Original Investigation

β-Blocker–Associated Risks in Patients With Uncomplicated Hypertension Undergoing Noncardiac Surgery

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IMPORTANCE Perioperative β-blocker strategies are important to reduce risks of adverse events. Effectiveness and safety may differ according to patients' baseline risk.

OBJECTIVE To determine the risk of major adverse cardiovascular events (MACEs) associated with long-term β-blocker therapy in patients with uncomplicated hypertension undergoing noncardiac surgery.

DESIGN, SETTING, AND PARTICIPANTS Association study based on in-hospital records and out-of-hospital pharmacotherapy use using a Danish nationwide cohort of patients with uncomplicated hypertension treated with at least 2 antihypertensive drugs (β-blockers, thiazides, calcium antagonists, or renin-angiotensin system [RAS] inhibitors) undergoing noncardiac surgery between 2005 and 2011.

INTERVENTIONS Various antihypertensive treatment regimens, chosen as part of usual care.

MAIN OUTCOMES AND MEASURES Thirty-day risk of MACEs (cardiovascular death, nonfatal ischemic stroke, nonfatal myocardial infarction) and all-cause mortality, assessed using multivariable logistic regression models and adjusted numbers needed to harm (NNH).

RESULTS The baseline characteristics of the 14 644 patients who received β-blockers (65% female, mean [SD] age, 66.1 [12.0] years) were similar to those of the 40 676 patients who received other antihypertensive drugs (57% female, mean [SD] age, 65.9 [11.8] years). Thirty-day MACEs occurred in 1.3% of patients treated with β-blockers compared with 0.8% of patients not treated with β-blockers ($P < .001$). β-Blocker use was associated with increased risks of MACEs in 2-drug combinations with RAS inhibitors (odds ratio [OR], 2.16 [95% CI, 1.54-3.04]), calcium antagonists (OR, 2.17 [95% CI, 1.48-3.17]), and thiazides (OR, 1.56 [95% CI, 1.10-2.22]), compared with the reference combination of RAS inhibitors and thiazides. Results were similar for all-cause mortality. Risk of MACEs associated with β-blocker use seemed especially pronounced for patients at least 70 years old (number needed to harm [NNH], 140 [95% CI, 86-364]), for men (NNH, 142 [95% CI, 93-195]), and for patients undergoing acute surgery (NNH, 97 [95% CI, 57-331]), compared with patients younger than 70 years, women, and patients undergoing elective surgery, respectively.

CONCLUSIONS AND RELEVANCE Antihypertensive treatment with a β-blocker may be associated with increased risks of perioperative MACEs and all-cause mortality in patients with uncomplicated hypertension.

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Use of β-blockers during noncardiac surgery is being reevaluated because of concerns about the validity of prior studies. Several randomized trials supporting the use of perioperative β-blocker therapy have been undermined by accusations of data fabrication and are no longer considered in formulating clinical practice guidelines.[1,2] Three recent meta-analyses, which excluded these undermined trials, reported that β-blockers lowered the risk of myocardial infarction but increased the risk of hypotension, stroke, and mortality, compared with placebo.[3-5] As a consequence, it is unknown which patients should receive perioperative β-blocker therapy. Among patients with ischemic heart disease, a recent observational study suggested that β-blocker therapy was associated with a lower risk of adverse perioperative events only among patients with specific high-risk conditions, such as recent myocardial infarction or chronic heart failure.[6]

Perioperative β-blocker therapy has been widely used to lower cardiac work, improve myocardial oxygenation, and stabilize coronary plaques.[7] Guidelines from the United States[8] and from Europe[9] suggest continuing β-blocker use perioperatively in patients already treated with them (class IB recommendations), even though the literature supporting this strategy is sparse and mainly drawn from high-risk patients undergoing vascular surgery.[10,11]

Anesthesia, blood loss, and the inflammatory response to surgery may each lead to hemodynamic instability and hypotension, which might be exacerbated by β-blocker therapy, as suggested by the POISE (Perioperative Ischemic Evaluation) trial.[12] Patients with hypertension may be especially susceptible to swings in blood pressure because they have increased vascular stiffness and higher thresholds for organ autoregulatory functions[13,14] although 2 smaller randomized trials suggested lower prevalence of myocardial ischemia among previously untreated patients with hypertension who received perioperative β-blockers, compared with patients who received placebo.[15,16]

In the present study, we tested the hypothesis that use of perioperative β-blockers in a population of hypertensive patients free of cardiac, renal, and liver disease might be associated with increased risks of major adverse cardiovascular events (MACEs) and all-cause mortality in the 30 days after noncardiac surgery.

Methods

The authors were granted full access to raw and deidentified encrypted data by Statistics Denmark (Central Authority on Danish Statistics), and the study was approved by the Danish Data Protection Agency. In Denmark, ethics committee approval and informed consent is not warranted for retrospective, register-based studies.

Registers and Study Population

The health care system in Denmark is fully tax financed and equally available to all inhabitants independent of social and financial status. The Danish government has for decades collected high-quality, nationwide health care data, which can be linked using the unique personal identification number given to every resident on birth or immigration,[17] as described in detail elsewhere.[18-20]

For the present study, we identified all noncardiac surgical procedures performed in Denmark during the period 2005 through 2011 in patients at least 20 years old. Information on body mass index, smoking, and alcohol consumption, and whether the surgery was acute or elective, was retrieved from the Danish Anesthesia Register. A complete medical history, based on diagnostic codes (according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10]*), was retrieved from the Danish National Patient Register. Information on vital status, date of birth, and cause of death was obtained from the National Population Register and the National Causes of Death Register. A full profile on pharmacotherapy used prior to surgery was retrieved from the Danish Register of Medicinal Product Statistics, which holds data on all prescriptions dispensed in Denmark, classified according to the Anatomical Therapeutic Classification system; this register is directly linked to the government for reimbursement and is accurate.[21]

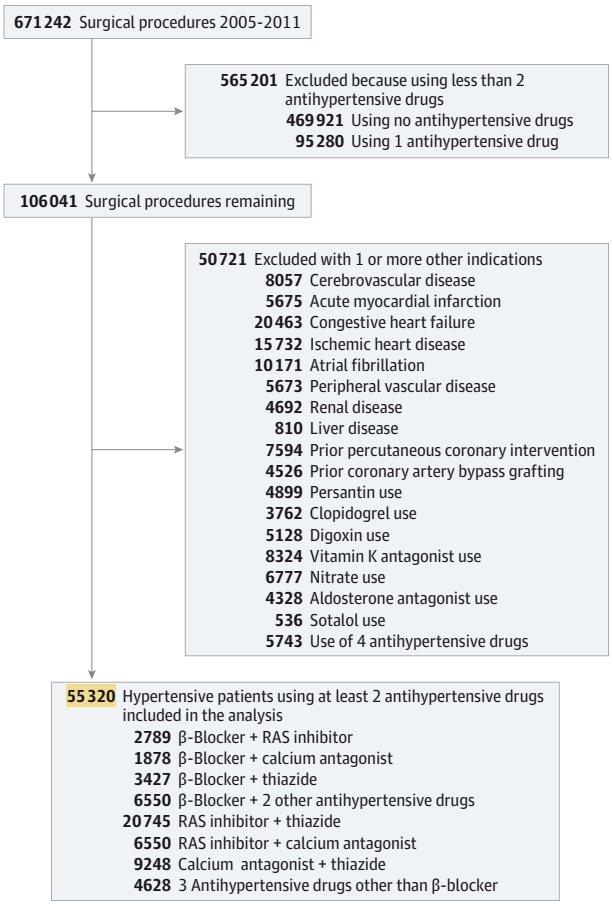
Hypertension is most often managed by patients' primary physicians, and so the in-hospital *ICD-10* diagnosis for essential hypertension (*ICD-10* I10) is used irregularly. We therefore identified the study population of hypertensive patients using a validated algorithm (positive predictive value of 80.0% and sensitivity of 94.7%) based on the use of at least 2 classes of antihypertensive drugs: β-blockers, renin-angiotensin system (RAS) inhibitors, calcium antagonists, or thiazides.[22] We excluded patients with various secondary cardiovascular conditions, renal disease, or liver disease and patients treated with the β-blocker sotalol hydrochloride (used primarily to treat arrhythmias) to ensure that antihypertensive drugs, especially β-blockers, were prescribed for hypertension. Patients treated with all 4 study drugs were excluded as a result of lack of relevant controls for these patients and because they may have more severe hypertension. The selection process for the study population is illustrated in **Figure 1**.

Definition of Pharmacotherapy, Comorbidity, and Surgery Risk

Use of specific drugs was defined as at least 1 claimed prescription during the 120 days prior to surgery (eTable 1 in the Supplement), as package size is most often 100 tablets in Denmark. Comorbidities were identified through *ICD-10* codes, and diagnoses were considered obsolete if the last diagnosis was registered more than 5 years prior to surgery. In addition to *ICD-10* codes, use of glucose-lowering agents was used as a proxy for diabetes mellitus and use of loop diuretics as a proxy for heart failure, as done previously (eTable 1 in the Supplement).[23,24] Diagnoses from the National Patient Register included in the Charlson comorbidity index have been validated, with positive predictive values of 96% to 100%.[25]

Types of surgery in 17 categories were considered in sensitivity analyses. All surgical procedures were identified from codes based on the Nordic Medicostatistical Committee's Classification of Surgical Procedures[26] and classified in accordance with previous work (eTable 1 in the Supplement).[6,27] In

Figure 1. Flowchart Showing Cohort Definitions



We used a validated algorithm for identification of arterial hypertension, with high positive predictive value (80.0%) and sensitivity (94.7%).[22]
RAS indicates renin-angiotensin system.

accordance with American guidelines, noncardiac surgery risk was categorized as low risk (estimated 30-day MACE or mortality <1%) or elevated risk (estimated 30-day MACE or mortality ≥1%). Low-risk procedures consisted of breast, plastic, endocrine, and eye surgery, whereas the remaining surgery types were considered elevated risk (eTable 1 in the Supplement).[8]

Outcomes

The primary outcomes were MACEs and all-cause mortality within 30 days of surgery, including events on the day of surgery. Major adverse cardiovascular events was defined as a composite end point consisting of nonfatal acute myocardial infarction (*ICD-10* I21), nonfatal ischemic stroke (*ICD-10* I63-64), and cardiovascular death (*ICD-10* "I" diagnosis listed as cause of death). The MACE components were analyzed individually as secondary outcomes.

Statistics and Analyses

Differences in baseline characteristics for patients with and without β-blocker use were tested using χ^2 test and analysis of variance. For patients treated with β-blockers, we calculated numbers needed to harm (NNH) adjusted for all variables in the **Table**, using the method and SAS macro by Bender and Vervölgyi.[28,29] Multivariable logistic regression models were used to estimate odds ratios (OR) and their 95% confidence intervals (CIs), adjusted for sex, age as continuous variable, body mass index, calendar year, all comorbidities, pharmacotherapies, and surgery risk from the Table, hereafter referred to as full adjustment. All models were indirectly adjusted for 2- vs 3-drug therapy because this variable was a linear combination of the 4 study drugs. Eight possible combinations of the 4 study drugs (hereafter antihypertensive treatment regimens) were evaluated, with patients treated with RAS inhibitors and thiazides designated as the reference category (because it was the largest group); these models are hereafter referred to as main results.

β-Blocker–associated risks of MACE were estimated in several subgroups based on clinical relevance, with the reference being patients not treated with β-blockers. Formal tests for interaction between β-blockers and each subgroup variable were performed. For these analyses, patients were stratified by urgency, sex, age (<70 or ≥70 years), diabetes, RAS inhibitor use, calcium antagonist use, thiazide use, surgery risk, smoking, alcohol consumption, and guideline changes for treatment of hypertension. In 2009, Danish guidelines were changed so β-blockers were considered as fourth-line rather than first-line drug therapy for blood pressure control in patients without ischemic heart disease or chronic heart failure, so we tested for interaction between β-blocker therapy and patients undergoing surgery in the periods 2005 through 2008 and 2010 through 2011, respectively (patients undergoing surgery in 2009 were excluded from this analysis only).

Supplemental analyses were performed estimating risks of MACE and mortality in the 8 antihypertensive treatment regimens. We did 2 analyses of patients with a hospital-verified diagnosis of essential hypertension (*ICD-10* I10), 1 for the primary study cohort and 1 additionally including patients treated with a single antihypertensive drug (1-drug treatment and a diagnosis of hypertension). Risks in metoprolol-treated (64% of β-blocker–treated patients) or atenolol-treated (17% of β-blocker–treated patients) subgroups of patients were estimated separately to create a more homogenous β-blocker group. Risks of the individual MACE components were estimated. We repeated the main model with additional adjustment for 17 types of surgery. Because of missing values in smoking and alcohol consumption, we performed multiple imputations using the multiple imputation procedure in SAS. Missing values were considered missing at random, 20 imputed data sets were created, and the model included all variables from the main analyses. The main model was redone with adjustment for imputed variables for smoking and alcohol consumption using the "mianalyze" and "logistic regression" procedures in SAS. Body mass index was missing in 1%, and the remaining variables were complete. Sensitivity analyses including patients treated with all 4 study drugs were performed. The formal results for all input variables in the model estimating 30-day risks of MACE by antihypertensive treatment regimen were presented. Two-sided $P < .05$ was consid-

Table. Population Characteristics

Characteristic	Treated Patients, No. (%)[a]		P Value
	β-Blockers (14 644)	Other Antihypertensive Drugs Only (40 676)	
Female sex	5133 (64.9)	17 443 (57.1)	<.001
Age, mean (SD)	66.1 (12.0)	65.9 (11.8)	.046
BMI			
Mean (SD)	27.7 (5.3)	27.8 (5.2)	.04
Missing	160 (1.1)	419 (1.0)	.52
Smoking			
Former[b]	2608 (23.5)	8101 (25.8)	<.001
Current[c]	3080 (27.7)	7674 (24.5)	<.001
Missing	3542 (24.2)	9321 (22.9)	.002
Alcohol use[d]	6261 (51.6)	18 724 (55.4)	<.001
Missing	2509 (17.1)	6904 (17.0)	.66
Pharmacotherapy			
2 Drugs	8094 (55.3)	31 428 (77.3)	<.001
3 Drugs	6550 (44.7)	9248 (22.7)	<.001
Renin-angiotensin system inhibitors	8254 (56.4)	36 048 (88.6)	<.001
Calcium antagonists	4223 (28.8)	19 931 (49.0)	<.001
Thiazides	8717 (59.5)	34 621 (85.1)	<.001
Lipid-lowering therapy	4300 (29.4)	12 188 (30.0)	.17
Acetylsalicylic acid	3942 (26.9)	8731 (21.5)	<.001
Comorbidities			
Chronic obstructive pulmonary disease	285 (1.9)	924 (2.3)	.02
Anemia	345 (2.4)	793 (1.9)	.003
Cancer	395 (2.7)	1023 (2.5)	.23
Rheumatologic disease	239 (1.6)	447 (1.1)	<.001
Venous thromboembolism	136 (0.9)	356 (0.9)	.55
Diabetes mellitus	1548 (10.6)	5985 (14.7)	<.001
Elevated surgery risk	12 503 (85.4)	35 014 (86.1)	.04

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Data are given as number (percentage) unless otherwise indicated.

[b] Defined as prior use, with no use at the procedure date.

[c] Defined as any daily use at the day of the procedure.

[d] Defined as any amount not equal to zero.

ered statistically significant. Data management and calculations were performed with SAS, version 9.4 (SAS Institute).

Results

A total of 55 320 hypertensive patients underwent noncardiac surgery in Denmark between 2005 and 2011 and were included in the study. Baseline clinical characteristics were generally similar between the 14 644 patients treated with β-blockers and the 40 676 patients treated with other antihypertensive drugs (Table), although slightly more women received β-blockers (64.9% of women vs 57.1% men). Use of β-blockers declined between 2005 (35.0%) and 2011 (29.5%).

Absolute Risks

The incidence of 30-day MACEs and mortality was 1.32% and 1.93% in patients treated with β-blockers compared with 0.84% and 1.32% in patients treated with other drugs only (both $P < .001$). For the individual components of MACE, incidence of cardiovascular death was statistically significantly higher in patients treated with β-blockers (0.90% vs 0.45%; $P < .001$), but not nonfatal stroke (0.23% vs 0.21%; $P = .68$) and nonfatal acute myocardial infarction (0.18% vs 0.17%; $P = .81$).

Antihypertensive Drug Regimens

All regimens that included a β-blocker were associated with a statistically significantly increased risk of MACE and all-cause mortality, compared with a regimen of RAS inhibitors and thiazides (**Figure 2**), with the exception of patients treated with β-blockers and 2 other antihypertensive drugs, who were not at statistically significantly increased risks of MACE (OR, 1.22 [95% CI, 0.90-1.64]). Patients treated with any combination of other antihypertensive drugs only were not at increased risks of MACE or mortality, compared with the reference.

β-Blocker–Associated Risks, Numbers Needed to Harm, and Interaction by Subgroup

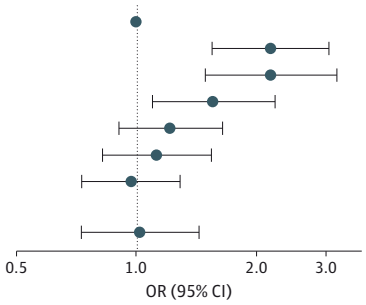
We compared users of β-blockers to nonusers by subgroups (**Figure 3**). β-Blocker–associated risks did not differ within the levels of each subgroup, with the exception of patients with diabetes (OR, 1.91 [95% CI, 0.98-3.74]) vs without diabetes (OR, 1.22 [95% CI, 0.93-1.60]) (P for interaction = .047), and low risk (OR, 1.19 [95% CI, 0.46-3.07]) vs elevated risk (OR, 1.27 [95% CI, 0.98-1.65]) (P for interaction = .046). β-Blocker–associated risks did not differ with type of other antihypertensive drug (all P for interaction >.05) (Figure 3).

Taking the absolute event rates into account, the associated NNH for β-blocker treatment was especially pronounced

Figure 2. Main Model, Risks of Major Adverse Cardiovascular Events (MACEs) and Mortality by Antihypertensive Drug Regimen

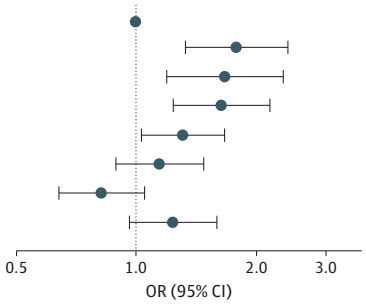
A 30-day MACEs

Subgroups	OR (95% CI)	Events/ Sample Size
RAS inhibitors + thiazides	1 [Reference]	161/20745
β-blocker + RAS inhibitors	2.16 (1.54-3.04)	46/2789
β-blocker + calcium antagonists	2.17 (1.48-3.17)	35/1878
β-blocker + thiazides	1.56 (1.10-2.22)	41/3427
β-blocker + 2 others	1.22 (0.90-1.64)	71/6550
RAS inhibitors + calcium antagonists	1.12 (0.82-1.54)	55/6055
RAS inhibitors, thiazides, and calcium antagonists	0.97 (0.73-1.29)	77/9248
Calcium antagonists + thiazides	1.02 (0.73-1.44)	49/4628



B 30-day all-cause mortality

Subgroups	OR (95% CI)	Events/ Sample Size
RAS inhibitors + thiazides	1 [Reference]	256/20745
β-blocker + RAS inhibitors	1.79 (1.33-2.42)	58/2789
β-blocker + calcium antagonists	1.68 (1.20-2.35)	44/1878
β-blocker + thiazides	1.65 (1.24-2.18)	73/3427
β-blocker + 2 others	1.31 (1.03-1.67)	107/6550
RAS inhibitors + calcium antagonists	1.15 (0.89-1.48)	93/6055
RAS inhibitors, thiazides, and calcium antagonists	0.82 (0.64-1.05)	95/9248
Calcium antagonists + thiazides	1.24 (0.96-1.60)	94/4628



Patients treated with renin-angiotensin system (RAS) inhibitors and thiazides in combination were used as reference. Major adverse cardiovascular events included nonfatal acute myocardial infarction, nonfatal stroke, and cardiovascular death. OR indicates odds ratio.

for patients at least 70 years old (NNH, 140 [95% CI, 86-364]), men (NNH, 142 [95% CI, 93-195]), and patients undergoing acute surgery (NNH, 97 [95% CI, 57-331]), compared with patients younger than 70 years, women, and patients undergoing elective surgery, respectively (Figure 3).

Sensitivity Analyses

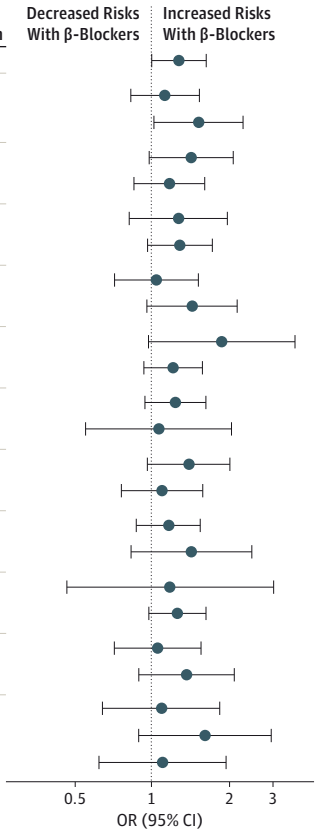
Analyses of the individual MACE components showed that the risk of cardiovascular death was consistent with our main findings with increased risks associated with the different regimens including β-blockers, whereas no statistically significant associations were observed for nonfatal acute myocardial infarction or nonfatal stroke for any of the β-blocker treatment regimens (eFigure 1 in the Supplement). Analyses only including the β-blockers metoprolol (64% of β-blocker-treated patients) or atenolol (17% of β-blocker-treated patients) were comparable to our main findings, although the power was reduced (eTable 2 and eFigure 2 in the Supplement). In a subgroup of patients with a diagnosis of hypertension (34% of the study population), findings mirrored the main analyses with the exception of patients treated with β-blockers and thiazides, who were not at increased risk when compared with patients treated with RAS inhibitors and thiazides (eFigure 3 in the Supplement). In a separate analysis, we included patients treated with only 1 antihypertensive drug and a diagnosis of hypertension. Patients treated with β-blockers as monotherapy were at increased risk of MACEs (OR, 1.67 [95% CI, 0.95-2.93), compared with patients treated with RAS inhibitors and thiazides, although the result was not statistically significant (eFigure 3 in the Supplement). Adjusting the main model for type of surgery in 17 categories did not change the results (eTable 3 and eFigure 4 in the Supplement). Compared with patients not treated with the specific drug (all patients received at least 2 antihypertensive drugs), use of thiazides (OR, 0.67 [95% CI, 0.52-0.87]) was associated with statistically significantly lowered risks of MACE, whereas use of RAS inhibitors (OR, 0.73 [95% CI, 0.59-0.90]) and thiazides (OR, 0.73 [95% CI, 0.59-0.91]) was associated with statistically significantly lower risks of mortality (eFigure 5 in the Supplement). Adjusting the main model for smoking and alcohol after imputation of missing values did not change the results markedly (eFigure 6 in the Supplement). Key variables for patients with and without missing values are presented in eTable 4 in the Supplement. Patients treated with all 4 study drugs had an associated statistically significantly increased risk of MACE (OR, 1.79 [95% CI, 1.26-2.56]) and mortality (OR, 1.46 [95% CI, 1.06-2.01]) (eFigure 7 in the Supplement). Formal results for all input variables in the main analysis are presented in eFigure 8 in the Supplement.

Discussion

This nationwide study of patients with uncomplicated hypertension demonstrated that, compared with other classes of antihypertensive drugs, treatment with an antihypertensive 2-drug regimen including a β-blocker was associated with a statistically significant increase in the rate of MACEs and death within 30 days of noncardiac surgery. Although this study was

Figure 3. β-Blocker–Associated Risks by Subgroup, Numbers Need to Harm (NNH), and Test for Interaction

Subgroups	Adjusted OR (95% CI)	Events/Sample Size: β-Blocker Use	Events/Sample Size: No β-Blocker Use	Adjusted NNH (95% CI)	*P* for Interaction
Overall	1.29 (1.01-1.65)	193/14 451	342/40 334	210 (147-367)	NA
Acute surgery	1.14 (0.83-1.56)	120/3285	223/8497	97 (57-331)	.20
Elective surgery	1.55 (1.02-2.33)	73/11 359	119/32 179	366 (230-896)	
Men	1.44 (0.98-2.12)	80/5133	149/17 443	142 (93-195)	.19
Women	1.18 (0.85-1.64)	113/9511	193/23 233	280 (165-906)	
Age <70 y	1.29 (0.82-2.02)	65/9068	105/25 673	325 (201-851)	.40
Age >70 y	1.30 (0.96-1.75)	128/5576	237/15 003	140 (86-364)	
2005-2008	1.05 (0.71-1.54)	113/9511	193/23 233	483 (197-1075)	.46
2010-2011	1.45 (0.96-2.20)	65/9068	105/25 673	218 (128-762)	
Patients with diabetes	1.91 (0.98-3.74)	29/1548	48/5985	93 (56-278)	.047
Patients without diabetes	1.22 (0.93-1.60)	164/13 096	294/34 691	247 (162-523)	
Treated with RAS inhibitors	1.29 (0.98-1.71)	103/8254	293/36 048	230 (145-561)	.87
Not treated with RAS inhibitors	1.07 (0.55-2.09)	90/6390	49/4628	286 (131-1583)	
Treated with calcium antagonists	1.41 (0.97-2.06)	67/4223	181/19 931	147 (93-358)	.95
Not treated with calcium antagonists	1.10 (0.76-1.60)	126/10 421	161/20 745	231 (148-522)	
Treated with thiazides	1.17 (0.87-1.57)	94/8717	287/34 621	401 (206-8027)	.12
Not treated with thiazides	1.45 (0.83-2.52)	99/5927	55/6055	131 (86-280)	
Low risk	1.19 (0.46-3.07)	24/2141	24/5662	143 (85-454)	.046
Elevated risk	1.27 (0.98-1.65)	169/12 503	318/35 014	226 (149-459)	
Nondrinkers	1.06 (0.71-1.58)	55/6261	110/18 724	213 (125-747)	.64
Drinkers	1.38 (0.89-2.14)	81/5874	137/15 048	343 (183-2839)	
Nonsmokers	1.10 (0.64-1.88)	37/5414	75/15 580	495 (224-2333)	.80
Former smokers	1.64 (0.89-3.01)	31/2608	54/8101	192 (103-1429)	
Current smokers	1.11 (0.62-1.99)	32/3080	64/7674	488 (162-2140)	



Risks of 30-day major adverse cardiovascular events were estimated. Patients not treated with β-blockers served as reference in all analyses. Analyses should not be directly compared between subgroups because the reference group differed. The NNH was adjusted for sex, age, body mass index, calendar year, surgery risk, comorbidities, and pharmacotherapy. The effects associated with β-blocker use were comparable when stratifying by subgroup where *P* for interaction >.05. Stratification by date is based on a change in Danish guidelines for antihypertensive treatments (see Methods section). Alcohol consumption and smoking had missing values (see Methods section). OR indicates odds ratio.

not randomized, the availability of multiple different classes of drugs to treat hypertension led to considerable variation in prescription patterns. Consequently, the clinical characteristics of patients who received either β-blockers or an alternative medication were similar, and statistical adjustments controlled for differences between patients receiving different antihypertensive drugs. Findings were consistent in subgroup and sensitivity analyses. Numbers needed to harm were in the range of 150 to 400 and thus clinically relevant due to the large number of patients with uncomplicated hypertension in everyday clinical practice (>8% of all noncardiac surgical procedures in our population). The use of a large, real-world population for this study enhances the generalizability of these findings, and the consistency of these findings with recent research enhances their plausibility.

β-Blocker Therapy in Noncardiac Surgery

Several trials have investigated the risks of perioperative adverse events associated with use of different types of β-blockers, route of administration, and dose titration, but important shortcomings have later been identified in some of the studies. The credibility of several of the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography) trials has been undermined by suspicions of data fabrication.[1,2] In addition, the POISE trial, which is the only large trial remaining addressing these issues, has been controversial for starting a high dose of metoprolol (200 mg) close to surgery. Several meta-analyses have suggested a reduced risk of myocardial infarction, but possibly a higher risk of all-cause mortality and perioperative stroke, associated with the use of β-blockers.[30-37] The 3 most recent meta-analyses, which excluded trials suspected of fraud, demonstrated a 27% to 30% increased risk of all-cause mortality associated with perioperative β-blocker therapy and noted that the results from the largest study, the POISE trial, dominated the meta-analyses.[3-5] In our study, risks of cardiovascular death were increased, whereas no statistically significant differences were observed for nonfatal stroke or nonfatal myocardial infarction. The reason for these discrepancies might be the lower incidence rate of 0.2% for stroke and 0.2% for myocardial infarction in the present study, compared with rates of 0.5% and 4.4%, respectively, in the POISE trial.[12]

In the wake of the ambiguous results from meta-analyses, a number of cohort studies have examined whether specific subgroups of patients received a beneficial effect of perioperative β-blocker therapy. Our group has previously observed that among patients with established ischemic heart disease, β-blocker therapy was associated with decreased perioperative adverse outcomes in patients who had either chronic heart failure or recent myocardial infarction, but not in patients who had stable ischemic heart disease.[6] Two other major cohort studies stratifying patients by revised cardiac risk index (RCRI) score concluded that β-blocker therapy was associated with lowered risks of 30-day all-cause mortality in higher-risk patients (RCRI score of ≥2) but was associated with higher 30-day mortality in lower-risk patients (RCRI score of 0 or 1).[38,39] A subanalysis from 1 of these studies included hypertensive patients with an RCRI score of 0 undergoing noncardiac surgery. The analysis showed no increased risk of all-cause mortality for patients treated with β-blockers (OR, 0.96 [95% CI, 0.82-1.13]), but the study defined β-blocker treatment as an in-hospital prescription within the first 2 days of hospital admission, which differed from our definition.[38] In this same study, the authors found that the NNH for β-blocker treatment in patients with an RCRI score of 1, diabetes, ischemic heart disease, or cerebrovascular disease ranged from 209 to 504, which is similar to the NNH for hypertension in our study. It is important to recognize differences between the study cohorts because in-hospital β-blocker therapy initiation was included in both studies focusing on RCRI, whereas our patients were exposed only to long-term treatment, which may have effects different from those of recent initiation. We did not conduct subgroup analyses for patients at high risk because of lack of power. Calcium antagonist use has been associated with lowered risks of mortality and myocardial infarction following aortic aneurysm repair in a matched cohort study and noncardiac surgery in a systematic review, dependent on selectivity of these drugs.[40,41] Our results did not confirm these associations, which could be related to the pooling of these drugs despite differences in selectivity. Use of RAS inhibitors was associated with reduced risks of all-cause mortality but not MACE in our low-risk population, which has also recently been reported in another cohort study,[42] whereas guidelines, and a single observational study in high-risk patients undergoing vascular surgery, suggested that these drugs did not reduce mortality and MACEs but increased the risks of hypotension.[9,43] Finally, guidelines describe the perioperative use of thiazides to be safe, which is confirmed by the findings in our study, in which thiazides were associated with reduced risks of MACE and mortality. The risk estimates should be interpreted with the caveat that all patients received at least 2 antihypertensive drugs, although no statistically significant interactions were found, and that thiazide use appeared to be associated with lower risks of adverse events than use of the 3 other types of drugs.[9] Perioperative use of thiazides has received limited attention to date, and further investigation into this class of drugs is warranted.

β-Blockers as an Antihypertensive Drug

The general use of β-blockers as an antihypertensive drug has been questioned after several studies suggested that β-blockers were inferior to RAS inhibitors and calcium antagonists, especially for stroke prevention.[44-46] Danish guidelines on antihypertensive therapy were changed in 2009 to remove β-blockers from the first-line therapies for hypertension, but β-blockers are still used in antihypertensive polypharmacy.[47] Patients undergoing surgery after these guidelines were adopted showed a similar association of β-blocker use and MACEs as patients who underwent surgery prior to the change in guidelines. One study suggested that risks associated with general β-blocker therapy may be modified by sex and age older and younger than 70 years, neither of which could be demonstrated in our population.[48]

Strengths and Limitations

Our study included a large nationwide cohort undergoing various types of surgery during a 7-year period. The procedure distribution for the study cohort was representative for a noncardiac surgery population,[27] but the high prevalence of use of at least 2 antihypertensive drugs may compromise generalizability.

Because no reliable diagnostic code is available for identifying whether hypertension was diagnosed in hospital vs out of hospital, we used a conservative approach based on a validated algorithm for identifying hypertensive patients. This algorithm was derived using a sample of the general Danish population, and by applying additional exclusion criteria we believe that a diagnosis of hypertension would have a higher positive predictive value in our cohort than in the derivation cohort, yet this was unknown and therefore a limitation of the study. These definitions may have resulted in misclassification of some patients as hypertensive, and exclusion of patients with complicated hypertension may be incomplete if patients were only treated by their general practitioner and never hospitalized because only in-hospital diagnostic codes were available. The exclusion criteria removed essentially all patients with cardiac disease, but a few patients may still have been prescribed β-blockers for cardiac, renal, or liver disease. Nitrates are sold over the counter in Denmark; thus, patients may have used these drugs undetected by the register data. Information on drug titration or withdrawal during hospitalization or on the day of surgery could not be retrieved because in-hospital medication use is not recorded. However, specifically for β-blockers, the similar results in elective and acute surgery may indicate that perioperative β-blocker withdrawal might not be a major problem because acute surgery does not allow for dose titration or withdrawal. Furthermore, perioperative guidelines in effect during the study period recommended continuation of β-blocker use throughout surgery in patients with hypertension, suggesting that discontinuation was not a major issue in our population. Because of the observational design, we lacked information on perioperative variables such as heart rate, blood pressure, hypotension, electrocardiographic changes, perioperative troponin concentrations, fluid administration schemes, and need for inotropic therapy. Although we considered both mortality and MACEs as main end points, no statistical adjustment was performed for the numbers of tests performed, given the explorative nature of the study. Also, some of the subgroups were based on small numbers of events (as evident by the wide confidence limits on estimates) and albeit statistically significant, some of the associations might not be clinically important.

Conclusions

In this nationwide cohort of patients treated with 2 or more antihypertensive drugs who underwent noncardiac surgery, a 2-drug antihypertensive treatment regimen with a β-blocker was associated with an increased risk of MACEs and all-cause mortality. This association was seen irrespective of the antihypertensive drug combination and was consistent across subgroups. This observation may suggest that perioperative management of patients with hypertension should receive specific attention in clinical practice and future guidelines, but additional randomized clinical trials on this question may be warranted.

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