



Cohort study of preoperative chronic beta blocker prescription in elderly patients as a risk factor for postoperative mortality stratified by preoperative blood pressure.

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4 **Cohort study of pP**reoperative chronic beta blocker prescription in
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7 **elderly patients as a risk factor for postoperative mortality**
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10 **stratified by preoperative blood pressure: a cohort study**
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Brief Title: Preoperative medications and surgical mortality

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13 **Editor's key points** **Total word count: 2678**
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19 The role of preoperative antihypertensive drug therapy as a risk factor for postoperative
20 mortality as a function of preoperative arterial pressure was investigated in a large
21 retrospective data set.
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28 A propensity score-matched cohort study of primary care data from the UK Clinical Practice
29 Research Datalink including 84,633 elderly patients 65 years or over analysed mortality
30 following elective noncardiac surgery.
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36 Beta blockers were associated with increased risk of 30-day mortality in patients with
37 elevated preoperative blood pressure.
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41 Renin angiotensin system inhibitors, calcium channel blockers, and loop diuretics were not
42 associated with mortality, while thiazides and statins were associated with reduced risk.
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47 Prospective randomised trials are needed to confirm these findings with important
48 implications for perioperative management.
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Abstract

Background: Recent data suggest that beta blockers are associated with increased perioperative risk in hypertensive patients. We investigated whether beta blockers were associated with increased risk in elderly patients with raised preoperative arterial blood pressure (BP).

Methods: We conducted a propensity score-matched cohort study of primary care data from the United Kingdom Clinical Practice Research Datalink (2004-2013) including 84,633 patients aged 65 years or over. Conditional logistic regression models, including factors that were significantly associated with the outcome, were constructed for 30-day mortality following elective, non-cardiac surgery. The effects of beta blockers (primary outcome), renin angiotensin system (RAS) inhibitors, calcium channel blockers, thiazides, loop diuretics and statins were investigated at systolic, and diastolic BP thresholds.

Results: Beta blockers were associated with ~~an~~ increased odds of postoperative 30-day mortality in patients with systolic hypertension (defined as systolic BP >140 mmHg, adjusted odds ratio [aOR]: 1.92, 95% CI: 1.05-3.51). After excluding patients for whom prior data suggest benefit from perioperative beta blockade (patients with prior myocardial infarction or heart failure), rather than adjusting for them, the point estimate shifted slightly (aOR: 2.06, 95% CI: 1.09-3.89). Compared to no use, statins (aOR: 0.35; 95% CI: 0.17-0.75) and thiazides (aOR: 0.28; 95% CI: 0.10-0.78) were associated with lower mortality in patients with systolic hypertension.

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3 Conclusions: These data suggest that the safety of perioperative beta blockers may be
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5 influenced by preoperative BP thresholds. A ~~randomized~~randomised controlled trial of beta
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7 blocker withdrawal, in select populations, is required to identify ~~any~~a causal relationship.
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Introduction

For many years, beta blockers were considered ~~as~~ protective medications in the perioperative period, however, recent trials and meta-analyses have challenged this notion¹⁻³. Most notably the POISE study suggested that *de novo* institution of a high dose of ~~slow-slow~~-release metoprolol ~~may reduce~~s the risk of myocardial infarction but ~~increases~~s the risk of stroke, sepsis and mortality⁴. Accumulating data from observational studies suggests that beta blockers exert a class effect⁵ and may be harmful in ~~low-low~~-risk patients (defined as low revised cardiac risk index scores^{6,7}) but beneficial in those with a recent myocardial event or heart failure⁸ (~~reviewed in ref 3 for review see~~³). When excluding ~~high-high~~-risk cardiac patients, Jorgensen ~~et al. recently and colleagues~~⁹ found that among hypertensive patients, use of beta blockers was associated with increased risk of postoperative major adverse complications⁹. Based on this work, our primary hypothesis ~~herein was to verify whether that~~ beta blockers ~~were~~-are associated with increased 30-day mortality in patients with numerically ~~raised-high~~ preoperative blood pressure. The working hypothesis is that in patients with hypertension, the effects on cardiac output, renin-angiotensin system (RAS) and vascular tone by beta blockers in the perioperative period, outweigh ~~the benefit of~~ any direct cardioprotective ~~effect~~benefit. As secondary ~~hypotheses-aims~~ we tested the association of other cardiovascular medications and postoperative 30-day mortality at different blood pressure thresholds defined as hypotension (<80 mm Hg diastolic or <120 mm Hg systolic), normotension (80-89 mm Hg diastolic or 120-139 mm Hg systolic), ~~and-or~~ hypertension (>90 mm Hg diastolic or >140 mm Hg systolic). There ~~are is~~ limited guidance on the impact of other cardiovascular medications in the perioperative period, though RAS inhibitors are suggested to be withheld in some situations¹⁰. It is important to note that in our recent analysis of these

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3 data, hypertensive level BP values in the elderly were not associated with increased 30-day
4 mortality¹¹. This *a priori* planned secondary analysis focuses on whether cardiovascular
5 medications may be an important determinant of perioperative outcomes at different BP
6 values in ~~the~~ elderly patients undergoing elective noncardiac surgery.
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Methods

Data source and study design

The data source for this study was the UK Clinical Practice Research Datalink (CPRD) which is a ~~UK~~ primary care database representing about 6% of the country's population. We used medical codes (as listed in the Appendix of our original paper¹²) to identify patients who underwent specific non-cardiac surgeries between 1st January 2004 and 31st December 2013. We ~~then~~ retained longitudinal data for patients aged 65 ~~years~~ and over, and who were registered at the GP practice for ~~at least~~ \geq 1 year prior to their elective non-cardiac surgery. This study was approved by the Independent Scientific Advisory Committee (ISAC) for the Medicines and Healthcare Products Regulatory Agency, UK (ISAC protocol number: 11_138A).

Exposure variables

Preoperative cardiovascular medications were ~~our~~ the main exposure variables. They included beta blockers (primary outcome) and as secondary outcomes ~~of~~ statins, calcium-channel blockers, angiotensin converting enzyme inhibitors and angiotensin 2 receptor blockers referred to as RAS inhibitors, thiazide diuretics, and loop diuretics prescribed within 30 days of surgery (compared to non-users).

Outcome variable

Our outcome variable was perioperative mortality, defined as death occurring within 30 days following non-cardiac surgery. In the UK, death certificates issued by the GP are entered directly into the primary care database. Potential biases that may arise from misclassification

of death are likely to be non-differential, i.e. similar between both groups:— death and survival. We ~~have~~ discussed this in more detail in our previous publication¹².

Covariates

We included the following as covariates in our multivariable models: age, ~~gender~~sex, alpha2 agonists, aspirin, other antiplatelet agents, atrial fibrillation, unstable angina, valvular heart disease, myocardial infarction, cerebrovascular disease, peripheral vascular disease, chronic pulmonary disease (including asthma), heart failure, diabetes mellitus, renal disease, liver disease, cancer, body mass index (BMI) as a categorical variable (<18.5, 18.5–24.99, 25–29.99 and >30 kg m⁻²), smoking status, alcohol consumption, and socioeconomic status [using the 2010 Index of Multiple Deprivation (IMD) scores in quintiles]. We used the surgical risk score to adjust for ~~the~~ varying levels of risk posed by the ~~various~~ included surgery types. Our surgical procedural risk score was based on ~~the a~~ validated surgical risk scale^{13,14} and was included as an ordinal categorical variable ranging from 1 to 5 with 1 a ~~low~~low-risk procedure and 5 a ~~high~~high-risk procedure.

Statistical analysis

Based on our prior study¹¹, we considered the most recent BP measurement prior to surgery and stratified our study population by BP thresholds as ~~follows: hypotension (<80mm Hg diastolic or <120 mm Hg systolic), normotension (80–89 mm Hg diastolic or 120–139 mm Hg systolic), and hypertension (>90mm Hg diastolic or >140 mm Hg systolic)~~above. We first computed propensity scores¹⁵ using multivariable logistic regression models for each of ~~our~~ six drugs of interest (statins, beta blockers, calcium-channel blockers, RAS inhibitors, thiazide diuretics, and loop diuretics) using the method ~~described by~~of Hirano and Imbens¹⁶.

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3 Covariates that informed the propensity score derivation models were ~~the following~~
4 ~~comorbidities~~: myocardial infarction, unstable angina, heart failure and atrial fibrillation. We
5
6 ~~then~~ generated propensity score quintiles for each drug of interest, and matched individuals
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8 on propensity score quintile, using an interval matching approach¹⁷, with a minimum 1:1
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10 variable matching ratio.
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16 For each ~~of the~~ BP threshold, we performed conditional logistic regression to investigate ~~the~~
17
18 association between preoperative cardiovascular medication and postoperative mortality.
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20 We ran unadjusted and adjusted models for each of the ~~five-six~~ cardiovascular drugs
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22 separately comparing the effect of exposure to a given medication to non-exposure. In our
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24 adjusted models we included those covariates that were statistically significantly (p-
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26 ~~value~~<0.05) associated with postoperative mortality. Conditional logistic regression models
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28 for each of the ~~five-six~~ drugs had the following covariates in common as well as their individual
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30 propensity score: age, aspirin, other antiplatelet agents, atrial fibrillation, unstable angina,
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32 MI, cerebrovascular disease, peripheral vascular disease, chronic pulmonary disease, diabetes
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34 ~~mellitus~~, renal disease, cancer, BMI, smoking status and surgical score. ~~Additionally,~~
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36 ~~{Significantly associated}~~ covariates included for specific models are presented below:
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44 Statins: ~~gendersex~~, beta blockers, RAS inhibitors, ~~Ca~~calcium-channel blockers, loop diuretics,
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46 heart failure, alcohol consumption, number of BP measurements, and IMD 2010 scores.
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48 Beta blockers: ~~gendersex~~, statins, RAS inhibitors, ~~Ca~~calcium-channel blockers, loop diuretics,
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50 heart failure, liver disease, alcohol consumption, number of BP measurements, and IMD 2010
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52 scores.
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54 Calcium-channel blockers: ~~gendersex~~, beta blockers, RAS inhibitors, statins, loop diuretics,
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56 heart failure, and alcohol consumption.
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3 RAS inhibitors: gendersex, statins, beta blockers, Ca-channel blockers, loop diuretics, heart
4 failure, liver disease, alcohol consumption, number of BP measurements, and IMD 2010
5 scores.
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10 Thiazides: statins, beta blockers, Cacalcium-channel blockers, loop diuretics, RAS inhibitors,
11 liver disease, number of BP measurements, and IMD 2010 scores.
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15 Loop diuretics: gendersex, statins, beta blockers, Cacalcium-channel blockers, thiazides, RAS
16 inhibitors, heart failure, liver disease, alcohol consumption, number of BP measurements, and
17 IMD 2010 scores.
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24 Drugs were omitted from the adjusted analysis where-if the sample size was insufficient.
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26 Interaction terms were specified between all drug covariates included in the multivariable
27 model to account for the impact of drug combinations. All analyses were performed using
28 Stata 15.0 (StataCorp, College Station, TX, USA).
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Results

~~Our The~~ study population included 84,633 patients aged 65 years or over who underwent elective, non-cardiac surgery (**Figure 1**). For ~~the~~ systolic BP thresholds, there were: 7,924 hypotensive patients (89.9% were also diastolic hypotensive), 34,531 normotensive patients (36.4% were also diastolic normotensive) and 41,527 hypertensive patients (17.7% were also diastolic hypertensive; **Supplementary Figure 1** and **Supplementary Table 1**). For ~~the~~ diastolic BP thresholds, there were: 42,821 hypotensive patients, 32,721 normotensive patients, and 8,422 hypertensive patients. ~~There were 495 Four hundred ninety five (1.16%) events of~~ postoperative mortality ~~were events~~ recorded ~~in our study population~~ (**Table 1**). Systolic BP was missing for 651 patients and diastolic BP was missing for 669 patients.

Of ~~these~~ patients who had received cardiovascular drugs, 15,578 (18.4%) ~~only~~ had only one prescribed cardiovascular drug, and 21,870 (25.8%) patients did not have any prescriptions for cardiovascular drugs (**Table 1**). ~~There were~~ 12,148 patients ~~in our study population who~~ had received a current prescription for beta blockers. Of these, atenolol 50 mg was the most commonly prescribed beta blocker (29.6% of all beta blocker prescriptions), followed by atenolol 25 mg (17.3% of all beta blocker prescriptions) and bisoprolol 2.5mg (10.5% of all beta blocker prescriptions).

Primary Outcome

~~Our primary p~~Propensity-matched analysis showed that, after adjustment for statistically significant confounders, in patients with systolic hypertension, beta blockers were associated with a statistically significant increase in odds of postoperative mortality (adjusted odds ratio (aOR): 1.92, 95% confidence intervals (95% CI): 1.05-3.51; **Figure 2**).

Secondary Outcomes

~~Our~~ In a secondary analysis, that should be considered at most ~~hypothesis-hypothesis-~~ generating, ~~showed that in the systolic hypotensive group,~~ statins were associated with a statistically significant decrease in the adjusted odds of postoperative mortality (aOR: 0.35, 95% CI: 0.17-0.75) in the systolic hypotensive group. For patients with systolic hypertension, statins (aOR: 0.35; 95% CI: 0.17-0.75; **Figure 2**) and thiazides (aOR: 0.28; 95% CI: 0.10-0.78; **Figure 2**) were associated with a protective effect on postoperative mortality. No significant results were observed based on diastolic BP thresholds.

Sensitivity Analyses

In 2011, beta blockers were ~~demoted-lowered~~ from first-line treatment to third-line treatment for hypertension¹⁸. In order to address any resulting confounding, we performed a *post-hoc* sensitivity analysis in those patients who underwent non-cardiac surgery prior to 31 December 2011. ~~There were~~ Of 69,686 such patients, ~~of whom~~ 9,952 (14.3%) had been prescribed beta blockers. In this population, we found that beta blockers were associated with a two-fold increase in postoperative mortality in the systolic hypertension group (aOR: 2.07; 95% CI: 1.09 to 3.95).

Since confounding by indication could influence the observed associations above and beta blockers are associated with perioperative protection in patients with heart failure and prior myocardial infarction⁸, we conducted a *post hoc* secondary analysis by excluding patients with heart failure (n=3,063) and running our models again. In the remaining 81,570 patients, beta blockers remained statistically significant in systolic hypertension (aOR: 2.13; 95% CI: 1.18 to

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3 3.85; **Table 2**). We conducted further analyses excluding patients with prior acute myocardial
4 infarction (aOR: 1.95; 95% CI: 1.04 to 3.67) or both heart failure and acute myocardial
5 infarction (aOR: 2.06; 95% CI: 1.09 to 3.89). In these groups, significant associations were
6 observed between beta blocker uses and mortality in patients with systolic hypertension
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13 **(Table 2)**.
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Discussion

Our main finding confirmed ~~our the~~ hypothesis that beta blockers ~~were are~~ associated with increased perioperative mortality in patients with raised blood pressure. This hypothesis was based on the recent finding that beta blockers may be harmful in hypertensive ~~ve patients on~~ ~~based determined with on~~ a different dataset⁹. The effects of beta blockers on raised systolic BP remained throughout sensitivity analyses adjusted for year of administration and confounding ~~from by~~ indication ~~of for~~ heart failure or prior MI.

Before further inference, it is essential to note that due to the observational nature of this study, ~~our the~~ data do not address whether beta blocker withdrawal (or non-compliance) may be responsible for these findings as we do not have data on within hospital administration of beta blockers. ~~This is an important limitation of our data though beta blocker continuation has been advocated by guidelines throughout the study period. Furthermore, exclusion of patients for whom continuation of beta blockers are thought to be critical (high-high-risk patients with prior MI or heart failure), did not affect our the results.~~ Our data support the notion that continuing beta blocker exposure in the perioperative period may not be advantageous in all patients ~~as we have discussed in our a recent review~~³. Further epidemiological evidence is required to understand which patients may benefit from beta blocker withdrawal and ~~who which~~ may come to harm. ~~However, t~~The only way to address these issues definitively will be to conduct an appropriately powered ~~randomized randomised~~ controlled trial, ~~likely targeting lower risk patients.~~

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3 Beta blocker withdrawal has been associated with adverse outcomes in **important**
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5 epidemiological studies^{6,19}, though a more recent study provided less clear evidence with
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7 both increased mortality and lower morbidity²⁰. Our data highlight that it is unclear whether
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9 the risk/benefit ratio is the same for all levels of patient risk, with patient factors such as BP
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11 influencing the potential risk, supporting our prior work^{8,9}. One hypothesis may be, that
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13 patients with hypertension ~~may be~~ vulnerable to swings in perioperative ~~blood pressure~~BP
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15 due to increased vascular stiffness, or suppression of the renin-angiotensin system, combined
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17 with higher BP thresholds for organ autoregulation⁹. ~~Simultaneously, w~~We also hypothesize
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19 that they are of low ~~enough~~ cardiac risk so to not benefit at a population level from the
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21 cardioprotective effects of beta blockers. Hence the hypothesis is that the risk/benefit ratio
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23 of the medications is unclear in this population, though we acknowledge that we are ~~merely~~
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25 ~~at the beginning of~~ early in evaluating this hypothesis ~~and that much work is required~~.
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27 However, this study validates the prior finding that beta blockers ~~may~~ can be associated with
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29 harm in patients with hypertension⁸. ~~Our approach leveraged the availability of preoperative~~
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31 ~~BP measures that are often used by anaesthesiologists to gauge perioperative risk. We~~
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33 ~~acknowledge that this is slightly discordant with the study by Jorgensen et al. and colleagues⁶,~~
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35 ~~in which BP measures were not available. As such, o~~Our results suggest that it is not the
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37 ~~diagnosis of hypertension that is most critical but the actual numerical value of blood pressure~~
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39 ~~(i.e. any such that increased risk may not pertain to well-controlled hypertensive~~
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41 ~~patients).~~
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In our secondary analyses, we observed that chronic statins and thiazide diuretics were associated with protective effects against postoperative mortality in elderly patients with

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3 systolic hypertension. If ~~true (as these are hypothesis generating analyses)~~ findings are
4 confirmed, we suspect that patients on statins may have benefited from improved
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6 autoregulation, anti-inflammatory action and/or organ protection that statins are thought to
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8 afford²¹. While ~~many~~ observational studies have suggested that statins ~~may~~ improve
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10 perioperative outcomes^{22,23}, the recent Lowering the Risk of Operative Complications Using
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12 Atorvastatin Loading Dose (LOAD) ~~randomized-randomised~~ controlled trial did not suggest
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14 benefit of *de novo* institution of statins in the perioperative period (and showed no trend ~~to~~
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16 of benefit in elderly patients)²⁴. Hence the actual benefit of *de novo* perioperative statin
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18 therapy is unproven. The finding that thiazides may be protective is harder to explain.
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20 ~~Nonetheless the finding with thiazides but~~ should not necessarily be dismissed as we recently
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22 observed that thiazides are relatively protective (compared to other anti-hypertensive
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24 medications) in a cohort of Danish patients⁹. If real, ~~any~~ their protective effect may relate to
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26 their small stimulatory effect on the renin angiotensin system ~~that these drugs afford~~²⁵.
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43 **Limitations**

44 Our data ~~suffers~~ from the limitations that affect all observational analyses, particularly that
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46 causation cannot be proven. Causality can only be concluded in the setting of experimental
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48 studies such as ~~randomized-randomised~~ controlled trials. ~~Furthermore, s~~ Selection bias and
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50 confounding by indication cannot be excluded from influencing these results, hence the
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52 importance of specific hypotheses and the conduct of sensitivity analyses (such as excluding
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54 patients with heart failure). For example, it is possible that beta blockade in patients without
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56 prior MI or heart failure constitutes resistant hypertension. In this context, the risk may be
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58 conferred by the underlying pathophysiology, not the drug itself. ~~Nonetheless g~~ Given the
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3 accumulating data suggesting poor adverse outcomes ~~may be~~ associated with beta blocker
4 exposure in lower risk populations, ~~it appears a~~ randomized-randomised controlled trial of
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6 the safety of beta blockers is warranted. ~~Further, it~~ is important to note that similar to all
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8 observational studies, the analysis is vulnerable to unmeasured confounding such as from
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10 variables on which we lacked data ~~such as~~ including comorbidities such as stable angina or
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12 specific subtypes of heart failure. Similar to ~~many~~ other perioperative epidemiology studies,
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14 we also lack detailed data on perioperative events that ~~will also~~ influence postoperative
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16 mortality, ~~such as~~. ~~These perioperative events include~~ non-compliance and withdrawal of
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18 medication. ~~In particular, f~~urther information is ~~required~~ needed from epidemiological
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20 datasets about the withdrawal of perioperative medications. Hence, we regard our data as
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22 hypothesis generating and ~~require~~ requiring confirmation in future epidemiological studies
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24 and ~~randomized-randomised~~ controlled trials.
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37 **Conclusions**

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40 ~~Our data suggest that b~~Beta blockers may be associated with increased risk of mortality at
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42 raised preoperative blood pressure thresholds in ~~the~~ elderly patients undergoing elective
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44 noncardiac surgery. Future epidemiological studies and ~~randomized-randomised~~ trials should
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46 consider analysing ~~results-outcomes~~ based on preoperative BP-blood pressure thresholds.
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54 **Authors' Contributions**

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57 RDS, SV and PM designed the research question and study analysis plan with input from the
58
59 co-authors. SV performed the analysis with input from PM and RDS. SV had full access to all
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3 of the data in the study and takes responsibility for the integrity of the data and the accuracy
4
5 of the data analysis. All co-authors advised on the analyses. RDS and SV wrote the manuscript
6
7 with significant input from PM. All authors advised on the manuscript content and
8
9 contributed to editing and scientific direction. All authors approved the final manuscript.
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16 ***Declaration of Interests***

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19 All authors have completed the Unified Competing Interest form at
20
21 www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and
22
23 declare no competing interests that may be relevant to the submitted work.
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51 ***Figure Legends***

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55 Figure 1: STROBE diagram
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3 Figure 2: Forest plots for the impact of ~~various~~-preoperative cardiovascular medications on
4 postoperative mortality for different preoperative systolic blood pressure thresholds. Top
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8 confounders. Columns refer to different blood pressure thresholds.
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14 Figure 3: Forest plots for the impact of ~~various~~-preoperative cardiovascular medications on
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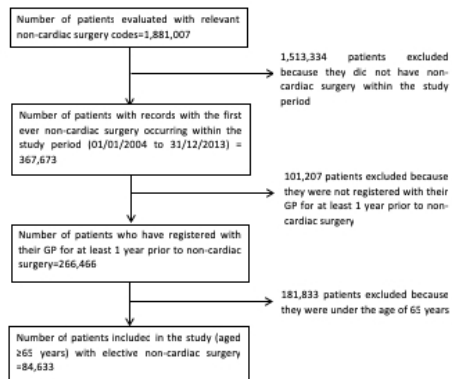


Figure 1: STROBE diagram

338x190mm (54 x 54 DPI)

Table 1: Demographic and clinical/Subject characteristics. *'0' refers to those patients who never received a prescription for any of the cardiovascular drugs of interest examined.

	All (n=84,633)	Survived (n=84,138)	30-day mortality (n=495)	p-value
Mean age, in years (SD)	74.7 (6.9)	74.7 (6.9)	81.5 (8.4)	<0.001
Sex				
Male (%)	44,349 (52.4)	44,088 (52.4)	261 (52.7)	0.884
Female (%)	40,284 (47.9)	40,050 (47.6)	234 (47.3)	
Body Mass Index (m kg ²)				
Underweight (<18.5)	1,528 (1.8)	1,495 (1.8)	33 (6.7)	<0.001
Normal range (18.5 to 24.99)	25,107 (29.7)	24,914 (29.6)	193 (39.0)	
Overweight (25 to 29.99)	31,194 (36.9)	31,060 (36.9)	134 (27.1)	
Obese (≥30)	18,992 (22.4)	18,937 (22.5)	55 (11.1)	
Missing	7,812 (9.2)	7,732 (9.2)	80 (16.2)	
Smoking status				
Non-smoker	43,780 (51.7)	43,557 (51.8)	223 (45.1)	<0.001
Current Smoker	8,371 (9.9)	8,297 (9.9)	74 (15.0)	
Ex-smoker	31,193 (36.9)	31,007 (36.9)	186 (37.6)	
Missing	1,289 (1.5)	1,277 (1.5)	12 (2.4)	
Alcohol consumption status				
Below limit	38,937 (46.0)	38,753 (46.1)	184 (37.2)	<0.001
Above limit	5,858 (6.9)	5,836 (6.9)	22 (4.4)	
Missing	39,838 (47.1)	39,549 (47.0)	289 (58.4)	
Comorbidities				
Atrial fibrillation (%)	6,934 (8.2)	6,845 (8.1)	89 (18.0)	<0.001
Other cardiac arrhythmia (%)	48 (0.1)	48 (0.1)	0 (0)	0.595
Unstable angina (%)	1,097 (1.3)	1,086 (1.3)	11 (2.2)	0.068
Valvular heart disease (%)	28 (0.03)	28 (0.03)	0 (0)	0.685
Myocardial infarction (%)	7,671 (9.1)	7,586 (9.0)	85 (17.2)	<0.001
Congestive heart disease (%)	3,063 (3.6)	2,998 (3.6)	65 (13.1)	<0.001
Peripheral vascular disease (%)	5,704 (6.7)	5,618 (6.7)	86 (17.4)	<0.001
Cerebrovascular disease (%)	5,864 (6.9)	5,795 (6.9)	69 (13.9)	<0.001
Chronic pulmonary disease (%)	17,023 (20.1)	16,902 (20.1)	121 (24.4)	0.016
Liver disease (%)	390 (0.5)	385 (0.5)	5 (1.0)	0.070

Commented [HCH1]: Add range

Diabetes mellitus (%)	10,690 (12.6)	10,617 (12.6)	73 (14.8)	0.155
Renal disease (%)	11,421 (13.5)	11,305 (13.4)	116 (23.4)	<0.001
Cancer (%)	20,036 (23.7)	19,853 (23.6)	183 (37.0)	<0.001
Statins	21,617 (25.5)	21,532 (25.6)	85 (17.2)	0.001
Beta blockers	12,148 (14.4)	12,078 (14.4)	70 (14.1)	0.401
ACE-Angiotensin converting enzyme inhibitors	20,888 (24.7)	20,799 (24.7)	89 (18)	0.192
Calcium channel blockers	11,786 (13.9)	11,743 (13.9)	43 (8.7)	0.005
Alpha-2 agonists	1,145 (1.4)	1,137 (1.4)	8 (1.6)	0.611
Thiazide diuretics	11,657 (13.8)	11,627 (13.8)	30 (6.1)	<0.001
Loop diuretics	6,047 (7.1)	5,977 (7.1)	70 (14.1)	<0.001
Aspirin	35,336 (41.8)	35,052 (41.7)	284 (57.4)	<0.001
Other antiplatelet drugs	6,941 (8.2)	6,877 (8.2)	64 (12.9)	<0.001
Number of cardiovascular drugs*				
0	21,870 (25.8)	21,771 (25.9)	99 (20)	
1	15,578 (18.4)	15,489 (18.4)	89 (18)	
2	13,385 (15.8)	13,327 (15.8)	58 (11.7)	
3	8,773 (10.4)	8,735 (10.4)	38 (7.7)	
4	3,200 (3.8)	3,183 (3.8)	17 (3.4)	
5	538 (0.6)	538 (0.6)	0 (0)	
6	11 (0.01)	11 (0.01)	0 (0)	0.327
Surgical risk score				
Score-1	0 (0)	0 (0)	0 (0)	
Score-2	8,142 (9.6)	8,114 (9.6)	28 (5.7)	
Score-3	15,033 (17.8)	14,993 (17.8)	40 (8.1)	
Score-4	8,574 (10.1)	8,533 (10.1)	41 (8.3)	
Score-5	52,884 (62.5)	52,498 (62.4)	386 (78.0)	<0.001
Socio-economic status (IMD 2010 quintiles)				
1	13,153 (15.5)	13,101 (15.6)	52 (10.5)	
2	13,491 (15.9)	13,409 (15.9)	82 (16.6)	
3	10,104 (11.9)	10,026 (11.9)	78 (15.8)	
4	7,745 (9.15)	7,688 (9.1)	57 (11.5)	
5	5,302 (6.3)	5,261 (6.3)	41 (8.3)	
Missing	34,838 (41.2)	34,653 (41.2)	185 (37.4)	<0.001

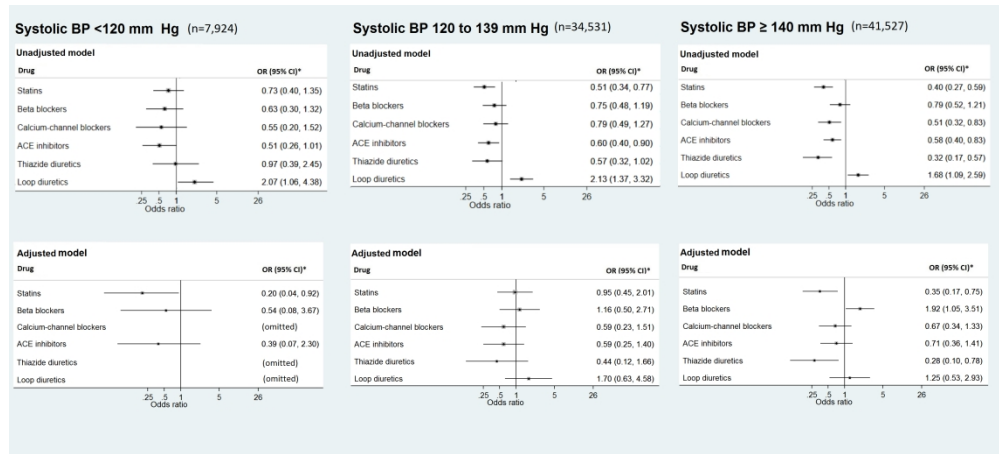


Figure 2: Forest plots for the impact of various preoperative cardiovascular medications on postoperative mortality for different preoperative systolic blood pressure thresholds. Top row shows unadjusted data and bottom row shows the results after adjusting for confounders. Columns refer to different blood pressure thresholds.

Table 2: Sensitivity analysis: Impact of beta blockers on postoperative mortality at various **BP-arterial pressure** thresholds in patient groups excluding specific disease groups.

Systolic threshold	No <u>Myocardial-myocardial Infarction</u>		No <u>Heart-heart Failure</u>		No <u>Myocardial-myocardial Infarction</u> or <u>Heart-heart Failure</u>	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
<120 mmHg	0.79 (0.33-0.89)	0.28 (0.04-1.84)	0.60 (0.26-1.43)	0.28 (0.04-1.84)	0.61 (0.22-1.73)	0.28 (0.04-1.84)
120-139 mmHg	1.07 (0.64-1.77)	1.31 (0.50-3.43)	1.18 (0.75-1.87)	1.29 (0.54-3.11)	1.11 (0.65-1.90)	1.44 (0.50-4.13)
≥140 mmHg	0.91 (0.57-1.47)	1.95 (1.04-3.67)*	0.89 (0.57-1.41)	2.13 (1.18-3.85)*	0.83 (0.50-1.38)	2.06 (1.09-3.89)*

*p-value <0.05

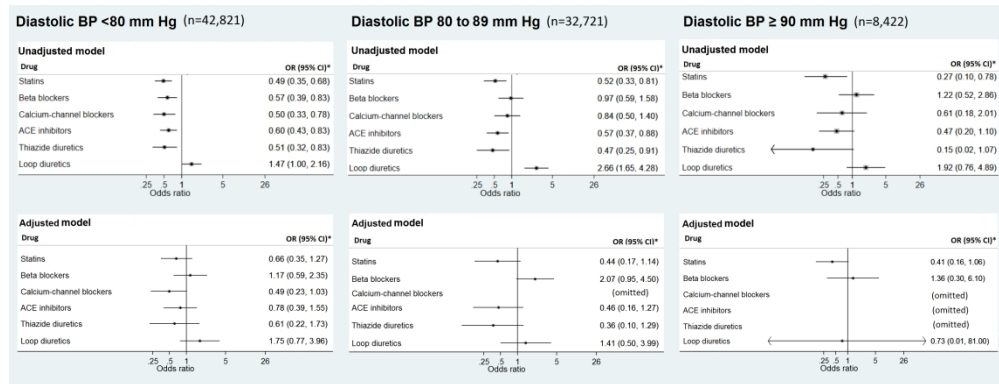


Figure 3: Forest plots for the impact of various preoperative cardiovascular medications on postoperative mortality for different preoperative diastolic blood pressure thresholds. Top row shows unadjusted data and bottom row shows the results after adjusting for confounders. Columns refer to different blood pressure thresholds.