statins, respectively.

The results of our study showed a beneficial effect on the perioperative mortality of β -blockers in the entire strata of surgical procedures. In a recently published paper, Lindenauer *et al.* [11] reported the results of a large retrospective cohort study on perioperative β -blocker therapy and perioperative mortality reduction in patients undergoing major noncardiac surgery. Perioperative β -blockade was associated with significantly reduced in-hospital mortality rates in higher risk subgroups of the total cohort. In contrast, perioperative β -blockade was associated with significantly increased in-hospital mortality rates among the lowest risk patients. The protective effect of perioperative β -blockade in our patient population was consistent in all types of surgical procedures, including low-risk and low-intermediate risk surgery. The possible harmful effect of β -blocker therapy in low-risk patients undergoing major surgical procedures, found by Lindenauer and colleagues, could be contributed to the design of that study. Patients who were treated with

a β -blocker on the first or second hospital day were assumed to be on prophylaxis. This seems, however, unlikely in lower risk patients. In these patients, β -blocker therapy might have been a response to a cardiovascular complication, rather than the prevention of one [13].

The protective effect of β -blocker therapy is caused by perioperative heart rate control and reduced myocardial contractility, resulting in a prolonged coronary diastolic filling time and a subsequent correction of the myocardial oxygen demand and supply mismatch in patients with fixed coronary artery lesions. Our results support this cardioprotective mechanism. In the subgroup of patients with an established diagnosis of coronary artery disease (previous myocardial infarction, history of angina pectoris), a stronger effect in perioperative mortality reduction on β -blocker therapy was present, compared with those without symptomatic disease (Fig. 2).

A considerable proportion of the surgical population had undiagnosed, asymptomatic coronary artery disease, characterized by nonblood flow limiting, vulnerable atherosclerotic plaques [14]. Acute coronary plaque rupture, owing to an increased stress response to surgery, may be the first expression of cardiac disease. In our study, the estimate of treatment effect favored statin therapy in all prognostically relevant subgroups. Our data, however, suggested a larger perioperative mortality reduction in patients without previously diagnosed coronary artery disease (Fig. 2). These patients could have silent cardiac disease, characterized by nonblood flow limiting vulnerable plaques. The beneficial effect of statin therapy can be ascribed to the stabilization of these plaques, a result of the antiinflammatory action and reversal of endothelial dysfunction.

An interaction was found between β -blocker use and statin therapy. In the presence of each other, both β -blockers and statins failed to show a statistically significant effect. A protective effect in simultaneous β -blocker and statin use could not be, however, excluded on the basis of our results. A part of the interaction between both drugs can be explained by a similar treatment effect between statins and β -blockers. Antiinflammatory effects after prolonged β -blocker therapy have previously been described in long-time users [15]. Nevertheless, the amount of patients who used both drugs simultaneously (nine cases and 29 controls) was small and data on therapy duration and dose were not available.

Physicians should continue β -blocker and/or statin therapy in their patients undergoing low-risk and intermediate-risk surgery. The results of our study confirm the individual protective effects of both therapies. In addition, withholding therapy in chronic β -blocker users resulted in a rebound effect, causing tachycardia and hypertension, with possible myocardial ischemia [16]. Future studies are needed to provide information on duration, dose and effect of prophylactic β -blocker and statin use in patients undergoing low-risk and intermediate-risk types of surgery.

Our study has several limitations that are common with any case-control study relying on retrospective data collection. Firstly, we should mention that cases and controls might have been misclassified because of inappropriate information on vital status at discharge, although we consider this highly unlikely. Secondly, and this is a more realistic scenario, information on β -blocker and statin use might have been missed, probably differently so in cases and controls because of observer bias prejudice. Thirdly, multivariable adjustment for potential confounders is obviously limited to the available data elements, and unknown, unmeasured confounders

might still be present. Consequently, our estimates of the beneficial effects of β -blockers and statins might be overestimated. Therefore, we would like to emphasize that this early evidence needs confirmation by adequately powered randomized clinical trials.

Conclusion

This case-control study provides evidence that β -blockers and statins are individually associated with a reduction of perioperative mortality in patients undergoing noncardiac, nonvascular surgery.

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