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Beta-Blocker Therapy Is Associated With Increased 1-Year Survival After Hip Fracture Surgery: A Retrospective Cohort Study

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BACKGROUND: The high mortality rates seen within the first postoperative year after hip fracture surgery have remained relatively unchanged in many countries for the past 15 years. Recent investigations have shown an association between beta-blocker (BB) therapy and a reduction in risk-adjusted mortality within the first 90 days after hip fracture surgery. We hypothesized that preoperative, and continuous postoperative, BB therapy may also be associated with a decrease in mortality within the first year after hip fracture surgery.

METHODS: In this retrospective cohort study, all adults who underwent primary emergency hip fracture surgery in Sweden, between January 1, 2008 and December 31, 2017, were included. Patients with pathological fractures and conservatively managed hip fractures were excluded. Patients who filled a prescription within the year before and after surgery were defined as having ongoing BB therapy. The primary outcome of interest was postoperative mortality within the first year. To reduce the effects of confounding from covariates due to nonrandomization in the current study, the inverse probability of treatment weighting (IPTW) method was used. Subsequently, Cox proportional hazards models were fitted to the weighted cohorts. These analyses were repeated while excluding patients who died within the first 30 days postoperatively. This reduces the effect of early deaths due to surgical and anesthesiologic complications as well as the higher degree of advanced directives present in the study population compared to the general population, which allowed for the evaluation of the long-term association between BB therapy and mortality in isolation. Results are reported as hazard ratios (HR) with 95% confidence intervals (CI). Statistical significance was defined as a 2-sided *P* value <.05.

RESULTS: A total of 134,915 cases were included in the study. After IPTW, BB therapy was associated with a 42% reduction the risk of mortality within the first postoperative year (adjusted HR = 0.58, 95% CI, 0.57–0.60; *P* < .001). After excluding patients who died within the first 30 days postoperatively, BB therapy was associated with a 27% reduction in the risk of mortality (adjusted HR = 0.73, 95% CI, 0.71–0.75; *P* < .001).

CONCLUSIONS: A significant reduction in the risk of mortality in the first year following hip fracture surgery was observed in patients with ongoing BB therapy. Further investigations into this finding are warranted. (Anesth Analg 2021;133:1225–34)

KEY POINTS

- **Question:** Is ongoing beta-blocker therapy associated with a reduction in mortality within the first postoperative year after hip fracture surgery?
- **Findings:** When adjusting for available confounders, beta-blocker therapy was associated with a statistically significant reduction in the risk of mortality within the first year after hip fracture surgery.
- **Meaning:** The results emphasize the importance of maintaining beta-blocker therapy in hip fracture patients throughout surgery and provide further evidence for the imperative nature of investigating the value of initiating beta-blocker therapy in this patient population.

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The principles of the Declaration of Helsinki and STROBE guidelines were adhered to while conducting this study. Ethical approval was obtained from the Regional Ethical Review Authority (reference 2019-02094).

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GLOSSARY

ASA = American Society of Anesthesiologists; **ASD** = absolute standardized difference; **BB** = beta-blocker; **BB$^+$** = ongoing beta-blocker therapy; **BB$^-$** = no beta-blocker therapy; **CCI** = Charlson Comorbidity Index; **CI** = confidence interval; **COPD** = chronic obstructive pulmonary disease; **HR** = hazard ratio; **IPTW** = inverse probability of treatment weighting; **IQR** = interquartile range; **IRR** = Incidence rate ratio; **N/A** = not applicable; **POISE** = Perioperative Ischemic Evaluation; **RR** = relative risk; **SD** = standard deviation; **STROBE** = STrengthening the Reporting of OBservational studies in Epidemiology

Recent investigations have shown an association between beta-blocker (BB) therapy and a reduction in risk-adjusted 90-day mortality after hip fracture surgery.[1,2] These results are in line with several other studies showing the same positive effect between BB therapy and short-term mortality after major noncardiac surgery or severe traumatic injuries.[3–10] This may be explained by the physiological stress response induced by both the physical and surgical trauma associated with hip fractures. Trauma induces a hyperadrenergic state characterized by the activation of the sympathetic nervous system and the subsequent release of catecholamines.[11,12] This increases the strain on the cardiovascular system and other vital organs, which results in damage and complications, such as arrhythmias or myocardial infarction, where patients with preoperative cardiac conditions are at higher risk for such adverse events.[6] It is therefore postulated that the protective effect is a result of BB therapy inducing a downregulation of the trauma- and surgically induced hyperadrenergic state.[11–14]

The incidence of hip fractures is expected to increase during the coming decades as the global population continues to age.[15–18] Hip fractures primarily occur in a subpopulation that is older and suffers from a high overall disease burden.[1,2,19,20] The postoperative mortality rates within the first year for hip fracture surgery are reported to be as high as 27%, with the most common cause of death being cardiovascular events.[15,20–25] Despite better overall health care, mortality rates in many countries have remained relatively unchanged for the last 15 years in this patient population.[20] Several studies have indicated a protective effect of BBs beyond the immediate postoperative period with better long-term survival after major noncardiac surgery.[4,5,26] However, there is no study investigating the association between ongoing perioperative BB therapy and long-term survival exclusively after hip fracture surgery. The purpose of the current study is to investigate if the association between BB therapy and survival extends beyond the immediate postoperative period after hip fracture surgery. We hypothesized that ongoing preoperative BB therapy, which is continued postoperatively, is associated with a decrease in mortality within the first year after hip fracture surgery.

METHODS

Ethical approval was obtained from the Regional Ethical Review Authority of Uppsala/Orebro (reference 2019-02094). Due to the retrospective nature of the study, the need for informed consent was waived by the regional ethical review authority. The principles of the Declaration of Helsinki and the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines were adhered to while conducting this study.[27] The study population was obtained from the prospectively collected National Quality Registry for Hip Fracture Patients in Sweden, Rikshoft.[28] All adult cases (18 years or older) of primary emergency hip fracture surgery in Sweden, between January 1, 2008 and December 31, 2017, were included. Patients with pathological fractures and conservatively managed hip fractures were excluded from the analysis. Variables including date of hospital admission, age, sex, fracture type, American Society of Anesthesiologists (ASA) physical status, surgical method, date of surgery, and date of hospital discharge were retrieved from the National Quality Registry for Hip Fracture Patients. The selected cases were cross referenced with the Patient and Cause of Death registers maintained by the Swedish National Board of Health and Welfare to retrieve the date of death and comorbidity data. The comorbidity data were used to calculate the age adjusted Charlson Comorbidity Index (CCI) for each patient.[29]

Data concerning BB prescriptions (ATC codes C07AA, C07AB, C07AG) were obtained from The Swedish Prescribed Drug registry. The Swedish Prescribed Drug registry is a population-based database that records all drug prescriptions issued by physicians in Sweden within both primary and secondary care facilities. Patients who filled a prescription within the year before and after surgery were defined as having ongoing BB therapy. Patients who were only prescribed to take BBs as needed were not included as having ongoing BB therapy. An inclusion period of 12 months before and after surgery was selected since BBs are rarely discontinued once initiated and therefore commonly issued on a long-term basis covering up to a 1-year period with a single prescription.

Statistical Analysis

Patients were divided into 2 groups: ongoing BB therapy (BB$^+$) and no BB therapy (BB$^-$). Patient

demographics and clinical characteristics were compared between the groups. Categorical variables are reported with percentages while continuous variables are reported as a mean and standard deviation (SD).

The primary outcome of interest was postoperative mortality within the first year after surgery. A secondary analysis was performed where patients who died within the first 30 days after surgery were excluded. Studying the association between BB use and mortality in the first year, conditional on patients surviving 30 days or more after surgery, allowed for the evaluation of the long-term association between BB therapy and mortality in isolation. This reduces the effect of early deaths due to surgical and anesthesiologic complications as well as the higher degree of advanced directives present in the study population compared to the general population.

To reduce the effects of confounding from the covariates due to nonrandomization in the current observational study, the inverse probability of treatment weighting (IPTW) method was used in our survival analysis. The probability of treatment was determined using a logistic regression model, which included BB therapy as the response variable, and age, sex, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes, hemiplegia, chronic kidney disease, local tumor, metastatic carcinoma, ASA physical status, type of fracture, type of surgery, and year of surgery as the predictors. The weights were calculated as $\frac{1}{\text{probabilty of BB}^+ \text{ treatment}}$ for BB^+ patients and $\frac{1}{1-\text{probability of BB}^+ \text{ treatment}}$ for BB^- patients. These weights were converted from unstabilized to stabilized weights by multiplying the weights of BB^+ patients by the proportion of patients who were BB^+ and by multiplying the weights of BB^- patients by the proportion of patients who were BB^-. Differences between the cohorts, both before and after weighting, were evaluated using absolute standardized differences (ASD). An ASD <0.1 was considered balanced. Finally, Cox proportional hazards models were fitted to the weighted cohorts. As a sensitivity analysis, a multilevel survival model with a Weibull distribution (which is suitable for a proportional hazards model or an accelerated failure time model) and propensity score matched pairs included as random effects was also fitted to the data (Supplemental Digital Content, Table 1, http://links.lww.com/AA/D597). Each of these steps were repeated separately with the dataset containing all patients as well as a dataset excluding patients who died within the first 30 days postoperatively. Results are reported as hazard ratios (HR) with 95% confidence intervals (CI). Statistical significance was defined as a 2-sided *P* value <.05.

As can be seen in Table 1, <2% of cases had any missing data. This is within the acceptable limits of what can be expected to be missing at random when dealing with a retrospective database. Multiple imputation by chained equations was used to compensate for these missing values; logistic regression was used for sex, a proportional odds model for ASA physical status, as well as Bayesian polytomous regression for type of fracture and type of surgery. The variables included as predictors were 30-day mortality, 1-year mortality, follow-up time, the presence of right censoring, BB therapy, age, sex, type of BB therapy, age, sex, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes, hemiplegia, chronic kidney disease, local tumor, metastatic carcinoma, CCI, ASA physical status, type of fracture, type of surgery, and year of surgery. This resulted in 5 imputed datasets containing all patients and 5 imputed datasets excluding those who died within the first 30 days postoperatively. All imputations were performed before calculating the probability of treatment. Analyses were performed using the statistical programming language R (R Foundation for Statistical Computing).[30]

RESULTS

A total of 134,915 hip fracture cases met the inclusion criteria, of whom only 1187 (0.9%) were under the age of 50. Depicted in Table 1 are the distribution of sex, age, fracture, and surgery type within the groups. Metoprolol was the most common BB prescribed (57.4%), followed by bisoprolol (18.7%) and atenolol (13.5%). The BB^+ group had more comorbidities (CCI ≥7: 23.8% vs 15.2%, ASD 0.271) and was less fit for surgery (ASA ≥3: 65.8% vs 52.1%, ASD 0.351). Dementia and metastatic carcinoma were the only comorbidities included that were more common in the BB^- group, while all other comorbidities were more prevalent in the BB^+ group. After excluding patients who died within 30 days postoperatively, a total of 124,707 hip fracture cases remained. The differences observed in the full dataset remained unchanged after the exclusion (Table 1).

After performing IPTW, all the covariates used to calculate the weights were balanced with ASDs <0.1. The results from the imputed and weighted datasets are presented in Table 2.

Crude mortality within the first year postoperatively was lower in the BB^+ group in the full dataset both before (19.3% vs 25.6%, ASD 0.152) and after IPTW (18.2% vs 28.6%, ASD 0.248; Table 3). Crude mortality within the first year postoperatively was also

Table 1. Demographics and Clinical Characteristics in Patients With Ongoing Beta-Blocker Therapy and Without Ongoing Beta-Blocker Therapy Undergoing Surgery for Hip Fractures

Variable	All patients			Excluding 30-d postoperative mortality		
	BB+ (N = 52,500)	BB− (N = 82,415)	ASD	BB+ (N = 50,567)	BB− (N = 74,140)	ASD
Age, mean (SD)	82.8 (±8.5)	81.4 (±10.8)	0.144	82.6 (±8.6)	80.8 (±11.0)	0.183
Sex, n (%)			0.066			0.038
Female	36,755 (70.0)	55,158 (66.9)		35,557 (70.3)	50,822 (68.5)	
Male	15,738 (30.0)	27,250 (33.1)		15,003 (29.7)	23,311 (31.4)	
Missing	7 (0.0)	7 (0.0)		7 (0.0)	7 (0.0)	
Type of beta-blocker, n (%)			N/A			N/A
Metoprolol	30,143 (57.4)	0 (0.0)		28,997 (57.3)	0 (0.0)	
Bisoprolol	9805 (18.7)	0 (0.0)		9497 (18.8)	0 (0.0)	
Atenolol	7094 (13.5)	0 (0.0)		6859 (13.6)	0 (0.0)	
Other	5458 (10.4)	0 (0.0)		5214 (10.3)	0 (0.0)	
Comorbidities, n (%)						
Myocardial infarction	5496 (10.5)	2567 (3.1)	0.295	5146 (10.2)	1643 (2.2)	0.335
Congestive heart failure	12,845 (24.5)	8252 (10.0)	0.390	11,934 (23.6)	5541 (7.5)	0.457
Peripheral vascular disease	3041 (5.8)	2849 (3.5)	0.111	2897 (5.7)	2339 (3.2)	0.125
Cerebrovascular disease	10,849 (20.7)	12,533 (15.2)	0.143	10,309 (20.4)	10,727 (14.5)	0.156
Dementia	8477 (16.1)	18,827 (22.8)	0.170	7702 (15.2)	16,087 (21.7)	0.167
COPD	6454 (12.3)	9123 (11.1)	0.038	6158 (12.2)	7775 (10.5)	0.053
Connective tissue disease	3057 (5.8)	3430 (4.2)	0.076	2960 (5.9)	3076 (4.1)	0.078
Peptic ulcer disease	1956 (3.7)	2372 (2.9)	0.047	1865 (3.7)	2053 (2.8)	0.052
Liver disease	587 (1.1)	783 (1.0)	0.017	568 (1.1)	664 (0.9)	0.023
Diabetes	10,251 (19.5)	9605 (11.7)	0.218	9831 (19.4)	8335 (11.2)	0.229
Hemiplegia	1351 (2.6)	1560 (1.9)	0.046	1301 (2.6)	1414 (1.9)	0.045
Chronic kidney disease	4018 (7.7)	2927 (3.6)	0.179	3742 (7.4)	2032 (2.7)	0.214
Local tumor	5940 (11.3)	8620 (10.5)	0.027	5690 (11.3)	7418 (10.0)	0.040
Metastatic carcinoma	937 (1.8)	2025 (2.5)	0.047	898 (1.8)	1600 (2.2)	0.028
Charlson Comorbidity Index, n (%)			0.271			0.325
≤4	19,449 (37.0)	40,162 (48.7)		19,163 (37.9)	38,471 (51.9)	
5–6	20,542 (39.1)	29,705 (36.0)		19,748 (39.1)	25,985 (35.0)	
≥7	12,509 (23.8)	12,548 (15.2)		11,656 (23.1)	9684 (13.1)	
ASA physical status, n (%)			0.351			0.397
I	881 (1.7)	5775 (7.0)		864 (1.7)	5672 (7.7)	
II	16,128 (30.7)	32,136 (39.0)		15,877 (31.4)	30,630 (41.3)	
III	29,687 (56.5)	37,170 (45.1)		28,546 (56.5)	32,311 (43.6)	
IV	4833 (9.2)	5701 (6.9)		4356 (8.6)	4103 (5.5)	
V	46 (0.1)	89 (0.1)		38 (0.1)	41 (0.1)	
Missing	925 (1.8)	1544 (1.9)		886 (1.8)	1383 (1.9)	
Type of fracture, n (%)			0.064			0.070
Nondisplaced cervical (garden 1–2)	6308 (12.0)	11,560 (14.0)		6146 (12.2)	10,694 (14.4)	
Displaced cervical (garden 3–4)	19,654 (37.4)	30,518 (37.0)		18,905 (37.4)	27,343 (36.9)	
Basicervical	1681 (3.2)	2799 (3.4)		1624 (3.2)	2502 (3.4)	
Peritrochanteric (2 fragments)	10,668 (20.3)	16,191 (19.6)		10,240 (20.3)	14,535 (19.6)	
Peritrochanteric (multiple fragments)	9708 (18.5)	14,785 (17.9)		9333 (18.5)	13,154 (17.7)	
Subtrochanteric	4455 (8.5)	6533 (7.9)		4293 (8.5)	5885 (7.9)	
Missing	26 (0.0)	29 (0.0)		26 (0.1)	27 (0.0)	
Type of surgery, n (%)			0.089			0.101
Pins or screws	8167 (15.6)	15,291 (18.6)		7866 (15.6)	13,983 (18.9)	
Screws or pins with sideplate	13,452 (25.6)	21,450 (26.0)		12,941 (25.6)	19,205 (25.9)	
Intramedullary nail	13,024 (24.8)	18,968 (23.0)		12,514 (24.7)	16,982 (22.9)	
Hemiarthroplasty	14,022 (26.7)	20,574 (25.0)		13,438 (26.6)	18,035 (24.3)	
Total hip replacement	3809 (7.3)	6080 (7.4)		3783 (7.5)	5893 (7.9)	
Missing	26 (0.0)	52 (0.1)		25 (0.0)	42 (0.1)	

Abbreviations: ASA, American Society of Anesthesiologists; ASD, absolute standardized difference; BB−, no beta-blocker therapy; BB+, ongoing beta-blocker therapy; COPD, chronic obstructive pulmonary disease; N/A, not applicable; SD, standard deviation.

lower in the dataset that excluded patients who died within 30 days postoperatively both before (16.2% vs 17.3%, ASD 0.029) and after IPTW (14.8% vs 19.8%, ASD 0.248; Table 3). No covariates were included in the Cox proportional hazards model since all available covariates were balanced after weighting. The risk of mortality within 1 year postoperatively was reduced by 42% in the BB+ group compared to the BB− group (adjusted HR = 0.58, 95% CI, 0.57–0.60; $P < .001$; Table 4; Figure 1). After excluding patients who died within the first 30 postoperative days, the risk of mortality was 27% lower in the BB+ group compared to the BB− group (adjusted HR = 0.73, 95% CI, 0.71–0.75; $P < .001$; Table 4; Figure 2).

Table 2. Demographics and Clinical Characteristics in Patients With Ongoing Beta-Blocker Therapy and Without Beta-Blocker Therapy Undergoing Surgery for Hip Fractures, After Multiple Imputation and IPTW

Variable	All patients			Excluding 30-d postoperative mortality		
	BB^+ (N = 52,500)	BB^- (N = 82,415)	ASD	BB^+ (N = 50,567)	BB^- (N = 74,140)	ASD
Age, mean (SD)	82.3 (8.9)	82.1 (10.4)	0.017	81.9 (9.0)	81.7 (10.5)	0.014
Sex, n (%)			0.003			0.007
Female	35,535 (68.1)	56,367 (68.0)		34,826 (69.4)	51,730 (69.1)	
Male	16,646 (31.9)	26,578 (32.0)		15,381 (30.6)	23,176 (30.9)	
Comorbidities, n (%)						
Myocardial infarction	3207 (6.1)	5499 (6.6)	0.020	2794 (5.6)	4765 (6.4)	0.034
Congestive heart failure	8356 (16.0)	13,655 (16.5)	0.012	7186 (14.3)	11,377 (15.2)	0.025
Peripheral vascular disease	2375 (4.6)	3878 (4.7)	0.006	2192 (4.4)	3489 (4.7)	0.014
Cerebrovascular disease	9256 (17.7)	14,704 (17.7)	<0.001	8672 (17.3)	13,003 (17.4)	0.002
Dementia	10,519 (20.2)	16,692 (20.1)	0.001	9565 (19.1)	14,227 (19.0)	0.001
COPD	6120 (11.7)	9653 (11.6)	0.003	5712 (11.4)	8472 (11.3)	0.002
Connective tissue disease	2531 (4.9)	3992 (4.8)	0.002	2454 (4.9)	3632 (4.8)	0.002
Peptic ulcer disease	1720 (3.3)	2722 (3.3)	0.001	1633 (3.3)	2468 (3.3)	0.002
Liver disease	562 (1.1)	860 (1.0)	0.004	526 (1.0)	769 (1.0)	0.002
Diabetes	7825 (15.0)	12,481 (15)	0.001	7450 (14.8)	11,198 (14.9)	0.003
Hemiplegia	1145 (2.2)	1814 (2.2)	0.001	1114 (2.2)	1679 (2.2)	0.002
Chronic kidney disease	2791 (5.3)	4654 (5.6)	0.012	2389 (4.8)	3884 (5.2)	0.020
Local tumor	5716 (11)	9045 (10.9)	0.002	5349 (10.7)	7968 (10.6)	0.001
Metastatic carcinoma	1158 (2.2)	1807 (2.2)	0.003	1015 (2.0)	1485 (2.0)	0.003
Charlson Comorbidity Index[a], n (%)			0.028			0.033
≤4	22,524 (43.2)	36,487 (44.0)		22,720 (45.3)	34,259 (45.7)	
5–6	19,744 (37.8)	30,271 (36.5)		18,719 (37.3)	26,879 (35.9)	
≥7	9913 (19.0)	16,186 (19.5)		8767 (17.5)	13,768 (18.4)	
ASA physical status, n (%)			0.008			0.015
I	2518 (4.8)	4132 (5.0)		2536 (5.1)	3944 (5.3)	
II	18,934 (36.3)	29,938 (36.1)		19,045 (37.9)	28,109 (37.5)	
III	26,419 (50.6)	41,976 (50.6)		25,064 (49.9)	37,372 (49.9)	
IV	4254 (8.2)	6813 (8.2)		3528 (7.0)	5437 (7.3)	
V	55 (0.1)	85 (0.1)		33 (0.1)	45 (0.1)	
Type of fracture, n (%)			0.003			0.003
Nondisplaced cervical (garden 1–2)	6873 (13.2)	10,925 (13.2)		6758 (13.5)	10,083 (13.5)	
Displaced cervical (garden 3–4)	19,335 (37.1)	30,821 (37.2)		18,522 (36.9)	27,604 (36.9)	
Basicervical	1718 (3.3)	2737 (3.3)		1643 (3.3)	2450 (3.3)	
Peritrochanteric (2 fragments)	10,428 (20.0)	16,586 (20.0)		10,021 (20.0)	15,036 (20.1)	
Peritrochanteric (multiple fragments)	9557 (18.3)	15,092 (18.2)		9152 (18.2)	13,598 (18.2)	
Subtrochanteric	4270 (8.2)	6784 (8.2)		4110 (8.2)	6135 (8.2)	
Type of surgery, n (%)			0.003			0.004
Pins or screws	9008 (17.3)	14,373 (17.3)		8723 (17.4)	13,066 (17.4)	
Screws or pins with sideplate	13,545 (26.0)	21,512 (25.9)		12,986 (25.9)	19,423 (25.9)	
Intramedullary nail	12,438 (23.8)	19,743 (23.8)		11,954 (23.8)	17,855 (23.8)	
Hemiarthroplasty	13,444 (25.8)	21,323 (25.7)		12,724 (25.3)	18,859 (25.2)	
Total hip replacement	3745 (7.2)	5995 (7.2)		3820 (7.6)	5704 (7.6)	
Year of surgery, n (%)			0.006			0.006
2008	5230 (10.0)	8278 (10.0)		4527 (9.0)	6665 (8.9)	
2009	5368 (10.3)	8503 (10.3)		4565 (9.1)	6770 (9.0)	
2010	5374 (10.3)	8559 (10.3)		4991 (9.9)	7429 (9.9)	
2011	5545 (10.6)	8893 (10.7)		5149 (10.3)	7671 (10.2)	
2012	5551 (10.6)	8800 (10.6)		5105 (10.2)	7639 (10.2)	
2013	5402 (10.4)	8606 (10.4)		5342 (10.6)	8033 (10.7)	
2014	5105 (9.8)	8156 (9.8)		5382 (10.7)	8006 (10.7)	
2015	5177 (9.9)	8294 (10.0)		5217 (10.4)	7806 (10.4)	
2016	5230 (10.0)	8278 (10.0)		4929 (9.8)	7348 (9.8)	
2017	5368 (10.3)	8503 (10.3)		4999 (10)	7541 (10.1)	

Counts and percentages are based on the stabilized weights. They will therefore not add up exactly to the number of patients in each cohort.

Abbreviations: ASA, American Society of Anesthesiologists; ASD, absolute standardized difference; BB^-, no beta-blocker therapy; BB^+, ongoing beta-blocker therapy; COPD, Chronic obstructive pulmonary disease; IPTW, inverse probability of treatment weighting; SD, standard deviation.

[a]Charlson Comorbidity Index was not used in the weighting since the individual comorbidities were used instead.

DISCUSSION

This is the first study investigating the association between BB therapy and mortality within the first year after hip fracture surgery. BB therapy was associated with a 42% reduced risk of mortality within the first postoperative year after adjusting for age, sex, comorbidities, ASA physical status, fracture, and surgery type. When excluding patients who died within the

Table 3. Crude Postoperative Outcomes in Patients With Ongoing Beta-Blocker Therapy and Without Beta-Blocker Therapy Undergoing Surgery for Hip Fractures, Before and After IPTW

	All patients				Excluding 30-d postoperative mortality			
Outcome measure	BB+ (N = 52,500)	BB− (N = 82,415)	ASD	RR (95% CI)	BB+ (N = 50,567)	BB− (N = 74,140)	ASD	RR (95% CI)
Before IPTW, n (%)								
30-d mortality	1933 (3.7)	8275 (10.0)	0.254	0.37 (0.35–0.38)	N/A	N/A	N/A	N/A
1-y mortality	10,138 (19.3)	21,115 (25.6)	0.152	0.75 (0.74–0.77)	8205 (16.2)	12,840 (17.3)	0.029	0.93 (0.91–0.96)
After IPTW, n (%)								
30-d mortality	1784 (3.4)	10,128 (12.2)	0.332	0.28 (0.27–0.29)	N/A	N/A	N/A	N/A
1-y mortality	9477 (18.2)	23,706 (28.6)	0.248	0.64 (0.62–0.65)	7450 (14.8)	14,805 (19.8)	0.131	0.75 (0.73–0.77)

Abbreviations: ASA, American Society of Anesthesiologists; ASD, absolute standardized difference; BB−, no beta-blocker therapy; BB+, ongoing beta-blocker therapy; CI, confidence interval; COPD, chronic obstructive pulmonary disease; IPTW, inverse probability of treatment weighting; N/A, not applicable; RR, relative risk.

Table 4. Hazard Ratios for BB Therapy for Mortality Within 1 y After Hip Fracture Surgery, Calculated Using a Cox Proportional Hazards Model With Weights Based on IPTW

Variable	All patients		Excluding 30-d postoperative mortality	
	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
BB therapy				
No	Ref.		Ref.	
Yes	0.58 (0.57–0.60)	<.001	0.73 (0.71–0.75)	<.001

Cox proportional hazards models with weights are based on IPTW. No adjustments were made for any covariates as all were balanced after IPTW, defined as an absolute standardized difference <0.1.

Abbreviations: BB, beta-blocker; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting.

first 30 days after surgery, BB therapy was associated with a 27% reduction in the risk of mortality.

Mortality within the first postoperative year after hip fracture surgery has been reported to be up to 27%, with one-third of the deaths being of cardiovascular origin.[20,31,32] In a previous study by our research team, using the same patient population, a significant reduction in the incidence of all-cause mortality within first 30 days postoperatively was observed (adjusted incidence rate ratio [IRR] = 0.28, 95% CI, 0.26–0.29; $P < .001$). Furthermore, a 76% reduction in cardiovascular mortality was also detected in patients with ongoing BB therapy (adjusted IRR = 0.24, 95% CI, 0.22–0.26; $P < .001$).[2] Consequently, we opted to exclude patients who died within the 30-day postoperative period in our secondary analysis to better study the association between BB therapy and long-term mortality.

Previous studies, including major general surgical procedures, have demonstrated a positive association between BBs and mortality beyond the immediate postoperative period.[4,5,26] In a double-blinded randomized, placebo-controlled trial conducted by Mangano et al,[5] a reduced risk in 2-year all-cause mortality after noncardiac surgery was detected in patients receiving perioperative atenolol. The authors postulated that the protective long-term effect of atenolol is generated by an attenuation of the heart rate which lowers the strain on the heart and further limits the development of ischemia, reducing long-term cardiac complications.[5] Similar results were also seen in patients who underwent elective abdominal colon cancer resection surgery in a study conducted by Ahl et al.[26] In that study, the authors detected that patients receiving regular BB therapy before admission had a 43% decrease in postoperative mortality within the first year (adjusted HR = 0.57, 95% CI, 0.52–0.63; $P < .001$). Maghami et al[4] could also see a survival benefit after emergency laparotomy in geriatric (≥65 years) patients, with a 35% reduction in the incidence of mortality 1 year postoperatively (adjusted IRR = 0.65, 95% CI, 0.44–0.98; $P = .04$). Similar to the current study, these previous investigations included patient cohorts that consisted mainly of elderly patients burdened by several comorbidities.[4,5,26] Perioperative BB therapy has been viewed with caution since the Perioperative Ischemic Evaluation (POISE) study, a randomized controlled trial that assigned BB naive patients to receive extended release metoprolol 2 to 4 hours before surgery.[33] Patients who received metoprolol had a lower rate of myocardial infarction but a higher rate of stroke and 30-day mortality. The POISE study was criticized for its large, fixed dose of BBs, but the uncertainty around the benefit of BB therapy in perioperative care has continued,[34] despite several studies showing no increased risk of stroke and some even demonstrating a decrease in mortality in the intensive care setting or major abdominal surgery.[9,26,35–37] There are several differences between the POISE study and the current study that needs to be highlighted. In our epidemiological study, BB therapy was not initiated because the patient required surgery, but was already being administered due to a previous prescription. The POISE study included a potpourri of surgical patients, for example, vascular, orthopedic, and general surgery, without distinguishing between the surgical procedures. There are significant differences between these patient populations in terms of both their general condition and risk of adverse events. In contrast, the current study consists of a more homogenous patient population.

The apparent protective effect of BB therapy appears to be the greatest during the first 30 days

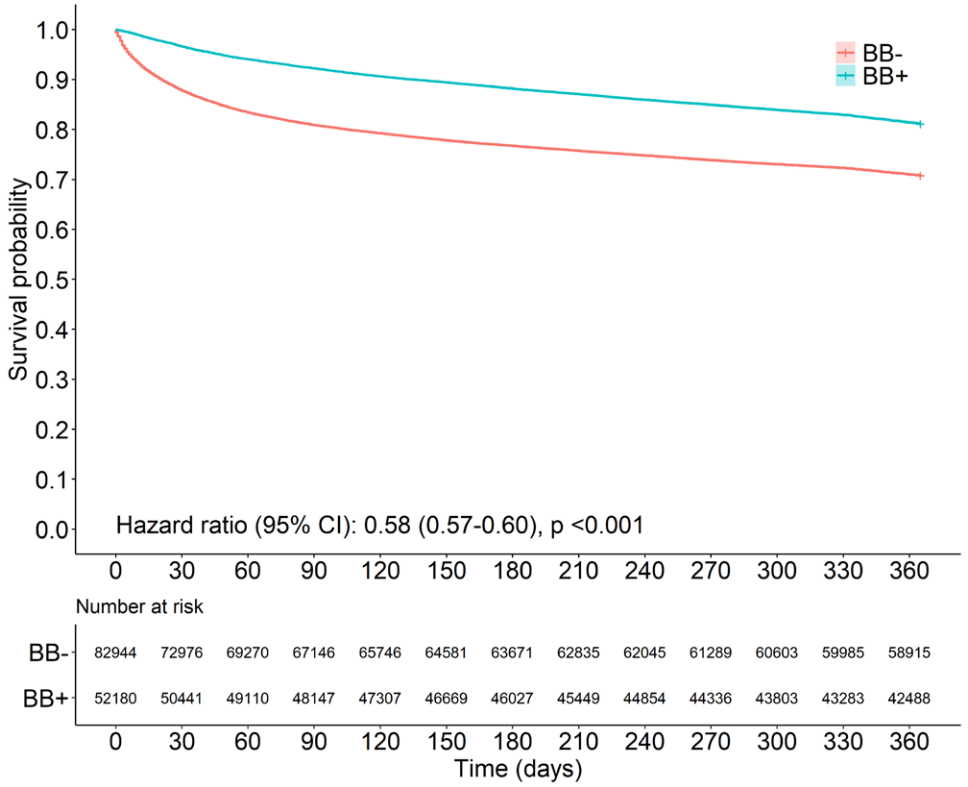

Figure 1. Kaplan Meier curve describing 1-y survival with and without beta-blocker therapy, after inverse probability of treatment weighting. BB+ = ongoing beta-blocker therapy; BB- = no beta-blocker therapy CI, confidence interval.

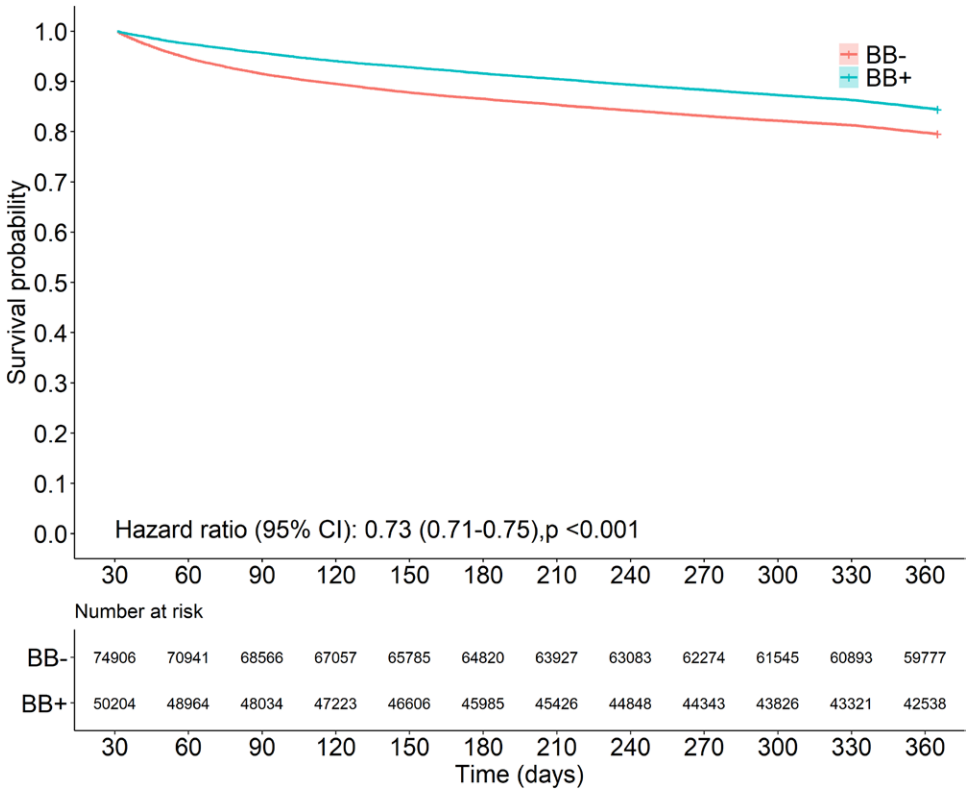

Figure 2. Kaplan Meier curve describing 1-y survival with and without beta-blocker therapy, excluding 30-d mortality, after inverse probability of treatment weighting. BB+ = ongoing beta-blocker therapy; BB- = no beta-blocker therapy; CI, confidence interval.

after hip fracture surgery. This might be attributed to the recent trauma and subsequent surgery causing the largest release of catecholamines in the immediate aftermath of the initial injury; consequently, most deaths resulting from the hyperadrenergic state occur in this period. Since BBs are hypothesized to counteract the initial spike in catecholamines, a larger reduction in mortality would be expected to be seen during this period. However, when expanding the studied time span the effect of BB appears to decrease. A reason for this may be the presence of a number of comorbidities in the BB^+ group, which start to take their toll as time passes by. As such, they may result in and contribute to deaths that BB therapy does not protect against. Nevertheless, the association between BB therapy and survival remains up to 1 year postoperatively for hip fracture patients.

The evidence presented emphasizes the importance of maintaining BB therapy in hip fracture patients. BB therapy remains significantly underused for a large proportion of surgical patients.[38] With the evidence currently available, it is not possible to recommend initiating BB therapy in BB naive patients; however, the aspiration is that this study will provide further evidence for the imperative nature of investigating this possibility using an interventional study design. These findings also lend further credence to considering factors other than surgical variables when managing hip fracture patients.[39]

This investigation has the advantage of a large sample size from a nationwide database, rather than being limited to a single center. The Rikshoft registry is used by all orthopedic departments in Sweden and is well known for its high case coverage, ranging between 80% and 90%.[40] Furthermore, limiting the study to patients treated in Sweden allows for a more homogenous patient management since there is a consensus on how hip fracture patients should be managed on a national level. Nonetheless, Sweden also differs slightly compared to the rest of the world since it has one of the highest incidences of hip fractures globally.[21] The study is limited by its retrospective nature, which restricts the data to the variables available in the registers. The authors acknowledge that individual patient's compliance with their prescribed BB therapy cannot be determined; nevertheless, a 2012 study found that the Swedish population is highly compliant regarding filling their prescriptions.[41] Consequently, we do not believe that this has had any significant effect on the outcomes of this study. Since Rikshoft is an orthopedic database, there was regrettably no data regarding anesthesiologic variables such as type of anesthesia, hemodynamic variables, fluid therapy, blood loss, and antiplatelet medication. However, since we have focused on a homogenous patient population, that is, isolated hip fracture patients, and also controlled for the year of operation when matching patients, it is highly unlikely that there are major differences in the anesthesiologic management between the cohorts. Furthermore, all the covariates included have been previously shown to be associated with an increased risk of postoperative mortality in patients subjected to hip fracture surgery. No conclusions about a causal relationship could be made due to the retrospective nature of the study. Further research in the form of a randomized controlled trial is encouraged to answer the question of a causal relationship between BB therapy and postoperative mortality in hip fracture patients.

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