Ther Adv Gastroenterol
2017, Vol. 10(12) 919–929
DOI: 10.1177/1756283X17734116

Use of beta-blockers and risk of serious upper gastrointestinal bleeding: a population-based case-control study

Mette Reilev, Per Damkier, Lotte Rasmussen, Morten Olesen, Martin Thomsen Ernst, Rikke Mie Rishøj, Morten Rix Hansen, Anne Broe, Alexander Steenberg Dastrup, Maja Hellfritzsch, Sidsel Arnspang, Anton Pottegård and Jesper Hallas

Abstract

Background: Some studies indicate a reduced risk of serious upper gastrointestinal bleeding (UGIB) for users of beta-blockers, but the association remains to be confirmed in larger studies and characterized with respect to differences among beta-blockers. We aimed to assess whether beta-blocker use decreases the risk of UGIB.

Methods: We conducted a register-based, population-based case-control study in Denmark. We identified cases with a first validated discharge diagnosis of UGIB during the period 1995–2006. Controls were selected by risk-set sampling in a ratio of 10:1. We estimated crude and adjusted odds ratios (ORs) of the association between current beta-blocker use and the risk of UGIB by using conditional logistic regression and further stratified by selective and non-selective beta-blockers, respectively.

Results: We identified 3571 UGIB cases and 35,582 controls. Use of beta-blockers was not found to be associated with a decreased risk of UGIB (adjusted OR 1.10; 95% CI: 1.00–1.21). The association remained neutral after stratification by selective and non-selective beta-blockers, and by single beta-blocker substances. Similarly, we found no association between current beta-blocker use and the risk of UGIB within different subgroups.

Conclusions: We found no association between beta-blocker use and UGIB.

Keywords: beta-blocker use, non-variceal, pharmaco-epidemiology, population-based, upper gastrointestinal bleeding

Received: 30 March 2017; revised manuscript accepted: 7 August 2017.

Correspondence to:
Jesper Hallas
Clinical Pharmacology and Pharmacy, University of Southern Denmark, J. B. Winsløws Vej 19, 2, 5000 Odense C, Denmark
jhallas@health.sdu.dk

Mette Reilev
Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Denmark The Research Unit of General Practice, Department of Public Health, University of Southern Denmark, Denmark

Per Damkier
Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Denmark Department of Clinical Research, University of Southern Denmark, Denmark

Lotte Rasmussen
Morten Olesen
Martin Thomsen Ernst
Rikke Mie Rishøj
Morten Rix Hansen
Anne Broe
Alexander Steenberg Dastrup
Maja Hellfritzsch
Sidsel Arnspang
Anton Pottegård
Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Denmark

Introduction

Upper gastrointestinal bleeding (UGIB) is associated with a markedly increased mortality and morbidity.[1,2] Despite an improvement in medical care, UGIB is still a common gastrointestinal emergency with an incidence rate of 78 per 100,000 persons annually[1,3,4] and a case fatality of about 10 deaths per 100 patients.[5,6]

Risk of UGIB is known to be associated with use of drugs, in particular non-steroidal anti-inflammatory drugs (NSAIDs) and oral anticoagulants.[7,8] Beta-blockers have a well-documented protective effect on variceal bleeding in cirrhotic patients,[9] and several observational studies have suggested that beta-blocker use is also protective against UGIB in general.[10–15] However, these were generally small studies, resulting in imprecise results and further did not discriminate between selective and non-selective beta-blockers (see Supplementary Table 1).

It has been suggested that a gastro-protective effect of beta-blockers on UGIB might be mediated through effects on the secretion of prostaglandins and gastrin.[16–18] A decrease in the portal venous pressure may also influence the risk of UGIB, as seen in cirrhotic patients with variceal

bleeding.[19–21] However, the exact biological mechanisms behind the suggested protective effect of beta-blockers on non-variceal UGIBs remain uncertain.

As beta-blockers are widely used in the treatment of cardiovascular disease, including hypertension, heart failure, myocardial infarction and stroke, a potential protective effect on UGIBs is important to uncover.[22] In this large population-based case-control study, our aim was to evaluate the suggested protective effect of beta-blockers on UGIB and elucidate possible differences between different types of beta-blockers.

Methods

This study was a register-based, population-based case-control study. We compared the use of beta-blockers among individuals with UGIB (cases) with the use among individuals without UGIB (controls) to estimate the odds ratio (OR) for UGIB associated with beta-blocker use.

Data sources

Data were retrieved from three sources: the Danish Central Person Register (CPR), the Funen County Patient Administrative System (FPAS) and Odense Pharmaco-epidemiological Database (OPED). All three registers contain detailed longitudinal data at an individual level. The CPR covers the entire Danish population, while FPAS and OPED cover the population of Funen County (470,000 individuals). All Danish citizens are assigned a unique civil registration number, which is used in all records and enables flawless linkage between registers.[23,24]

The CPR contains information on date of birth, sex, current and historic residency, migrations to and from Denmark and date of death.[24] The data were used to extract controls and to ensure that cases and controls had permanent residence on Funen for at least 365 days prior to their index date.

FPAS holds information on hospital contact among Funen County residents, including discharge diagnoses since 1973. Diagnoses have been encoded by the International Classification of Diseases 10th edition (ICD-10) since 1994.

OPED has information on all reimbursed drug dispensation from Funen County since 1990. Each prescription record includes, among other information, the substance, the date of dispensation, the formulation of the drug and quantity dispensed for each prescription given by number, strength and defined daily dose (DDD).[25,26] Dosing instructions and indications are not recorded. All drugs are registered according to the Anatomical Therapeutical Chemical (ATC) index.[27] All beta-blockers (ATC: C07) require a prescription.

The dataset has been used and described in detail in a previous study concerning the association between SSRI use and UGIB.[28]

Cases and controls

Our source population was the residents of Funen County during a study period of 1 August 1995 to 31 July 2006. This population has been shown to be representative of the population in Denmark in general.[29] We included as cases all individuals who fulfilled the following three criteria: (1) admission to a hospital in Funen County within the study period, with peptic ulcer or gastritis as the main diagnosis; (2) mention of melena, a subnormal hemoglobin, or the need for transfusion in the discharge summary or medical record; and (3) a potential bleed source in the stomach or duodenum verified by endoscopy or surgery. Bleedings caused by gastric varices were excluded.

All discharge summaries (n = 12,607) with a main diagnosis of peptic ulcer (complicated or not) or gastritis in the study period were manually reviewed in order to include cases coded under less specific diagnoses not indicating bleeding. During the review, the study group was blinded to the exposure status of potential cases. Each case was assigned an index date defined as the first registered date of a UGIB diagnosis.

Controls were selected by risk-set sampling strategy – that is, for each case we randomly selected 10 controls among the individuals in our source population who matched the case by sex and birth year. Controls were assigned an index date identical to the index date of the corresponding case. We allowed that cases could be selected as controls before they had their case-defining event. Thereby, the calculated OR is an unbiased estimate of the incidence rate ratio that would have emerged from a cohort study, based on the same source population.[30]

We required that both cases and controls had been residents of Funen County for at least one year on the index date. We excluded cases and controls with a diagnosis of liver disease before their index date. Patients with liver cirrhosis use unselective beta-blockers as prophylaxis against variceal bleeding and have a strongly elevated risk of peptic ulcer bleeding,[31] thereby constituting a potential confounder. As this exclusion was performed after the matching and as some of the very old cases had fewer than 10 eligible controls, the final control:case ratio deviated slightly from 10:1.

Exposure

Subjects who had their latest beta-blocker prescription within the past 120 days before or at the index date were categorized as current users. In Denmark, chronic medication is usually dispensed in supplies of 100 days. We added a grace period of 20% to account for minor non-adherence or irregular prescription filling due to stockpiling, thus arriving at a window of 120 days. This assumption was validated by an analysis of the waiting-time distribution.[32] Individuals whose latest beta-blocker prescription was redeemed between 240 and 120 days before the index date were categorized as recent users; individuals whose last beta-blocker prescription was redeemed more than 240 days before the index date were categorized as past users. The reference for all analyses was never-users of beta-blockers.

In supplementary analyses, beta-blockers were subdivided into non-selective (alprenolol, oxprenolol, pindolol, propranolol, timolol, sotalol, tertatolol) and selective (metoprolol, atenolol, acebutolol, betaxolol, bisoprolol). The two combined alpha- and beta-blockers (carvedilol and labetalol) were both classified as non-selective based on the profile of their beta-blocker action.[33,34]

The daily dose of beta-blockers for a treatment episode was calculated by dividing the cumulative number of DDDs dispensed for all prescriptions (except the last) within the episode by the number of days between the first and the last prescription. We considered a chain of successive beta-blocker prescriptions to belong to the same treatment episode if the interval between them never exceeded 120 days (i.e. consistent with our exposure definition). For episodes consisting of only one beta-blocker prescription, the daily dose could not be calculated. The categorization of daily doses (0–0.49, 0.50–0.99 and ⩾1.00 DDD/day) was based on explorative analyses of prescription renewals.

Data analysis

By using conditional logistic regression, we estimated the crude and adjusted ORs with 95% confidence intervals (CIs). Confounding by age, sex and calendar time was accounted for by the matching and conditional analysis. For the adjusted ORs, the following potential confounders were included: (1) current use of the following drugs: vitamin K antagonists (VKA), aspirin, other antiplatelet drugs, NSAIDs, selective serotonin reuptake inhibitors (SSRIs), systemic corticosteroids, proton pump inhibitors (PPIs), H2 receptor antagonists, statins, nitrates, spironolactone, calcium antagonists, bisphosphonates; (2) any history of the following events: UGIB, *Helicobacter pylori* (HP) eradication, peptic ulcer, chronic obstructive pulmonary disease (COPD), diabetes, ischemic heart disease, heart failure, stroke, hypertension, inflammatory bowel disease, malignant disease, renal failure; and (3) prescription or diagnosis markers of smoking or excessive alcohol consumption. For all drugs, current drug use was defined by the filling of a prescription within fewer than 120 days before the index date.

For information on codes used to define the covariates, see Appendix.

Supplementary analyses

In order to appraise the influence of confounding by unmeasured lifestyle covariates, we performed a number of supplementary analyses. We estimated the association between use of beta-blockers (all types) and UGIB within subgroups defined by: (1) any ulcer antecedent (i.e. no history of peptic ulcer or use of anti-ulcer drugs); (2) any use of NSAIDs; (3) any use of antiplatelet drugs; (4) a history of gastrointestinal cancer; (5) any markers of alcohol abuse; and (6) different categories of Charlson score (0, 1–2 and 3 or more).[35] We performed the subgroup analysis stratified on beta-blocker class – that is, non-selective and selective beta-blockers. Finally, we

performed an analysis nested within ever-users of antihypertensives other than beta-blockers (i.e. inhibitors of the renin-angiotensin system, thiazides and related drugs or calcium channel blockers). The rationale was that if the apparent effect of beta-blockers was explained by unmeasured confounders related to the presence of hypertension, this particular analysis would show no association.

All main analyses were carried out independently in duplicate and found to reproduce results accurately.

Others

All analyses were performed using STATA 14.2 (StataCorp, College Station, TX, USA). This study was approved by the Danish Data Protection Agency. According to Danish legislation, neither approval from the ethics committee nor informed consent from the study populations is required for registry-linkage studies.[23]

Results

We identified 3571 UGIB cases and 35,582 controls. Their median age was 75 (interquartile range: 64–83) and 50.7% were male. All included comorbidities and currently used drugs were more common among UGIB cases than controls, as was the use of ulcerogenic medications (Table 1). As an example, 34.2% of cases were classified as current users of NSAIDs compared with 11.3% of controls.

Both ever and current use of beta-blockers were more prevalent among cases than controls (26.9% *versus* 18.1% and 13.6% *versus* 9.1%, respectively). The crude OR for the association between ever-use of beta-blockers and UGIB was 1.70 (95% CI: 1.57–1.85). After adjustment for confounding, use of beta-blockers was not found to be associated with risk of UGIB (adjusted OR 1.10; 95% CI: 1.00–1.21), emphasizing that the increased risk suggested in the crude analysis can be explained by the higher level of comorbidity and polypharmacy among cases. The association remained neutral after stratification by recency, daily dosage, selective and non-selective beta-blockers and the most commonly used single beta-blocker substances (Table 2).

The association between current beta-blocker use and UGIB within subgroups is illustrated in Table 3. Stratifying by age and sex revealed no association. Restricting to non-users of PPI, NSAIDs and antiplatelets, and by the absence of gastrointestinal cancers, ulcer antecedents and alcohol abuse likewise showed no association (Table 3). Similarly, we found no association among ever-users of antihypertensives other than beta-blockers. Finally, we demonstrated no association within subgroups with different severities of comorbidity assessed by the Charlson score (Table 3).

For all confounders adjusted for in the analyses, we performed a post-hoc analysis to evaluate the contribution from each of them. Ischemic heart disease was identified as having the largest contribution, as the beta-blocker–UGIB estimate adjusted for this variable alone came closest to the fully adjusted value (Supplementary Table 2).

Discussion

In this population-based case-control study, we found no decreased risk of UGIB associated with beta-blocker use, neither overall nor within specific classes or types of beta-blockers. This finding was consistent after stratification by recency and dosage, as well as within subgroups of patients with an increased risk of UGIB.

The association between beta-blocker use and the risk of gastrointestinal bleeding has previously been assessed in six observational studies (Supplementary Table 1).[10–13,15,36] In a case-control study nested among new users of antihypertensive agents, Suissa and colleagues found that use of beta-blockers decreased the risk of gastrointestinal bleeding (adjusted rate ratio (RR) 0.66 (95% CI: 0.44–0.98).[12] Though not statistically significant, the ORs from a case-control study by Lanas and colleagues[36] supported this finding. Similarly, two cohort studies suggested a protective effect of beta-blockers compared with ACE inhibitors or calcium antagonists.[11,15] A recent study by Nagata and colleagues[10] could not support an association, but the number of exposed cases was very low and confidence intervals wide. Lastly, García Rodriguez and colleagues[13] investigated the association between multiple exposures, including beta-blocker use and verified UGIB. They found an increased risk of UGIB with use of

Table 1. Characteristics of cases and controls at the index date.

	Cases (*n* = 3571)	Controls (*n* = 35,582)		
		All	Exposed (*n* = 3221)	Unexposed (*n* = 29,144)
Age				
Median (IQR)	75 (64–83)	75 (64–83)	78 (71–84)	75 (62–83)
Sex				
Men	1811 (50.7%)	18,029 (50.7%)	1502 (46.6%)	15,061 (51.7%)
Current drug use				
VKA	183 (5.1%)	823 (2.3%)	237 (7.4%)	413 (1.4%)
Low-dose aspirin	696 (19.5%)	3436 (9.7%)	779 (24.2%)	2109 (7.2%)
Other antiplatelet drugs	197 (5.5%)	782 (2.2%)	168 (5.2%)	481 (1.7%)
NSAID	1220 (34.2%)	4005 (11.3%)	453 (14.1%)	3139 (10.8%)
SSRI	429 (12.0%)	2038 (5.7%)	215 (6.7%)	1496 (5.1%)
Systemic corticosteroids	384 (10.8%)	1638 (4.6%)	150 (4.7%)	1295 (4.4%)
PPI	521 (14.6%)	2037 (5.7%)	320 (9.9%)	1395 (4.8%)
H2 receptor antagonists	294 (8.2%)	958 (2.7%)	105 (3.3%)	732 (2.5%)
Statins	237 (6.6%)	1572 (4.4%)	520 (16.1%)	695 (2.4%)
Nitrates	318 (8.9%)	1678 (4.7%)	497 (15.4%)	820 (2.8%)
Spironolactone	208 (5.8%)	599 (1.7%)	110 (3.4%)	380 (1.3%)
Calcium antagonists	588 (16.5%)	3829 (10.8%)	613 (19.0%)	2363 (8.1%)
Bisphosphonates	70 (2.0%)	439 (1.2%)	50 (1.6%)	333 (1.1%)
History of				
UGIB	95 (2.7%)	175 (0.5%)	18 (0.6%)	119 (0.4%)
HP eradication	160 (4.5%)	467 (1.3%)	51 (1.6%)	331 (1.1%)
Peptic ulcer	218 (6.1%)	535 (1.5%)	62 (1.9%)	375 (1.3%)
COPD	256 (7.2%)	1044 (2.9%)	74 (2.3%)	834 (2.9%)
Diabetes	404 (11.3%)	2167 (6.1%)	327 (10.2%)	1533 (5.3%)
Ischemic heart disease	867 (24.3%)	5272 (14.8%)	1301 (40.4%)	2822 (9.7%)
Heart failure	279 (7.8%)	1164 (3.3%)	244 (7.6%)	670 (2.3%)
Stroke	353 (9.9%)	1835 (5.2%)	250 (7.8%)	1264 (4.3%)
Hypertension	412 (11.5%)	1863 (5.2%)	532 (16.5%)	839 (2.9%)
Inflammatory bowel disease	23 (0.6%)	107 (0.3%)	9 (0.3%)	87 (0.3%)
Malignant disease	244 (6.8%)	1711 (4.8%)	213 (6.6%)	1318 (4.5%)
Renal failure	94 (2.6%)	205 (0.6%)	45 (1.4%)	108 (0.4%)
Alcohol-related markers	166 (4.6%)	336 (0.9%)	32 (1.0%)	271 (0.9%)
Tobacco-related markers	1148 (32.1%)	8364 (23.5%)	778 (24.2%)	6637 (22.8%)

COPD, chronic obstructive pulmonary disease; HP, *Helicobacter pylori*; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitors; SSRI, selective serotonin reuptake inhibitors; UGIB, upper gastrointestinal bleeding; VKA, vitamin K antagonists.

Table 2. Association between use of beta-blockers and UGIB.

	Cases (*n* = 3571)	Controls (*n* = 35,582)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Non-use	2610	29,121	1.00 (reference)	1.00 (reference)
Ever-use	958	6431	1.71 (1.57–1.85)	1.10 (1.00–1.21)
Beta-blocker class (current use)				
Selective	376	2354	1.79 (1.58–2.01)	1.12 (0.97–1.30)
Metoprolol	281	1679	1.90 (1.66–2.19)	1.15 (0.97–1.36)
Atenolol	61	465	1.37 (1.04–1.80)	1.00 (0.74–1.37)
Non-selective	111	886	1.39 (1.13–1.71)	0.85 (0.67–1.08)
Propranolol	38	338	1.24 (0.88–1.75)	1.03 (0.71–1.51)
Carvedilol	31	173	2.14 (1.43–3.21)	0.77 (0.48–1.25)
Usage				
Current	484	3218	1.70 (1.52–1.89)	1.07 (0.94–1.21)
Recent	60	388	1.76 (1.32–2.33)	1.25 (0.91–1.72)
Past	414	2825	1.66 (1.48–1.86)	1.06 (0.93–1.21)
Dosage, current use (DDD/day)				
0–0.49	140	1070	1.45 (1.20–1.74)	0.96 (0.77–1.19)
0.5–1.0	195	1361	1.60 (1.36–1.88)	0.96 (0.79–1.16)
>1.0	108	614	2.03 (1.63–2.52)	1.32 (1.03–1.69)
Unknown	41	173	2.40 (1.68–3.41)	1.48 (0.98–2.23)

ASA, acetylsalicylic acid; COPD, chronic obstructive pulmonary disease; DDD: Defined daily doses; HP, Helicobacter pylori; NSAID, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitors; SSRI, selective serotonin reuptake inhibitors; UGIB, upper gastrointestinal bleeding; VKA, vitamin K antagonists.
*Adjusted for: current use of: VKA, ASA, other antiplatelet drugs, NSAID, SSRIs, systemic corticosteroids, PPIs, H2 receptor antagonists, statins, nitrates, spironolactone, calcium antagonists, bisphosphonates; any history of: UGIB, HP eradication, peptic ulcer, COPD, diabetes, ischemic heart disease, heart failure, stroke, hypertension, inflammatory bowel disease, malignant disease, renal failure; and prescription or diagnosis markers of smoking or excessive alcohol consumption.

antihypertensive agents (RR: 1.7; 95% CI: 1.4–2.1); however, users of beta-blockers alone were found to have no increased risk of UGIB (RR: 1.0; 95% CI: 0.7–1.4) (see Appendix). All of these studies were small, including only 4–65 cases exposed to beta-blockers, and did not attempt to differentiate between selective and non-selective beta-blockers. In comparison, we included 484 exposed cases, more than twice the cumulative number from prior studies.

Our study has several important strengths. First and foremost, a manual validation of all cases was performed, thereby minimizing the risk of outcome misclassification. Even admissions that did not specify UGIB were reviewed in order to capture cases that were imprecisely coded. Due to the high quality of our case data, we were able to reproduce all the well-established risk factors for UGIB as demonstrated in Table 1. Second, our approach was truly population based as Danish health care offers full tax-funded coverage to all citizens and we had access to data on their medical history since 1994 and their drug use since 1990. It is unlikely that patients would suffer severe UGIB without this being captured in our data.

Information bias or confounding by variables not included in this study cannot be fully excluded. First, we did not have data on lifestyle factors that could potentially be confounders. Instead, we

Table 3. Association between current use of beta-blockers and UGIB within subgroups.

Subgroup	Cases exposed/ unexposed	Controls exposed/ unexposed	Crude odds ratio 95% CI	Adjusted * odds ratio 95% CI
All	484/2610	3218/29,121	1.70 (1.52–1.89)	1.07 (0.94–1.21)
Sex				
Men	226/1363	1501/15,044	1.69 (1.45–1.98)	0.97 (0.80–1.17)
Women	258/1247	1717/14,077	1.70 (1.47–1.98)	1.16 (0.97–1.38)
Age (years)				
<55	34/350	120/4053	3.23 (2.16–4.83)	1.04 (0.54–1.99)
55–75	207/962	1125/11,172	2.14 (1.81–2.52)	1.14 (0.92–1.40)
>75	243/1298	1973/13,896	1.34 (1.15–1.55)	1.00 (0.84–1.19)
Drug use				
PPI	77/361	320/1393	0.96 (0.58–1.58)	0.58 (0.28–1.20)
No PPI use	407/2249	2898/27,728	1.69 (1.50–1.90)	1.11 (0.96–1.28)
NSAID	176/884	453/3137	1.27 (0.96–1.66)	0.95 (0.68–1.33)
No NSAID use	308/1726	2765/25,984	1.76 (1.53–2.01)	1.09 (0.92–1.28)
Antiplatelet drugs	201/430	849/2,306	1.19 (0.98–1.43)	1.17 (0.93–1.47)
No use of antiplatelet drugs	443/2,546	3120/28,840	1.65 (1.47–1.84)	1.05 (0.92–1.20)
Medical history				
No GI cancer	444/2,461	3005/27,805	1.69 (1.51–1.89)	1.06 (0.92–1.21)
No ulcer antecedents	448/2465	3156/28,748	1.67 (1.49–1.87)	1.05 (0.92–1.20)
No markers of alcohol abuse	464/2483	3186/28,850	1.69 (1.51–1.89)	1.08 (0.94–1.23)
Ever use of other antihypertensives	269/698	1639/5491	1.20 (1.00–1.45)	0.99 (0.78–1.25)
Charlson comorbidity index				
0	228/1477	1975/21,778	1.76 (1.50–2.06)	1.03 (0.85–1.26)
1–2	138/748	871/5708	1.17 (0.91–1.50)	0.88 (0.64–1.22)
3 or more	118/385	372/1635	1.68 (1.06–2.65)	1.45 (0.74–2.87)

ASA, acetylsalicylic acid; COPD, chronic obstructive pulmonary disease; DDD: Defined daily doses; HP, Helicobacter pylori; NSAID, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitors; SSRI, selective serotonin reuptake inhibitors; UGIB, upper gastrointestinal bleeding; VKA, vitamin K antagonists.
*Adjusted for: current use of: VKA, ASA, other antiplatelet drugs, NSAID, SSRIs, systemic corticosteroids, PPIs, H2 receptor antagonists, statins, nitrates, spironolactone, calcium antagonists, bisphosphonates; any history of: UGIB, HP eradication, peptic ulcer, COPD, diabetes, ischemic heart disease, heart failure, stroke, hypertension, inflammatory bowel disease, malignant disease, renal failure; and prescription or diagnosis markers of smoking or excessive alcohol consumption.

used proxies for smoking and excessive alcohol use. Smoking is associated with cardiovascular disease and hence the use of beta-blockers. However, smoking is not a strong risk factor for peptic ulcer bleeding.[37,38] Excessive drinking is a risk factor for peptic ulcer bleeding.[39] There is no clinical reason to prefer beta-blockers in patients with high alcohol consumption, if they have not developed liver disease. However, if patients with high alcohol consumption use beta-blockers more often than others, this would elevate the OR and might conceal a true protective effect. To this end, we did exclude patients with liver disease as they represent a special subgroup with confounding

factors that may be difficult to account for in registry data. Second, we did not have data on use of ulcerogenic over-the-counter (OTC) drugs, such as high-dose aspirin. The prescription coverage of low-dose aspirin and NSAIDs was in the order of 85% and 70% during our study period,[40] but there is no reason to suspect more OTC drug exposure among users of beta-blockers than among others. Though of very high quality, our data are somewhat old. However, this allowed us to analyze the difference between selective and non-selective beta-blockers. The use of non-selective beta-blockers has decreased substantially in recent years,[40] and more recent data would thus contribute little to elucidating the possible effect modification by receptor selectivity. In addition, antithrombotic use has become increasingly complex and aggressive over recent years,[41] thereby leaving more room for confounding.

In conclusion, there was no association between beta-blocker use and serious UGIB in this large population-based study.

Author contributions

All authors had access to the data in the study. Jesper Hallas takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: all authors.
Acquisition and analysis of data: Jesper Hallas, Anton Pottegård, Morten Olesen and Martin Thomsen Ernst.
Interpretation of data: all authors.
Drafting of the manuscript: all authors
Critical revision of the manuscript for important intellectual content: all authors.
Statistical analysis: Jesper Hallas, Anton Pottegård, Morten Olesen and Martin Thomsen Ernst.
All authors have approved the final version of the manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflict of interest statement

Dr Reilev, Dr Rishøj, Dr Arnspang, Dr Pottegård, Dr Broe, Dr Damkier, M. Olesen, M. Ernst, Dr Dastrup, Dr Rasmussen and Dr Hansen have nothing to disclose.
Dr Hellfritzsch has received speaker honoraria from Pfeizer and Bristol-Myers Squibb, outside the submitted work.
Dr Hallas reports grants from Pfizer, grants from Takeda and grants from Merini, outside the submitted work.

Transparency declaration

Jesper Hallas affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Accessibility of protocol, raw data and programming code

Due to Danish legislation, raw data cannot be transferred. The study protocol as well as all programming codes (STATA) are available on request.

References

1. Tielleman T, Bujanda D and Cryer B. Epidemiology and risk factors for upper gastrointestinal bleeding. *Gastrointest Endosc Clin N Am* 2015; 25: 415–428.
2. Rosenstock SJ, Møller MH, Larsson H, *et al.* Improving quality of care in peptic ulcer bleeding: nationwide cohort study of 13,498 consecutive patients in the Danish Clinical Register of Emergency Surgery. *Am J Gastroenterol* 2013; 108: 1449–1457.
3. Abougergi MS, Travis AC and Saltzman JR. The in-hospital mortality rate for upper GI hemorrhage has decreased over 2 decades in the United States: a nationwide analysis. *Gastrointest Endosc* 2015; 81: 882–888.e1.
4. Longstreth GF. Epidemiology of hospitalization for acute upper gastrointestinal hemorrhage: a population-based study. *Am J Gastroenterol* 1995; 90: 206–210.
5. Button LA, Roberts SE, Evans PA, *et al.* Hospitalized incidence and case fatality for upper gastrointestinal bleeding from 1999 to 2007: a record linkage study. *Aliment Pharmacol Ther* 2011; 33: 64–76.
6. Wehbeh A, Tamim HM, Abu Daya H, *et al.* Aspirin has a protective effect against adverse outcomes in patients with nonvariceal upper gastrointestinal bleeding. *Dig Dis Sci* 2015; 60: 2077–2087.
7. Lamberts M, Olesen JB, Ruwald MH, *et al.* Bleeding after initiation of multiple antithrombotic drugs, including triple therapy,

in atrial fibrillation patients following myocardial infarction and coronary intervention: a nationwide cohort study. *Circulation* 2012; 126: 1185–1193.

8. Gutthann SP, García Rodríguez LA and Raiford DS. Individual nonsteroidal antiinflammatory drugs and other risk factors for upper gastrointestinal bleeding and perforation. *Epidemiol Camb Mass* 1997; 8: 18–24.
9. Ilyas JA and Kanwal F. Primary prophylaxis of variceal bleeding. *Gastroenterol Clin North Am* 2014; 43: 783–794.
10. Nagata N, Niikura R, Sekine K, *et al*. Risk of peptic ulcer bleeding associated with *Helicobacter pylori* infection, nonsteroidal anti-inflammatory drugs, low-dose aspirin, and antihypertensive drugs: a case-control study. *J Gastroenterol Hepatol* 2015; 30: 292–298.
11. Pahor M, Guralnik JM, Furberg CD, *et al*. Risk of gastrointestinal haemorrhage with calcium antagonists in hypertensive persons over 67 years old. *Lancet* 1996; 347: 1061–1065.
12. Suissa S, Bourgault C, Barkun A, *et al*. Antihypertensive drugs and the risk of gastrointestinal bleeding. *Am J Med* 1998; 105: 230–235.
13. García Rodríguez LA, Cattaruzzi C, Troncon MG, *et al*. Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. *Arch Intern Med* 1998; 158: 33–39.
14. He Y, Chan EW, Leung WK, *et al*. Systematic review with meta-analysis: the association between the use of calcium channel blockers and gastrointestinal bleeding. *Aliment Pharmacol Ther* 2015; 41: 1246–1255.
15. Kaplan RC, Heckbert SR, Koepsell TD, *et al*. Use of calcium channel blockers and risk of hospitalized gastrointestinal tract bleeding. *Arch Intern Med* 2000; 160: 1849–1855.
16. Brandsborg O, Brandsborg M and Christensen NJ. The role of the beta-adrenergic receptor in the secretion of gastrin: studies in normal subjects and in patients with duodenal ulcers. *Eur J Clin Invest* 1976; 6: 395–401.
17. Bhandare P, Diniz-D'Souza R, Mainker A, *et al*. Protective effect of propranolol on ethanol-induced gastric lesions in mice. *Eur J Pharmacol* 1990; 191: 167–172.
18. Rataboli PV, Bhandare PN, D'Souza RS, *et al*. Protective effect of propranolol on ethanol-induced gastric lesions in rats: probable mechanism of action. *Indian J Physiol Pharmacol* 1992; 36: 35–38.
19. Lebrec D, Nouel O, Corbic M, *et al*. Propranolol: a medical treatment for portal hypertension? *Lancet* 1980; 2: 180–182.
20. Brett BT, Hayes PC and Jalan R. Primary prophylaxis of variceal bleeding in cirrhosis. *Eur J Gastroenterol Hepatol* 2001; 13:349–358.
21. Brooks J, Warburton R and Beales ILP. Prevention of upper gastrointestinal haemorrhage: current controversies and clinical guidance. *Ther Adv Chronic Dis* 2013; 4: 206–222.
22. Wilcox CM and Clark WS. Causes and outcome of upper and lower gastrointestinal bleeding: the Grady Hospital experience. *South Med J* 1999; 92: 44–50.
23. Thygesen LC, Daasnes C, Thaulow I, *et al*. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health* 2011; 39: 12–16.
24. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011; 39(Suppl. 7): 22–25.
25. WHO Collaborating Centre for Drug Statistics Methodology (WHOCC). Definition and general considerations, www.whocc.no/ddd/definition_and_general_considera/ (2010, accessed 24 November 2016).
26. Kildemoes HW, Sørensen HT and Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011; 39: 38–41.
27. WHO Collaborating Centre for Drug Statistics Methodology (WHOCC). Structure and principles, www.whocc.no/atc/structure_and_principles/ (2011, accessed 24 November 2016).
28. Dall M, Schaffalitzky de Muckadell OB, Lassen AT, *et al*. An association between selective serotonin reuptake inhibitor use and serious upper gastrointestinal bleeding. *Clin Gastroenterol Hepatol* 2009; 7: 1314–1321.
29. Henriksen DP, Rasmussen L, Hansen MR, *et al*. Comparison of the five Danish regions regarding demographic characteristics, healthcare utilization, and medication use: a descriptive cross-sectional study. *PloS One* 2015; 10: e0140197.
30. Rothman KJ. *Epidemiology, an introduction*. 2nd ed. New York: Oxford Press, 2012.
31. Hsu Y-C, Lin J-T, Chen T-T, *et al*. Long-term risk of recurrent peptic ulcer bleeding in patients with liver cirrhosis: a 10-year nationwide cohort study. *Hepatology* 2012; 56: 698–705.

32. Pottegård A and Hallas J. Assigning exposure duration to single prescriptions by use of the waiting time distribution. *Pharmacoepidemiol Drug Saf* 2013; 22: 803–809.

33. MacCarthy EP and Bloomfield SS. Labetalol: a review of its pharmacology, pharmacokinetics, clinical uses and adverse effects. *Pharmacotherapy* 1983; 3: 193–219.

34. Sponer G, Bartsch W, Strein K, *et al.* Pharmacological profile of carvedilol as a beta-blocking agent with vasodilating and hypotensive properties. *J Cardiovasc Pharmacol* 1987; 9: 317–327.

35. Charlson ME, Pompei P, Ales KL, *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373–383.

36. Lanas A, Serrano P, Bajador E, *et al.* Risk of upper gastrointestinal bleeding associated with non-aspirin cardiovascular drugs, analgesics and nonsteroidal anti-inflammatory drugs. *Eur J Gastroenterol Hepatol* 2003; 15: 173–178.

37. Weil J, Langman MJ, Wainwright P, *et al.* Peptic ulcer bleeding: accessory risk factors and interactions with non-steroidal anti-inflammatory drugs. *Gut* 2000; 46: 27–31.

38. Stack WA, Atherton JC, Hawkey GM, *et al.* Interactions between *Helicobacter pylori* and other risk factors for peptic ulcer bleeding. *Aliment Pharmacol Ther* 2002; 16: 497–506.

39. Opatrny L, Delaney JA and Suissa S. Gastrointestinal haemorrhage risks of selective serotonin receptor antagonist therapy: a new look. *Br J Clin Pharmacol* 2008; 66: 76–81.

40. Sundhedsdatastyrelsen. The danish health data authority. *Statistics* [Statistikker], http://medstat.dk/ (2016, accessed 17 November 2016).

41. Lamberts M, Olesen JB, Ruwald MH, *et al.* Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation patients following myocardial infarction and coronary intervention: a nationwide cohort study. *Circulation* 2012; 126: 1185–1193.

Appendix

Table A1. ATC codes used to define covariates.

	ATC code
VKA	B01AA
ASA	B01AC06 (excl. B01AC30)
Other antiplatelet drugs	B01AC (excl. B01AC06)
NSAIDs	M01A (excl. M01AX)
SSRI	N06AB
Systemic corticosteroids	H02AB
PPI	A02BC
H2 receptor antagonists	A02BA
Statins	C10AA
Nitrates	C01DA
Spironolactone	C03DA01
Calcium antagonists	C08
Bisphosphonates	M05BA, M05BB

Table A2. ICD-10 codes used to define covariates.

	ICD-10 codes
Stroke	I60, I61, I62, I63, I64, I65, I66, I67, I69, G45
Hypertension	I10, I11, I12, I13, I15
Inflammatory bowel disease	K50, K51, K528C
Malignant disease	C (excl. C44, C98), D45, D46, D471, D473, D474, D475
Renal failure	E102, E112, E122, E132, E142, I12, N01, N03, N083, N085, N118C, N14, N150, N16, N18, N19, N26, P960, Q601, Q602, Z992 (excl. I129 N160 N181)
Alcohol-related diagnoses	E244, E529A, F10, G312A, G312B, G312C, G312D, G312E, G405B, G621, G721, I426, K292, K70, K860, O354, P043, T519, Z502, Z714, Z721
Tobacco-related diagnoses	J40, J41, J42, J43, J44, C34
UGIB	K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290
Peptic ulcers	K25, K26, K27, K28
COPD	J40, J41, J42, J43, J44
Diabetes	E10-14, E145D, E891A, G590, G632, G730A, G990C, H280, H360, I792A, M142, N083, O240, O241, O242, O243
Ischemic heart disease	I200, I201, I201A, I201B, I208, I208A, I209, I210, I211, I212, I212A, I212B, I212C, I212D, I212E, I212F, I212G, I212H, I213, I214, I219, I22, I220, I220A, I220B, I220C, I221, I221A, I221B, I221C, I228, I228A, I228B, I228C, I228D, I228E, I228F, I228G, I228H, I229, I23, I230, I232, I236, I236A, I236B, I238, I241, I252, Z951
Heart failure	I110, I42, I50, J819