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Does Aspirin Detract from the Benefits of Mineralocorticoid Receptor Antagonists in Patients with Heart Failure and a Reduced Left Ventricular Ejection Fraction? Probably!

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There is a wealth of data to show that mineralo-corticoid antagonists (MRA) reduce morbidity and mortality in patients with heart failure when left ventricular ejection fraction (LVEF) is reduced (HFrEF) and perhaps also when LVEF is fairly well-preserved (HFpEF)(1-5). Chin et al investigated whether the benefits of MRA were reduced amongst
patients prescribed aspirin. They concluded that no important interaction could be observed. If true, this is good news but still does not justify prescription of aspirin for patients with heart failure and coronary artery disease (CAD). The evidence that chronic aspirin therapy is safe or effective, regardless of LVEF, for any cardiovascular condition is not robust (7-10). Admittedly, there is good evidence that aspirin reduces coronary events and mortality when given for 4-12 weeks after an acute vascular event but any suggestion of a long-term effect owes more to the fertile imagination of cardiologists rather than to clinical trial data. In this era, which we pretend is one of evidence-based medicine, it is not to the credit of the medical community that aspirin enjoys such widespread abuse.

Many patients with heart failure have CAD as a cause of cardiac dysfunction and heart failure and it may be an important co-morbidity in others. There is a widespread belief that these patients should receive an antiplatelet agent, usually aspirin, in order to reduce the risk of vascular events and prolong life. Unfortunately, there is no evidence to support such a view. Adequate randomized controlled trials comparing aspirin to placebo in patients with heart failure are lacking but the few data that exist are not reassuring (10, 11). There are concerns that aspirin might detract from the therapeutic benefits of agents that are known to improve outcome in heart failure, including ACE inhibitors and beta-blockers, possibly by blocking prostaglandin production resulting in impaired vasodilatation, renal dysfunction, sodium and water retention and hyponatraemia (7). Aspirin will also increase gastro-intestinal blood loss and may be at the root of the current epidemic of iron deficiency in the heart failure population (12). A key attribute of MRAs is that they increase sodium excretion, which may be attenuated by aspirin (13); a key problem with MRAs is a fall in glomerular filtration rate, which may be exacerbated by aspirin (14); each provides grounds for concern that aspirin may detract from the benefits of MRA.
Several trials have compared aspirin either against clopidogrel or warfarin in patients with heart failure in sinus rhythm(11, 15, 16). Compared to aspirin, treatment with clopidogrel was associated with an improvement in renal function and a decline in natriuretic peptides but this has not, so far, translated into improved outcome(7, 17). For patients in sinus rhythm, warfarin reduces the risk of stroke but is not otherwise superior to aspirin(15, 16). An increased risk of heart failure hospitalizations with aspirin compared to warfarin noted in two studies(11, 15) was not substantiated in a third (16). Patients with heart failure and atrial fibrillation should, of course, receive an anti-coagulant. Newer anticoagulant agents appear associated with lower risks of stroke, intra-cranial haemorrhage and major bleeding compared to warfarin(18). For those in sinus rhythm, low-dose rivaroxaban (2.5mg twice daily) is being compared on top of background therapy(19); predominantly aspirin, unfortunately. However, there is also a head-to-head study of aspirin 100mg/day compared to rivaroxaban 5mg twice daily in patients with coronary or peripheral artery disease due to complete in 2018, although the study excludes patients with an LVEF <30%(20).

Why, in the face of a lack of a positive trial do doctors continue to prescribe aspirin to patients with CAD? In the largest randomized controlled trial comparing aspirin and placebo after a myocardial infarction there were more deaths on aspirin (246 of 2267; 10.9%) than on placebo (219 of 2257; 9.7%)(21). Admittedly, patients were treated with aspirin at a dose of 1,000mg/day but no large, long-term, placebo-controlled trial of aspirin after a myocardial infarction has ever used <300mg/day. Altogether, there were 10,859 patients in the six valid, randomized trials of long-term aspirin therapy after myocardial infarction. This showed a borderline significant 13% reduction in vascular deaths and 10% reduction in all-cause mortality (22). There is strong evidence of publication bias; the smaller the trial the larger the apparent effect(10). The subset of patients with heart failure in the two largest of these studies
had a higher mortality on aspirin than placebo(10). How much data is required to show how useless chronic aspirin therapy is?

There has been only one clearly positive trial of aspirin for coronary disease(23). In the ISIS (International Study of Infarct Survival)-2 study, a course of aspirin lasting only 28 days reduced mortality at 35 days (the primary endpoint) compared to placebo, given double-blind. Importantly, the benefits of this 28 day course of aspirin persisted for at least 10 years, long after the course of aspirin was complete. Information on aspirin use after completion of the double-blind phase of ISIS-2 is lacking but as only 5% of patients in ISIS-1 were given aspirin and as there was no reason to change practice between these trials, the presumption must be that most patients did not receive aspirin after the randomized phase. More recent trials of aspirin and alternative anti-platelet agents initiated late after myocardial infarction have also failed to reduce mortality(24). Thus, it would appear that aspirin should be used after a myocardial infarction in much the same way as an antibiotic for pneumonia; a course of treatment is prescribed and then stopped.

An oft quoted reason for prescribing antiplatelet agents is that they reduce platelet adhesion and occlusive thrombus formation and therefore the risk of myocardial infarction. However, the trigger for many coronary vascular events may be haemorrhage from fragile capillary ingrowth from the vasa vasorum(25). Thus, in stable disease, any benefit of anti-thrombotic agents from reduced thrombosis may be offset by an increase in plaque haemorrhage and rupture. Plaque is rich in red cell membrane derived lipids and haemosiderin suggesting that such events are common and might account for reports that aspirin accelerates plaque growth.

So, are the conclusion of Chin et al valid? Probably not. The study was not powered to investigate the effects of eplerenone in subgroups. Of the 2,737 patients enrolled, more than 30% of patients had atrial fibrillation and presumably most of these patients were not taking
aspirin because they were anti-coagulated. More patients taking aspirin developed hyperkalaemia on eplerenone (12.7% compared to 8.7%). The reduction in heart failure hospitalizations exerted by eplerenone was significantly lower amongst patients taking aspirin compared to those who were not (31% versus 52%; p=0.05) with similar trends, albeit not significant, for cardiovascular death (14% versus 31%) and all-cause mortality (18% versus 31%). These results could reflect the play of chance but with more data perhaps more of these trends would have become significant. An individual patient-data meta-analysis of randomized controlled trials of MRAs is warranted to address this issue. In the RALES (Randomized Aldactone Evaluation Study), AREA IN-CHF (Anti-remodelling Effect of Canrenone in Patients with Mild Chronic Heart Failure) and TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) studies, 37%, 57% and 65% respectively were reported to be taking aspirin. However, observational data are no substitute for a randomized controlled trial of aspirin withdrawal in heart failure, which is sorely needed.

In conclusion, this analysis does not justify the use of aspirin in patients with heart failure with or without coronary artery disease. Moreover, these data do not provide reassurance that aspirin does not detract from the benefits of eplerenone; rather the opposite. Whether or not there is an interaction between MRA and aspirin, there are concerns that aspirin has deleterious effects on haemodynamics, renal function, symptoms and outcome in patients with heart failure. There is no evidence that aspirin is of benefit for patients with heart failure.


19. Zannad F, Greenberg B, Cleland JG, Gheorghiade M, Van Veldhuisen DJ, Mehra MR, Anker SD, Byra WM, Fu M, Mills RM. Rationale and design of a randomized, double-blind, event-driven, multicentre study comparing the efficacy and safety of oral rivaroxaban with placebo for reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an exacerbation of heart failure: the COMMANDER HF trial. *Eur J Heart Fail* 2015;17(7):735-742.


