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

John GF Cleland. MD, PhD, FRCP, FACC, FESC

Director of the Robertson Centre for Biostatistics and Professor of Clinical Trials, University of Glasgow.

Honorary Consultant Cardiologist, Greater Glasgow & Clyde Health Board

Professor of Clinical Cardiology, National Heart & Lung Institute, Royal Brompton & Harefield Hospitals, Imperial College, London

Address for Correspondence:-

Robertson Centre for Biostatistics and Glasgow Clinical Trials Unit

Boyd-Orr Building, University Avenue. Glasgow UK. G12 8QQ

Telephone: +44-141-330-4744. Fax: +44-141-330-5094

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(6). 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 in-growth 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.

Reference List

1. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Witte J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;**341**(10):709-717.

2. Zannad F, McMurray JJ, Krum H, Van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**(1):11-21.

3. Lewis EF, Kim HY, Claggett B, Spertus J, Heitner JF, Assmann SF, Kenwood CT, Solomon SD, Desai AS, Fang JC, McKinlay SA, Pitt BA, Pfeffer MA. Impact of Spironolactone on Longitudinal Changes in Health-Related Quality of Life in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial. *Circ Heart Fail* 2016;**9**(3):e001937.

4. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, O'Meara E, Shah SJ, Mckinlay S, Fleg JL, Sopko G, Pitt B, Pfeffer MA. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J* 2016;**37**(5):455-462.

5. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014;**370**(15):1383-1392.

6. Chin LE, Collier TJ, Pitt B, McMurray JJV, Swedberg K, van Velhuisen DJ, Pocock SJ, Vincent J, Turgonyi E, Zannad F, Krum H. Aspirin does not reduce the clinical benefits of the mineralocorticoid receptor antagonist eplerenone in patients with systolic heart failure and mild symptoms. An analysis of EMPHASIS-HF study. *European Journal of Heart Failure* 2016.

7. Cleland JG, Parsons S. Aspirin for heart failure: theory- or evidence-based? *Circ Heart Fail* 2014;**7**(2):237-238.

8. Cleland JG. Is aspirin useful in primary prevention? *Eur Heart J* 2013;**34**(44):3412-3418.

9. Cleland JG, Mumtaz S, Cecchini L. Role of Antithrombotic Agents in Heart Failure. *Curr Cardiol Rep* 2012;**14**(3):314-325.

10. Cleland JGF. Is aspirin 'The Weakest Link' in cardiovascular prophylaxis. The surprising lack of evidence supporting the use of aspirin for cardiovascular disease. *Prog Cardiovasc Dis* 2002;**44**:275-292.

11. Cleland JGF, Findlay I, Jafri S, Sutton G, Falk R, Bulpitt C, Prentice C, Ford I, Trainer A, Poole-Wilson PA. The Warfarin/Aspirin Study in Heart Failure (WASH): A randomized trial comparing antithrombotic strategies for patients with heart failure. *Am Heart J* 2004;**148**:157-164.

12. Cleland JG, Zhang J, Pellicori P, Dicken B, Dierckx R, Shoaib A, Wong K, Rigby A, Goode K, Clark AL. Prevalence and Outcomes of Anemia and Hematinic Deficiencies in Patients With Chronic Heart Failure. *JAMA Cardiol* 2016;**1**(5):539-547.

13. Tweeddale MG, Ogilvie RI. Antagonism of spironolactone-induced natriuresis by aspirin in man. *N Engl J Med* 1973;**289**(4):198-200.

14. de Silva R, Nikitin NP, Witte KK, Rigby AS, Loh H, Nicholson A, Bhandari S, Clark AL, Cleland JG. Effects of applying a standardised management algorithm for moderate to severe renal dysfunction in patients with chronic stable heart failure. *Eur J Heart Failure* 2007;**9**:415-423.

15. Massie B, Collins JF, Ammon SE, Armstrong PW, Cleland JGF, Ezekowitz M, Jafri SM, Krol WF, O'Connor CM, Schulman KA, Teo K, Warren SR, for the WATCH Trial Investigators. Randomized Trial of Warfarin, Aspirin and Clopidogrel in Patients with Chronic Heart Failure. The Warfarin and Antiplatelet Therapy in Chronic Heart Failure WATCH) Trial. *Circulation* 2009;**119**(12):1616-1624.

16. Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, Ammon SE, Graham S, Sacco RL, Mann DL, Mohr JP, Massie BM, Labovitz AJ, Anker SD, Lok DJ, Ponikowski P, Estol CJ, Lip GY, Di Tullio MR, Sanford AR, Mejia V, Gabriel AP, del Valle ML, Buchsbaum R. Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med* 2012;**366**(20):1859-1869.

17. Meune C, Wahbi K, Fulla Y, Cohen Solal A, Duboc D, Mahe I, Simoneau G, Bergmann JF, Weber S, Mouly S. Effects of aspirin and clopidogrel on plasma brain natriuretic peptide in patients with heart failure receiving ACE inhibitors. *Eur J Heart Fail* 2007;**9**(2):197-201.

18. van Gelder IC, Van Veldhuisen DJ, Lip GY. New oral anticoagulants in heart failure. *Eur J Heart Fail* 2013;**15**(9):966-973.

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.

20. Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease (COMPASS).clinicaltrials.gov: 2016.

21. Aspirin Myocardial Infarction Study Research Group. A randomised, controlled trial of aspirin in persons recovered from myocardial infarction. *JAMA* 1980;**243**:661-668.

22. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;**373**(9678):1849-1860.

23. Baigent C, Collins R, Appleby P, Parish S, Sleight P, Peto R, on behalf of the ISIS-2 Collaborative Group. ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both or neither. *BMJ* 1998;**316**:1337-1343.

24. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Oude OT, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;**372**(19):1791-1800.

25. Michel JB, Virmani R, Arbustini E, Pasterkamp G. Intraplaque haemorrhages as the trigger of plaque vulnerability. *Eur Heart J* 2011;**32**(16):1977-85, 1985a, 1985b, 1985c.