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REVIEW

Proton Pump Inhibitors and Cardiovascular Events: A Systematic Review

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Background Proton pump inhibitors (PPIs) are a commonly prescribed medication that recent data has linked to an increased risk of cardiovascular morbidity and all cause morbidity. The current study sought to perform a systematic review to investigate the link between PPIs and morbidity and mortality

Methods A systematic review was carried out as per the PRISMA guidelines, with information databases including Pubmed, Medline, and the Cochrane Review Database. English-language studies of all types published from January 1990 to October 2016 were considered. Dichotomous analysis generating odds ratios was performed using RevMan Version 5.3.

Results Thirty-seven studies were considered, of which five directly compared the effect of PPI use on mortality and/or cardiovascular morbidity (including 22,427 patients in mortality datasets, and 354,446 patients in morbidity datasets). For patients taking PPIs, all cause mortality (OR 1.68 [95% CI 1.53–1.84), $p < 0.001$) and rate of major cardiovascular events (OR 1.54 [95% CI 1.11–2.13], $p = 0.01$) were significantly higher.

Conclusions The current systematic review demonstrates that, in patients using PPIs, there was a significant increase in morbidity due to cardiovascular disease. Careful consideration should be given to the prescription of PPIs while clinical equipoise remains. Further research in the area is required.

Keywords Proton pump inhibitor • Myocardial infarct • Cardiovascular disease • AMDA • Nitric oxide • Mortality

Introduction

Proton pump inhibitors (PPIs) are indicated in gastroesophageal reflux disease (GORD), and are often the first line in anti-acid therapy as they have been demonstrated to be superior to H2 receptor antagonists [1]. Internationally, over 113 million PPI prescriptions are filled annually, accounting for $13 billion in sales [2]. However, PPIs are not free of side effects, with evidence for increased risks of diarrhoea, pneumonia and fractures in long-term users [1]. PPIs are often also prescribed to counteract the gastrointestinal complications of the antiplatelet aspirin, itself given to prevent atherosclerotic disease.

In the past decade, a number of studies have suggested there was a marked increase in cardiovascular morbidity and mortality in patients taking PPIs concomitantly with clopidogrel [3–5], to the extent that the FDA issued a formal warning about this interaction [6]. However, this has recently been suggested not to be a true interaction [7], especially as an increase in mortality and cardiac events has been seen even in patients not taking clopidogrel [8,9], and mechanisms for this increased thrombotic risk have recently been proposed [10]. Subsequent meta-analyses agree that there is an increase in adverse cardiac events in patients even not taking clopidogrel [11–16] and work by Sherwood *et al*. suggested that degree of cardiovascular risk

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even differs between individual PPIs [12]. Debate remains as to whether PPIs do truly carry an increase in cardiovascular morbidity and mortality [17–19], and to what extent.

We sought to investigate the impact of proton pump inhibitor use on both mortality, and morbidity due to thrombotic complications, namely ischaemic heart disease and vascular disease (including cerebrovascular accidents and limb ischaemia), variables not included in previous meta-analyses. We sought studies that included a control group not using PPIs, and excluded studies investigating PPI interaction with clopidogrel. With ischaemic heart disease and stroke causing one in three and one in 20 deaths in the USA annually respectively [20], proton pump inhibitors should be thoroughly investigated for any contribution to atherosclerotic disease.

Methods

This systematic review was carried out as per PRISMA guidelines [21].

Regarding study selection, eligibility criteria are as follows. Studies were included if they examined death or atherosclerotic events (including myocardial infarct, stroke, or peripheral arterial events), and compared a group exposed to proton pump inhibitors with a control group (not exposed to PPIs), in any group of patients. Duration of follow-up was not an exclusion criteria, as the authors were aware the data is limited.

Information sources included medical databases Pubmed, Medline, and the Cochrane Review Database. Search strategy involved using the terms 'proton pump inhibitor' combined separately with 'atherosclerosis', 'myocardial infarct', 'ischemia', 'endovascular', and 'death', with the phrase 'clopidogrel' excluded. English-language studies from January 1990 to October 2016 were considered, with date last searched 11 November 2016. Attempt was made to contact authors of two of the eligible studies, with response from one. Study designs to be considered included randomised controlled trials, cohort, and case-control studies.

Data was abstracted by one reviewer, with a second reviewer assessing for completeness and errors. The data

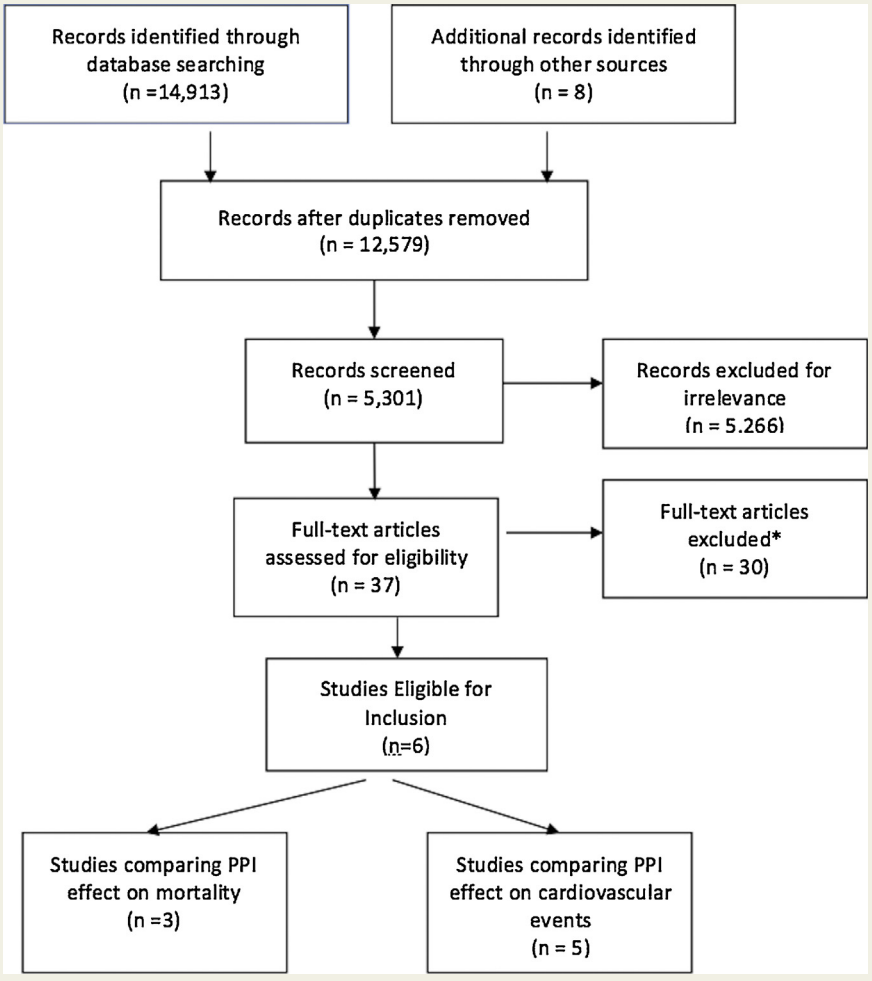

Figure 1 PRISMA study selection flow diagram.
Abbreviation: PPI = proton pump inhibitor. * See text for reasons for exclusion.

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