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Original article

Proton pump inhibitors and the risk of cardiovascular events and cardiovascular mortality: A systematic review and meta-analysis of observational studies

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ABSTRACT

Background and Aims: Observational research has indicated that proton pump inhibitors (PPIs) might increase the long-term risk of cardiovascular events. This study evaluated the evidence from observational studies for an effect of PPI monotherapy on the risk of incident cardiovascular events and cardiovascular mortality.
Methods: The databases MEDLINE, EMBASE, and Scopus were systematically searched up to September 2021. The primary outcome was first cardiovascular event, i.e. first myocardial infarction or first ischaemic stroke. The secondary outcome was cardiovascular mortality. Studies were included following a detailed risk of bias assessment with the ROBINS-I tool. Sensitivity and bias analyses adjusted for potential publication bias, immortal time bias, and unmeasured confounding.
Results: We included ten studies with 75,371 first cardiovascular events, as well as seven studies on cardiovascular mortality with 50,329 cardiovascular deaths in total. The pooled hazard ratios (HRs) for PPI use and cardiovascular events were 1.05 with a 95% confidence interval of (0.96; 1.15) before and 0.99 (0.93; 1.04) after adjusting for observational study design bias. The pooled HRs for PPI use and cardiovascular mortality were 1.27 (1.11; 1.44) before and 1.06 (0.96; 1.16) after adjusting for publication bias and observational study design bias.
Conclusion: It is questionable, whether PPI monotherapy constitutes a cardiovascular risk factor.

1. Introduction

1.1. Rationale

Proton pump inhibitors (PPIs) are widely used to treat disorders characterized by excessive gastric acid production [1] and have been sold over-the-counter for more than one decade. Alongside, PPIs are used for gastroprotection in patients on dual antiplatelet therapy consisting of asprin in combination with a $P2Y_{12}$ inhibitor such as clopidogrel, prasugrel or ticagrelor to prevent secondary myocardial infarctions and ischaemic strokes. Two different questions, therefore, arise regarding a potentially increased cardiovascular risk associated with PPI intake. The effect of PPI intake on secondary events as part of dual antiplatelet therapy is a question of short-term effects in a high-risk population and is examined most appropriately by clinical trials [2,3]. The effect of PPI intake as a treatment of gastroesophageal diseases on primary events is a question of long-term effects in a low-risk population requiring both a large study population and long study period and thus

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best addressed by an observational study design.

Unfortunately, observational studies examining the effect of PPI intake on cardiovascular outcomes are especially prone to bias as PPI intake might be associated with cardiovascular morbidity. Associations between PPI intake and cardiovascular outcomes could therefore indicate a causal effect of PPI intake or stem from residual confounding. Since the most recent meta-analyses [4–7] found a higher risk of cardiovascular outcomes associated with PPI therapy, several large observational studies have been published that analysed this association in more detail.

It is therefore time to have an updated look at the evidence regarding the relationship between PPI therapy and incident cardiovascular outcomes and to apply a rigorous risk of bias assessment of the included studies [8].

1.2. Objectives

We performed a systematic review and meta-analysis to evaluate the effect of PPI therapy on the risk of first acute cardiovascular events, i.e. first myocardial infarction or first ischaemic stroke. In addition, we examined the effect on cardiovascular mortality.

2. Methods

2.1. Eligibility criteria

2.1.1. Population

We included observational studies in populations free of prevalent cardiovascular disease at inclusion for the analysis of first myocardial infarction. Likewise, populations free of prevalent cerebrovascular disease at inclusion were considered for the analysis of first stroke. For the analysis of cardiovascular mortality, we included study populations with and without prior cardiovascular events.

2.1.2. Intervention

The intervention under investigation was intake of PPIs (ATC Code A02BC). We included studies addressing an as-started [9] effect as well as studies addressing an on-treatment [9] effect. The as-started effect (also known as intention-to-treat analysis) is the effect of the initial treatment, regardless of treatment continuation. It assumes an irreversible long-term effect of a point treatment. The on-treatment effect (similar to a per-protocol analysis) is the effect of continuous treatment and assumes a reversible effect of treatment. More generally, under a reversible effect model time under risk is attributed to the current exposure, whereas in an irreversible effect model all time under risk after a point treatment is attributed to this baseline exposure.

2.1.3. Comparators

We included effect estimates comparing PPI intake versus H2RA (histamine-2 receptor antagonist; ATC Code A02BA) intake as an active comparator [10] as well as estimates comparing PPI intake versus no intake.

2.1.4. Outcomes

The primary outcomes were first myocardial infarction and first ischaemic stroke. The secondary outcomes were the combined outcome of incident cardiovascular events (i.e. the combination of first myocardial infarction or first ischaemic stroke) and cardiovascular mortality.

2.1.5. Information sources, search strategy and study selection

We searched for peer-reviewed studies in English language in the PubMed / MEDLINE, EMBASE, and Scopus electronic databases from their respective inception dates until 16 September 2021. The search strings used for each of the databases can be found in Supplementary Table S1.

Two authors (MN, IR) independently screened all titles and abstracts after initial removal of duplicates. Original research articles reporting treatment effect estimates and meeting our eligibility criteria were included. Single-case studies, cross-sectional studies, case-control studies without density sampling and randomized controlled trials were disregarded. Then, two authors (MN, IR) independently performed full-text reviews to decide on the inclusion of studies for the detailed risk of bias assessment. Studies were excluded if they had an unsuitable study design, inept selection of treatment controls or used a qualitative study design. All discrepancies were resolved by consensus.

2.2. Risk of bias assessment and data extraction

The risk of methodological bias was assessed by two review authors (MN, IR) independently, using the "Risk Of Bias In Non-randomised Studies - of Interventions" (ROBINS-I) [8] tool. This tool draws on the concept of considering each study as an emulated target trial [11]. In this context, risk of bias is separately judged in seven domains using signalling questions and the ratings within each domain are carried forward to an overall risk of bias judgement. Disagreements were resolved by discussion. Details about the reasons that lead to attributing overall serious risk of bias to individual studies are given in Supplementary Table S2.

We performed double data extraction for details on the study design and on the statistical analysis. Where data were missing or unclear, we contacted the corresponding author. The authors of one article [12] provided additional information upon request. For one study [13] we had to estimate the number of events. Where studies reported multiple effect estimates, we used data from the analysis with the lowest risk of bias and the longest follow up time. We used adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) to present and synthesize the results.

2.3. Statistical analysis

We used the Hartung-Knapp-Sidik-Jonkman random-effects meta-analysis approach with inverse-variance weighting which showed to produce adequate standard errors even when the number of studies is small [14,15] to estimate the between-study variance (τ^2) and combine study-specific log HRs. We estimated pooled HRs, with corresponding 95% CIs and 95% prediction intervals (PIs) [16]. The 95% CI from a random-effects model contains highly probable values for the pooled HR. The 95% PI estimates where the true HR is to be expected in 95% of future studies under similar conditions factoring in the variability of the effect over different settings [17]. We reported the percentage of total variation due to heterogeneity (I^2). Cochran's Q statistic was used to test for between-study heterogeneity.

Subgroup analyses examined the effects of geographic region (Asia, Europe, United States), follow up time (up to or more than 5 years), study size (up to or more than 2,000 events), proportion of prevalent cardiovascular disease at study inclusion (up to or more than 20%), use of an active comparator / new user design (yes, no) and risk of bias (moderate, serious). All statistical tests were two-sided. The statistical software R (version 4.1.2, Foundation for Statistical Computing, Vienna, Austria; packages meta, metafor, metamisc [18], and metasens [19]) was used.

2.4. Sensitivity and bias analyses

Random-effects meta-analysis of observational studies can produce biased estimates of pooled effect sizes if the synthesized individual studies are subject to unmeasured confounding or selection bias [20]. Thus, in order to detect outliers and influential studies we analysed Baujat plots [21,22]. We then examined possible effects due to inclusion of small studies, selective publication of positive findings, and sensitivity to unobserved confounding and selection bias. Publication bias and small study effects (funnel plot asymmetry) were examined using the

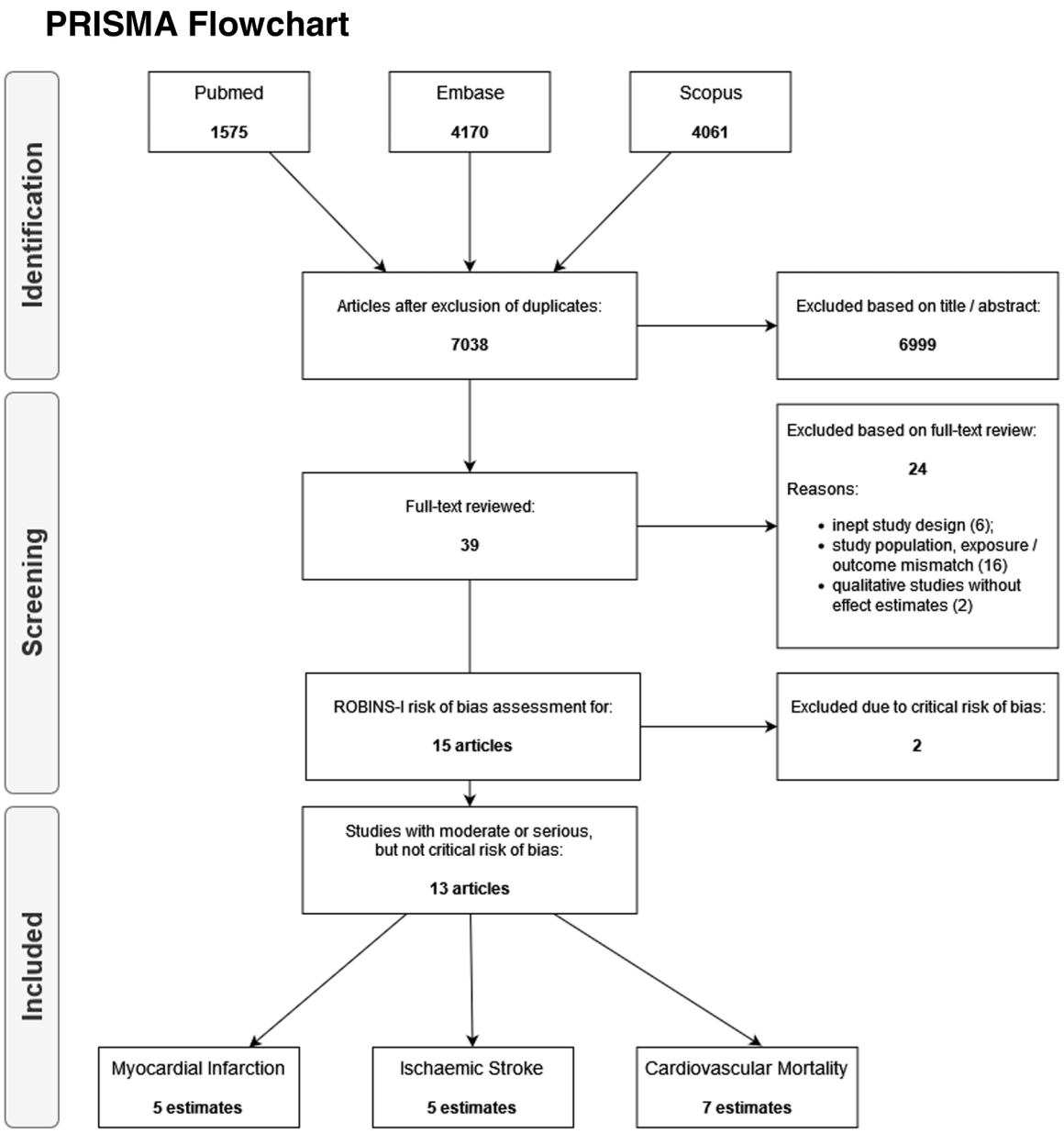

Fig. 1. PRISMA Flowchart Flowchart of the inclusion of studies in the review. Four studies each yielded two separate effect estimates.

regression-based tests proposed by Debray et al. [18]. If the tests indicated bias, we applied the trim-and-fill method [19], the Copas selection model [19] and adjusted for small study bias using the Rücker regression-based shrinkage estimator [19].

In addition, we quantified bias introduced by analytical and clinical study design choices using meta-regression. Due to the small number of studies we calculated the p-value for the meta-regression model using a permutation test [23]. Following a two-stage approach [24], we further adjusted each study individually for bias introduced by publication bias and study design choices. Finally, random-effects meta-analysis of these bias-adjusted HRs was performed to estimate a pooled bias-adjusted HR.

3. Results

3.1. Systematic review and qualitative analysis

After removal of duplicate publications our literature search identified a total of 7,038 publications (Fig. 1). Examination of titles and abstracts and a full-text review of 39 studies left us with 17 studies for a detailed risk of bias assessment [8]. Only studies with moderate or serious risk of bias were included in the analyses. Studies with critical risk of bias were excluded (Supplementary Table S3). Two studies [25,26] estimated the effect on myocardial infarction and ischaemic stroke separately in their study populations. Rooney et al. [27] estimated the effect on ischaemic stroke and cardiovascular mortality in one study population, while Landi et al. [28] estimated the effect on myocardial infarction in two separate study populations. Thus, in total, five estimates regarding myocardial infarction [25,26,28,29] and five estimates regarding ischaemic stroke [25–27,30,31] were combined for the analysis of acute cardiovascular events (24,547 cases of first ischaemic stroke and 50,824 cases of first myocardial infarction). In the analysis of cardiovascular mortality, the estimates of seven studies with 50,329 cardiovascular deaths were included [12,13,27,32–35].

Studies differed in size (58–28,207 events), study design (comparator H2RA or non-user; new use or prevalent use), duration of follow-up (maximum follow-up between 4 and 231 months), study population characteristics (age and sex structure, prevalence of comorbidities), and statistical analysis (reversible/irreversible effect model, adjusted

Table 1
Characteristics of included studies (ordered by outcome, year).

Author, year	Data Source	Continent, Country	Outcome, No. cases	Comparator	Max follow-up	HR (95% CI)	Robins-I	Effect model	Statistical Model	New user design
Nolde, 2021 (MI)	Claims Data	Europe, Germany	MI, 4,606	H2RA	120 months	0.96 (0.80-1.16)	Moderate	Irreversible	Weighted Cox	Yes
Landi, 2018 (a)	Claims Data (Truven Marketscan Commercial)	North America, US	MI, 21,670	H2RA	36 months	0.94 (0.88-0.99)	Moderate	Irreversible	Weighted Cox	Yes
Landi, 2018 (b)	Claims Data (Truven Marketscan Medicare)	North America, US	MI, 23,556	H2RA	36 months	0.96 (0.92-1.01)	Moderate	Irreversible	Weighted Cox	Yes
Sehested, 2018 (MI)	Linked registers	Europe, Denmark	MI, 863	Non-user	12 months	1.12 (0.95-1.27)	Serious	Irreversible	Multi-variable Cox	No
Shih, 2014	Claims Data	Asia, Taiwan	MI, 129	Non-user	4 months	1.58 (1.11-2.25)	Serious	Irreversible	Matched Cox	Yes
Nolde, 2021 (IS)	Claims Data	Europe, Germany	IS, 18,393	H2RA	120 months	0.98 (0.89-1.08)	Moderate	Irreversible	Weighted Cox	Yes
Rooney, 2020 (IS)	Cohort Study	North America, US	IS, 122	Non-user	84 months	0.92 (0.60-1.44)	Serious	Irreversible	Multi-variable Cox	No
Nguyen, 2018	Cohort Studies (Nurses' Health Study & Health Professionals Follow-up Study)	North America, US	IS, 2,599	Non-user	144 months	1.08 (0.91-1.27)	Serious	Reversible	Time-varying Cox	No
Sehested, 2018 (IS)	Linked registers	Europe, Denmark	IS, 1,198	Non-user	12 months	1.20 (1.06-1.36)	Serious	Irreversible	Multi-variable Cox	No
Wang, 2017	EHR	Asia, Taiwan	IS, 2,235	H2RA	143 months	1.11 (1.02-1.21)	Moderate	Irreversible	Matched Cox	Yes (30 days washout)
Brown, 2021	EHR (General Practice Research Database)	Europe, UK	CVM, 28,207	H2RA	231 months	1.14 (1.07-1.22)	Moderate	Irreversible	Weighted Cox	Yes
He, 2021	EHR (UK Biobank)	Europe, UK	CVM, 352	H2RA (regular use)	121 months	1.26 (0.89-1.79)	Moderate	Irreversible	Multi-variable Cox	No
Rooney, 2020 (CVM)	Cohort Study	North America, US	CVM, 121	Non-user	84 months	1.36 (0.87-2.12)	Serious	Irreversible	Multi-variable Cox	No
Xie, 2019	EHR (US Department of Veterans Affairs)	North America, US	CVM, 18,148	H2RA	120 months	1.25 (1.10-1.44)	Moderate	Irreversible	Weighted Cox	Yes
Adelborg, 2018	Linked registers	Europe, Denmark	CVM, 3,220*	H2RA	60 months	1.23 (1.08-1.41)	Serious	Irreversible	Matched Cox	Yes
De Francisco, 2018	EHR (European Clinical Database)	Europe, Spain	CVM, 223	Non-user	30 months	1.67 (1.03-2.71)	Serious	Irreversible	Matched Cox	No
Shah, 2015	Cohort Study	North America, US	CVM, 58	Non-user	96 months	2.00 (1.07-3.78)	Serious	Irreversible	Multi-variable Cox	No

HR: hazard ratio; MI: myocardial infarction; IS: ischaemic stroke; CVM: cardiovascular mortality;
EHR: Electronic health records; H2RA: H2 receptor antagonists
Weighted Cox: Cox regression model using balancing weights to adjust for baseline confounding
* estimated

Table 2
Additional characteristics of included studies (ordered by outcome, year).

Author, year	Study Population	PREV CVD	Adjusted Covariates	Remarks	The seven domains of the ROBINS-I						
					CF	SEL	INT	DEV	MISS	OUT	REP
Nolde, 2021 (MI)	Age $\geq$ 18	No	Age, Sex, COME, COMO, TI, ASP, CLO		o	+	+	+	+	+	+
Landi, 2018 (a)	Working population; age 18–65	1.4 % stroke	Age, Sex, COME, COMO, TI, CLO, health care utilization	Additional on-treatment effect estimate	o	+	+	+	+	+	+
Landi, 2018 (b)	Retired population; age $\geq$ 65	8.9 % stroke	Age, Sex, COME, COMO, TI, CLO, health care utilization	Additional on-treatment effect estimate	o	+	+	+	+	+	+
Sehested, 2018 (MI)	Patients after elective upper endoscopy; age 30–99	No	Age, Sex, COME, COMO, TI, ASP, SES	In patients after upper endoscopy	-	+	+	+	+	+	+
Shih, 2014	Age 18–80	12.4 % CEVD	Age, Sex, COME, COMO, ASP, CLO, SES, health care utilization		o	-	+	+	+	+	o
Nolde, 2021 (IS)	Age $\geq$ 18	No	Age, Sex, COME, COMO, TI, ASP, CLO		o	+	+	+	+	+	+
Rooney, 2020 (IS)	5th visit of a cohort study; age 69–90	No	Age, Sex, Race, Education, COME, Diabetes, Livestyle, Lab		-	-	-	+	o	+	o
Nguyen, 2018	Age 30–75	5.0 % CVD	Age, Sex, COME, COMO, TI, ASP, Livestyle	Only study assuming reversible causal effect	-	o	o	+	o	+	+
Sehested, 2018 (IS)	Patients after elective upper endoscopy; age 30–99	No	Age, Sex, COME, COMO, TI, ASP, SES	In patients after upper endoscopy	-	+	+	+	+	+	+
Wang, 2017	Age $\geq$ 20	17.4 % CAD 1.2 % MI	Age, Sex, COME, COMO, ASP, CLO, SES, health care utilization		o	o	+	+	+	+	+
Brown, 2021	Age $\geq$ 18	8.2 % CHD; 4.5 % CEVD	Age, Sex, COME, COMO, ASP, CLO, Livestyle, SES, health care utilization		o	+	+	+	+	+	+
He, 2021	Age 37–73	No	Age, Sex, Race, COME, COMO, TI, ASP, SES, Education, Livestyle		o	o	o	+	o	+	+
Rooney, 2020 (CVM)	5th visit of a cohort study; age 69–90	No	Age, Sex, Race, Education, COME, Diabetes, Livestyle, Lab		-	-	-	+	o	+	o
Xie, 2019	Veterans; 96% male	25.2 % CVD	Age, Sex, Race, COME, COMO, TI, Livestyle, SES, health care utilization, Lab		o	o	o	o	+	+	+
Adelborg, 2018	Patients hospitalized with first-time heart failure; mostly older	53.6 % CAD; 14.8 % stroke	Age, Sex, COME, COMO, TI, SES	In patients with heart failure	o	-	o	+	+	+	+
De Francisco, 2018	Hemodialysis Patients; age $\geq$ 18, mostly older	40.0 % on anti-platelets	Age, Sex, COME, COMO, Lab, ASP/CLO combined	In patients on hemodialysis	-	-	+	+	o	+	+
Shah, 2015	Patients after non-emergent elective coronary angiogram	76% CAD	Age, Sex, Race, COME, COMO, Lab, Livestyle	In patients after coronary angiogram	-	-	-	+	o	+	o

MI: myocardial infarction; IS: ischaemic stroke; CVM: cardiovascular mortality;
PREV CVD: prevalent cardiovascular disease; CF: confounding; SEL: selection; INT: intervention; DEV: deviations; MISS: missing; OUT: outcome; REP: reporting; MI: myocardial infarction; CEVD cerebrovascular disease; CVD cardiovascular disease; CHD: coronary heart disease; CAD: coronary artery disease; COME: comedications; COMO: comorbidities; TI: treatment indications; SES: socio-economic status; ASP: aspirin; CLO: clopidogrel; +: low risk of bias; o: moderate risk of bias; -: serious risk of bias

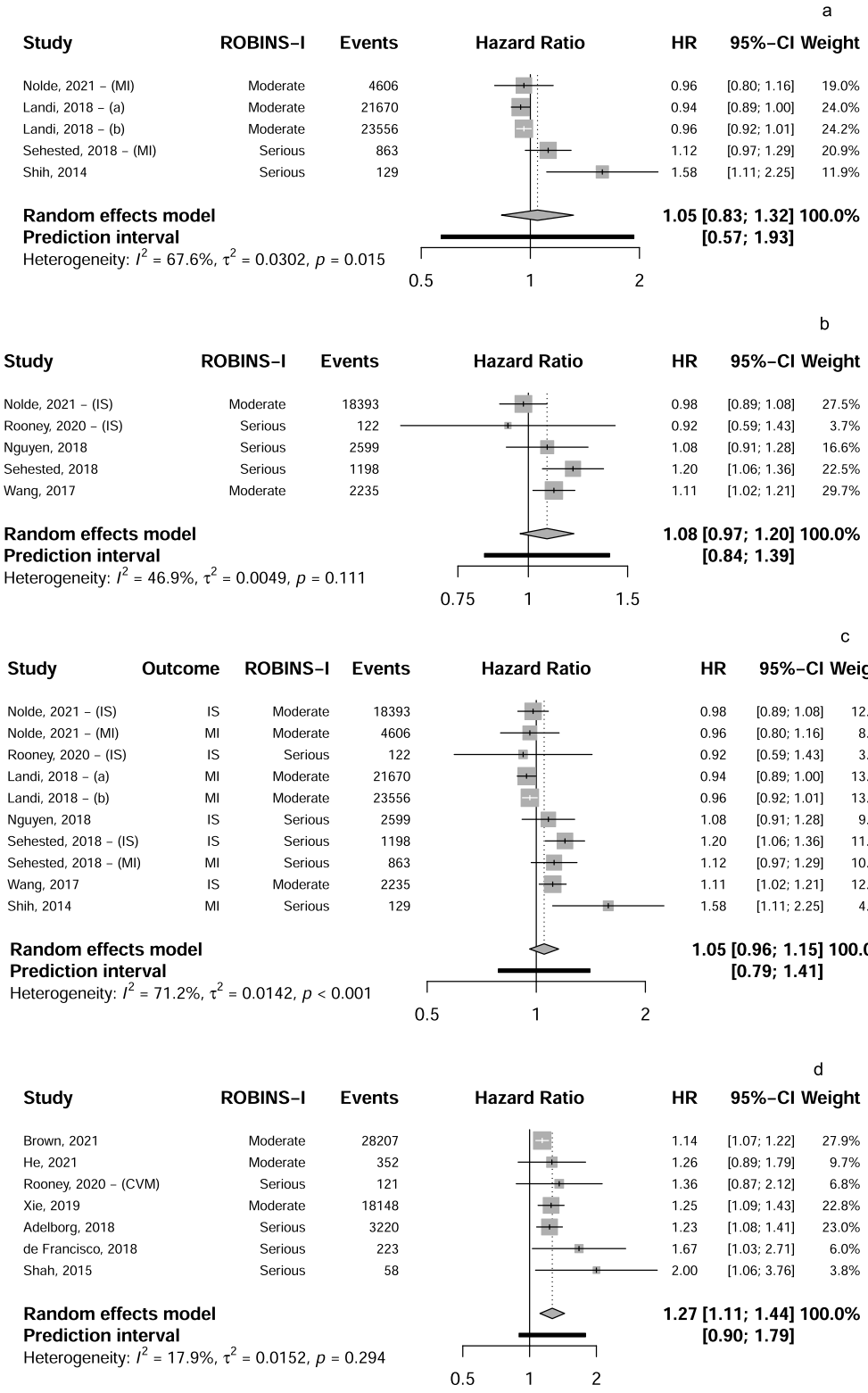

Fig. 2. (a–d). Forest plot of random-effects meta-analyses for (a) myocardial infarction, (b) ischaemic stroke, (c) acute cardiovascular events, (d) cardiovascular mortality Study-specific hazard ratios (HR) are represented by black diamonds (with their 95% confidence interval [CI] as error bars). HRs were combined using a Hartung-Knapp-Sidik-Jonkman random-effects model, yielding a pooled HR and its 95% CI and 95% prediction interval. The dotted line represents the pooled HR. Two-sided *P* value for between-study heterogeneity based on Cochran Q statistic.

covariates). Detailed characteristics of all included studies are shown in Tables 1 and 2. Among studies with a cardiovascular mortality endpoint there was large variation of the proportion of prevalent cardiovascular disease at study inclusion and some studies [13,32,34] were undertaken in clinical populations with high cardiovascular morbidity. In particular, the two large studies [12,35] on cardiovascular mortality examined all-cause mortality and reported cause-specific mortality as part of their subgroup analyses. This broader scope also meant that eligibility criteria were not tailored specifically for studying cardiovascular mortality and patients with prevalent cardiovascular disease were included, which possibly biased effect estimates due to confounding by indication.

3.2. Meta-analysis

3.2.1. Cardiovascular events

The random-effects meta-analysis yielded pooled HRs of 1.05 with a

Table 3
Subgroup meta-analyses.

Cardiovascular Events (10 studies)					
Subgroup	**No. of studies**	**HR (95% CI)**	**I^2, %**	**T^2**	**P**
Risk of bias (ROBINS-I)					0.031
moderate	5	0.99 (0.91–1.07)	63.0	0.0029	
serious	5	1.16 (0.96–1.40)	23.3	0.0185	
Follow-up time					0.53
short studies (≤ 5 years)	5	1.09 (0.87–1.37)	82.7	0.0294	
long studies (> 5 years)	5	1.04 (0.95–1.13)	18.1	0.0024	
Number of events					0.062
small studies (≤ 2000)	4	1.18 (1.08–1.29)	59.0	0.0249	
big studies (> 2000)	6	0.98 (0.95–1.01)	32.2	0.0030	
Geographic region					0.084
Asia	2	1.13 (1.04–1.23)	72.4	0.0402	
Europe	4	1.06 (0.99–1.13)	62.4	0.0073	
US	4	0.96 (0.92–0.99)	0	0.0017	
Cardiovascular Mortality (7 studies)					
Subgroup	**No. of studies**	**HR (95% CI)**	**I^2, %**	**T^2**	**P**
Risk of Bias (ROBINS-I)					0.097
moderate	3	1.17 (1.03–1.34)	0	0.0320	
serious	4	1.39 (1.02–1.89)	14.1	0.0195	
Active comparator / new user design					0.033
yes	3	1.18 (1.04–1.34)	3.3	0.0010	
no	4	1.46 (1.08–1.99)	0	0.0142	
Prevalent cardiovascular disease					0.16
≤ 20%	3	1.16 (1.01–1.32)	0	0.0017	
> 20%	3	1.27 (0.98–1.66)	0	0.0095	
Follow-up time					0.72
short studies (≤ 5 years)	2	1.32 (0.26–6.78)	29.9	0.0195	
long studies (> 5 years)	5	1.25 (1.05–1.50)	18.6	0.0173	
Number of events					0.033
small studies (≤ 2000)	4	1.46 (1.08–1.99)	0	0.0142	
big studies (> 2000)	3	1.18 (1.04–1.34)	3.3	0.0010	
Geographic region					0.37
Europe	4	1.22 (1.02–1.45)	11.2	0.0098	
US	3	1.36 (0.84–2.21)	5.3	0.0242	

CI: confidence interval; HR: hazard ratio (calculated in the Hartung-Knapp-Sidik-Jonkman random-effects model); I^2: percentage of total variance explained by τ^2; τ^2: between-study variance; P: *p*-value of Q test for subgroup differences.

95% confidence interval of (0.83; 1.32) (Fig. 2a) for first myocardial infarction, 1.08 (0.97; 1.20) (Fig. 2b) for first ischaemic stroke and 1.05 (0.96; 1.15) (Fig. 2c) for first cardiovascular events. All CIs and all PIs included the null. There was moderate to substantial heterogeneity (46.9%-71.2%) between studies. Stratified analyses suggested that studies with a serious risk of bias (HR 1.16), small studies (HR 1.18), and studies conducted in an Asian population (HR 1.13) resulted in higher risk estimates (Table 3).

3.2.2. Cardiovascular mortality

The pooled HR for PPI use and cardiovascular mortality was 1.27 (1.11; 1.44) (Fig. 2d). Heterogeneity between studies was low (17.9%). In the stratified analyses, we found smaller effect estimates in large studies and in studies following an active comparator new user design [10] (Table 3).

3.3. Sensitivity and bias analyses

3.3.1. Cardiovascular events

The Baujat plot confirmed that the studies of Landi et al. [28] had the largest influence on the effect estimate (Supplementary Fig. S1).

Analysis of funnel plot asymmetry (Supplementary Fig. S2), Egger test (*p*-value 0.069) and Debray test (*p*-value 0.095) (Supplementary Table S4) showed little evidence for small study bias. According to the contour-enhanced funnel plot (Supplementary Fig. S2) the reported estimates were sufficiently explained under the null.

Meta-regression analysis estimated the effect of study design choices summarized by the ROBINS-I assessment (moderate or serious) to 0.16 on the log(HR) scale with a standard error of 0.06 and a *p*-value of 0.030. We adjusted the reported HRs and CIs accordingly (Supplementary Table S5). Meta-analysis of these bias-adjusted HRs yielded a pooled bias-adjusted HR of 0.99 (0.93; 1.04) (Fig. 3a).

3.3.2. Cardiovascular mortality

The Baujat plot (Supplementary Fig. S3) identified the study of Brown et al. [12] as the most influential study for the effect estimate. Despite the small number of studies included, analysis of funnel plot asymmetry (Supplementary Fig. S4), Egger test (p-value 0.005) and Debray test (*p*-value 0.039) (Supplementary Table S4) showed strong evidence for small study bias. We calculated pooled HRs adjusted for small study bias (Supplementary Table S6) using the trim-and-fill method [HR 1.19 (1.01; 1.39)] (Supplementary Fig. S5), Copas selection model [HR 1.17 (1.09; 1.25)] and Rücker's shrinkage procedure [HR 1.16 (1.07; 1.26)] (Supplementary Fig. S6).

Multiple meta-regression analysis estimated the bias introduced on the log(HR) scale by deviating from an active comparator, new user design to 0.21 (standard error 0.07) and by including patients with prevalent cardiovascular disease to 0.0025 (standard error 0.0009) per 1% increase (Supplementary Fig. S7) with a p-value of 0.019 for the meta-regression model. Reported HRs and CIs were adjusted for both publication bias according to Rücker's shrinkage procedure and design bias (Supplementary Table S5). Meta-analysis of these bias-adjusted HRs yielded a bias-adjusted pooled HR of 1.06 (0.96; 1.16) (Fig. 3b).

4. Discussion

Our study adds information to the safety evaluation of PPIs, a question of high clinical relevance [36,37], as PPIs are amongst the most frequently used medications [1]. This meta-analysis combined ten studies on cardiovascular events including 24,547 cases of first ischaemic stroke and 50,824 cases of first myocardial infarction, as well as seven studies on cardiovascular mortality with 50,329 cardiovascular

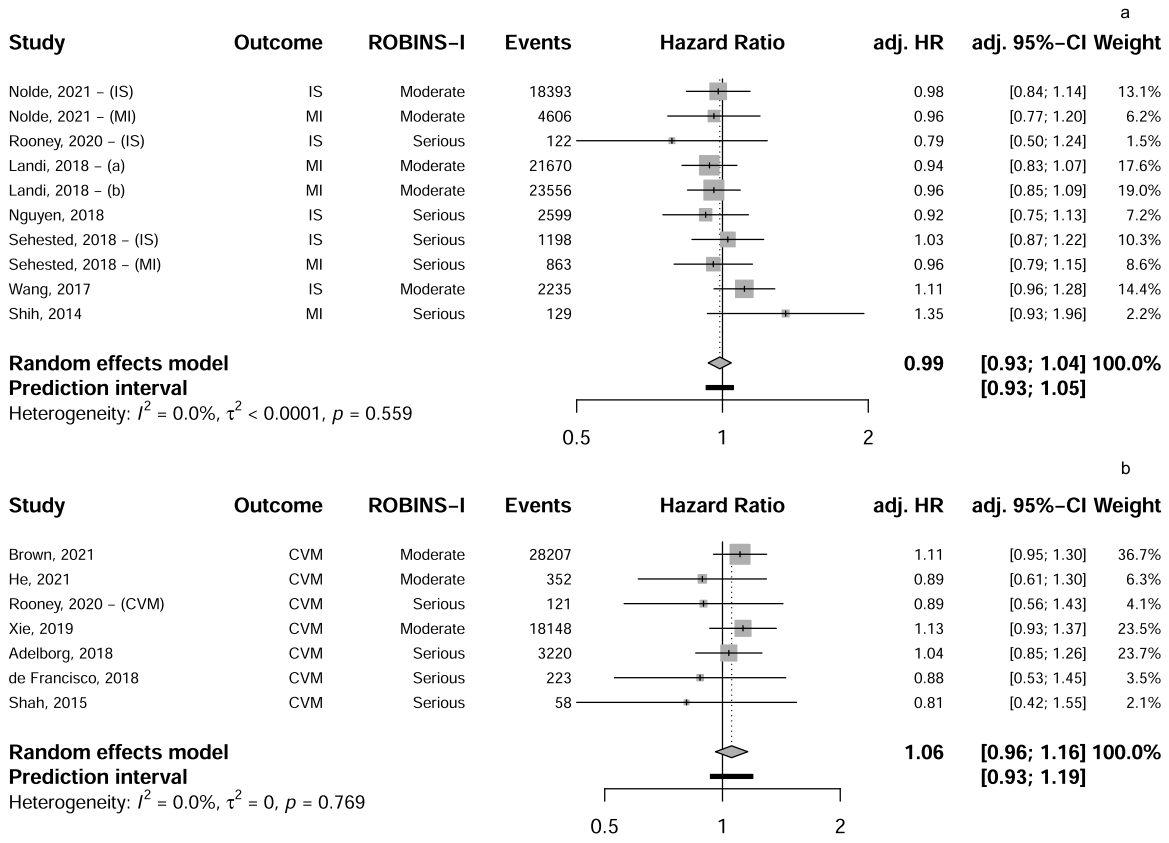

Fig. 3. (a,b). Forest plot of bias-adjusted random-effects meta-analyses for (a) acute cardiovascular events, (b) cardiovascular mortality Study-specific hazard ratios (HR) are represented by black diamonds (with their 95% confidence interval [CI] as error bars). HRs were combined using a Hartung-Knapp-Sidik-Jonkman random-effects model, yielding a mean hazard ratio and its 95% CI and 95% prediction interval. The dotted line represents the pooled HR. Two-sided P value for between-study heterogeneity based on Cochran Q statistic.(a) HR and 95%-CI adjusted for bias introduced by study design (serious risk of bias) (b) HR and 95%-CI adjusted for publication bias and bias introduced by study design (prevalent cardiovascular disease, prevalent use, non-user control).

deaths in total. The pooled HRs for PPI use and cardiovascular events were 1.05 (0.96; 1.15) before and 0.99 (0.93; 1.04) after adjusting for observational study design bias. The pooled HRs for PPI use and cardiovascular mortality were 1.27 (1.11; 1.44) before and 1.06 (0.96; 1.16) after adjusting for publication bias and observational study design bias.

An effect of PPI intake on cardiovascular events has been discussed for more than a decade. PPIs, especially omeprazole, seem to attenuate clopidogrel's antiplatelet effects by inhibiting CYP2C19, which metabolises clopidogrel to its active metabolites [2]. Besides that, several mechanisms have been suggested, by which PPIs might directly affect cardiovascular risk via impaired vascular endothelial function [38,39] or accelerated endothelial aging [40]. Evidence for an effect independent of clopidogrel inhibition was conflicting between randomized trials and observational studies [5]. While randomized trials showed no differences between PPI users and placebo-users [3,5], observational studies indicated a potentially increased cardiovascular risk for PPI users [4,5]. This seemed concerning, as observational studies are better suited to detect long-term effects and the combined CI of (0.25; 5.73) from randomized trials [5] could not reject the observational effect estimate.

Our analyses showed that this discrepancy can be resolved by adjusting for observational study design bias. First, we minimized the effects of clopidogrel inhibition by observing first cardiovascular events only. Second, we analysed each study's risk of bias in detail using the ROBINS-I tool [8] and excluded studies with critical risk of bias. Finally, we adjusted individual study estimates for bias introduced by study design choices and combined the adjusted estimates to the pooled bias-adjusted HR of 0.99 (0.93; 1.04), which coincides with estimates from randomized trials [3]. Especially, risk of bias in individual studies could have been reduced by applying a new user design, as prevalent PPI therapy might be a sign of a pre-existing cardiovascular condition and the inclusion of prevalent PPI users would therefore introduce indication bias. By design, studies on cardiovascular mortality included patients with prior cardiovascular disease, which increased the potential for bias due to interaction with clopidogrel and confounding by indication. Furthermore, we found considerable publication bias among studies on cardiovascular mortality. After adjusting individual study estimates for publication and study design bias we yielded a bias-adjusted pooled HR of 1.06 (0.96; 1.16) consistent with the analysis of cardiovascular events.

Although we did not find an overall effect of PPI therapy on the risk of cardiovascular events, the subgroup analysis revealed that the two studies [29,31] in Asian populations reported substantially higher effect estimates than studies from other regions. Unfortunately, the number of studies was not sufficient to decide, whether this is pure coincidence or actual effect modification.

The limitations of this meta-analysis stem mostly from the limitations of the data used in the individual studies. Especially, exposure to PPI therapy was usually identified using dispensed prescriptions and use of over-the-counter medications and combination products was not captured. PPI therapy was considered a point treatment. Effects of long-term intake or cumulative dose-dependent effects were not accessible. Long-term and high-dose users of PPIs were part of the analyses, but their cardiovascular risk might have been diluted by mostly short-term and low-dose PPI users.

In conclusion, this qualitative and quantitative synthesis of all available prospective observational studies suggests that PPI intake as a limited treatment of gastroesophageal diseases does not increase the risk

of first cardiovascular events. Reports of increased cardiovascular mortality can largely be explained by publication bias and observational study design biases, such as indication bias and unmeasured confounding. In combination with results from randomized trials it seems therefore questionable, whether PPI intake constitutes a cardiovascular risk factor independent of any possible interaction with clopidogrel. Further studies might investigate the cardiovascular risk of PPI therapy in Asian populations.

5. Registration and protocol

This review was registered at the PROSPERO database (CRD42020197513). It was designed and conducted in accordance with the Cochrane Handbook of Systematic Reviews [41] and has been authored according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline [42].

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Availability of data and materials

Data derived from public domain resources

Declaration of Competing Interest

UA is member of the advisory board of Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.09.021.

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