Editorials

Aspirin for primary prevention of CVD in CKD:

where do we stand?

CHRONIC KIDNEY DISEASE IS A POWERFUL AND POTENTIALLY MODIFIABLE RISK FACTOR FOR CARDIOVASCULAR DISEASE

Chronic kidney disease (CKD) is defined as any abnormality of kidney function or structure with implications for health that is present for more than 3 months. It is classified according to the estimated glomerular filtration rate (eGFR) and urine albumin:creatinine ratio (ACR). The presence of an eGFR <60 mL/min/1.73 m^2 or an ACR ≥3 mg/mmol for >90 days is diagnostic of CKD.

CKD is common. Data from the 2016 Health Survey of England reveal that 15% of people aged ≥35 years have CKD (stage 1 to 5), with 7% in CKD stages 3 to 5.[1] An important minority of people with CKD will progress to end-stage renal disease and require renal replacement therapy, but the greatest significance of CKD is as a powerful and potentially modifiable risk factor for cardiovascular disease (CVD). Large-scale robust epidemiological data indicate that the risks of both all-cause mortality and cardiovascular (CV) mortality in the general population increase with eGFR <60 mL/min/1.73 m^2 or an ACR ≥1 mg/mmol. The risks are graded: compared to eGFR 95 ml/min/1.73 m^2, hazard ratios for CV mortality at eGFR 60, 45, and 15 ml/min/1.73 m^2 are approximately 1.5, 2, and 3 respectively; a similar pattern is seen with rising urine ACR. eGFR and ACR are multiplicatively associated with mortality risk with no evidence of interaction.[2]

The pattern of vascular events in people with CKD varies according to disease severity. In less severe renal disease, atherothrombotic events dominate. With severe impairment of eGFR and in particular in those receiving renal replacement therapy, atherosclerotic events are proportionally less common and serious arrhythmia and heart failure more important.

ASPIRIN AND SECONDARY PREVENTION IN THE GENERAL POPULATION

There is good evidence that antiplatelet therapy reduces the risk of subsequent vascular events in patients with pre-existing CVD (secondary prevention) and that overall the benefits outweigh the risks of major bleeding (the principal complication of therapy). A meta-analysis conducted by the Antithrombotic Trialists' Collaboration (ATC) found a relative risk reduction of 22% in major vascular events (MVE: non-fatal myocardial infarction [MI], non-fatal stroke and CV death) in those treated with antiplatelet agents (primarily aspirin), compared with controls.

Overall, in this high-risk group (annual absolute risk of MVE >3%) aspirin prevented 10–20 MVE per 1000 patient-years.[3] Aspirin is recommended internationally for the secondary prevention of CV events in people with established CVD.

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ASPIRIN AND PRIMARY PREVENTION IN THE GENERAL POPULATION

In lower risk populations without pre-existing CVD the benefits of aspirin for the primary prevention of CVD are smaller and largely offset by the risks of bleeding, assuming equivalence of impact of CV and bleeding events. Consequently, current guidance does not support this use of aspirin, either for the general low-risk population or for those with diabetes.

An ATC meta-analysis of six primary prevention studies reported a 12% proportional reduction in MVE in a low-risk population: the annual rate of MVE was 0.51% in aspirin-treated patients versus 0.57% in controls, with major bleeding experienced by 0.10% and 0.07% per year in the two groups respectively. Only 1-3 MVE per 1000 patient-years were prevented.[4]

Broadly similar results were seen in ASCEND, a large trial of aspirin for primary prevention of CVD in people with diabetes published in 2018.[5] Two further primary prevention trials published the same year (ARRIVE, in people at moderate CV risk; and ASPREE in healthy older people) found no statistically significant benefits on major vascular events.

However, it is noteworthy that in all three trials the baseline CV risk of the populations studied was not dissimilar to that of the aforementioned low-risk historical primary prevention populations (annual rate of MVE 0.9–1.3% in control subjects), probably reflecting uptake of effective contemporary risk management strategies.

IS THERE A ROLE FOR ASPIRIN PRIMARY PREVENTION IN CKD?

Despite the existence of a substantial body of evidence, uncertainties still remain over whether and under what circumstances aspirin should be used for primary prevention. A key group in whom the balance of benefits and risk remains uncertain is those with CKD.

CKD substantially increases the risks of CV events, with a graded relationship between advancing stages of CKD and rates of fatal and non-fatal MI, and the probability of death following MI.[6]

In the Renal Risk in Derby cohort (mean eGFR 52 mL/min/1.73 m^2, 16% with albuminuria, 22% with pre-existing CVD) the annual rate of fatal and non-fatal CVD was 2.5%. The absolute benefits of aspirin may therefore be higher in the CKD population than in lower risk groups even if the relative risk reductions are similar.[7]

It is also possible that the relative risk reductions in CVD with aspirin are greater in people with CKD than in those with normal kidney function. Some support for this contention is found in a post-hoc CKD subgroup analysis from the HOT (Hypertension Optimal Treatment) primary prevention trial where overall, aspirin reduced the risk of major vascular events by 15%. Per 1000 patient years aspirin prevented 1 (95% confidence interval [CI] = −1 to 2), 2 (95% CI = −2 to 5) and 20 (95% CI = 6 to 32) major CV events for patients with baseline eGFR of ≥60, 45–59, and <45 mL/min/1.73 m^2 respectively. On sensitivity analysis eGFR appeared to define the threshold for benefit.[8] However, it is unclear to what extent any benefits may be offset because people with CKD are also

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at increased risk of major bleeding. Many people with CKD are older, which is a risk factor for aspirin-associated bleeding. There are additional specific mechanisms through which the bleeding tendency is increased in CKD, including defective platelet adhesion to the sub-endothelium, defective platelet aggregation, and other intrinsic platelet defects.

A systematic review in 2016 exploring the use of aspirin for primary prevention of CVD in CKD concluded that insufficient randomised control trial data exists to recommend either universal use or avoidance of aspirin for primary prevention of CV events in CKD and that the limitations of the evidence highlighted the need for definitive CKD-specific randomised controlled trials.[9] Dad and Weiner concluded, in their review of 2016 US guidance on primary prevention with aspirin, that:

'Given existing clinical equipoise, the affordability of aspirin, the wide acceptance of aspirin as potentially therapeutic by patients, and the high risk for CVD in advanced kidney disease, adequately powered clinical trials are urgently needed and should be a priority for funding agencies.'[10]

In 2014, the National Institute for Heath and Care Excellence recommended a definitive trial of aspirin for primary prevention of CVD in people with CKD.

While large trials have been published since these commentaries and recommendations, people with CKD have not been well-represented in these studies; for example, the proportion with an eGFR <60 mL/min/1.73 m^2 in ASCEND and ASPREE was 12% and 19% respectively.

CONCLUSION

The burden of CVD in CKD is substantial and the financial impact is large: assuming unit costs of £12 200 for a stroke and £7734 for an MI and incidence of stroke, and MI of 12.0 and 11.9 per 1000 patient-years respectively in people with CKD,[11] the annual costs of strokes and MI in people with CKD in England is in the order of £1 billion.

Although there is good evidence to support lipid lowering therapy for primary prevention of CVD in CKD (statins are recommended in all stages), our understanding of how to further reduce CV risk in CKD is limited. These limitations drive uncertainty and variation in practice.

In the UK it has been estimated that there are more than 3 million people with CKD and no CVD who are not prescribed aspirin but around 1 million that are receiving aspirin for primary prevention in the absence of definitive evidence, potentially contributing to treatment burden.[12]

Pragmatic trial evidence to guide future practice in this high-risk group is urgently required.

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