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Effect of preadmission beta-blockade on mortality in multiple trauma

M. Eriksson[1,2] , E. von Oelreich[1,2], O. Brattström[1,2], J. Eriksson[1,2], E. Larsson[1,2] and A. Oldner[1,2]

[1]Perioperative Medicine and Intensive Care, Karolinska University Hospital, Solna, and [2]Section of Anaesthesiology and Intensive Care Medicine, Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden
Correspondence to: Dr M. Eriksson, Perioperative Medicine and Intensive Care, Karolinska University Hospital, Solna, SE-171 76 Stockholm, Sweden (e-mail: mikael.er.eriksson@sll.se; @MikaelEriksson4, @EOelreich, @Olobra, @kn_haddock, @larsson_em, @OldnerAnders)

Background: High levels of circulating catecholamines after multiple trauma have been associated with increased morbidity and mortality. Beta-adrenergic receptor antagonist (beta-blocker) therapy has emerged as a potential treatment option, but the effect of preinjury beta-blockade on trauma-induced mortality is unclear. The aim of this study was to assess whether preinjury beta-blocker therapy is associated with reduced mortality after multiple trauma.

Methods: Severely injured patients, aged at least 50 years, admitted to a level one trauma centre over a 10-year interval were linked to national and local registries of co-morbidities, prescription drug use and level of education. The association between preinjury beta-blocker use and 30-day mortality was explored using logistic regression analysis.

Results: Some 1376 patients were included; 338 (24·6 per cent) were receiving beta-blockers at the time of trauma. Beta-blocker users had an increased crude 30-day mortality rate compared with that for non-users: 32·8 *versus* 19·7 per cent respectively ($P < 0·001$). After adjustment for baseline imbalances and injury-related factors, there was no association between preinjury beta-blocker use and mortality (OR 1·09, 95 per cent c.i. 0·70 to 1·70). Separate analyses of individuals with or without severe head injury did not significantly change this association. There was no significant difference in the rate of shock between beta-blocker users and non-users.

Conclusion: Pretrauma beta-blockade is not associated with 30-day mortality beyond the effects of age, co-morbidity and injury severity.

Introduction

In recent years the harmful effects of high levels of catecholamines and the potential benefit of beta-adrenergic receptor antagonist (beta-blocker) therapy have gained widespread interest[1,2]. Beta-blocker administration has emerged as a possible therapeutic intervention in the trauma setting and has been recommended for patients with severe traumatic brain injury (TBI) without haemodynamic instability[3]. Post-trauma administration of beta-blockers has been reported[4–6] to be associated with improved outcome in different settings, mainly TBI, but

large RCTs are lacking. The mechanism of the potential benefit of beta-blockers is unclear, and could be mediated by a decreased sympathetic activation and thus a decrease in oxygen consumption and metabolism, a modulation of the immune response to trauma, decreased endothelial damage or some other process[1,7,8].

Reports[9–13] on pretrauma beta-blocker therapy have been conflicting, with no effect, or even increased mortality, in multiple trauma and a protective effect in TBI. The different results between preinjury and postinjury beta-blocker administration might be explained by a higher prevalence of associated co-morbidities in the pretrauma

beta-blocker cohort or a blunted initial haemodynamic response to severe injury[10,11,14]. In addition to an effect in the trauma setting, beta-blocker use before admission might be protective among general patients in the ICU and those with sepsis[15,16]. With these reports suggesting a benefit among other groups of patients, and with conflicting results in previous studies of injured patients, there is an obvious gap of knowledge regarding the association between pretrauma beta-blocker use and outcome.

The aim of this study was to assess the effect of preinjury beta-blocker treatment on 30-day mortality after multiple trauma.

Methods

The regional ethical review board in Stockholm, Sweden, approved this study (approval numbers 2015/1137-31/4 and 2016/810-22/04).

The study was conducted at the Karolinska University Hospital, a level one trauma centre serving the Greater Stockholm area of more than two million inhabitants. The study adhered to the STROBE guidelines[17] for cohort studies.

Trauma registry and patient selection

Injured patients aged at least 15 years admitted to the trauma bay with full trauma team activation are included in a trauma registry. In addition, injured patients admitted to the emergency department without trauma team activation but retrospectively found to have an Injury Severity Score (ISS) above 9 are included. Patients with isolated fractures of the upper or lower extremity, drowning, chronic subdural haematoma, burn injury and hypothermia without concomitant trauma are not included in the registry. The Abbreviated Injury Scale (AIS) 1990 edition (for 2006) and 2005 edition (from 2007) were used.

All injured patients aged at least 50 years with an ISS of more than 15, admitted between January 2006 and December 2015, were included in the present study. Patients younger than 50 years were excluded owing to an expected low prevalence of beta-blocker treatment. Individuals with an ISS of 75 were excluded as they were unlikely to survive regardless of treatment. Individuals without a valid personal identity number (non-Swedish citizens and immigrants without Swedish citizenship) and thus unable to link to registries were excluded.

National registries and definitions

The Swedish personal identity number system enables linkage between different national and local health registries[18]. Information on education was retrieved from the Longitudinal Integration Database for Health Insurance and Labour Market Studies managed by Statistics Sweden. Highest educational achievement at the time of trauma was categorized in three levels (low, medium, high), corresponding to 9 years or less (elementary school only), 10–12 years (senior high school) and more than 12 years (university level) respectively.

Information on co-morbidity was collected from the national inpatient and outpatient registries managed by the Swedish Board of Health and Welfare (NBHW). The registries hold information on care episodes from hospitals and outpatient care not classified as primary care, including ICD-10 codes[19]. Co-morbidity was assessed for up to 8 years before trauma admission. Charlson Co-morbidity Index, and included diagnosis, was defined by the presence of corresponding ICD-10 codes as suggested by Quan and colleagues[20]. Hypertension was defined as the presence of a diagnosis in ICD-10 groups I10–I15, ischaemic heart disease as I20–I25, psychiatric co-morbidity as F20–F99 and substance abuse as F10–F19.

The Swedish Prescribed Drug Register, managed by the NBHW, contains information on all prescribed dispensed drugs in Sweden. It includes personal identity numbers from 1 July 2005, thus enabling linkage to other registries from that date. The register is considered to have 100 per cent coverage; all dispensed drugs that require a prescription are included[21]. In Sweden, beta-blockers are only dispensed with a prescription at community pharmacies.

Beta-blocker use at the time of trauma was defined as having filled at least one prescription with Anatomical Therapeutic Chemical Classification (ATC) code C07* in the 180 days preceding the trauma. Most prescriptions in Sweden cover 3 months' use to get full reimbursement, but expanding the time frame to 6 months to define users from prescription registries has been shown to increase sensitivity without decreasing specificity[22–24]. To evaluate the impact of eventual misclassification, additional analyses were performed, with beta-blocker use defined as having filled at least two prescriptions with the latest within 100 days before the trauma. Users of warfarin and novel oral anticoagulants were defined using ATC codes B01AA03 (warfarin), B01AE07 (dabigatran), B01AF01 (rivaroxaban), B01AF02 (apixaban) and B01AF03 (edoxaban).

Severe injury to an AIS region was defined as AIS greater than 2. Shock on arrival was defined as a first recorded systolic BP below 90 mmHg. Thirty-day mortality was assessed from the trauma registry, and date of death was extracted from the Cause of Death Register managed by the NBHW.
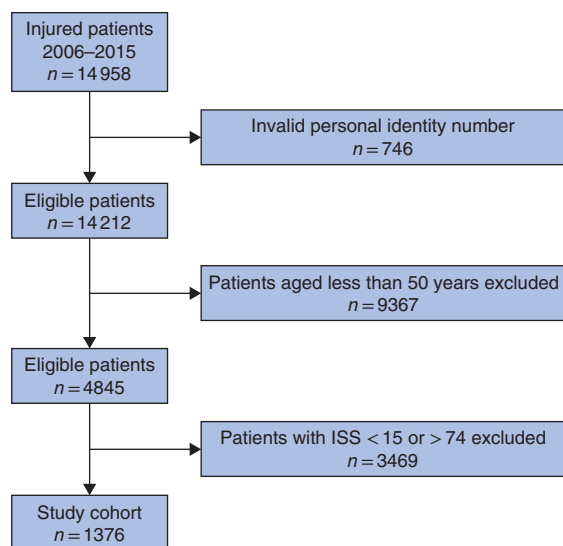
Fig. 1 Flow chart of patients included in the study. ISS, Injury Severity Score

Statistical analysis

Categorical data were compared with the χ^2 test, and continuous data with the Mann–Whitney U test. Kaplan–Meier survival curves were plotted for 30-day mortality, using the log rank test to examine differences between the groups. The association between beta-blocker use and 30-day mortality was examined by means of logistic regression analysis. Factors known or suspected to be associated with beta-blocker use and mortality were analysed with univariable logistic regression; included variables were age, sex, education, ischaemic heart disease (IHD), congestive heart failure (CHF), hypertension, diabetes mellitus, anticoagulation therapy, injury severity, shock on arrival and severe head injury. A restricted model for the association between beta-blocker use and mortality, adjusted for age, sex and injury-related variables, was constructed. In the full model, all variables with $P < 0.100$ in univariable analysis were included in a multivariable logistic regression model. Results are presented as odds ratios (ORs) with corresponding 95 per cent confidence intervals.

Data were analysed as complete cases. As missing data were noted for education (less than 10 per cent), the analysis was repeated after multiple imputations. Educational category was imputed from a logistic regression model and predicted by 30-day mortality, age, sex, IHD, CHF, hypertension, diabetes mellitus, anticoagulation therapy, beta-blocker therapy, injury severity, severe head injury and shock on arrival. Ten imputed data sets were created and analysed. To investigate the impact of more

Table 1 General characteristics and clinical outcome in the study cohort stratified by beta-blocker therapy

	No beta-blocker ($n = 1038$)	Beta-blocker ($n = 338$)	$P\ddagger$
Age (years)*	63·5 (56–73)	71·5 (63–82)	<0·001§
Sex ratio (M : F)	733 : 305	223 : 115	0·108
Educational level			0·175
Low	240 (25·1)	88 (30·6)	
Medium	444 (46·3)	125 (43·4)	
High	274 (28·6)	75 (26·0)	
CCI*	0 (0–1)	1 (0–2)	<0·001§
CCI category	($n = 958$)	($n = 288$)	<0·001
0	693 (66·8)	118 (34·9)	
1	168 (16·2)	88 (26·0)	
>1	177 (17·1)	132 (39·1)	
Ischaemic heart disease	27 (2·6)	96 (28·4)	<0·001
Congestive heart failure	28 (2·7)	60 (17·8)	<0·001
Hypertension	118 (11·4)	141 (41·7)	<0·001
Diabetes mellitus	69 (6·6)	62 (18·3)	<0·001
Anticoagulation therapy	31 (3·0)	65 (19·2)	<0·001
Psychiatric co-morbidity	142 (13·7)	39 (11·5)	0·312
Substance abuse	172 (16·6)	48 (14·2)	0·302
ISS*	24 (17–27)	25 (17–26)	0·911§
ISS category			0·181
16–24	525 (50·6)	164 (48·5)	
25–40	433 (41·7)	156 (46·2)	
>40	80 (7·7)	18 (5·3)	
Blunt trauma	1020 (98·3)	331 (97·9)	0·689
Type of injury			0·698
Accident	954 (91·9)	312 (92·3)	
Self-inflicted	51 (4·9)	16 (4·7)	
Assault	26 (2·5)	6 (1·8)	
Unknown	7 (0·7)	4 (1·2)	
Severe head injury	651 (62·7)	216 (63·9)	0·694
Severe thoracic injury	400 (38·5)	132 (39·1)	0·865
Severe abdominal injury	89 (8·6)	28 (8·3)	0·868
SAP*†	144 (120–164)	150 (120–170)	0·073§
SAP < 90 mmHg†	83 (8·0)	32 (9·5)	0·396
ICU admission	602 (58·0)	190 (56·2)	0·565
30-day postinjury mortality	205 (19·7)	111 (32·8)	<0·001

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). †On arrival in the trauma unit. CCI, Charlson Co-morbidity Index; ISS, Injury Severity Score; SAP, systolic arterial pressure. ‡χ^2 test, except §Mann–Whitney U test.

active co-morbidity, the analysis was repeated with all co-morbidities defined by the presence of a corresponding ICD code in the last year before the trauma. Logistic regression was also performed in patients with and without head injury separately. Potential interactions between beta-blocker use and head injury, and beta-blocker use and shock on arrival, were examined. Finally, the analysis was repeated with patients with an ISS of 15 or less included.

Model performance was analysed with Hosmer–Lemeshow goodness-of-fit test and the area under the receiver operating characteristic curve (AUC) was calculated. $P < 0.050$ was considered statistically significant; all tests were two-tailed. Data analysis was performed
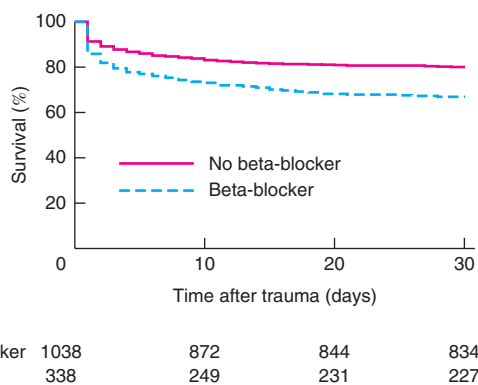
Fig. 2 Kaplan–Meier curves of 30-day survival of patients categorized as beta-blocker users or non-users. $P < 0.001$ (log rank test)

using Stata® SE 14.2 (StataCorp, College Station, Texas, USA).

Results

A total of 14 958 patients were included in the trauma registry between 2006 and 2015. After exclusion of individuals with an invalid personal identity number, less severe or direct fatal injuries, and individuals younger than 50 years old, 1376 severely injured patients were included in the final analysis (*Fig. 1*).

In the study cohort, 338 (24·6 per cent) were receiving beta-blockers at the time of trauma. Beta-blocker users were older and had a higher rate of somatic co-morbidity. There was no significant difference in injury severity expressed as ISS or in the proportion of patients with severe injuries to central AIS regions between beta-blocker users and non-users. The first recorded BP was similar, and patients from both groups presented with shock on arrival and were treated in the ICU to the same extent (*Table 1*).

Of all included patients, 316 (23·0 per cent) died within 30 days (*Table S1*, supporting information). Beta-blocker users had a significantly higher crude 30-day mortality rate than non-users: 32·8 *versus* 19·7 per cent respectively ($P < 0.001$) (*Fig. 2*). In univariable regression analysis, patients treated with beta-blocker had increased odds of death (OR 1·99, 95 per cent c.i. 1·51 to 2·61; $P < 0.001$) (*Table 2*). When adjusted for age, sex and injury-associated variables (restricted model), this association was no longer statistically significant. In the full model, adjusted for age, sex, education, cardiovascular co-morbidity and diabetes, the presence of anticoagulation therapy, injury severity, shock on arrival and severe head injury, there was no

Table 2 Univariable regression analysis of unadjusted associations with 30-day mortality

	Odds ratio	P
Age (years)		
50–59	1·00 (reference)	
60–69	1·44 (0·94, 2·20)	0·095
70–79	3·47 (2·30, 5·24)	< 0·001
80–89	10·93 (7·08, 16·86)	< 0·001
> 89	28·00 (14·39, 54·47)	< 0·001
Male sex	0·72 (0·50, 0·94)	0·015
Educational category		
Low	1·00 (reference)	
Medium	0·63 (0·45, 0·89)	0·008
High	0·71 (0·49, 1·03)	0·067
Ischaemic heart disease	2·54 (1·73, 3·73)	< 0·001
Congestive heart failure	5·32 (3·41, 8·30)	< 0·001
Hypertension	2·74 (2·05, 3·67)	< 0·001
Diabetes mellitus	1·48 (1·00, 2·20)	0·053
Anticoagulation therapy	2·60 (1·70, 3·98)	< 0·001
Beta-blocker therapy	1·99 (1·51, 2·61)	< 0·001
ISS category		
16–24	1·00 (reference)	
25–40	4·27 (3·18, 5·74)	< 0·001
> 40	6·23 (3·91, 9·94)	< 0·001
SAP < 90 mmHg*	4·12 (2·79, 6·08)	< 0·001
Severe head injury	2·33 (1·74, 3·10)	< 0·001

Values in parentheses are 95 per cent confidence intervals. *On arrival in the trauma unit. ISS, Injury Severity Score; SAP, systolic arterial pressure.

Table 3 Univariable unadjusted and multivariable adjusted analyses of associations between beta-blocker use before injury and 30-day mortality

	Odds ratio	P	z	Coefficient
Unadjusted	1·99 (1·51, 2·61)	< 0·001	4·92	0·687
Restricted model*	1·35 (0·96, 1·90)	0·085	1·72	0·300
Full model†	1·09 (0·70, 1·70)	0·703	0·38	0·086
Full model‡	1·09 (0·73, 1·61)	0·675	0·42	0·084

Values in parentheses are 95 per cent confidence intervals. *Adjusted for age, sex, injury severity, severe head injury and shock on arrival. †In addition to the restricted model, adjusted for education, ischaemic heart disease, congestive heart failure, hypertension, diabetes mellitus and anticoagulation therapy. ‡Full model with multiple imputations of missing data for education.

association between pretrauma beta-blockade and mortality (OR 1·09, 0·70 to 1·70; $P = 0.703$) (*Table 3* and *Fig. 3*; *Table S2*, supporting information).

When analysed separately, there was no significant association between pretrauma beta-blockade and mortality for individuals with or without severe head injury (data not shown). In addition, there were no significant interactions between beta-blocker use and head injury, or beta-blocker use and shock on arrival. Model testing showed good calibration (Hosmer–Lemeshow goodness-of-fit test) and excellent discrimination (AUC 0·856).
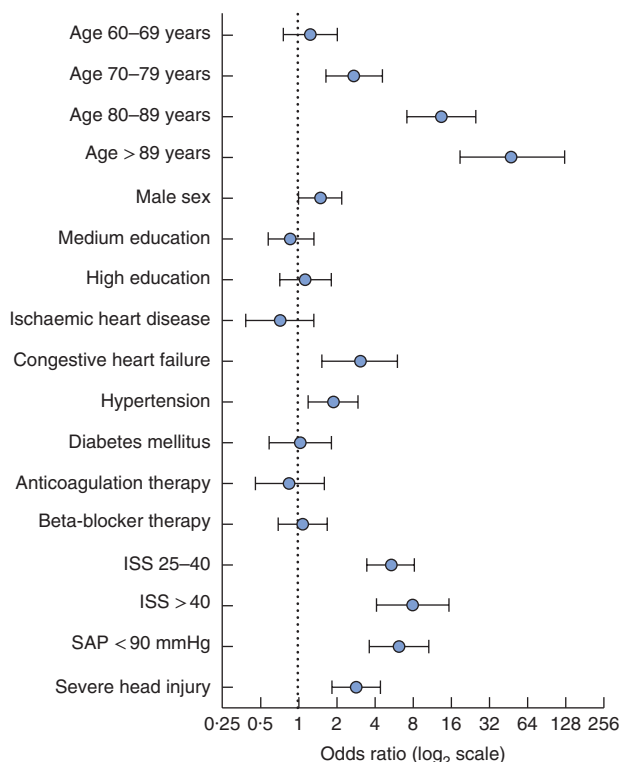
Fig. 3 Multivariable model for 30-day mortality, odds ratio and 95 per cent confidence interval. ISS, Injury Severity Score; SAP, systolic arterial pressure

Defining users of beta-blockers as those who filled at least two prescriptions, with the latest within 100 days of trauma, did not change the association between pretrauma beta-blockade and mortality (OR 1·08, 95 per cent c.i. 0·68 to 1·70; $P = 0.750$). Including only co-morbidities registered in the last year before trauma yielded similar results (OR 1·29, 0·86 to 1·95; $P = 0.217$). Finally, including individuals with minor injury (ISS 15 or less) did not change the results significantly (OR 0·91, 0·65 to 1·29; $P = 0.611$).

Discussion

In this study of severely injured patients there was no significant association between pretrauma beta-blocker therapy and 30-day mortality when adjusted for important confounders.

Several plausible mechanisms for a protective effect of beta-blockade in multiple trauma have been proposed. Beta-blockers are widely used in cardiovascular disease and reduce mortality following myocardial infarction, and in CHF. As shown in the present study, many injured patients have a history of cardiovascular co-morbidity. These high-risk patients could be protected against myocardial

injury or other cardiovascular events by beta-blockers[25,26]. Indeed, a small multicentre RCT[27] reported a lower incidence of myocardial injury with the administration of atenolol compared with placebo in injured patients.

Raised levels of catecholamines contribute to a hypermetabolic state that may be particularly harmful in TBI. Treatment with the non-selective beta-blocker propranolol has been shown to attenuate this hypermetabolism and to decrease muscle catabolism in children with severe burns[28]. However, it is unclear whether blockade of cerebral beta-adrenoreceptors and subsequent decreased cerebral metabolic rate is a protective mechanism after TBI in humans[7,29]. In addition, adrenergic stimulation may increase total body oxygen consumption and interfere with insulin and glucose homeostasis, leading to hyperglycaemia and increased lactate production. This may be associated with inflammation and negative effects on endothelial glycocalyx and microcirculation[7,30].

The haematological and immunological effects of catecholamines are extremely complex and not fully understood[7,30]. Levels of the proinflammatory cytokine interleukin 6 are decreased by post-trauma administration of beta-blockers (esmolol or metoprolol), but the clinical implication is unknown[31]. Increased levels of noradrenaline (norepinephrine) mobilize haematopoietic progenitor cells (HPCs) from the bone marrow to the peripheral blood, a potential mechanism for post-trauma anaemia. A prospective randomized trial showed a significant decrease in HPCs in peripheral blood and a non-significant increase in haemoglobin at discharge following post-trauma administration of propranolol compared with placebo[32]. Thus, beta-blockers might have a protective effect on the bone marrow in this setting.

Recently a proposed link between severe trauma and endothelial injury with subsequent coagulopathy, mediated through sympathoadrenal hyperactivation, has been presented[1]. An increase in plasma catecholamines has been associated with markers of endothelial and glycocalyx damage, as well as signs of hypocoagulability[1,8]. Animal data indicate that administration of beta-blockers might have antifibrinolytic and endothelial protective effects mediated via reduced sympathetic hyperactivity, thus suggesting a causal link[33]. It remains to be proven whether early blockade of beta-adrenergic receptors can prevent endothelial damage and trauma-induced coagulopathy in humans.

The results of the present study differ slightly from those of earlier studies on pretrauma beta-blockade in multiple trauma. In a 2008 study from the USA, Neideen and co-workers[9] found that patients receiving beta-blockers at the time of trauma had an increased mortality compared

with non-users, despite adjustment for confounders. This association, however, could be seen only among those without head injury. Two other studies[10,12] of patients with multiple trauma from the USA showed similar associations between pretrauma beta-blockade and increased mortality. In contrast, a case–control study from the USA[11] did not find any increased risk of death with preinjury beta-blockade. The apparent differences with the present study could have several explanations. The patients in the study by Neideen *et al.*[9] were older and less severely injured. The presence of co-morbidities, with beta-blockers as a potential proxy for co-morbidity, might be of greater importance for mortality in that setting. In addition, methodological differences could be of importance. In the large study by Ferraris and colleagues[10], over 40 per cent of screened patients and the majority of trauma deaths were excluded because medical and cardiovascular history could not be assessed. The use of validated registries for detection of co-morbidity could be an advantage in this context.

The present study is retrospective in design and thus definite answers regarding patient care cannot be expected. A protective, or detrimental, effect that was undetected due to a lack of power cannot be ruled out, but the results suggest that the use of beta-blockers at the time of trauma does not contribute to mortality beyond the influence of age, co-morbidity and injury severity. Moreover, beta-blocker use does not seem to contribute to shock or worsen outcome in case of shock. In the light of several recent studies[34,35] indicating harm from the cessation of beta-blockers in other acute conditions, it may be argued that the present study supports the in-hospital continuation of beta-blocker administration.

This is the first study outside the USA to investigate the association between preinjury beta-blockade and outcome after severe multiple trauma. The use of validated national registries with extensive coverage is a strength. The included co-morbidity variables are considered robust; this is further supported by sensitivity analyses yielding virtually unchanged results regardless of co-morbidity definitions. The data were also adjusted for the use of anticoagulants, a known risk factor for mortality, and efforts were made to adjust for a potential 'healthy user effect' by including education in the logistic regression[10,36]. Furthermore, there was no loss to follow-up.

There are several limitations in the present study, many due to the retrospective and register-based design. Trauma registries may not be complete and undiagnosed injuries cannot be ruled out. In addition, the patient registries do not include diagnoses from primary care. Moreover, it is not known whether patients who were prescribed beta-blockers had taken them on the day of trauma (whether they had circulating plasma levels of beta-blockers). Several studies[22,37,38] have shown very high concordance between register data on prescribed cardiovascular drugs, beta-blockers in particular, and actual usage verified by interviews. The robustness of these results, regardless of user definition, supports this. Unfortunately, information on whether beta-blockade treatment was continued in hospital was not available. The limited number of patients did not allow a separate analysis of different types of beta-blocker that might have different effects[39]. As over 90 per cent of the prescriptions were selective β1-receptor blockers (metoprolol, bisoprolol and atenolol), this might be less important.

In addition, ICD-based ISS (ICISS) may outperform ISS for risk adjustment[40]. Adding ICISS to the logistic regression analysis may have been an advantage compared with ISS. Differences in healthcare systems may reduce the generalizability and external validity of these results. In Sweden, inpatient and outpatient care is tax-funded and available to all citizens. As a comparison, 68 per cent of patients with CHF in the present study were using beta-blockers, compared with 15 per cent in the US studies[10]. The single-centre design may also reduce the external validity.

Preinjury beta-blockade was not associated with reduced mortality among patients with predominantly blunt trauma. There was no association, however, between beta-blocker use and shock. Given the negative effects of beta-blockade cessation in similar conditions, these findings may support early reinstitution of beta-blockers in previous users after trauma in the absence of haemodynamic compromise. Further prospective randomized trials will help determine a potential role for post-trauma beta-blockade.

Acknowledgements

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.