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Original research

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

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Background

- 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.
- To date, there is limited evidence from randomized studies regarding the effect of PPIs on UGIB in NOAC-treated patients with AF.
- 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, a statement that was, however, removed in the most recent guidelines.

AIM of the study

- To assess the association between PPI use and UGIBs in patients with AF treated with a NOAC in three Western European countries.

Methods

- Population-based cohort study
- Data from three different databases: the Swedish Healthcare Database in the Stockholm region (complete population, n=2.3million), the nationwide Danish health registers (complete population, n=5.8million) and the PHARMO Database (random sample from the Dutch population, n=4million).
- The primary outcome was a UGIB diagnosed in a secondary care inpatient setting.

Results (I)

- 164 290 NOAC users with AF were included in the study, of whom 46 708 (28%) used a PPI at some point during follow-up.
- The mean age of the PPI users was slightly higher than for non-users, and women used PPIs more often in all three databases.
- Both the mean HAS-BLED and CHA2DS2-VASc scores were higher in PPI users compared with non-users.
- Patients receiving PPIs more often had GI comorbidities.

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.

Results (II)

- 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).
- 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.

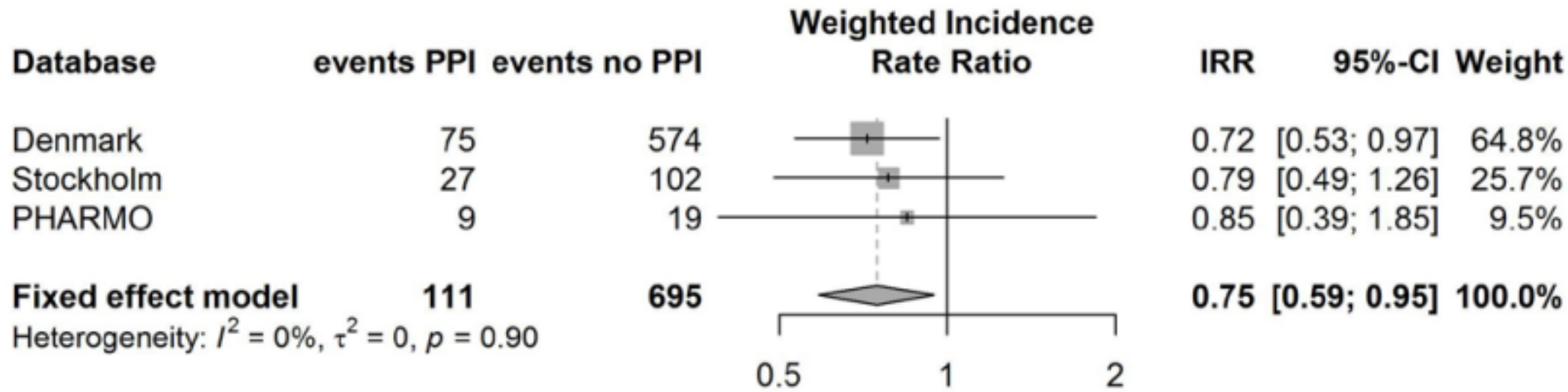

Figure 1 Results from the meta-analysis on the inverse probability weighted incidence rate ratio (IRR) of upper gastrointestinal bleeds. PPI, proton pump inhibitor.

Results (III)

- The incidence of UGIB increased with increasing age groups, as did the protective effect of PPIs, which was greatest in patients aged 75-84 years (number needed to treat for 1 year (NNTY): 787), aged ≥85 years (NNTY: 667), with a HAS-BLED score ≥3 (NNTY: 378) or on concomitant antiplatelet therapy (NNTY: 373).
- The protective effect of PPIs on UGIB was only present in patients receiving apixaban or dabigatran but not in patients receiving rivaroxaban.

Conclusions

- In this large european population-based study, PPI use was associated with a 25% reduced risk of UGIB during NOAC treatment.
- The protective effect was most pronounced in high-risk patients, that is, patients above the age of 75 years, and patients with a HASBLED score of 3 or higher and/or on concomitant antiplatelet therapy.
- These findings suggest that PPI co-treatment can be considered for the prevention of UGIBs in high-risk NOAC-treated patients with AF.