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Non-vitamin K antagonist oral anticoagulants, proton pump inhibitors and gastrointestinal bleeds

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ABSTRACT

Objective To evaluate if proton pump inhibitor (PPI) treatment reduces the risk of upper gastrointestinal bleeding (UGIB) in patients with atrial fibrillation (AF) treated with non-vitamin K antagonist oral anticoagulants (NOACs).

Design We used a common protocol, common data model approach to conduct a cohort study including patients with AF initiated on a NOAC in Stockholm, Denmark and the Netherlands from April 2011 until July 2018. The outcome of interest was a UGIB diagnosed in a secondary care inpatient setting. We used an inverse probability weighted (IPW) Poisson regression to calculate incidence rate ratios (IRRs), contrasting PPI use to no PPI use periods.

Results In 164 290 NOAC users with AF, providing 272 570 years of follow-up and 39 938 years of PPI exposure, 806 patients suffered a UGIB. After IPW, PPI use was associated with lower UGIB rates (IRR: 0.75; 95% CI: 0.59 to 0.95). On an absolute scale, the protective effect was modest, and was found to be largest in high-risk patients, classified as age 75–84 years (number needed to treat for 1 year (NNTY): 787), age ≥85 years (NNTY: 667), HAS-BLED score ≥3 (NNTY: 378) or on concomitant antiplatelet therapy (NNTY: 373).

Conclusion Concomitant treatment with a PPI in NOAC-treated patients with AF is associated with a reduced risk of severe UGIB. This indicates that PPI cotreatment can be considered, in particular among the elderly patients, patients with a HAS-BLED score ≥3, and/or in patients on concomitant antiplatelet therapy.

INTRODUCTION

Pooled results from clinical trials showed that treatment with non-vitamin K antagonist oral anticoagulants (NOACs) significantly increased the risk of upper gastrointestinal bleeding (UGIB) compared with warfarin.[1] Proton pump inhibitors (PPIs) reduce gastric acid production and prevent ulcer recurrence.[2] In patients on aspirin treatment, which increases the risk of GIB,[3] PPIs have been shown to reduce the risk of GIB.[4] Therefore, PPI use is recommended for patients on aspirin treatment with certain comorbidities and comedications.[5] Since clinical trials show an overall increased risk of UGIB associated with NOAC treatment, it is hypothesised that cotreatment with a PPI could decrease the risk of UGIB in NOAC users as well.

An observational study from the USA showed markedly reduced risks of UGIB associated with PPI use in patients treated with NOACs.[6] In contrast, the COMPASS trial showed no protective effect with respect to GI bleeding overall, while a subanalysis on gastroduodenal bleeding showed a clearly reduced risk.[7] However, this trial was in patients with stable cardiovascular disease and peripheral artery disease receiving a lower dose of rivaroxaban than in atrial fibrillation (AF) (5 mg two times per day).

In the absence of convincing results, the guidelines state that PPI treatment *may be* considered to reduce the risk of GIB, especially in those with a history of GI bleeding or ulcer and patients requiring concomitant use of (dual) antiplatelet therapy,[8] a statement that was, however, removed in the most recent guidelines.[9] As there is currently limited evidence from randomised studies regarding the effect of PPIs on UGIB in NOAC-treated patients with AF, observational data are the main source of guidance for this clinically relevant topic. Therefore, the aim of the current study was to assess the association between PPI use and UGIBs in patients with AF treated with a NOAC in three Western European countries.

METHODS

Database

For this population-based cohort study, we used three different databases: the Swedish Healthcare Database in the Stockholm region (complete population, n=2.3 million), the nationwide Danish health registers (complete population, n=5.8 million) and the PHARMO Database (random sample from the Dutch population, n=4 million). The databases are described in detail elsewhere.[10–12] All three databases contain prescription claims data from community pharmacies, registered by Anatomical Therapeutic Chemical codes, and all three databases contain medical diagnostic data from secondary care, registered by 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes. In addition, the Stockholm database also contains medical diagnostic data from primary care, also registered by ICD-10 codes. We used a common protocol and a common data model to combine the data from the different databases.

Study population

From each database, we included all patients dispensed a NOAC with a known history of AF, defined by a registration of the ICD-10 code I48 any time prior to or within 90 days after the first NOAC dispensing, to account for diagnostic lag.[13] Patients entered the cohort at the date of their first ever NOAC prescription (cohort entry date), and we included patients from April 2011 until July 2018. We considered a patient to be on continued NOAC treatment when the patient claimed a prescription for a NOAC within 30 days after the calculated end of the previous prescription (see online supplemental figure 1). We censored patients at an outcome of interest, at the calculated end of their last prescription, when they died, moved out of the region or database, or switched to warfarin treatment. Patients could re-enter the cohort after they stopped their treatment if restarting NOAC therapy, and follow-up was defined in a similar manner after re-entering the cohort. All patients had to have at least 3 years of follow-up time prior to cohort entry, in order to adequately assess baseline characteristics.

Exposure definition

During follow-up, patients were considered to be exposed to PPIs when they claimed a PPI prescription (see online supplemental figure 1). They were considered exposed until the end of the duration of their last consecutive PPI prescription. We considered PPI treatment to be consecutive if a new prescription was claimed within the duration of the prior prescription, with another 30-day grace period added to account for irregular fill patterns and minor non-compliance. We calculated the duration of the prescription using the number of tablets dispensed, thus assuming a one tablet a day dosing regimen. To avoid bias from reverse causality (ie, that patients receive a PPI because of suspected or early symptoms of a UGIB), we used a lag time of 7 days after a first PPI prescription before we considered a patient exposed to PPI.

Outcome definition

The outcome of interest was a diagnosis code indicating a severe UGIB (see online supplemental table 1 for ICD-10 codes). We defined a severe UGIB as a registration of such a bleed in secondary inpatient care. Using this approach for the outcome, validation studies have shown a positive predictive value (PPV) of 98.1 and sensitivity of 82.3% for the Stockholm database,[14] and a PPV of 98.0 and a sensitivity of 89.5% for the Danish database.[12]

Covariate assessment

Given the non-random allocation of PPIs, potentially introducing confounding by indication, adjustment was needed. We adjusted for age, sex, year of inclusion, days from cohort entry date as well as relevant baseline comorbidities, time-varying comorbidities and time-varying comedications.

Baseline covariates included comorbidities in the HAS-BLED score (except labile international normalised ratio): hypertension, renal disease, liver disease, stroke history, prior bleeding or anaemia, and alcohol abuse; and comorbidities in the CHA_2DS_2-VASc score, not represented in the HAS-BLED score: heart failure, vascular disease and diabetes (see online supplemental table 1 for ICD-10 codes). We searched for registrations of relevant diagnosis codes in the 3 years prior to each patient's cohort entry date.

Time-varying comorbidities included: peptic ulcer, GI cancer, gastritis, oesophagitis, gastro-oesophageal reflux disease or dyspepsia, abdominal pain, lower GI problems and other GI problems (see online supplemental table 1 for ICD-10 codes). As these comorbidities might be markers for an already present UGIB, we added a 7-day lag period to the actual registration date of the diagnosis, to avoid reverse causality in the assessment of covariates. In addition, as these confounders might change over time, and affect both the risk of UGIB and the chance of PPI prescription, we partitioned follow-up time into 91-day periods, with the individual patient's initial cohort entry date as starting point. We searched for registrations of these diagnosis codes in the 3 years prior to the first day of the 91-day period. We defined the time-varying comorbidities as acute if the code was registered in the 30 days prior to the first day, as current if it was registered in the 30–90 days prior to the first day, as recent if it was registered in the 90–365 days prior to the first day, and as long-term if it was registered in the 365 days—3 years prior to the first day.

The comedications assessed were aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), clopidogrel, other antiplatelets, oral corticosteroids, diuretics, beta blockers, calcium channel blockers, renin–angiotensin–aldosterone system inhibitors, statins, oral antidiabetic drugs, insulins and antidepressants (see online supplemental table 1 for ATC codes). As comedications may change over time, we used the same 91-day periods as for the time-varying confounders. We looked for a prescription in the 180 days prior to the first day of the 91-day period.

Statistical analysis

We used descriptive statistics to present baseline characteristics for each database. To describe PPI users and non-users, we defined patients as users of a PPI if they received a PPI at some point during follow-up. This division was only done to describe the cohorts, as for all other analyses we used time-varying exposure definitions to define PPI exposed periods in order to avoid immortal time bias.[15]

Given the time-varying exposure and time-varying covariates, we used time-varying Poisson regression to calculate adjusted incidence rate ratios (IRRs) with 95% CIs for the association between PPI use and UGIB (see online supplemental file 1 for the rationale for the statistical analysis). We used time-varying inverse probability weights (IPWs) to account for confounding introduced by the included covariates. We calculated 90-day period-specific probabilities of receiving PPI treatment conditional on the aforementioned covariates using a logistic regression model. The time-varying covariates were included as categorical variables, with the timing of the diagnoses considered, as described above. For each 91-day period, the IPW was calculated by dividing the prevalence of observed PPI treatment during follow-up by the probability of receiving treatment, to obtain a stabilised IPW. All statistical analyses were performed with statistical software R V.4.0.0 and RStudio Desktop V.1.1.463. We considered a p value of <0.05 as statistically significant.

Meta-analysis

The analyses could not be conducted centrally on a pooled database due to privacy regulations but were performed locally and separately in the three databases. All study centres used the same protocol, same programming code, and same ICD-10 codes for outcomes and comorbidity codes through a common data model. For all analyses, the results from each database were pooled using a meta-analysis. We performed a Cochran's Q statistic to test for heterogeneity across the databases and used a fixed effects meta-analysis based on the results from this test.

Table 1 Summary of baseline characteristics per database

	Stockholm		Denmark		PHARMO	
	Total (N=35 031)		Total (N=110 225)		Total (N=19 034)	
	PPI user	PPI non-user	PPI user	PPI non-user	PPI user	PPI non-user
Number of patients	11 682	23 349	26 220	84 005	8806	10 228
Follow-up (person-years)	9993	45 586	21 762	169 226	8183	17 820
Age, sex, risk scores						
Female, n (%)	5771 (49.6)	10 028 (42.9)	12 323 (47.0)	36 962 (44.0)	3954 (44.9)	4146 (40.5)
Age, mean (SD)	75.31 (10.36)	74.30 (11.07)	75.83 (10.19)	74.50 (11.11)	73.26 (10.11)	70.97 (10.96)
CHA_2DS_2-VASc, median (IQR)	3 (2–5)	3 (2–5)	3 (2–5)	2 (1–4)	2 (1–4)	2 (1–4)
HAS-BLED, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	1 (1–3)	1 (1–3)	1 (1–3)
≥1 GI comorbidity, n (%)	2330 (20.0)	1951 (8.4)	2944 (11.2)	5159 (6.1)	562 (6.4)	450 (4.4)
NOAC						
Apixaban, n (%)	7154 (61.5)	15 876 (68.0)	8299 (31.7)	28 439 (33.9)	2072 (23.5)	2548 (24.9)
Dabigatran, n (%)	2526 (21.7)	3930 (16.8)	9154 (34.9)	23 957 (28.5)	3673 (41.7)	3711 (36.3)
Rivaroxaban, n (%)	1929 (16.6)	3486 (14.9)	8506 (32.4)	30 295 (36.1)	2649 (30.1)	3362 (32.9)
Edoxaban, n (%)	19 (0.2)	57 (0.2)	261 (1.0)	1314 (1.6)	412 (4.7)	607 (5.9)

Summary of the baseline characteristics of PPI users compared with PPI non-users stratified by database. The full baseline characteristics are in online supplemental table 2.
GI, gastrointestinal; NOAC, non-vitamin K antagonist oral anticoagulant; PPI, proton pump inhibitor.

Supplementary analyses

In addition to the main analyses, we performed several stratified and sensitivity analyses. These analyses are described in the eMethods in the online supplemental file 1. In short, we stratified by sex, age, bleeding risk and individual NOAC. We performed six sensitivity analyses to test the robustness of our findings when varying our analytical choices.

RESULTS

Cohort characteristics

In total, we included 164 290 NOAC users with AF in the study, of whom 46 708 (28%) used a PPI at some point during follow-up (see table 1 for a summary and online supplemental table 2 for all baseline characteristics). The mean age of the PPI users was slightly higher than for non-users, and women used PPIs more often in all three databases. In Stockholm, apixaban was the most frequently used NOAC (>60%), while in Denmark and PHARMO all NOACs, except edoxaban, were used to approximately the same extent during the study period. Both the mean HAS-BLED and CHA_2DS_2-VASc scores were higher in PPI users compared with non-users. Patients receiving PPIs more often had GI comorbidities. In total, the cohorts accumulated 272 570 person-years (pys) of NOAC use of which 39 938 pys were exposed to PPIs. PPIs were most commonly used in the PHARMO Database with 31% of all follow-up time being exposed to PPI, while this was 11% in Denmark and 18% in Stockholm. In Stockholm, omeprazole was the most frequently used PPI (72%), while in Denmark this was pantoprazole (60%), and in the PHARMO both were used approximately equally (51% pantoprazole and 41% omeprazole).

Associations between PPI use and UGIB

A total of 806 severe UGIBs occurred during 272 570 pys of follow-up yielding an overall IR of 0.30%/py. The pooled unadjusted (crude) IRR for exposed versus non-exposed person-time was 1.06 (95% CI: 0.86 to 1.30). The cohorts were however imbalanced regarding several baseline characteristics. After IPW, all covariates had a standardised mean difference below 0.1, indicating successful weighting (online supplemental figure 2A–C). Taking the time-varying IPW into account, the pooled IRR for UGIB was 0.75 (95% CI: 0.59 to 0.95), indicating a protective effect of PPIs on UGIBs (see figure 1). The adjusted IRRs were consistent in all three databases: 0.79 (95% CI: 0.49 to 1.26) in Stockholm, 0.72 (95% CI: 0.53 to 0.97) in Denmark and 0.85 (95% CI: 0.39 to 1.85) in PHARMO.

Stratified results

The incidence of UGIB increased with increasing age groups, as did the protective effect of PPIs, which was greatest in patients above the age of 75 years (75–84 IPW IRR: 0.60; 95% CI: 0.39 to 0.93, ≥85 IPW IRR: 0.64; 95% CI: 0.40 to 1.03). The numbers needed to treat for 1 year (NNTYs) in these groups were 788 and 668, respectively. Patients with a HAS-BLED score of 3 or more experienced twice as many UGIBs as patients with a score below 3 (0.52%/py vs 0.22%/py), and the protective effect of PPIs was largest in this group as well (IPW IRR 0.51; 95% CI: 0.35 to 0.77, NNTY: 378). Patients with concomitant antiplatelet use had the highest crude rate of UGIB (0.64%/py) and the protective effect of PPI treatment was significantly greater than in patients without concomitant antiplatelet use (IPW IRR: 0.64; 95% CI: 0.39 to 1.05, NNTY: 374). Stratifying by sex and concomitant NSAID use yielded no statistically different results.

The protective effect of PPIs on UGIB was only present in patients receiving apixaban or dabigatran (IPW IRR: 0.65; 95% CI: 0.43 to 0.98 and 0.65; 95% CI: 0.39 to 1.08, respectively) but not in patients receiving rivaroxaban (1.06; 95% CI: 0.73 to 1.54) (see table 2).

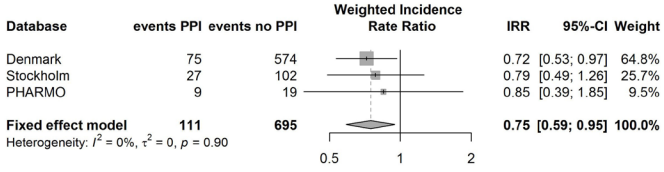

Figure 1 Results from the meta-analysis on the inverse probability weighted incidence rate ratio (IRR) of upper gastrointestinal bleeds. PPI, proton pump inhibitor.

Table 2 Crude and adjusted incidence rate ratios (IRRs) of upper gastrointestinal bleeds per subgroup

	n events	Follow-up time (person-years)	Incidence rate (%/year)	Crude IRR (95% CI)	IPW IRR (CI)	LRT significant*
Age						2 out of 3
0–64	53	43 542	0.12	2.55 (1.33 to 4.88)	1.09 (0.48 to 2.48)	
65–74	252	101 012	0.25	1.50 (1.06 to 2.11)	0.99 (0.65 to 1.49)	
75–84	294	87 954	0.33	0.71 (0.49 to 1.03)	0.58 (0.37 to 0.89)	
≥85	207	40 063	0.52	0.74 (0.49 to 1.12)	0.67 (0.42 to 1.07)	
Sex						0 out of 3
Female	457	149 597	0.31	1.02 (0.77 to 1.34)	0.66 (0.47 to 0.92)	
Male	349	122 974	0.28	1.12 (0.83 to 1.51)	0.88 (0.62 to 1.24)	
HAS-BLED						3 out of 3
Low (0–2)	472	209 553	0.23	1.14 (0.86 to 1.52)	0.95 (0.7 to 1.29)	
High (≥3)	334	63 018	0.53	0.76 (0.57 to 1.03)	0.54 (0.36 to 0.8)	
Concomitant NSAID						1 out of 3
No	691	249 520	0.28	1.01 (0.81 to 1.27)	0.74 (0.57 to 0.96)	
Yes	115	23 050	0.50	1.15 (0.72 to 1.86)	0.84 (0.46 to 1.54)	
Concomitant AP						2 out of 3
No	585	239 339	0.24	1.10 (0.87 to 1.4)	0.80 (0.61 to 1.06)	
Yes	221	33 232	0.67	0.79 (0.54 to 1.16)	0.63 (0.38 to 1.04)	
NOAC						2 out of 3
Apixaban	282	93 566	0.30	0.93 (0.67 to 1.31)	0.67 (0.45 to 1.01)	
Dabigatran	240	100 105	0.24	1.06 (0.71 to 1.58)	0.64 (0.39 to 1.07)	
Rivaroxaban	278	76 842	0.36	1.29 (0.92 to 1.80)	1.03 (0.71 to 1.50)	

Number of events, follow-up time, incidence rate, crude IRR and IPW IRR of PPI versus no PPI exposure in different subgroups.
*The number of databases in which the LRT was significant. If this test was significant in two or more databases, we considered a subgroup as a relevant effect modifier.
AP, antiplatelet; IPW, inverse probability weighted; LRT, likelihood ratio test; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

Sensitivity analysis

The results from the sensitivity analyses are presented in the eResults section in the online supplemental file 1. None of the sensitivity analyses showed different results compared with the main analysis.

DISCUSSION

In this large multicountry population-based study, covering 162 333 NOAC-treated patients with AF, we found that PPI use was associated with a 25% reduced risk of UGIB during NOAC treatment. This result was consistent in all three databases. The protective effect was most pronounced in high-risk patients, that is, patients above the age of 75 years, and patients with a HAS-BLED score of 3 or higher and/or on concomitant antiplatelet therapy. Interestingly, the protective effect of PPIs was only observed in those treated with apixaban or dabigatran and not in those treated with rivaroxaban.

Our results are in line with prior observational research and evidence from the only randomised controlled trial available.[6 7] The COMPASS trial, comparing pantoprazole with placebo in patients treated with rivaroxaban 5 mg two times per day, reported an HR of 0.93 (95% CI: 0.60 to 1.47) for all upper GI events, while for a UGIB confirmed by endoscopy or radiography, the HR was 0.25 (95% CI: 0.07 to 0.89).[7] However, these results were from patients with stable cardiovascular disease instead of patients with AF, and using a lower dose of rivaroxaban than recommended in AF (5 mg two times per day instead of 15–20 mg once daily). A recent large observational study from the USA reported an adjusted IRR of 0.66 (95% CI: 0.52 to 0.85) for UGIB in OAC-treated patients with AF using PPIs, however, this study also included patients on warfarin therapy.[6] In line with our findings, this study also reported the largest risk reduction in patients receiving apixaban and dabigatran (adjusted IRRs of 0.50 and 0.51, respectively), but contrary to our findings, they also found a protective effect in patients receiving rivaroxaban, although lower (IRR 0.68). Potential explanations could be that rivaroxaban is taken only once daily resulting in higher peak plasma concentrations or that rivaroxaban should always be taken with food, both of which could influence PPI effectiveness. However, given the wide CIs in our NOAC subgroups, we believe these differences between the NOACs could also be a play of chance.

Clinical implications

As there is currently no randomised trial assessing the efficacy of PPIs in NOAC-treated patients with AF, and our results are in line with the COMPASS trial and another large observational study,[6 7] we believe that PPI cotreatment can be considered for the prevention of UGIBs in high-risk NOAC-treated patients with AF (age above 75 years, a HAS-BLED score above 2, and/or receiving concomitant antiplatelet therapy). The NNTYs were 788 (age 75–84 years), 668 (age ≥85 years), 378 (HAS-BLED >2) and 374 (antiplatelet). Given that NOAC treatment is lifelong, more realistic NNTYs might be for a 5-year period, which would yield NNTYs of 158, 134, 76 and 75, respectively. In addition, we used a conservative endpoint by only including specific ICD-10 codes in hospitalised patients. Therefore, the absolute risk of UGIB in our study was low (approximately three times lower than in the clinical trials[1]) and with that, the absolute risk reduction could potentially be higher if the absolute risks were as high as in the clinical trials. It is also conceivable that our results are to some extent affected by residual confounding, since PPIs were primarily channelled to high-risk patients. However, this implies that the true effect is most likely larger than we could demonstrate.

Limitations

Our study has several limitations. First, despite using time-varying IPW, there is still the potential for residual confounding,

for example, due to lifestyle factors such as smoking. Second, there was potential misclassification of exposure, as we used prescription claims data, which have potentially biased the point estimate towards a neutral association.[16] In addition, in all three settings, PPIs can be bought over-the-counter. Therefore, we might have classified some patients as non-users, while in reality they were using over-the-counter PPIs. Third, we used a conservative approach to define the outcome of interest and might therefore underestimate the true number of events. On the other hand, a conservative approach leads to a higher PPV for the outcome and a lower risk of detection bias. Fourth, NOACs can also be prescribed for other indications than AF, and we have not included patients with those diagnoses. Fifth, as we lacked data on renal function, we were not able to assess the appropriateness of NOAC dosing.

Strengths

Our study has several strengths. First, we used data from three different European countries; two unselected populations and the PHARMO database which is a random sample, yielding generalisable results to similar populations, also supported by the consistent results in all databases. Second, our results were robust to all sensitivity analyses, indicating that our study results are independent of the analytical choices we made. Third, this is the first study addressing this clinically important question in a European healthcare setting, where prescribing patterns are probably different than in a US setting. In addition, there are currently no randomised trial data addressing the clinical question of the efficacy of PPI in NOAC users and thus observational research can provide guidance.

CONCLUSION

We found an association between PPI use and a lower risk of severe UGIB in an unselected NOAC-treated population with AF, which was consistent in three different Western European healthcare settings. Based on these findings, as well as the results of other studies, we believe PPIs can be useful to reduce the risk of UGIBs in NOAC-treated patients with AF with a high risk of bleeds.

Key messages

What is already known on this subject?

- Non-vitamin K antagonist oral anticoagulant (NOAC) use in patients with atrial fibrillation increases the risk of gastrointestinal bleeds.
- Treatment with proton pump inhibitors (PPIs) can reduce the risk of gastrointestinal bleeds.

What might this study add?

- In patients with atrial fibrillation from Stockholm, Denmark and the Netherlands receiving NOACs, 28% received a PPI somewhere during follow-up.
- PPI use was associated with a 25% risk reduction in hospitalisation for upper gastrointestinal bleeds.
- This protective effect was largest in patients above age 75 years, in patients with a high bleeding risk and in patients receiving concomitant antiplatelet therapy.

How might this impact on clinical practice?

- Especially in high-risk patients, PPI therapy may be considered in patients with atrial fibrillation treated with NOACs.

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Patient consent for publication Not required.

Ethics approval The study was approved by the Regional Ethical Review Board in Stockholm (EPN 2015/579-31/2). Informed consent was not required in this registry study of anonymised data.

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Contents Supplementary Material

eMethods

Stratified analyses

First, we stratified by sex, age-groups (0-64, 65 – 74, 75 – 85, >85), and bleeding risk (HAS-BLED 0-2 and ≥3). Second, we stratified by concomitant antiplatelet and concomitant NSAID use. Third, we stratified by the individual NOACs apixaban, dabigatran, and rivaroxaban (edoxaban was not considered due to the very small sample size). We included an interaction term in our models and used the likelihood ratio test to test whether the interaction terms were significant. As it is not possible to pool results from different likelihood ratio tests through a meta-analysis, we considered a subgroup as an effect-modifier if the likelihood ratio test was significant in two or more databases. In each subgroup, we calculated the number needed to treat for one year (NNTY), by taking the multiplicative inverse of the absolute risk reduction. The absolute risk reduction was estimated with the incidence rate from the untreated group and the adjusted IRR.

Sensitivity analyses

We conducted several sensitivity analyses to test the robustness of our findings. First, we calculated E-values to identify the minimum strength of association that an unmeasured confounder would need to have with both PPI use and UGIB, conditional on the measured confounders, to explain away the observed associations [1]. Second, we tested the association between PPI use and non-GI major bleeds. As PPI use should not affect the risk for those bleeds, they could serve as falsification endpoints and we could assess potential residual confounding [2]. Third, we assessed how the results would be affected by including information on primary care diagnostic data by assessing the association between PPI use and UGIB in the Stockholm healthcare database with and without restricting the analyses to only secondary care data. Fourth, we conducted an analysis in which we had a maximum follow-up of one year. Fifth, we conducted an analysis in which we kept all covariates fixed at baseline. Finally, we conducted an analysis in which we excluded all patients suffering from the outcome of interest in the year prior to inclusion to remove high risk patients and an analysis where we excluded all patients suffering from any bleed or anemia in the year prior to inclusion.

To assess for each covariate how it influenced the exposure-outcome association, and thus what the effect of confounding adjustment is per covariate, we performed an additional analysis in which we created several adjusted Poisson regression models (i.e., without taking IPW into account). In these models we first: added each aforementioned covariate univariately, but still time-dependently; second: added groups of covariates (i.e., age-sex, CHADsVASc- and HAS-BLED comorbidities, GI comorbidities, comedication), and third: performed a full time-dependent covariate adjusted Poisson regression model.

eResults

The E-value for the point estimate for UGIB was 2.01. This indicates that a potential unobserved confounder would have required a relative risk of 2.01 with both the outcome and PPI use to move the point estimate to neutral.

We found a neutral association between PPI use and the first falsification endpoint of non-GI major bleed (IRR: 1.04; CI: 0.89 – 1.23). Censoring patients after one year of follow-up yielded similar results as in the main analysis (IRR: 0.72; CI: 0.54 – 0.96), as did excluding patients with a UGIB in the year prior to inclusion (IRR: 0.76; CI: 0.60 – 0.97) and exclusion of patients with any bleed or anemia in the year prior to the event (IRR: 0.78; CI 0.60 – 1.01). Keeping the covariates fixed at baseline yielded no different results (IRR: 0.81; CI 0.64 – 1.03).

Baseline characteristics were comparable to those observed in the main analysis when analyzing only secondary care data (Appendix Table 3). We found comparable results when we used only data from secondary care in Stockholm (IRR: 0.67; CI: 0.34 – 1.20), compared to data from both primary and secondary care (IRR: 0.79; CI: 0.49 – 1.26).

The stepwise adjusted models showed that anemia had the largest univariate effect when adjusting the models, followed by vascular disease and diuretics, and all three moved the point estimate towards a protective effect (Appendix Table 4). All groups of covariates were effective in removing confounding, but no group was as effective as the fully adjusted model and the full IPW model, indicating that adjustment for all covariates was needed. The fully adjusted models showed a larger protective effect compared to the IPW model.

eReferences

1. Weele TJ Van Der, Ding P. Sensitivity analysis in observational research: Introducing the E-Value. *Ann Intern Med* American College of Physicians; 2017;**167**:268–274.

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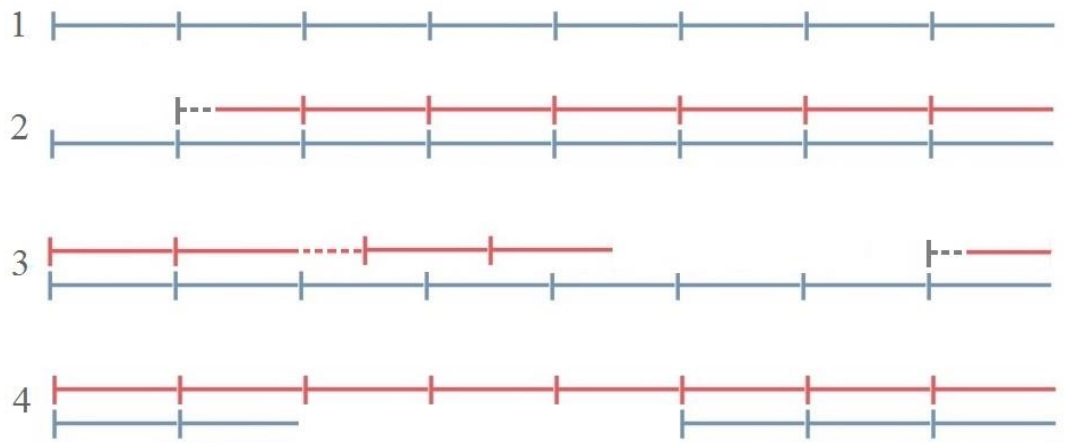
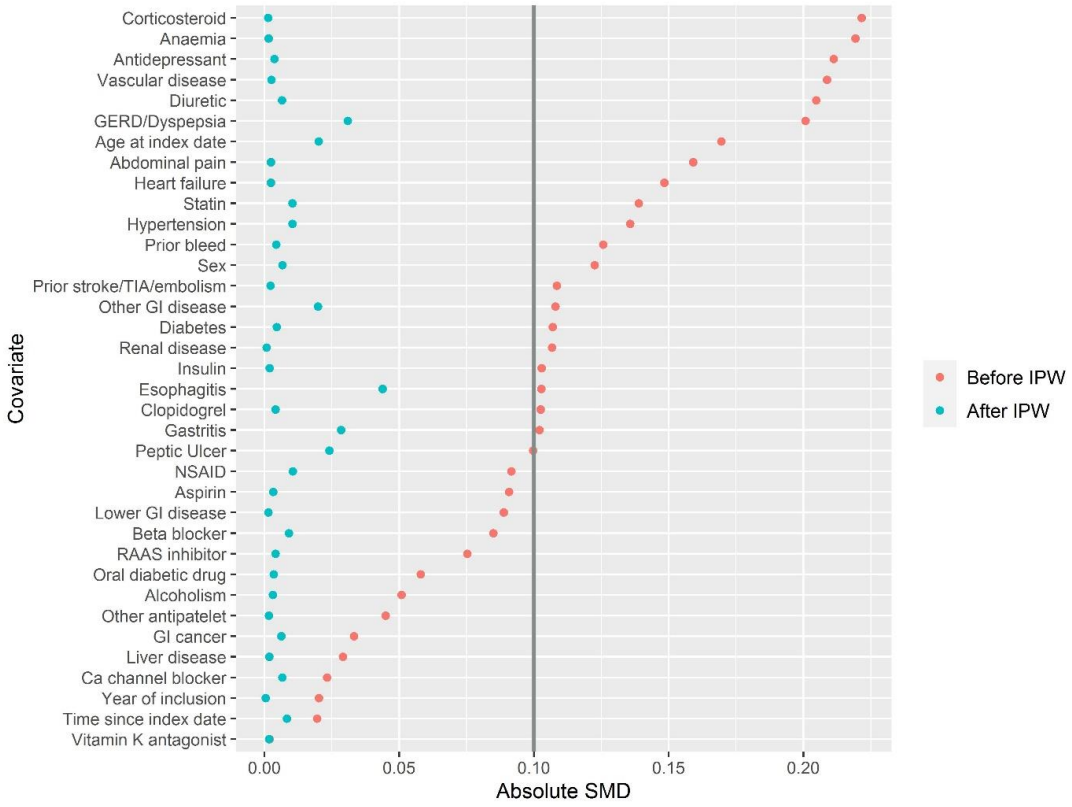
Appendix figure 1



Graphical presentation of four hypothetical patients with different exposure patterns. The vertical lines indicate that a patient claims a prescription and the horizontal lines indicate the duration of a prescription. A blue line is for a NOAC prescription and a red line is for a PPI prescription.

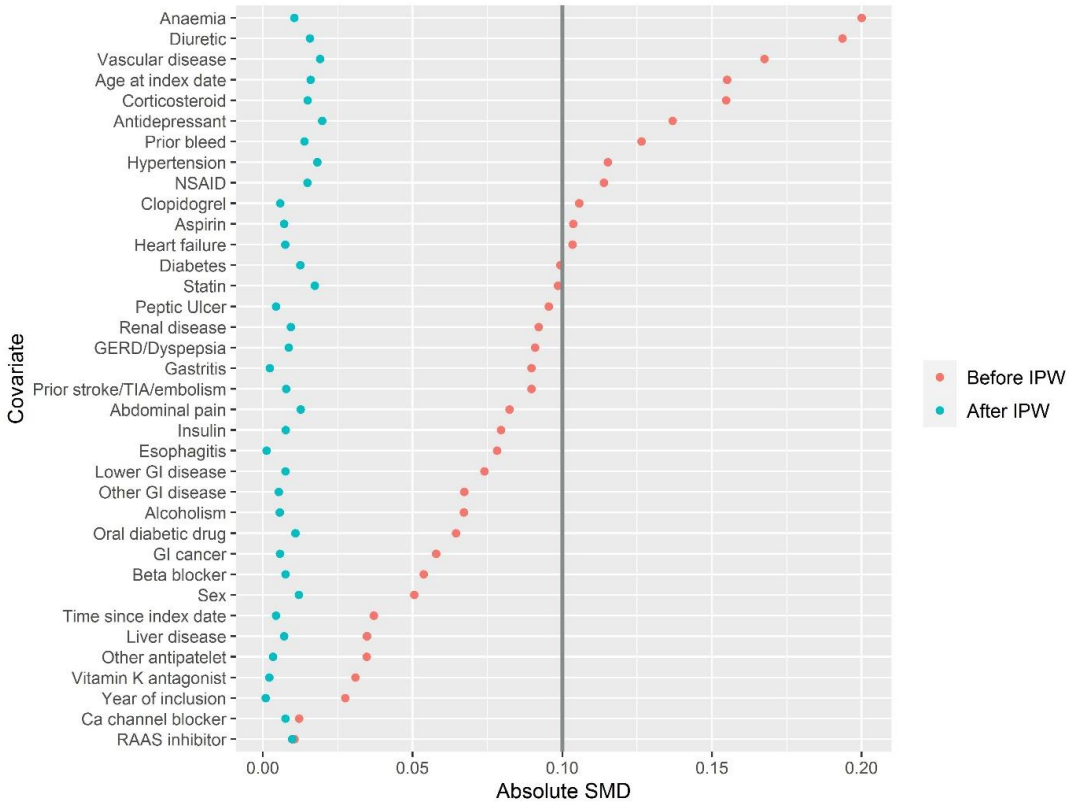
- Patient 1 is exposed to a NOAC the whole period and is therefore in the cohort the whole time, without any PPI exposure.
- Patient 2 claims a PPI prescription in the second period, and after a wash-in of 7 days (the grey area), the patient is considered exposed to a PPI the rest of the study period.
- Patient 3 is taking a PPI from the beginning of the study and is considered exposed to a PPI from the start. After the second PPI prescription, the patient claims a new PPI prescription after the calculated end of the second prescription, but within the 30-day grace period for non-compliance and, therefore, the patient is considered exposed to PPI treatment during that whole period. After the fourth PPI prescription, the patient fails to claim a new prescription within the 30-day grace period and is therefore considered unexposed from the end of the calculated end of the fourth prescription. At the end the patient claims a new PPI prescription and after a wash-in of 7 days the patient is considered exposed to PPI treatment.
- Patient 4 is taking a PPI from the beginning of the study and is considered exposed to a PPI from the start. After the second NOAC prescription, the patient fails to claim a new NOAC prescription within the 30-day grace period and, therefore, the patient is removed from the cohort during that period. After the patient claims a new NOAC prescription, the patient is once again included in the cohort.

Appendix figure 2a



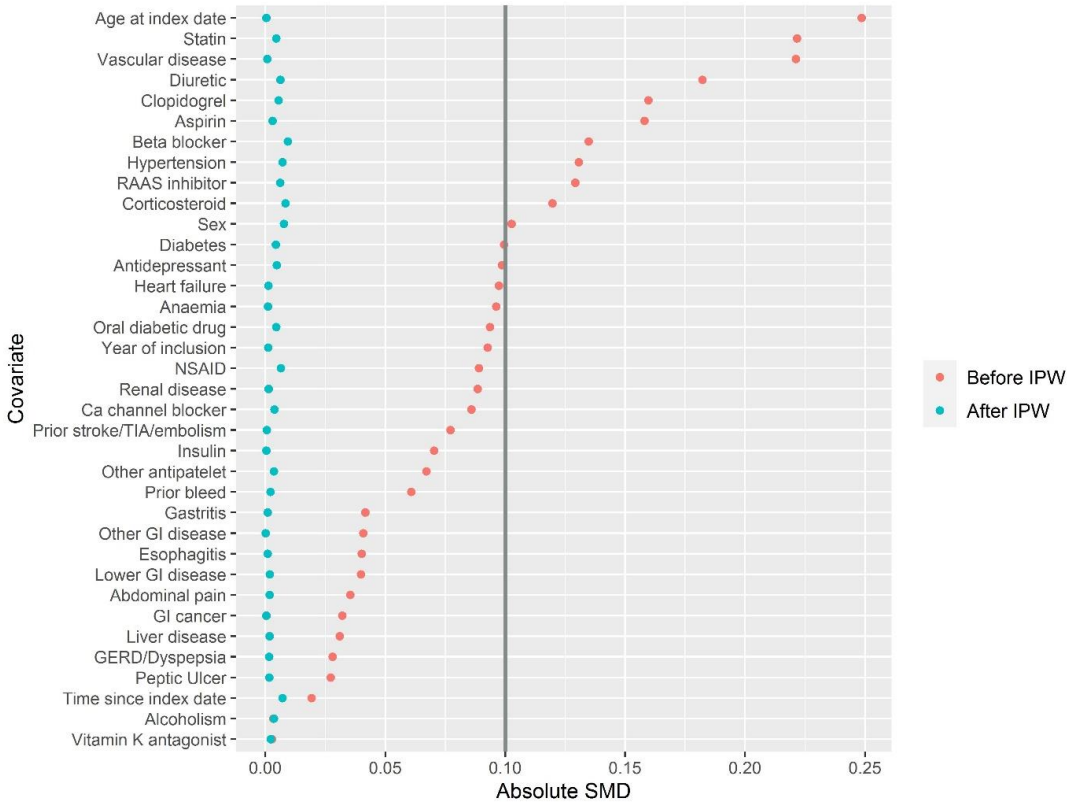
Standardized mean differences of covariates before and after applying inverse probability weighting in the Stockholm database.

Appendix table 2b



Standardized mean differences of covariates before and after applying inverse probability weighting in the Denmark database.

Appendix table 2c



Standardized mean differences of covariates before and after applying inverse probability weighting in the PHARMO database.

Appendix table 1

Outcome definition	**ICD-code beginning with**
Upper GI bleed	K25-K28 (sub codes 0, 2, 4, and 6 only) K290, K228, K298, I864
Baseline comorbidities	**ICD-code beginning with**
Hypertension	I10-I16
Renal disease	N183, N184, N185, N189, E102, E112, E122, E132, E142, I12, N03, N083, N085, N118C, N14, N150, N16, N19, N26, P960, Q601, Q602, Z992
Liver disease	K70-77
Stroke/TIA/embolism	I63, I64, I679, I693, I694, I698, I69, G453, G458, G459, I74, I26, I80, I81, I82
Prior bleed	I60, I61, I62, S064, S065, S066, I850, I983, K25-K28 (sub codes 0, 2, 4, and 6 only) K290, K228, K298, I864, K625, K922, D62, S063C, K920, G951A, I312, J942, K638B, K638C, K661, K868G, N02, R04, R31, R58
Anaemia	D50-59, D60-64
Alcohol abuse	E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, T51, Y90, Y91, Y91, Z502, Z714, E529A
Heart failure	I50, I099A, I971A, O754C, O291A, O742A, O754D, O891A, I30, Z035EA
Vascular disease	I20, I21, I22, I23, I24, I25, I70, I739
Diabetes	E10, E11, E12, E13, E14, G590, G632, H280, H360, N083, O240, O241, O242, O243
Peptic ulcer	K25-K28 (sub codes 1, 3, 5, 7, and 9 only)
GI cancer	C15-26
Gastritis	K29
Esophagitis	K20, K220, K2210, K222-229
GERD/dyspepsia	K21, K30
Abdominal pain	R10, R12
Lower GI problems	K57, K60-64
Other GI problems	K31, R11
Medication	**ATC code beginning with**
Apixaban	B01AF02
Dabigatran	B01AE07
Rivaroxaban	B01AF01
Edoxaban	B01AF03
PPI	A02BC
Aspirin	B01AC06
NSAID	M01A
Clopidogrel	B01AC04
Other antiplatelet	B01AC22, B01AC24, B01AC07
Corticosteroids	H02AA01, H02AA02, H02AA03, H02AB
Diuretic	C03A, C03B, C03C, C03D, C03E
Beta blocker	C07A, C07B, C07C, C07D, C07E, C07F
Ca channel blocker	C08C, C08D, C08E, C08G
RAAS inhibitor	C09A, C09B, C09C, C09D, C09X
Statin	C10AA
Oral antidiabetic drug	A10B
Insulin	A10A
Antidepressant	N06A
Falsification endpoint	**ICD code beginning with**
Non GI major bleed	I60, I61, I62, S064, S065, J942, I312, H431, H351

ATC and ICD-10 codes

Appendix table 2.

	Stockholm		**Denmark**		**PHARMO**	
	Total (N=34977)		**Total (N = 108322)**		**Total (N=19034)**	
	PPI user	**PPI non-user**	**PPI user**	**PPI non-user**	**PPI user**	**PPI non-user**
n	11 682	23 349	26 220	84 005	8 806	10 228
Person time (years)	9993	45586	21762	169226	8183	17820
Age, sex, risk scores						
Female	5771 (49.6%)	10028 (42.9%)	12323 (47.0%)	36962 (44.0%)	3954 (44.9%)	4146 (40.5%)
Age	75.31 (10.36)	74.30 (11.07)	75.83 (10.19)	74.50 (11.11)	73.26 (10.11)	70.97 (10.96)
CHADsVASc (mean (sd))	3.77 (1.84)	3.29 (1.78)	3.22 (1.68)	2.83 (1.66)	2.85 (1.66)	2.37 (1.63)
HAS-BLED (mean(sd))	2.55 (1.22)	2.16 (1.14)	2.19 (1.16)	1.86 (1.12)	1.89 (1.12)	1.52 (1.09)
≥1 GI comorbidity, n (%)	2330 (20.0%)	1951 (8.4%)	2944 (11.2%)	5159 (6.1%)	562 (6.4%)	450 (4.4%)
NOAC						
Apixaban	7154 (61.5%)	15876 (68.0%)	8299 (31.7%)	28439 (33.9%)	2072 (23.5%)	2548 (24.9%)
Dabigatran	2526 (21.7%)	3930 (16.8%)	9154 (34.9%)	23957 (28.5%)	3673 (41.7%)	3711 (36.3%)
Rivaroxaban	1929 (16.6%)	3486 (14.9%)	8506 (32.4%)	30295 (36.1%)	2649 (30.1%)	3362 (32.9%)
Edoxaban	19 (0.2%)	57 (0.2%)	261 (1.0%)	1314 (1.6%)	412 (4.7%)	607 (5.9%)
Main comorbidities						
Hypertension	7966 (68.5%)	14393 (61.6%)	9558 (36.5%)	25212 (30.0%)	2912 (33.1%)	2737 (26.8%)
Renal disease	906 (7.8%)	1135 (4.9%)	1142 (4.4%)	2460 (2.9%)	610 (6.9%)	522 (5.1%)
Liver disease	140 (1.2%)	189 (0.8%)	268 (1.0%)	580 (0.7%)	148 (1.7%)	124 (1.2%)
Prior stroke/TIA/embolism	2624 (22.6%)	4270 (18.3%)	5408 (20.6%)	14471 (17.2%)	1023 (11.6%)	994 (9.7%)
Alcoholism	368 (3.2%)	601 (2.6%)	677 (2.6%)	1423 (1.7%)	112 (1.3%)	127 (1.2%)
Prior bleed	1692 (14.6%)	2316 (9.9%)	3190 (12.2%)	6691 (8.0%)	410 (4.7%)	335 (3.3%)
Anaemia	1791 (15.4%)	1699 (7.3%)	2426 (9.3%)	3539 (4.2%)	720 (8.2%)	548 (5.4%)
Heart failure	3065 (26.4%)	4850 (20.8%)	4351 (16.6%)	11131 (13.3%)	1221 (13.9%)	1121 (11.0%)
Vascular disease	3031 (26.1%)	3755 (16.1%)	6228 (23.8%)	14048 (16.7%)	2188 (24.8%)	1459 (14.3%)
Diabetes	2414 (20.8%)	3895 (16.7%)	3459 (13.2%)	8566 (10.2%)	1362 (15.5%)	1237 (12.1%)
GI comorbidities						
Peptic ulcer	189 (1.6%)	42 (0.2%)	309 (1.2%)	191 (0.2%)	13 (0.1%)	3 (0.0%)
Gastrointestinal cancer	124 (1.1%)	149 (0.6%)	414 (1.6%)	765 (0.9%)	141 (1.6%)	109 (1.1%)
Gastritis	199 (1.7%)	72 (0.3%)	294 (1.1%)	265 (0.3%)	41 (0.5%)	16 (0.2%)
Esophagitis	136 (1.2%)	37 (0.2%)	227 (0.9%)	221 (0.3%)	36 (0.4%)	26 (0.3%)
GERD/dyspepsia	530 (4.6%)	188 (0.8%)	370 (1.4%)	495 (0.6%)	40 (0.5%)	16 (0.2%)
Abdominal pain	1028 (8.8%)	881 (3.8%)	857 (3.3%)	1868 (2.2%)	92 (1.0%)	77 (0.8%)
Lower GI problems	611 (5.3%)	681 (2.9%)	949 (3.6%)	2019 (2.4%)	193 (2.2%)	183 (1.8%)
Other GI problems	276 (2.4%)	184 (0.8%)	242 (0.9%)	402 (0.5%)	104 (1.2%)	81 (0.8%)
Comedication						
Aspirin	3837 (33.0%)	5892 (25.2%)	8748 (33.4%)	22930 (27.3%)	2448 (27.8%)	1680 (16.4%)
Vitamin K antagonist	1978 (17.0%)	2438 (10.4%)	6525 (24.9%)	19625 (23.4%)	2371 (26.9%)	2984 (29.2%)
Clopidogrel	560 (4.8%)	600 (2.6%)	2536 (9.7%)	6816 (8.1%)	734 (8.3%)	531 (5.2%)
Other antiplatelets	241 (2.1%)	253 (1.1%)	773 (2.9%)	1614 (1.9%)	348 (4.0%)	189 (1.8%)
NSAID	1380 (11.9%)	1737 (7.4%)	4467 (17.0%)	9975 (11.9%)	1164 (13.2%)	939 (9.2%)
Corticosteroid	1708 (14.7%)	1375 (5.9%)	3207 (12.2%)	6364 (7.6%)	1237 (14.0%)	983 (9.6%)
Diuretic	3663 (31.5%)	5492 (23.5%)	11557 (44.1%)	30465 (36.3%)	2904 (33.0%)	2624 (25.7%)
Beta blocker	7302 (62.8%)	13445 (57.6%)	12591 (48.0%)	36831 (43.8%)	5166 (58.7%)	5395 (52.7%)
Calcium channel blocker	3089 (26.6%)	5932 (25.4%)	7425 (28.3%)	21921 (26.1%)	2196 (24.9%)	2163 (21.1%)
RAAS inhibitor	5312 (45.7%)	9599 (41.1%)	12466 (47.5%)	37509 (44.7%)	4522 (51.4%)	4425 (43.3%)
Statin	4161 (35.8%)	6864 (29.4%)	10788 (41.1%)	30781 (36.6%)	4139 (47.0%)	3676 (35.9%)
Diabetic drug	1199 (10.3%)	2036 (8.7%)	3641 (13.9%)	9917 (11.8%)	1394 (15.8%)	1256 (12.3%)
Insulin	806 (6.9%)	1089 (4.7%)	1280 (4.9%)	3225 (3.8%)	481 (5.5%)	451 (4.4%)
Antidepressant	1978 (17.0%)	2438 (10.4%)	4147 (15.8%)	10768 (12.8%)	783 (8.9%)	657 (6.4%)

Full baseline characteristics per database

Appendix table 3.

	Primary + Secondary	**Secondary only**
Characteristic		
Female	15799 (45.2%)	12472 (46.6%)
Age	74.64 (10.85)	75.50 (11.05)
CHADsVASc (mean (sd))	3.45 (1.81)	3.25 (1.82)
HAS-BLED (mean(sd))	2.29 (1.18)	2.02 (1.15)
≥1 GI comorbidity	4281 (12.2%)	2302 (8.6%)
NOAC		
Apixaban	23030 (65.8%)	17335 (64.8%)
Dabigatran	6456 (18.5%)	5197 (19.4%)
Rivaroxaban	5415 (15.5%)	4156 (15.5%)
Edoxaban	76 (0.2%)	58 (0.2%)
Comorbidities		
Hypertension	22359 (63.9%)	12864 (48.1%)
Renal disease	2041 (5.8%)	1312 (4.9%)
Liver disease	329 (0.9%)	166 (0.6%)
Prior stroke/TIA/embolism	6894 (19.7%)	4776 (17.9%)
Alcoholism	969 (2.8%)	552 (2.1%)
Prior bleed	4008 (11.5%)	1921 (7.2%)
Anaemia	3490 (10.0%)	2035 (7.6%)
Heart failure	7915 (22.6%)	6100 (22.8%)
Vascular disease	6786 (19.4%)	4503 (16.8%)
Diabetes	6309 (18.0%)	3808 (14.2%)
GI comorbidities		
Peptic ulcer	231 (0.7%)	159 (0.6%)
Gastrointestinal cancer	273 (0.8%)	190 (0.7%)
Gastritis	271 (0.8%)	91 (0.3%)
Esophagitis	173 (0.5%)	84 (0.3%)
GERD/dyspepsia	718 (2.1%)	125 (0.5%)
Abdominal pain	1909 (5.5%)	212 (0.8%)
Lower GI problems	1292 (3.7%)	395 (1.5%)
Other GI problems	460 (1.3%)	130 (0.5%)
Comedication		
Aspirin	9729 (27.8%)	6783 (25.4%)
Vitamin K antagonist	4416 (12.6%)	3302 (12.3%)
Clopidogrel	1160 (3.3%)	822 (3.1%)
Other antiplatelets	494 (1.4%)	330 (1.2%)
NSAID	3117 (8.9%)	2150 (8.0%)
Corticosteroid	3083 (8.8%)	2647 (9.9%)
Diuretic	9155 (26.2%)	8157 (30.5%)
Beta blocker	20747 (59.3%)	17015 (63.6%)
Calcium channel blocker	9021 (25.8%)	6643 (24.8%)
RAAS inhibitor	14911 (42.6%)	11966 (44.7%)
Statin	11025 (31.5%)	8638 (32.3%)
Diabetic drug	3235 (9.2%)	2522 (9.4%)
Insulin	1895 (5.4%)	1655 (6.2%)
Antidepressant	4416 (12.6%)	3823 (14.3%)

Baseline characteristics of the Stockholm cohort with and without access to primary care data

Appendix table 4.

	Stockholm	Denmark	PHARMO	Pooled
Model	IRR	IRR	IRR	IRR
Main analysis (IPW)	**0,79 (0,48-1,23)**	**0,72 (0,53-0,96)**	**0,85 (0,37-1,78)**	**0,75 (0,59-0,95)**
Full covariate adjustment	**0,72 (0,45-1,13)**	**0,67 (0,52-0,86)**	**0,74 (0,30-1,66)**	**0,69 (0,56-0,85)**
Unadjusted	**1,21 (0,77-1,82)**	**1,02 (0,79-1,28)**	**1,03 (0,44-2,22)**	**1,06 (0,86-1,30)**
Age sex adjusted	**1,12 (0,72-1,82)**	**0,96 (0,74-1,27)**	**0,99 (0,42-2,23)**	**0,99 (0,81-1,29)**
Age	1,11 (0,71-1,67)	0,95 (0,74-1,20)	0,97 (0,41-2,10)	0,99 (0,81-1,21)
Sex	1,21 (0,77-1,82)	1,02 (0,79-1,29)	1,06 (0,46-2,29)	1,06 (0,87-1,30)
HASBLED CHADSVASC adjustment	**0,98 (0,62-1,49)**	**0,83 (0,64-1,05)**	**0,89 (0,38-1,94)**	**0,86 (0,70-1,06)**
Hypertension	1,17 (0,75-1,77)	0,99 (0,78-1,26)	0,99 (0,43-2,14)	1,03 (0,84-1,27)
Renal disease	1,15 (0,74-1,73)	1,02 (0,79-1,28)	1,04 (0,45-2,24)	1,05 (0,85-1,28)
Liver disease	1,21 (0,78-1,82)	1,00 (0,78-1,27)	1,04 (0,45-2,23)	1,05 (0,86-1,29)
Stroke/TIA/Embolism	1,15 (0,74-1,73)	1,00 (0,78-1,27)	1,03 (0,44-2,21)	1,03 (0,84-1,27)
Alcoholism	1,18 (0,76-1,78)	0,99 (0,77-1,25)	1,03 (0,44-2,22)	1,03 (0,84-1,26)
Prior bleed	1,14 (0,73-1,71)	1,00 (0,78-1,26)	0,99 (0,43-2,14)	1,03 (0,84-1,26)
Anaemia	1,02 (0,65-1,55)	0,91 (0,71-1,16)	0,89 (0,38-1,94)	0,94 (0,76-1,15)
Heart failure	1,11 (0,71-1,68)	0,98 (0,77-1,24)	1,00 (0,43-2,15)	1,01 (0,83-1,24)
Vascular disease	1,11 (0,71-1,67)	0,97 (0,75-1,22)	0,91 (0,39-1,98)	0,99 (0,81-1,22)
Diabetes	1,19 (0,76-1,79)	0,99 (0,77-1,25)	0,98 (0,42-2,11)	1,03 (0,84-1,27)
GI covariate adjustment	**1,08 (0,68-1,65)**	**0,94 (0,73-1,19)**	**0,94 (0,40-2,05)**	**0,97 (0,78-1,19)**
Peptic ulcer	1,14 (0,73-1,73)	0,98 (0,76-1,24)	1,03 (0,44-2,22)	1,02 (0,83-1,25)
GI cancer	1,21 (0,77-1,82)	1,00 (0,78-1,27)	1,04 (0,45-2,23)	1,05 (0,86-1,29)
Gastritis	1,19 (0,76-1,79)	1,01 (0,79-1,28)	0,99 (0,42-2,14)	1,05 (0,86-1,29)
Esophagitis	1,11 (0,71-1,69)	0,99 (0,77-1,25)	0,99 (0,42-2,14)	1,02 (0,83-1,25)
GERD/Dyspepsia	1,18 (0,76-1,79)	1,02 (0,79-1,28)	1,00 (0,43-2,15)	1,05 (0,86-1,29)
Abdominal pain	1,24 (0,79-1,86)	1,00 (0,78-1,26)	1,04 (0,45-2,23)	1,05 (0,86-1,29)
Lower GI disease	1,18 (0,76-1,78)	1,01 (0,79-1,27)	1,03 (0,44-2,21)	1,05 (0,85-1,28)
Other GI disease	1,22 (0,78-1,83)	1,00 (0,78-1,27)	1,04 (0,45-2,23)	1,05 (0,86-1,29)
Full drug adjustment	**0,98 (0,62-1,49)**	**0,83 (0,64-1,05)**	**0,89 (0,38-1,94)**	**0,86 (0,70-1,06)**
Aspirin	1,15 (0,74-1,74)	0,96 (0,75-1,21)	1,00 (0,43-2,17)	1,00 (0,82-1,23)
NSAID	1,20 (0,77-1,81)	0,99 (0,77-1,25)	1,01 (0,43-2,16)	1,03 (0,84-1,27)
Clopidogrel	1,18 (0,75-1,78)	0,98 (0,77-1,24)	1,08 (0,47-2,33)	1,03 (0,84-1,26)
Other antiplatelets	1,21 (0,78-1,83)	1,00 (0,78-1,27)	1,04 (0,45-2,24)	1,05 (0,86-1,29)
Corticosteroids	1,23 (0,79-1,86)	0,97 (0,76-1,23)	1,03 (0,44-2,22)	1,03 (0,84-1,26)
Diuretics	1,10 (0,70-1,65)	0,94 (0,73-1,18)	0,93 (0,40-2,01)	0,97 (0,79-1,19)
Beta blocker	1,21 (0,78-1,83)	1,02 (0,80-1,29)	1,05 (0,45-2,26)	1,06 (0,87-1,30)
Ca channel blocker	1,20 (0,77-1,81)	1,02 (0,79-1,28)	1,00 (0,43-2,16)	1,05 (0,86-1,29)
RAAS inhibitor	1,19 (0,76-1,79)	0,98 (0,76-1,24)	0,99 (0,42-2,13)	1,03 (0,84-1,26)
Statin	1,19 (0,76-1,79)	1,02 (0,80-1,29)	1,03 (0,44-2,23)	1,06 (0,86-1,30)
Oral diabetic drug	1,21 (0,77-1,82)	1,01 (0,79-1,27)	0,96 (0,41-2,07)	1,05 (0,85-1,28)
Insulin	1,13 (0,73-1,71)	1,01 (0,78-1,27)	1,02 (0,44-2,20)	1,04 (0,84-1,27)
Antidepressant	1,13 (0,72-1,70)	1,00 (0,78-1,26)	0,99 (0,43-2,15)	1,02 (0,84-1,26)
Vitamin K antagonist	1,21 (0,77-1,82)	1,01 (0,79-1,27)	1,03 (0,44-2,22)	1,05 (0,86-1,29)

Effect of adjustment on association per covariate or set of covariates. First three columns are for the databases separately, and the final column is for the pooled analysis.