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Aspirin and cardiovascular primary prevention in non-endstage chronic kidney disease: A meta-analysis

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ABSTRACT

Background and aims: Chronic kidney disease is a strong independent predictor of cardiovascular disease. No published meta-analyses on the use of aspirin for the primary prevention of cardiovascular disease in chronic kidney disease exist. We therefore performed a systematic review and meta-analysis of this subject.

Methods: We used a pre-defined and registered protocol (PROSPERO identification CRD42014008860). We searched Medline and Embase between 1996 and July 2015. Inclusion criteria were adult subjects with non-endstage chronic kidney disease (CKD) and no history of cardiovascular disease. The co-primary outcomes were major cardiovascular events and all-cause mortality. Secondary outcomes included bleeding-related events. We used a random effects model to pool data.

Results: Three trials were identified and two of these provided previously unpublished data. The studies included 4468 participants and 16,740 person-years of follow-up. There were no statistically significant reductions in the risk of major cardiovascular events (RR 0.92, 95% CI 0.49 to 1.73, $p = 0.79$, I^2 71%) or mortality (RR 0.74, 95% CI 0.55 to 1.00, $p = 0.05$, I^2 0%) with aspirin compared to the control group. Major bleeding events were increased with aspirin though (RR 1.98, 95% CI 1.11 to 3.52, $p = 0.02$, I^2 0%).

Conclusions: There is no clear benefit of aspirin for the primary prevention of cardiovascular events in CKD and no statistically significant reduction in mortality. Aspirin is likely to increase the risk of major bleeding events. Currently, insufficient randomised control trial data exists to recommend universal use or avoidance of aspirin for primary prevention of cardiovascular events in CKD.

1. Introduction

Chronic kidney disease (CKD) affects approximately 6–8% of the adult population [1]. It is an independent risk factor for atherosclerotic disease [2]. Aspirin irreversibly inhibits the production of thromboxane and hence prevents platelet aggregation. Its role is well established in the secondary prevention of cardiovascular disease (CVD) [3] and to a lesser degree in high risk groups for primary prevention, such as those with diabetes mellitus [4,5]. However, aspirin is associated with increased risk of bleeding, with gastrointestinal and cerebral haemorrhage contributing to morbidity and mortality [6].

Aspirin's role in the primary prevention of CVD in CKD has been identified as an important research priority [7,8]. However, only one relevant trial is presently registered with clinicaltrials.gov [9]. Whilst its efficacy may be higher in the prevention of CVD events [10], there is also a potentially greater risk of bleeding in CKD [11]. Previous meta-analyses have only considered the broader category of 'anti-platelets' and have included individuals with end-stage renal failure and established CVD [12].

Currently, aspirin use is recommended in national and international guidance in CKD for secondary prevention, but not primary prevention of CVD events [7,8]. European guidance specifically for diabetic CKD recommends that aspirin only be commenced for primary prevention in the absence of major bleeding risk factors [13].

In the general population, the Antithrombotic Trialists' (ATT)

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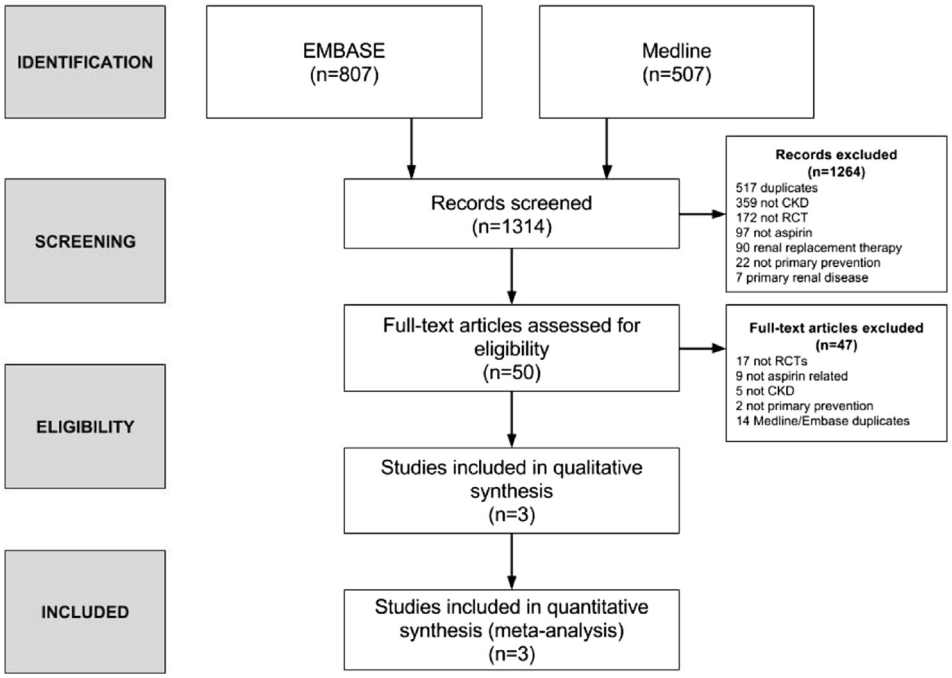

Fig. 1. Flowchart showing the number of papers identified, screened and included in the meta-analysis.

Collaboration [6] has provided perhaps the most comprehensive data in relation to CVD primary prevention with aspirin. Aspirin produced a 12% relative risk reduction in CVD events. However, in absolute terms this equated to a 0.06% per annum reduction in CVD events. Haemorrhagic strokes were increased by 32%, or 0.01% each year. Major extracranial bleeds showed a similar pattern with a 54% and 0.03% increase respectively. This reinforces the importance of event rates when trying to balance the risk and benefits in a primary prevention programme. CVD and bleeding prognostic models have not been validated in CKD. Since both the risk and potential benefit varies as estimated glomerular filtration rate (eGFR) changes [10], making an accurate assessment becomes problematic.

This systematic review and meta-analysis aimed to assess the role of aspirin for the primary prevention of CVD in CKD patients.

2. Patients and methods

We used a pre-defined and registered systematic review and meta-analysis protocol (PROSPERO identification CRD42014008860) [14]. We searched OVID Medline and Embase between 1996 and July 2015 using no language restrictions (see appendix 1 for full search strategy for OVID Medline). In addition, the National Institute of Health Research database of clinical trials and Cochrane databases were also searched. Other related reviews were also assessed for additional trials.

The inclusion criteria were randomised controlled trials in adult participants with any stage of non-endstage CKD and no history of CVD. Exclusion criteria were head-to-head studies of aspirin versus other anti-platelet medications, studies in primary renal disease (eg IgA nephropathy, vasculitis), or any trial with more than 5% of participants with a history of CVD.

The co-primary outcomes were major CVD events and all-cause mortality. Secondary outcomes included coronary heart disease events, stroke and major or minor bleeding-related adverse events. Major bleeding events were defined as any bleeding event leading to hospitalisation or death. Minor bleeding events encompassed any other bleeding event reported in the trial. All identified abstracts were independently assessed by two authors. Each reviewer shortlisted potential studies for further consideration. The full text of all identified papers was then reviewed independently by another two authors.

The quality of the studies' methodology, including bias and identification of CKD subgroups, were then assessed individually. All studies were assessed unblinded using a standardised proforma based on the Cochrane Handbook [15]. Assessments from the reviewers were compared and any differences were discussed until a consensus was achieved.

Outcome data were extracted using a predefined template by one reviewer and cross-checked to the original publication by another reviewer. Corresponding authors were contacted for additional unpublished data. Data were analysed using RevMan 5.2. Random effects model using Mantel-Haenszel (M-H) method were used to pool the data. A random effects model was chosen as heterogeneity was expected to be high. Relative and absolute pooled risk reductions were calculated as well as the number need to treat/harm over five years of treatment. Subgroup analyses were planned if heterogeneity was greater than I^2 >25% and included CKD stage, estimated glomerular filtration rate formula used, follow-up length (<2 years, >2 years) and the trials' proportion of diabetes mellitus and hypertension.

3. Results

One thousand three hundred and fourteen abstracts were reviewed. Fig. 1 shows the screening process including the number of studies identified and excluded.

The search identified three trials, and their key characteristics are described in Table 1 [10,16,17]. These trials included a total of 4469 individuals with CKD. All trial results were published in peer-review journals. Additional data were supplied by the authors of HARP and JPAD [16,17].

The assessment of the trials' quality showed medium to high levels of bias, mainly related to the suboptimal identification of CKD and assessment of endpoints in the trials. The full results of the bias assessment are available in appendix 2. Two trials reported