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Original Contribution

Intraoperative hypotension in noncardiac surgery patients with chronic beta-blocker therapy: A matched cohort analysis

Kristin H.J.M. Mol, Victor G.B. Liem, Felix van Lier, Robert Jan Stolker, Sanne E. Hoeks *

Department of Anesthesia, Erasmus University Medical Center, Rotterdam, the Netherlands

HIGHLIGHTS

- Chronic β-blocker therapy does not lead to increased intraoperative hypotension.
- Time, area and TwA under 55–75 mmHg MAP thresholds was similar compared to non-users.
- Patient subgroup and beta-blocker subtype analyses revealed similar results.
- Immediate postoperative myocardial injury did not differ between users and non-users.
- No difference in 30-day mortality and adverse cardiovascular events was observed.

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ABSTRACT

Study objective: To explore the incidence of intraoperative hypotension in patients with chronic beta-blocker therapy, expressed as time spent, area and time-weighted average under predefined mean arterial pressure thresholds.
Design: Retrospective analysis of a prospective observational cohort registry.
Setting: Patients ≥60 years undergoing intermediate- to high-risk noncardiac surgery with routine postoperative troponin measurements on the first three days after surgery.
Patients: 1468 matched sets of patients (1:1 ratio with replacement) with and without chronic beta-blocker treatment.
Interventions: None.
Measurements: The primary outcome was the exposure to intraoperative hypotension in beta-blocker users vs. non-users. Time spent, area and time-weighted average under predefined mean arterial pressure thresholds (55–75 mmHg) were calculated to express the duration and severity of exposure. Secondary outcomes included incidence of postoperative myocardial injury and thirty-day mortality, myocardial infarction (MI) and stroke. Furthermore, analyses for patient subgroup and beta-blocker subtype were conducted.
Main results: In patients with chronic beta-blocker therapy, no increased exposure to intraoperative hypotension was observed for all characteristics and thresholds calculated (all $P > .05$). Beta-blocker users had lower heart rate before, during and after surgery (70 vs. 74, 61 vs. 65 and 68 vs. 74 bpm, all $P < .001$, respectively). Postoperative myocardial injury (13.6% vs. 11.6%, $P = .269$) and thirty-day mortality (2.5% vs. 1.4%, $P = .055$), MI (1.4% vs. 1.5%, $P = .944$) and stroke (1.0% vs 0.7%, $P = .474$) rates were comparable. The results were consistent in subtype and subgroup analyses.
Conclusions: In this matched cohort analysis, chronic beta-blocker therapy was not associated with increased exposure to intraoperative hypotension in patients undergoing intermediate- to high-risk noncardiac surgery. Furthermore, differences in patient subgroups and postoperative adverse cardiovascular events as a function of treatment regimen could not be demonstrated.

* Corresponding author at: Department of Anesthesia, Erasmus University Medical Center, Room Na-1718, P.O. Box 2040, 3000 CA Rotterdam, the Netherlands.
E-mail addresses: k.mol@erasmusmc.nl (K.H.J.M. Mol), v.liem@erasmusmc.nl (V.G.B. Liem), f.vanlier@erasmusmc.nl (F. van Lier), r.stolker@erasmusmc.nl (R.J. Stolker), s.hoeks@erasmusmc.nl (S.E. Hoeks).

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1. Introduction

Perioperative adverse cardiovascular events are the leading cause of complications after intermediate-to high-risk noncardiac surgery. [1,2] Beta-blocker therapy, initiated for the reduction of surgery-related cardiovascular morbidity and mortality, showed promising at first. [3,4] However, the positive effects on cardiac outcome were offset by increased risks for perioperative stroke (hazard ratio (HR) 2.17 (95% confidence interval (CI); 1.26–3.74)) and all-cause mortality (HR 1.33 (95% CI; 1.03–1.74)) in patients receiving fixed-dose beta-blocker therapy shortly before surgery, as demonstrated in the POISE trial. [5] Routine initiation of beta-blockers prior to noncardiac surgery is therefore no longer recommended in current guidelines. [6,7] The risk for adverse effects with beta-blockers is believed to be related to increased incidence of intraoperative hypotension and bradycardia. [5,8] Whether extrapolation of these findings is justified in chronic users is unclear as observational studies on clinical outcome measures found both harm and benefit with beta-blockers in patient subgroups. [9–12] Because of possible withdrawal symptoms (i.e. a hyperadrenergic response to stress), perioperative continuation is advised for patients receiving chronic beta-blocker therapy. [6,7] Studies supporting continuation of beta-blocker treatment, however, are limited to clinical outcome measures and do not include hemodynamic data. [13–16] It is important to asses associations for intraoperative hypotension with perioperative beta-blockers as recent studies in noncardiac surgery patients have demonstrated adverse cardiovascular outcome with perioperative hypotension, regardless of beta-blocker regime. [17–20] Hemodynamic data is often subject to various and/or unclear definitions which limits direct comparability between studies. [21] Cumulative time spent and severity of hypotension under certain thresholds have shown to provide more detail on blood pressure patterns when compared to analyses of binary events (i.e. “yes” or “no” hypotension). [17,20,22] We conducted a matched cohort analysis to assess associations of chronic beta-blocker therapy with hypotension and postoperative adversity in patients undergoing intermediate- to high-risk noncardiac surgery. The primary endpoint was the incidence of intraoperative hypotension in patients with chronic beta-blocker therapy, using various predefined characteristics and MAP thresholds to define hypotension. Secondary endpoints included postoperative myocardial injury and hypotension in the first three postoperative days and 30-day all-cause mortality, myocardial infarction and stroke rate. Exploratory analysis on patient subgroups and beta-blocker subtype were conducted. Based on previous work, we hypothesized increased risk for intraoperative hypotension in patients with chronic beta-blocker therapy.

2. Materials and methods

2.1. Study design

This retrospective matched cohort analysis was derived from an ongoing single center prospective troponin cohort registry between July 2012 and July 2017 at the Erasmus University Medical Centre, Rotterdam, the Netherlands. [2,20]. Postoperative troponin was sampled on the first three days after surgery in all patients aged ≥60 years scheduled for intermediate- to high-risk noncardiac surgery with an expected postoperative hospital stay of at least 24 h. The sample size was based on the available data. The registry was reviewed by the Medical Ethical Committee of Erasmus University, Rotterdam (MEC-2013-397 and 2014-659), who approved the non-interventional character of the study and waived the requirement for informed consent. The study was conducted in compliance with the Helsinki declaration [23] and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria [24] for observational studies.

2.2. Patient characteristics

All consecutive patients enrolled into the study cohort were screened for baseline characteristics, including: age, sex, type of surgery, past medical history and use of cardiovascular medication at anesthesia preassessment. In case of multiple surgeries per patient, the first procedure was included for analysis. Intermediate- to high-risk noncardiac surgery included major abdominal, genitourinary, vascular, orthopedic and neurological surgery following ESC guidelines. [6] In the Netherlands, elective surgical procedures are preceded by outpatient pre-operative assessment well ahead of the date of surgery. During these visits and on admission, a patient’s record on pharmacotherapy is registered and checked by the hospital’s pharmacy as part of standard institutional procedures. For the present study, patients scheduled for emergency surgery were excluded because this procedure is not performed prior to surgery. In case of a beta-blocker prescription at both pre-operative assessment and the day of surgery, the time between these dates defined the minimum known duration of beta-blocker treatment and, subsequently, chronic treatment. All types beta-blocker prescriptions were allowed, including; atenolol, bisoprolol, carvedilol, celiprolol, labetalol, metoprolol, nebivolol, pindolol, propranolol and sotalol. Fixed-dose combinations of beta-blockers with other agents were coded by the beta-blocker component.

2.3. Endpoints

2.3.1. Hemodynamic data

Hemodynamic data were extracted from the hospital’s anesthesia information management system and linked to this cohort registry. Patients were excluded if the total intraoperative recording time was below 30 min. Preoperative blood pressure measurements were sampled at the outpatient clinic, surgical ward and in the preoperative holding area. Postoperative blood pressure readings were collected from the recovery unit and surgical wards. The intraoperative period was defined as the time between arrival and discharge from the operating room. On the wards, preoperative and postoperative day 1 to 3, blood pressure was measured noninvasive with 4- to 6-h intervals, following local policy. During surgery and at the recovery unit (postoperative day 0), measurements were acquired using arterial line measurements (continuous) or oscillometry (1- to 5-min intervals) according to local policy. Arterial line measurements were considered superior over non-invasive oscillometric measurements and used for analysis when both were available. Data were cleaned using a previously described protocol by Monk et al. [19]; systolic blood pressure readings (SBP) below 20 mmHg or above 300 mmHg; diastolic blood pressure readings (DBP) below 20 mmHg or above 200 mmHg; DBP > SBP and SBP – DBP difference of <20 mmHg were considered non-reliable and removed from the data. Intraoperative data were linearly interpolated.

Characteristics of hypotension

Mean arterial pressure (MAP) was used for analyses. Predefined MAP thresholds of 55 to 75 mmHg (with 5 mmHg increment) were used to characterize intraoperative hypotension. The severity of hypotension was expressed by **(i)** time spent, **(ii)** area and **(iii)** time-weighted average under these thresholds. [25] Time under threshold was defined as the cumulative length(duration(minutes)) a patient’s MAP had decreased below the specified threshold. The area under threshold (AuT (mmHg*min)) was calculated by multiplying the depth beneath the threshold times duration. To adjust for surgical time variation and operating under the assumption that the frequency of measurements varies between patients, time-weighted average (TwA (mmHg)) under the specified MAP threshold was calculated by dividing area under the specific threshold by the total duration of the intraoperative period.

2.3.2. Troponin T and clinical outcome measurements during follow-up

Postoperative high-sensitivity troponin T levels (hs-TnT) were systematically measured on the first three postoperative days using the

Roche fifth-generation Elecsys high-sensitivity troponin T assay (Roche Diagnostics, Germany). Troponin elevation was defined as a peak hs-TnT concentration above the 99th percentile of a normal population, i.e. 14 ng L^{-1}. [26] As previously published, myocardial injury was defined as troponin values >50 ng L^{-1}. [20] In this cohort, troponin measurements were not systematically evaluated for a non-ischemic origin (e.g. sepsis or pulmonary embolism). [27] Clinical outcome measures within 30-days after surgery included all-cause mortality, myocardial infarction and stroke rate. Both myocardial infarction and stroke were defined according to their universal definition in use during the inclusion period and required confirmation by a cardiologist or neurologist, respectively. [28,29] Information on thirty-day follow-up was collected from patients' own report on cardiovascular events and checked in the medical records, as described previously. [2] Survival status was obtained from the civil registry.

2.4. Statistical analyses

A matched cohort study was designed to balance baseline differences between beta-blocker users and non-users, addressing the concerns of treatment selection bias. The propensity score was estimated using a logistic regression model and defined as the conditional probability of receiving beta-blocker therapy given the following baseline measured covariates: age, gender, coronary heart disease, insulin dependent diabetes mellitus, stroke, chronic obstructive pulmonary disease, renal failure, peripheral arterial disease, chronic heart failure and cardiovascular medication. Covariate balance between beta-blocker users and non-users were assessed by estimation of the mean difference before and after matching and values <0.1 were considered balanced. [30] Genetic matching (1:1) with replacement was used to establish a cohort of matched pairs with similar baseline covariates (i.e. patient characteristics and type of surgery). [31] Genetic matching was preferred because it uses a combination of propensity score matching and Mahalanobis distance matching and has shown to be superior over propensity score matching alone and less sensitive to model specification. [32,33] It uses an iterative algorithm to find the most optimal set of weights for each covariate to achieve optimal balance after multivariate matching. [34] Replacement was allowed to reduce bias due to incomplete matching. Exploratory analyses for the most frequent prescribed beta-blockers and patient subgroups (congestive heart failure and/or prior myocardial infarction and uncomplicated hypertension) were conducted. [35] Uncomplicated hypertension was defined as a diagnosis of hypertension in the absence of established cardiovascular or renal disease. Descriptive statistics are presented as numbers and proportions. Continuous data are described as median with interquartile range (IQR). After matching, the Wilcoxon signed-rank and paired *t*-tests were used to adjust for control unit multiplicity and within-pair correlations. [36–38] No correction for multiple testing was performed due to the exploratory nature of this study. All reported *P*-values were 2-tailed and a value of <0.05 was considered significant. No statistical-analysis plan was pre-registered for this cohort registry. Genetic matching and further analyses were performed by calling functions of the MatchIt [39] and Survey package. [40] All statistical analyses were performed using R Statistical Software (v4.0.1, The R Foundation, Austria).

3. Results

This cohort registry consists of 4586 eligible patients aged ≥60 years undergoing noncardiac surgery with routine postoperative troponin measurements. A final of 4265 patients were available for matching of whom 1468 (34%) patients used beta-blockers on both preoperative assessment and the day of surgery (Fig. 1). All patients with chronic beta-blocker therapy were used in propensity score matching and as a result, a sample of 1468 matched pairs of treated and control patients was created through 1:1 matching with replacement. A total of 823 unique control patients were used, therefore, some control patients were matched to multiple cases.

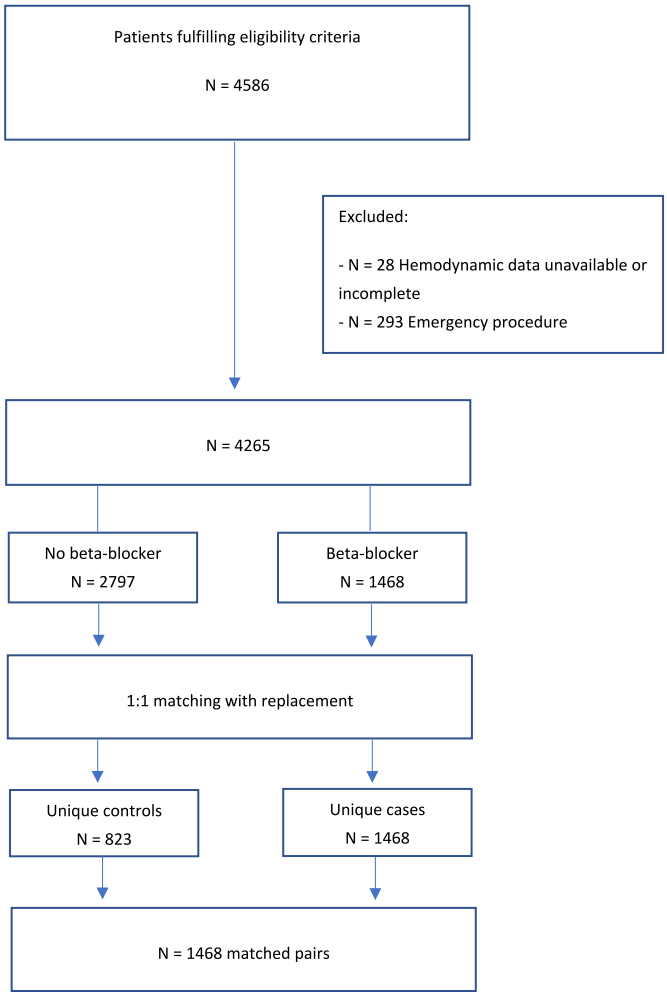

Fig. 1. Study flowchart.
Flowchart of the study cohort and matching. $N = 1468$ matched pairs were created using N = 1468 unique patients with beta-blocker therapy and $N = 823$ unique control patients.

3.1. Baseline characteristics

Patient characteristics before and after matching are presented in Table 1A. Before matching, beta-blocker users were older, more frequently male and showed a higher incidence of cardiovascular burden in prior medical history when compared to non-users. After matching, covariates that informed propensity score estimation were well balanced between the two treatment groups (Table 1A), as was the type and length of surgery. The minimum observed duration of beta-blocker treatment was 31 days [IQR; 12 - –66]. Metoprolol (727 (49.5%)) and bisoprolol (424 (28.9%)) were the two most commonly prescribed beta-blockers (Table 1B). Beta-blocker monotherapy wasobserved in 100 (6.8%) patients.

3.2. Intraoperative hypotension

Table 2 shows characteristics of intraoperative hypotension under the predefined MAP thresholds. Weighted analysis showed similar exposure to hypotension for time spent, area and time-weighted average below all MAP thresholds between beta-blocker users and non-users (all $P > .05$). Patients with chronic beta-blocker therapy had significant lower heart rate before and during surgery (all $P < .001$, Table 2). The

Table 1A
Patient characteristics before and after propensity score matching (1:1). Imbalance is presented as the standardized mean difference.

	Patients before PSM			Patients after PSM			
	No Beta-blocker	Beta-blocker	SMD	No Beta-blocker	Beta-blocker	SMD	*P*-value
Age (y)	68.8 [64.5, 74.3]	70.8 [66.2, 76.0]	0.228	71.1 [66.3, 76.3]	70.8 [66.2, 76.0]	0.033	0.317
Gender (male)	1594 (57.0)	904 (61.6)	0.094	64.2%	61.6%	0.054	0.888
Hypertension	1207 (43.2)	1149 (78.3)	0.771	78.6%	78.3%	0.008	0.526
Coronary artery disease	223 (8.3)	492 (33.5)	0.651	32.6%	33.5%	0.020	0.457
Myocardial Infarction	169 (6.0)	354 (24.1)	0.522	23.5%	24.1%	0.014	0.820
Congestive heart failure	75 (2.7)	163 (11.1)	0.337	10.5%	11.1%	0.020	0.971
Stroke	371 (13.3)	311 (21.2)	0.211	19.0%	21.2%	0.054	0.327
Peripheral Arterial Disease	231 (8.3)	283 (19.3)	0.324	18.0%	19.3%	0.033	0.722
Renal Disease	136 (4.9)	214 (14.6)	0.332	14.2%	14.6%	0.012	0.232
COPD	342 (12.2)	251 (17.1)	0.138	16.6%	17.1%	0.015	0.067
Diabetes Mellitus	194 (6.9)	171 (11.6)	0.163	11.2%	11.6%	0.013	0.833
Revised Cardiac Risk Index							
0	1569 (56.1)	427 (29.1)	0.568	31.2%	29.1%	0.032	0.514
1	851 (30.4)	526 (35.8)	0.115	39.1%	35.8%	0.051	0.319
≥2	329 (11.8)	483 (32.9)	0.525	29.7%	32.9%	0.084	0.111
Medication							
Statins	934 (33.4)	967 (65.9)	0.687	66.3%	65.9%	0.009	0.308
ACE-inhibitors	447 (16.0)	513 (34.9)	0.446	32.5%	34.9%	0.052	0.705
Angiotensin-II antagonists	427 (15.3)	356 (24.3)	0.227	24.1%	24.3%	0.003	0.821
Calcium Channel Blockers	465 (16.6)	444 (30.2)	0.326	30.0%	30.2%	0.006	0.612
Diuretics	581 (20.8)	619 (42.2)	0.473	40.6%	42.2%	0.032	0.231
Aspirin	614 (22.0)	660 (45.0)	0.503	42.5%	45.0%	0.049	0.187
Oral anticoagulants	195 (7.0)	293 (20.0)	0.388	19.9%	20.0%	0.002	0.678
Surgery							
General	484 (17.3)	210 (14.3)	0.082	13.4%	14.3%	0.028	0.564
Neurological	532 (19.0)	212 (14.4)	0.123	15.8%	14.4%	0.038	0.427
Orthopedic	324 (11.6)	193 (13.1)	0.048	11.7%	13.1%	0.043	0.386
Urologic/ sdfGynecologic	525 (18.8)	189 (12.9)	0.162	11.6%	12.9%	0.040	0.385
Vascular	725 (25.9)	557 (37.9)	0.260	41.4%	37.9%	0.071	0.169
Other	207 (7.4)	107 (7.3)	0.004	6.1%	7.3%	0.046	0.345
General Anesthesia	2709 (96.9)	1404 (95.6)	0.064	45.3%	95.6%	0.035	0.567
Days between pre-operative assessment and surgery	26 [9, 57]	31 [12, 66]	0.144	27 [11, 57]	31 [12, 66]	0.140	0.111

Covariates informing the propensity score estimation are presented in bold front.
Patients before PSM: N = 4265. Patients after PSM: N = 1468 matched pairs.
Results are expressed as median [IQR] and N (%). SMD: Standard Mean Difference.
COPD: chronic obstructive pulmonary disease. ACE-inhibitors: angiotensin converting enzyme inhibitors.

Table 1B
Type of Beta-blocker.

	N = 1468
Acebutolol	3 (0.2)
Atenolol	105 (7.2)
Bisoprolol	424 (28.9)
Carvedilol	25 (1.7)
Celiprolol	5 (0.3)
Labetalol	31 (2.1)
Metoprolol	727 (49.5)
Nebivolol	36 (2.5)
Propanolol	57 (3.9)
Sotalol	78 (5.3)

Data presented as absolute numbers (%).

observed crude ratio of patients receiving vasopressor support during surgery was comparable between the two groups.

3.3. Secondary outcomes

Postoperative MAP measured on the recovery unit was comparable between the two groups (beta-blocker users; 86 mmHg [IQR 76, 95] vs. non-users; 85 mmHg [IQR; 77, 94], $P = .954$; Table 3), in contrast to lower median heart rate with beta-blocker therapy (68 bpm [IQR; 60, 77] vs. 72 bpm [IQR; 64, 83], $P < .001$). In both groups, the majority of patients were discharged to the surgical wards. Consistent with pre- and intraoperative observations, beta-blocker users showed lower median heart rate on the first three postoperative days (all $P < .001$). Median postoperative high-sensitivity troponin T peak concentrations were comparable between beta-blocker users (18 ng L^{-1} [IQR; 11, 30]) and non-users (17 ng L^{-1} [IQ; 11, 30], $P = .677$), as was the incidence of postoperative myocardial injury (13.6% vs. 11.6%, $P = .269$, Table 3). Crude incidence rates of thirty-day all-cause mortality (2.5% vs 1.4%, $P = .055$), myocardial infarction (1.4% vs 1,5%, $P = .944$) and stroke (1.0% vs 0.7%, $P = .474$) did not differ between the two treatment groups.

3.4. Subgroup analyses

Exploratory analyses for the primary objective in patients with congestive heart failure and/or prior myocardial infarction and uncomplicated hypertension were conducted (online supplement A). The outcomes mirrored the main findings of the present study by showing no differences in exposure to intraoperative hypotension between the two treatment groups. For patients with congestive heart failure and/or prior myocardial infarction, exposure to hypotension was comparable to the matched sample of 1468 patients. For patients with uncomplicated hypertension, both the treatment and control group showed increased exposure to intraoperative hypotension (all characteristics) under all MAP thresholds when compared to the main analysis, but without differences between the two treatment groups. Comparison of the data of the two most frequent prescribed beta-blockers metoprolol and

Table 2
Intraoperative hypotension exposure for N = 1468 matched pairs.

	No Beta-blocker	Beta-blocker	*P*-value
Preoperative measurements			
Hemoglobin (mmol L^{-1})*	8.4 [7.4, 9.1]	8.2[7.4, 8.9]	0.044
Heart rate (bpm)	74 [68, 83]	70 [63, 77]	<0.001
MAP (mmHg)	97 [90, 105]	97 [89, 104]	0.661
Intraoperative measurements			
Total OR time (min)	171 [96, 279]	169 [98, 291]	0.492
Heart rate (bpm)	65 [58, 74]	61 [54, 69]	<0.001
MAP (mmHg)	81 [75, 89]	81 [75, 89]	0.924
Time (minutes) under MAP			
55 mmHg	0.0 [0.0, 3.0]	0.0 [0.0, 3.0]	0.056
60 mmHg	2.0 [0.0, 10.0]	3.0 [0.0, 12.0]	0.133
65 mmHg	8.0 [0.0, 29.0]	10.0 [1.0, 29.0]	0.184
70 mmHg	23.0 [5.0, 60.0]	24.0 [7.0, 60.0]	0.445
75 mmHg	47.0 [16.0, 111.0]	48.0 [17.0, 103.0]	0.868
Area under MAP			
55 mmHg	0.0 [0.0, 9.0]	0.0 [0.0, 11.0]	0.058
60 mmHg	4.0 [0.0, 46.0]	7.4 [0.0, 51.2]	0.111
65 mmHg	35.0 [0.0, 152.7]	44.2 [2.0, 155.9]	0.141
70 mmHg	127.2 [16.3, 365.3]	134.0 [24.4, 379.0]	0.263
75 mmHg	318.7 [82.3, 824.2]	328.0 [101.2, 793.1]	0.526
TwA under MAP			
55 mmHg	0.0 [0.0, 0.0]	0.0 [0.0, 0.1]	0.055
60 mmHg	0.0 [0.0, 0.2]	0.0 [0.0, 0.2]	0.080
65 mmHg	0.2 [0.0, 0.7]	0.2 [0.0, 0.7]	0.090
70 mmHg	0.7 [0.1, 1.8]	0.7 [0.1, 1.8]	0.171
75 mmHg	1.6 [0.5, 3.7]	1.8 [0.5, 3.7]	0.381
Vasopressor use			
Noradrenaline	32.5%	33.9%	0.567
Phenylephrine	56.1%	54.9%	0.624

All data are presented as median [IQR] and N (%).
BPM: beats per minute. MAP: Mean Arterial Pressure. TwA: Time weighted average under MAP.
* Total missing values: No BB: Hb 0.5%; BB: 0.6%.

Table 3
Postoperative adverse events for N = 1468 matched pairs.

	No Beta-blocker	Beta-blocker	*P*-value
Recovery Unit (day 0)			
Heart rate (bpm)	74 [64, 84]	68 [60, 77]	<0.001
MAP (mmHg)	85 [77, 94]	86 [76, 95]	0.954
Location of discharge			
Ward	54.2%	51.3%	0.246
Post Anesthesia Care Unit	41.0%	43.6%	0.301
Intensive Care Unit	4.8%	5.1%	0.760
Postoperative measurements (ward)			
Day 1			
Heart rate (bpm)	77 [69, 88]	73 [66, 82]	<0.001
MAP (mmHg)	89 [81, 98]	88 [80, 96]	0.077
Day 2			
Heart rate (bpm)	79 [70, 89]	75 [67, 85]	<0.001
MAP (mmHg)	93 [85, 102]	92 [83, 101]	0.152
Day 3			
Heart rate (bpm)	80 [70, 90]	74 [66, 84]	<0.001
MAP (mmHg)	94 [86, 103]	94 [85, 103]	0.856
Peak hs-TnT (ng L^{-1})	17 [11,30]	18 [11, 30]	0.677
≥50 ng L^{-1}	11.6%	13.6%	0.269
Follow-up event rate			
30-day MI	1.5% (1.0, 2.3)	1.4% (0.9, 2.2)	0.944
30-day Stroke	0.7% (0.4, 1.3)	1.0% (0.6, 1.7)	0.474
30-day Mortality	1.4% (0.9, 2.2)	2.5% (1.8, 3.4)	0.055

All data are presented as median [IQR] and N (%). MI, Stroke and Mortality presented as % (95% CI).
Total missing hemodynamic data due to patient discharge:
- No BB Day 1: 6.5%, Day 2: 8%, Day 3: 21.5%.
- BB: Day 1: 6.5%, Day 2: 10.8%, Day 3: 23.2%.
BPM: beats per minute. MAP: Mean Arterial Pressure. MI: Myocardial Infarction. hs-TnT: high-sensitive Troponin T.

bisoprolol yielded results similar to the main analysis (online supplement B).

4. Discussion

In this matched cohort analysis, associations of chronic beta-blocker treatment with intraoperative hypotension were assessed in patients scheduled for elective intermediate- to high-risk noncardiac surgery. Genetic matching showed similar exposure and severity of intraoperative hypotension in patients with chronic beta-blocker treatment when compared to non-users. Furthermore, no differences in postoperative adversity such as postoperative myocardial injury and hypotension could be observed. Crude thirty-day all-cause mortality, myocardial infarction and stroke rates were comparable between beta-blocker users and non-users.

4.1. Intraoperative hypotension and bradycardia with beta-blocker therapy

Understanding the hemodynamic effects of chronic beta-blocker treatment in noncardiac surgery patients is important given its common use in surgical patients. Intraoperative beta-blocker use ranges between 17% - 33% in the literature, which is similar to our cohort (34%). [41,42] A systematic review and meta-analysis by Blessberger et al. (2019) on perioperative beta-blocker therapy continues to show increased risk of bradycardia (RR 2.49, 95% CI 1.74–3.56; 49 studies, HR < 60 bpm) and hypotension (RR 1.40, 95% CI 1.29–1.51; 49 studies, SBP < 90 mmHg or requiring medical intervention) when compared to placebo or standard care, regardless of timing of treatment. [8] Continuation of beta-blocker therapy during surgery is a class I level B recommendation in European, American and Canadian guidelines, based on studies that predominantly report clinical outcome measures and/or harm observed with beta-blocker withdrawal and these studies do not report detailed intraoperative hemodynamic data. [6,7,43] Therefore, a gap of knowledge exists in current literature to guide evidence-based practice. By using various predefined characteristics and MAP thresholds to define hypotension, this study provided a detailed insight in intraoperative blood pressure patterns in patients with chronic beta-blocker therapy. The largest contributor to Blessberger's results is the POISE trial, investigating a strategy of an up-titrated dose of metoprolol administered to beta-blocker naïve patients 2 to 4 h before surgery. [5] Risks for hypotension and bradycardia were 1.55 (95% CI 1.38–1.74, $P < .001$) and 2.74 (95% CI 2.19–3.43, $P < .001$), respectively. The second and third largest contributors to the results are POBBLE (2015) [44] and MaVS (2006) [45], also investigating metoprolol vs. placebo, but only in vascular surgery patients. Similar to POISE, both studies showed associations of increased incidence of hypotension and bradycardia requiring treatment. We also observed lower heart rate in patients with beta-blocker treatment, but our results contrast by showing no significant effects on intraoperative MAP. Differences are likely explained by the lack of dose titration and opportunities for the sympathetic nervous system to reach steady state in these studies. Moreover, patients included in our prospective cohort generally have a lower incidence of cardiovascular burden in prior medical history when compared to these studies and the availability of various intermediate- to high-risk surgical procedures increases generalizability. Furthermore, in our study, the majority of patients received general

anesthesia (95%) whereas in POISE, nearly 50% received general anesthesia and almost 40% spinal or epidural anesthesia.

4.2. Comparison to other studies on intraoperative hypotension

Patients with and without beta-blocker therapy had comparable duration (time spent) and severity (area and time-weighted average) below the predefined 55–75 MAP thresholds. On a population basis, intraoperative MAP <65 mmHg is increasingly related to adverse cardiac outcome. [18,19,25,46] The absolute minimum duration and magnitude leading to harm, however, remains unknown, but risks for myocardial injury show a graded association with increased exposure. [17,25] Although assessment of harm with absolute thresholds is beyond the scope of the present study, we observed less time spent below MAP 65 mmHg in our cohort when compared to these studies and this may have influenced results.

4.3. Postoperative adverse cardiovascular events and subgroup analyses

Comparative analyses of crude thirty-day all-cause mortality and adverse cardiovascular event rates did not show differences between beta-blocker users and non-users. A non-significant trend towards increased 30-day mortality was noted in beta-blocker users; we have no clear explanation for this. The median time between pre-operative assessment and surgery was calculated to provide a minimum known duration of beta-blocker treatment, which was 31 days [IQR; 12, 66]. Our results are therefore in line with previous studies that report safe administration of beta-blockers when preoperative treatment duration exceeds 30 days and help in understanding why; by showing no associations of increased exposure to intraoperative hypotension. [6,7,47–50] Both Wallace [15] and London [14] found improved 30-day survival with intraoperative beta-blocker exposure in high-risk patients, which we did not observe. Similar to recent work by McKenzie, [51] stroke rate did not differ with chronic beta-blocker therapy and the incidence in our cohort was similar to work by others. [49,50,52] Previous studies suggested benefit from intraoperative beta-blockers in patients with congestive heart failure and/or prior myocardial infarction [11] and increased risks for postoperative thirty-day adverse events in patients with uncomplicated hypertension. [9,10] We were unable to identify differences between the two treatment groups in terms of exposure to intraoperative hypotension, as results were similar to the main analysis. However, we did obverse increased exposure to intraoperative hypotension in patients with uncomplicated hypertension, regardless of treatment regimen. Venkatesan demonstrated harm in hypertensive patients taking beta-blockers, by showing associations of preoperative beta-blockers with a doubling of postoperative death. [10] As we could not demonstrated differences in outcome between the two treatment groups, uncontrolled hypertension, not beta-blockers, might pose the higher observed risk for complications in that cohort. Interestingly, no favorable effect on clinical outcome from treatment with beta-blockers was observed in patients in whom beta-blockers are believed to be beneficial (i.e. high-risk patients with congestive heart failure and/or prior myocardial infarction). Moreover, and parallel to findings by Jørgensen investigating risks for thirty-day mortality and adverse cardiovascular events with beta-blocker subtypes, the risk for hypotension and adverse events did not differ by beta-blocker subtype in exploratory analyses. [11] However, we caution the interpretation of these results since absolute numbers are small and propensity score estimation was not aimed at such analyses.

4.4. Strengths and limitations

Strengths of the present study are a wide variety of surgical procedures that allows for generalizability of the findings together with the availability of a large-scale hemodynamic data during the intraoperative period. The use of multiple characterizations to define exposure to hypotension under various MAP thresholds allows an objective comparison between the two treatment groups and to work by others. Genetic matching with replacement was directed at lowering the risk for treatment selection bias by reducing the variability of baseline covariates in matched untreated subjects. Furthermore, with replacement, the formation of matched pairs was not affected by the order in which the matches were created, what otherwise could have led to bias due to incomplete matching and a dramatically reduced matched sample. Despite reviewing pharmacy records on both pre-assessment and the day of surgery, a risk for noncompliance bias remains present. Other important limitations include the lack of information on therapeutic indication of beta-blocker therapy and disease severity. Although well-known cardiovascular risk factors were included in propensity score matching, left ventricular function and other important predictors for hemodynamic compromise were not available for this analysis. Pharmacological and physiological diversity exists within the beta-blocker class, leading to diverse clinical effects indicated for different cardiovascular conditions. Though cardiovascular co-medication was included in propensity score estimation, this study did not evaluate interactions with other medical therapies. Furthermore, strategies for beta-blockers and other cardiovascular medication have changed over time and this might limit comparability to previous research. Data on anesthetics, quantities of vasopressor medication, intraoperative use of beta-blockers, fluid management and blood loss were incompletely available for the study sample. In this cohort, postoperative troponin levels were not systematically evaluated for noncardiac causes. Preoperative levels were not systematically measured in all patients and, therefore, incidence of chronic troponin elevation could not be assessed. Replicate studies are warranted to confirm our findings due to the exploratory nature of this study. Last, the presence of unmeasured confounding must be considered since intraoperative management was not dictated by protocol and practice variation exists among anesthetists.

In this matched cohort analysis, chronic beta-blocker therapy was not associated with increased exposure to intraoperative hypotension in patients undergoing intermediate- to high-risk noncardiac surgery. Furthermore, a difference in patient subgroups analysis and postoperative adverse cardiovascular events as a function of treatment regimen could not be demonstrated.

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CRediT authorship contribution statement

Kristin H.J.M. Mol: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft. **Victor G. B. Liem:** Investigation, Data curation. **Felix van Lier:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Robert Jan Stolker:** Writing – review & editing, Supervision. **Sanne E. Hoeks:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of Competing Interest

All authors declare no competing of interest.

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Appendix A. Supplementary data

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