Original Investigation

Association of β-Blocker Therapy With Risks of Adverse Cardiovascular Events and Deaths in Patients With Ischemic Heart Disease Undergoing Noncardiac Surgery
A Danish Nationwide Cohort Study

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IMPORTANCE Clinical guidelines have been criticized for encouraging the use of β-blockers in noncardiac surgery despite weak evidence. Relevant clinical trials have been small and have not convincingly demonstrated an effect of β-blockers on hard end points (ie, perioperative myocardial infarction, ischemic stroke, cardiovascular death, and all-cause death).

OBJECTIVE To assess the association of β-blocker treatment with major cardiovascular adverse events (MACE) and all-cause mortality in patients with ischemic heart disease undergoing noncardiac surgery.

DESIGN, SETTING, PARTICIPANTS, AND EXPOSURE Individuals with ischemic heart disease with or without heart failure (HF) and with and without a history of myocardial infarction undergoing noncardiac surgery between October 24, 2004, and December 31, 2009, were identified from nationwide Danish registries. Adjusted Cox regression models were used to calculate the 30-day risks of MACE (ischemic stroke, myocardial infarction, or cardiovascular death) and all-cause mortality associated with β-blocker therapy.

MAIN OUTCOMES AND MEASURES Thirty-day risk of MACE and all-cause mortality.

RESULTS Of 28 263 patients with ischemic heart disease undergoing surgery, 7990 (28.3%) had HF and 20 273 (71.7%) did not. β-Blockers were used in 4262 (53.3%) with and 7419 (36.6%) without HF. Overall, use of β-blockers was associated with a hazard ratio (HR) of 0.90 (95% CI, 0.79-1.02) for MACE and 0.95 (0.85-1.06) for all-cause mortality. Among patients with HF, use of β-blockers was associated with a significantly lower risk of MACE (HR, 0.75; 95% CI, 0.70-0.87) and all-cause mortality (0.80; 0.70-0.92), whereas among patients without HF, there was no significant association of β-blocker use with MACE (1.11; 0.92-1.33) or mortality (1.15; 0.98-1.35) ($P < .001$ for interactions). Among patients without HF, β-blockers were also associated with a lowered risk among those with a recent myocardial infarction (<2 years), with HRs of 0.54 (95% CI, 0.37-0.78) for MACE and 0.80 (0.53-1.21) for all-cause mortality ($P < .02$ for interactions between β-blockers and time period after myocardial infarction), but with no significant association in the remaining patients. Results were similar in propensity score–matched analyses.

CONCLUSIONS AND RELEVANCE Among patients with ischemic heart disease undergoing noncardiac surgery, use of β-blockers was associated with lower risk of 30-day MACE and mortality only among those with HF or recent myocardial infarction.

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Invited Commentary

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The effect of β-blockers on the cardiac risk of noncardiac surgery has been controversial for nearly 10 years. Clinical guidelines encourage the use of β-blockers but have been criticized because the evidence is weak. Relevant clinical trials have been small and have not convincingly shown an effect of β-blockers on hard end points (ie, perioperative myocardial infarction [MI], ischemic stroke, cardiovascular death, and all-cause death).[1-3]

For patients with systolic dysfunction or recent MI, β-blockers have been demonstrated to lower the risk of hard end points, but there is little evidence that β-blockers reduce risk among patients with stable ischemic heart disease.[4-6] Indeed, a recent large observational study showed no effect of β-blocker use on the risk of adverse cardiac events among patients with stable coronary artery disease, raising the question about the value of β-blockers for patients undergoing noncardiac surgery.[7] The potential benefits of β-blockers during noncardiac surgery must be weighed against the potential risks of bradycardia and hypotension.[8-10] The purpose of this study was to examine the association of the preoperative use of β-blockers with adverse cardiac outcomes and all-cause mortality after noncardiac surgery in a large, representative group of patients from a nationwide database.

Methods

Medical care in Denmark is tax financed, free of copayments, and universally available to all citizens. The Danish government maintains several registries with health care–related data for administrative purposes that have been linked for research purposes. We identified in the Danish National Patient Registry all patients with a history of ischemic heart disease who underwent noncardiac surgery between October 24, 2004, and December 31, 2009. We obtained medical diagnoses coded according to the *International Classification of Diseases, 10th Revision* (*ICD-10*), and surgical procedures coded according to the Nordic classification system for surgical procedures. We obtained information on all anesthetic procedures from the Danish Anesthesia Registry and included data on body mass index, smoking, type of anesthesia used, American Society of Anesthesiology score, whether the operation was elective or urgent, and the duration of surgery. Surgery was classified as cancer related if a cancer diagnosis was present within the year preceding surgery in the same area as the surgery was performed. We created 17 subgroups of surgery according to the surgical specialty involved and the extent of surgery, as listed in **Table 1**. This classification was partly based on prior studies and on clinical judgment.[2,3] We further classified surgery as low, intermediate, or high risk based on the method reported by Fleisher et al[2] and Poldermans et al.[3] Low-risk surgery included breast, endocrine, eye, female reproductive, reconstructive, orthopedic minor, and urologic minor; intermediate-risk surgery included abdominal, carotid, peripheral angioplasty, endovascular aneurism repair, head and neck, neurologic, orthopedic major, pulmonary, and urologic major; and high-risk surgery involved aortic and major vascular and peripheral vascular surgery.[3]

We identified pharmacologic treatment from the Danish Register of Medicinal Product Statistics, in which all claimed prescriptions have been registered since 1995. We identified treatment with β-blockers as at least 1 claimed prescription of β-blockers (anatomic therapeutic classification system code C07) within 4 months before surgery. We also identified treatment with vitamin K antagonists (B01AA0), low-dose aspirin (B01AC06), clopidogrel (B01AC04), calcium channel blockers (C08), angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (C09), and aldosterone blockers (C03D) by the same method. We classified patients as having diabetes mellitus if they had claimed at least 1 prescription for glucose-lowering medications (A10) within the same time frame.[11,12] The Danish Register of Medicinal Product Statistics does not contain medication dosage but does include information on strengths and number of dispensed tablets and dispensing time interval. On the basis of these data, we calculated the mean daily dosages of loop diuretics (C03CA01) used at the time of surgery as a proxy for HF severity (up to 3 consecutive prescription claims were considered in a retrospective manner).[13]

We collected information on deaths, date of birth, and sex from the National Population Register and on causes of deaths from the National Causes of Deaths register.

Study Population and Outcomes

We identified all patients with a history of ischemic heart disease based on *International Classification of Diseases, Eight Revision* (*ICD-8*), codes of 410 to 414 or *International Classification of Diseases, Tenth Revision* (*ICD-10*), codes of I20 to I25. We created 2 cohorts according to the presence or absence of HF, defined as an *ICD-10* code of I110, I42, I50, or J819. In the non-HF cohort, we excluded patients who used loop diuretics, took aldosterone blockers, or had atrial fibrillation because it was deemed likely that many of these patients may have had HF as well, and use of β-blockers in this group thus may have affected the associations between β-blockers and outcomes in the non-HF cohort (the HF diagnosis is very specific but has a sensitivity of only 29% in the Danish National Patient Registry).[14] Because of a potential differential effect of β-blockers in patients with and without MI in the non-HF cohort, we identified patients with a previous MI based on *ICD-8* code 410 or *ICD-10* code I21. We grouped patients according to their most recent diagnosis of MI: 2 years or less, 2 to 5 years, and more than 5 years.

The primary outcome was the 30-day risk of major adverse cardiovascular events (MACE), defined as acute MI (*ICD-10* code I21), ischemic stroke (*ICD-10* code I61), or cardiovascular death (*ICD-10* codes I00-I99). The secondary end point was all-cause mortality within 30 days of surgery.

Ethics

The study was approved by the Danish Data Protection Agency. Registries were deidentified by Statistics Denmark but included a unique variable that enabled individual-level linkage between registries.

Table 1. Baseline Characteristics

Characteristic	Heart Failure			No Heart Failure		
	β-Blockers (n = 4262)	No β-Blockers (n = 3728)	*P* Value for Difference	β-Blockers (n = 7419)	No β-Blockers (n = 12 854)	*P* Value for Difference
Age, mean (SD), y	73.4 (10.7)	76.1 (11.1)	<.001	68.8 (10.9)	68.8 (12.1)	.63
Male sex, No. (%)	2598 (61.0)	1981 (53.1)	<.001	4751 (64.0)	7505 (58.4)	<.001
Urgent surgery, No. (%)	1862 (43.7)	1912 (51.3)	<.001	2071 (27.9)	3909 (30.4)	<.001
Surgery type, No. (%)[a]						
Ear, nose, and throat	29 (0.7)	22 (0.6)	.61	95 (1.3)	148 (1.2)	.42
Orthopedic (major)	1393 (32.7)	1403 (37.6)	<.001	2364 (31.9)	4137 (32.2)	.64
Abdominal (nonbowel)	508 (11.9)	509 (13.7)	.02	1058 (14.3)	1979 (15.4)	.03
Abdominal (bowel)	238 (5.6)	243 (6.5)	.08	328 (4.4)	657 (5.1)	.03
Breast	24 (0.6)	34 (0.9)	.07	61 (0.8)	129 (1.0)	.20
Plastic	597 (14.0)	440 (11.8)	<.01	508 (6.8)	911 (7.1)	.52
Endocrine	16 (0.4)	10 (0.3)	.40	41 (0.6)	62 (0.5)	.50
Eye	48 (1.1)	54 (1.4)	.20	114 (1.5)	230 (1.8)	.18
Female reproductive	74 (1.7)	53 (1.4)	.26	277 (3.7)	489 (3.8)	.80
Intracranial	48 (1.1)	50 (1.3)	.38	96 (1.3)	196 (1.5)	.18
Male reproductive	52 (1.2)	46 (1.2)	.96	110 (1.5)	175 (1.4)	.48
Neurosurgery (excluding intracranial)	94 (2.2)	58 (1.6)	.03	328 (4.4)	575 (4.5)	.86
Non-arterial vessel	45 (1.1)	22 (0.6)	.02	149 (2.0)	257 (2.0)	.96
Orthopedic (minor)	274 (6.4)	196 (5.3)	.03	500 (6.7)	930 (7.2)	.18
Thoracic (excluding cardiac)	101 (2.4)	73 (2.0)	.21	139 (1.9)	223 (1.7)	.47
Urinary system	302 (7.1)	267 (7.2)	.88	686 (9.2)	1057 (8.2)	<.01
Vascular	419 (9.8)	248 (6.7)	<.001	565 (7.6)	699 (5.4)	<.001
Surgery time, mean (SD), min	71.9 (78.4)	70.1 (67.0)	.27	69.7 (76.8)	70.7 (79.1)	.36
ASA score, No. (%)						
1	48 (1.1)	49 (1.3)	.44	228 (3.1)	1252 (9.7)	<.001
2	921 (21.6)	841 (22.6)	.31	3960 (53.4)	6962 (54.2)	.28
3+	2719 (63.8)	2335 (62.6)	.28	2931 (39.5)	4086 (31.8)	<.001
Missing	62 (1.5)	66 (1.8)		96 (1.3)	193 (1.5)	
Cancer surgery, No. (%)	317 (7.4)	280 (7.5)	.9	687 (9.3)	1178 (9.2)	.82
Body mass index, mean (SD)[b]	26.4 (5.4)	25.5 (5.6)	<.001	26.8 (4.7)	26 (4.8)	<.001
Current smokers, No. (%)	719 (16.9)	706 (18.9)	.02	1667 (22.5)	3173 (24.7)	<.001
Previous conditions, No. (%)						
Cerebrovascular disease	917 (21.5)	1001 (26.9)	<.001	953 (12.8)	1808 (14.1)	.01
Chronic obstructive pulmonary disease	742 (17.4)	1175 (31.5)	<.001	419 (5.6)	1221 (9.5)	<.001
Anemia	811 (19.0)	817 (21.9)	<.01	422 (5.7)	920 (7.2)	<.001
Renal disease	712 (16.7)	605 (16.2)	.56	265 (3.6)	464 (3.6)	.89
Peripheral artery disease	905 (21.2)	814 (21.8)	.51	648 (8.7)	1093 (8.5)	.57
Myocardial infarction	2515 (59.0)	1725 (46.3)	<.001	3841 (51.8)	4520 (35.2)	<.001
Atrial fibrillation	1626 (38.2)	1422 (38.1)	.99			
CABG	947 (22.2)	539 (14.5)	<.001	1238 (16.7)	1240 (9.7)	<.001
PCI	1319 (31.0)	618 (16.6)	<.001	2927 (39.5)	1896 (14.8)	<.001
Diabetes mellitus	1019 (25.6)	749 (20.1)	<.001	1078 (14.5)	1488 (11.6)	<.001
Medication use, No. (%)						
Statins	2719 (63.8)	1437 (38.5)	<.001	5307 (71.5)	5044 (39.2)	<.001
Calcium blockers	786 (18.4)	988 (26.5)	<.001	1964 (26.5)	3295 (25.6)	.19
ACE inhibitors	2816 (66.1)	1590 (42.7)	<.001	3268 (44.0)	3922 (30.5)	<.001
Aldosterone blockers	994 (23.3)	618 (16.6)	<.001			
Clopidogrel	588 (13.8)	160 (4.3)	<.001	915 (12.3)	482 (3.7)	<.001
Vitamin K antagonists	982 (23.0)	670 (18.0)	<.001	241 (3.2)	351 (2.7)	.03
Aspirin	2882 (67.6)	1941 (52.1)	<.001	5587 (75.3)	5737 (44.6)	<.001

(continued)

Table 1. Baseline Characteristics (continued)

Characteristic	Heart Failure			No Heart Failure		
	β-Blockers (n = 4262)	No β-Blockers (n = 3728)	*P* Value for Difference	β-Blockers (n = 7419)	No β-Blockers (n = 12 854)	*P* Value for Difference
Loop diuretics, mg, No. (%)						
None	1584 (37.2)	1630 (43.7)	<.001	7419 (100)	12 854 (100)	...
≤40	1015 (23.8)	867 (23.3)		...	...	...
41-80	589 (13.8)	442 (11.9)		...	...	...
81-160	336 (7.9)	247 (6.6)		...	...	...
>160	738 (17.3)	544 (14.6)		...	...	...

Abbreviations: ACE, angiotensin-converting enzyme; ASA score, American Society of Anesthesiologists score; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention.

[a]"Thoracic" included pulmonary, mediastinal, and pleural surgery. "Abdominal (bowel)" included esophageal, gastric, duodenal, small intestine, colon, and rectal surgery. "Abdominal (nonbowel)" included all other kinds of abdominal surgical procedures. "Urology" included surgery of kidneys, ureters, and bladder. "Male reproductive" included surgery to the penis, urethra, scrotum, and prostate/seminal glands. "Orthopedic minor" included hand, antibrachial, and foot surgery. "Orthopedic major" included all other orthopedic surgical procedures. "Vascular (arteries)" included the entire artery system.

[b]Calculated as weight in kilograms divided by height in meters squared.

Statistical Analysis

We tested for differences in baseline characteristics between treatment with β-blockers and non–β-blockers using the χ^2 and *t* tests for discrete and continuous variables, respectively. We used the Kaplan-Meier method to create survival curves and the log-likelihood test to examine differences in survival. We used multivariable Cox proportional hazard regression analyses after adjustment for all variables in Table 1 to calculate the hazard ratios (HRs) associated with β-blocker treatment (a priori decided, irrespective of significance levels). We tested for differences in the association of β-blockers with outcomes between patients with and without HF by including a covariate interaction term in the model. Unless otherwise indicated, we analyzed all individuals in the same model and assessed the association of β-blockers with outcomes in different subgroups by use of dummy variables. The proportional hazards assumptions were evaluated visually by log minus log survival plots and found valid. To ensure that the results were not driven by major differences between the groups, we performed a sensitivity analysis using propensity score–matched subgroups, using the Greedy matching program (www.mayo.edu/research/documents/gmatch.sas/DOC-10027248). We calculated the propensity score based on calendar year for surgery and all variables in Table 1, except for surgery type and urgent vs elective surgery. β-Blocker users were matched with nonusers on their propensity score, surgery type, and urgent vs elective surgery. $P < .05$ was considered significant for all statistical tests. No adjustment was made for the numbers of tests performed. All statistical analyses were performed using SAS, version 9.2 (SAS Institute).

Results

Of 387 796 noncardiac surgical procedures performed in Denmark between October 24, 2004, and December 31, 2009, there were 37 166 (9.6%) procedures performed on patients with ischemic heart disease. Of this total, 28 263 procedures were included in the present analyses and 8903 were not analyzed further because patients had no registered HF but used loop diuretics, took aldosterone blockers, or had atrial fibrillation (and thus had possible but unverified HF). In total, 7990 (28.3%) of the included surgical procedures were performed on patients with HF and 12 601 (44.6%) were performed on patients with a history of MI. The median time between the most recent MI and index surgery was 6.0 (interquartile range [IQR], 2.2-12.8) years. In total, 3964 (14.0%) had undergone coronary artery bypass graft surgery before index surgery (median time between coronary artery bypass graft and index surgery, 5.1 [IQR, 2.1-8.1] years), and 6760 (23.8%) had received previous percutaneous coronary interventions (median time, 3.3 [IQR, 1.4-5.9] years). Of the surgical procedures, 7990 (28.3%) were performed on patients diagnosed with HF. Nearly 40% of all surgical procedures were of the orthopedic type and another 20% were abdominal interventions. Approximately one-third of all surgical procedures were for acute disorders.

β-Blockers were prescribed before surgery in 41.3% of the procedures. Patients who took β-blockers were more likely to have a history of MI than patients who did not receive β-blockers (50.4% vs 34.0%, respectively). Baseline characteristics for the HF and non-HF cohorts are shown in Table 1.

Outcomes

A total of 1374 (4.9%) patients experienced a MACE, of which 1024 (74.5%) were cardiovascular deaths, 48 (3.5%) were nonfatal strokes, and 302 (22.0%) were nonfatal MIs. A total of 1773 (6.3%) patients died of all causes.

Adverse events were significantly more frequent in the HF cohort (795 [10.0%] MACE and 985 [12.3%] deaths) compared with the non-HF cohort (579 [2.9%] MACE and 788 [3.9%] deaths) (**Table 2**).

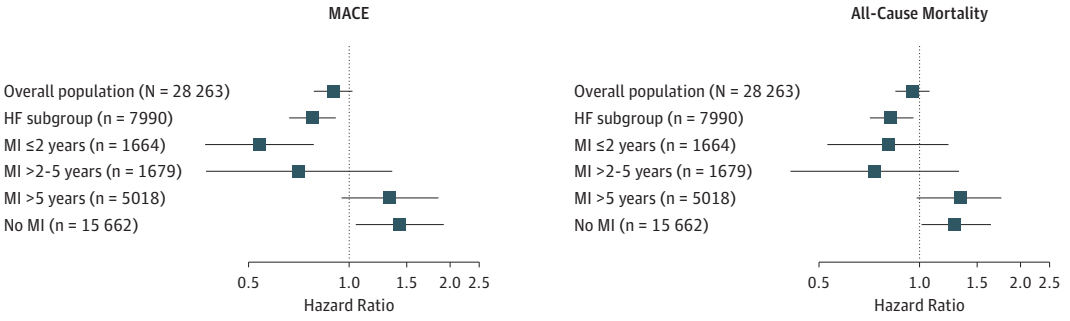
Overall, use of β-blockers preoperatively was associated with unadjusted HRs of 1.03 (95% CI, 0.92-1.14) for MACE and 0.94 (0.85-1.03) for all-cause mortality. Adjustment for multiple variables did not affect these estimates appreciably, with HRs of 0.90 (95% CI, 0.79-1.02) for MACE and 0.95 (0.85-1.06) for all-cause mortality.

Table 2. Crude Numbers of Events

Characteristic	No. (%)			
	Heart Failure		No Heart Failure	
	β-Blockers (n = 4262)	No β-Blockers (n = 3728)	β-Blockers (n = 7419)	No β-Blockers (n = 12 854)
30-d MACE	361 (8.0)	434 (12.0)	216 (3.0)	363 (3.0)
Nonfatal stroke	1 (0.02)	5 (0.1)	13 (0.2)	29 (0.2)
Nonfatal MI	67 (1.6)	57 (1.5)	57 (0.8)	121 (0.9)
Cardiovascular death	293 (7.0)	372 (10.0)	146 (2.0)	213 (2.0)
30-d All-cause mortality	427 (10.0)	558 (15.0)	279 (4.0)	509 (4.0)

Abbreviations: MACE, major adverse cardiovascular events; MI, myocardial infarction.

Figure 1. Hazard Ratios Associated With β-Blockers in Different Subgroups of Patients



The effects associated with β-blockers differed in patients with and without heart failure (HF) ($P < .001$ for interactions between β-blockers and HF for both end points). Among the subgroup without HF, the hazard ratios associated with β-blockers were further dependent on a history of MI and time elapsed since the most recent MI (for interaction between β-blockers and MI categories, $P < .001$ for MACE and $P = .02$ for all-cause mortality). Analysis was adjusted for all variables from Table 1 plus calendar year for surgery. MACE indicates major adverse cardiovascular events (nonfatal ischemic stroke, acute myocardial infarction, and cardiovascular death); MI, myocardial infarction.

The adjusted HR associated with β-blocker treatment for MACE was significantly lower among patients with HF (0.78; 95% CI, 0.66-0.91) than among patients without HF (1.11; 0.92-1.33) ($P < .001$ for interaction). The HR associated with β-blocker treatment for all-cause mortality was also lower for patients with HF (0.82; 95% CI, 0.71-0.95) than for patients without HF (1.15; 0.98-1.35) ($P < .001$ for interaction).

When we restricted the analyses to the cohort of patients without HF, we found a trend toward a differential prognostic importance of β-blockers according to time elapsed from MI ($P < .02$ for interaction between MI groups and β-blockers for both analyses). Patients with a recent MI had lowered HRs for MACE associated with β-blocker treatment (0.54; 95% CI, 0.37-0.78) but not for all-cause mortality (0.80; 0.53-1.21) (**Figure 1**). β-Blockers were associated with comparable effects in patients treated with and without percutaneous coronary interventions, as well as in those who did and did not receive a coronary artery bypass graft ($P = .19$ and .50 for MACE end points, and $P = .41$ and .67 for all-cause mortality). There were no differences in effects associated with β-blockers in men and women ($P > .05$ for interactions for MACE and all-cause mortality for all subgroups).

Association of β-Blockers With Outcomes in Specific Surgery Types

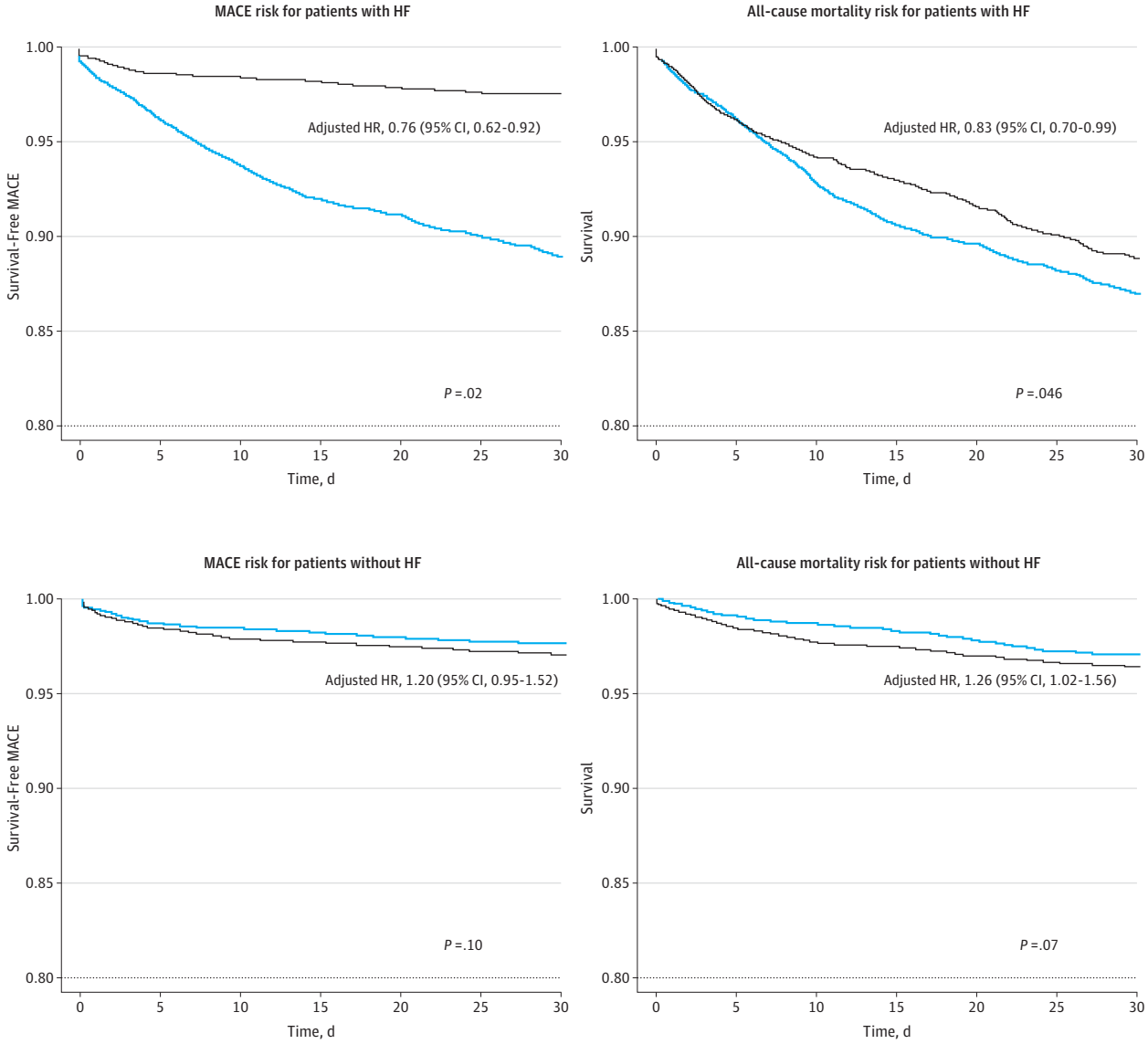
For patients with HF, the association of β-blockers with outcomes was similar for urgent and elective surgery, with HRs of 0.75 (95% CI, 0.63-0.89) and 0.86 (0.66-1.12) for MACE and 0.78 (0.67-0.92) and 0.95 (0.74-1.21) for all-cause mortality, respectively ($P = .27$ and $P = .05$ for interactions for MACE and all-cause mortality, respectively).

Similarly, for patients with an MI of 2 years or less without HF, the association of β-blockers with MACE was similar for urgent and elective surgery, with HRs of 0.48 (95% CI, 0.31-0.75) and 0.69 (0.39-1.22) ($P = .29$ for interaction), respectively, but differed for all-cause mortality ($P = .02$ for interaction). The association of β-blockers and lowered risk was greater among patients undergoing urgent surgery (HR, 0.64; 95% CI, 0.40-1.04) than among patients having elective surgery (1.26; 0.70-2.25). For patients without a recent MI (ie, no MI or MI >2 years before surgery), no differential effects of β-blockers were found between urgent and elective surgery for both end points, with HRs of 1.30 (95% CI, 1.00-1.69) and 1.31 (0.93-1.84), respectively (for interaction, $P = .18$ for MACE and $P = .15$ for all-cause mortality). For all groups, there was no evidence of a differential association of β-blockers with surgery risk ($P > .05$ for interactions between β-blockers and surgery risk).

Sensitivity Analyses

The Kaplan-Meier curves of the propensity score–matched cohorts are shown in **Figure 2**, and baseline characteristics of the 4420 patients with HF and the 10 940 patients without HF are available in eTable 1 in the Supplement. For patients with HF, the results of the propensity score–matched analyses were similar to the results of the main analyses, with an adjusted HR for

Figure 2. Kaplan-Meier Curves of Outcomes Associated With β-Blockers in Surgical Procedures Performed in Patients With and Without β-Blockers, Based on 1:1 Propensity Score–Matched Subgroups

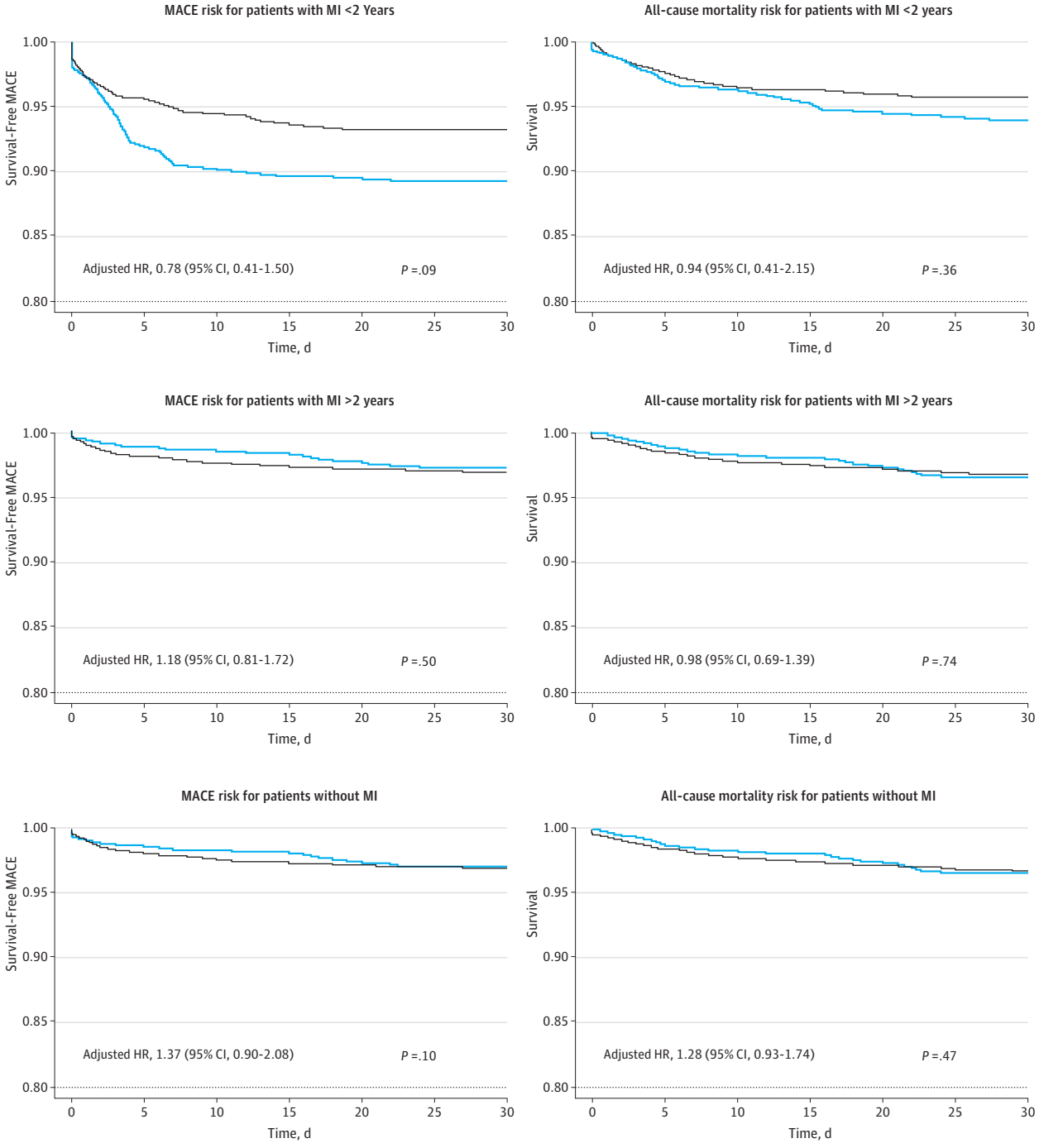


C statistics of the models were 0.74 and 0.75. HF indicates heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events (nonfatal ischemic stroke, acute myocardial infarction, and cardiovascular death). Baseline characteristics are available in eTables 1 and 2 in the Supplement. Patients treated with β-blockers are represented by the blue line; patients treated without β-blockers are represented by the black line.

β-blocker treatment of 0.76 (95% CI, 0.62-0.92) for MACE and 0.83 (0.70-0.99) for all-cause mortality. For patients without HF, use of β-blockers was associated with HRs of 1.20 (95% CI, 0.95-1.52) for MACE and 1.26 (1.02-1.56) for all-cause mortality. Analyses of propensity score-matched subgroups of patients without HF but with a history of recent MI (≤2 years before index surgery), late MI (>2 years before index surgery), or no prior MI are shown in **Figure 3**. Although not statistically significant, trends similar to the main analyses were found, with a tendency of lowered risks associated with β-blockers in patients with recent MI but no or increased risks associated with β-blockers in the other subgroups. Baseline characteristics of the 596 patients with an MI of 2 years or less, 3860 patients with and without β-blockers with an MI of more than 2 years, and 5778 patients without MI are available in eTable 2 in the Supplement.

Finally, we performed a sensitivity analysis without excluding the 8903 patients who had no registered HF but used loop diuretics, took aldosterone blockers, or had atrial fibrillation. Results similar to the main analyses were found. Overall, HRs associated with β-blocker treatment were 1.01 (95% CI, 0.92-1.12) for MACE and 1.00 (0.92-1.10) for all-cause mor-

Figure 3. Kaplan-Meier Curves of Outcomes of β-Blockers in Surgical Procedures Performed in Subgroups of Patients Without β-Blockers, Based on 1:1 Propensity Score–Matched Subgroups



C statistics of the models ranged from 0.75 to 0.80. MACE indicates major adverse cardiovascular events (nonfatal ischemic stroke, acute myocardial infarction, and cardiovascular death); HR, hazard ratio. Baseline characteristics are available in eTables 1 and 2 in the Supplement. Patients treated with β-blockers are represented by the blue line; patients treated without β-blockers are represented by the black line. In total, 298 patients with and 298 patients without β-blockers with a myocardial infraction (MI) of less than 2 years, 1930 patients with and 1930 patients without β-blockers with an MI of more than 2 years before the index surgery, and 2889 patients with and 2889 patients without β-blockers without an MI were included.

tality. As for the main analyses, HRs were significantly lower among patients with than without HF: 0.77 (95% CI, 0.66-0.90) vs 1.22 (1.07-1.38) ($P < .001$ for interaction) for the MACE end point and 0.82 (0.72-0.94) vs 1.15 (1.03-1.29) ($P < .001$ for interaction) for the all-cause mortality end point.

Discussion

This nationwide study of patients with ischemic heart disease undergoing noncardiac surgery suggests that perioperative use of β-blockers lowers the risks of MACE and all-cause mortality among patients with HF or a recent MI. Among patients with ischemic heart disease with neither HF nor recent MI, however, there was no evidence of an effect of β-blockers on the perioperative outcomes in our study.

Current US guidelines recommend that patients who use β-blockers preoperatively should continue treatment during surgery and state that it is reasonable to initiate treatment with β-blockers before intermediate- or high-risk noncardiac surgery (with the dose titrated to control blood pressure and heart rate) in patients with established coronary artery disease.[15] The European guidelines are a bit more aggressive and recommend β-blockers to all patients with known ischemic heart disease.[3] These recommendations are based on only a few clinical trials, one of which has recently been called into question.[16]

A systematic review of the effect of perioperative β-blockers, including 11 randomized trials, found that β-blockers significantly decreased ischemic episodes and significantly reduced the risk of nonfatal MI, but when the 2 most positive trials[16,17] were excluded, the results became neutral.[13] Another systematic review of 22 clinical trials concluded that the evidence by perioperative β-blockers for a reduction of major cardiovascular events was suggestive but not conclusive.[18] Both reviews found that the use of β-blockers significantly increased the risk of bradycardia, and 1 study also found an increased risk of hypotension.[18]

The potential for some risks, coupled with weak evidence for benefit from β-blockers among stable patients without HF or MI, calls into question the recommendation for the universal use of β-blockers among patients with coronary disease. The PeriOperative ISchemic Evaluation (POISE) trial, which randomly assigned patients with or at high risk of atherosclerotic disease undergoing noncardiac surgery to extended-release metoprolol succinate or placebo, found an even higher rate of all-cause mortality among patients receiving metoprolol (3.1% vs 2.3%).[10] However, the POISE trial has been criticized for using a high dose of metoprolol (200 mg/d), which makes it difficult to translate the results into everyday clinical practice.

Our finding that the association of β-blocker with MACE was modified significantly by the presence of HF or a recent MI offers a potential explanation for the inconsistent effect of β-blockers on outcomes in prior studies. Whereas the effect of β-blockers for reducing mortality among patients with HF or a recent MI is well established,[4-6] this effect in patients with stable ischemic heart disease has been questioned lately.[7] Our data show a similar pattern among patients undergoing noncardiac surgery, with β-blockers associated with reduced risk among patients with HF or a recent MI but not among the remaining lower-risk patients with coronary disease. Our findings are in agreement with those of a previous observational study, which found that β-blockers were associated with no benefit and even with harm among patients with the lowest cardiac risk.[19]

Strengths and Limitations

The main strength of this study is that it is based on a large representative population, including all noncardiac surgical procedures performed in Denmark during a 6-year period. Nevertheless, some subgroup comparisons were based on rather small numbers of individuals, and therefore a type II error cannot be excluded.

The national registries used in this study have been shown to have a good specificity and positive predictive values of the MI and ischemic stroke diagnoses.[20,21] However, the validity of the ischemic heart disease diagnosis is not known, and we had no information on the presence of inducible ischemia in our population. For the present study, the use of β-blockers was identified by claimed outpatient prescriptions, and we had no data on the use of β-blockers in the hospital. Furthermore, we did not have the exact indications for treatment with β-blockers or the doses used or whether patients had been adherent to the medication. A final limitation was that measures of troponins and electrocardiograms were not performed routinely postoperatively, and some nonfatal acute MIs may have been missed.[22] However, the mortality associated with missed postoperative MIs is high and would to some extent be reflected in the mortality analyses,[22] but the MACE end point still needs to be interpreted carefully.

In conclusion, use of β-blockers among patients with ischemic heart disease and HF or recent MI undergoing noncardiac surgery is associated with a substantially decreased risk of major adverse cardiovascular events and all-cause mortality within 30 days after surgery.

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