Aspirin for Heart Failure
Theory- or Evidence-Based?

John G.F. Cleland, MD; Sunaina Parsons, MB, ChB

There is fading evidence that chronic aspirin therapy reduces cardiovascular morbidity or mortality. One large trial (The Second International Study of Infarct Survival: ISIS-2) performed 30 years ago showed that aspirin, at a dose of 162.5 mg/d given for just 28 days, reduced mortality compared with placebo after an acute myocardial infarction. This success has never been repeated. Although aspirin must have been discontinued at the end of the double-blind period of ISIS-2, the effect of this short course of aspirin persisted for 10 years. Thus, there is good evidence, in the era before statin therapy or primary angioplasty, that aspirin, given at this dose for this duration, is effective. There is no robust evidence that any other antiplatelet regimen, in terms of dose, agent, or duration, is superior; most subsequent studies having permitted the inclusion of patients receiving lower, nonevidence-based doses of aspirin.

No substantial trial of long-term aspirin therapy for the primary or secondary prevention of cardiac events has ever confirmed this reduction in mortality. No long-term trial after myocardial infarction has ever even studied doses <300 mg/d. No substantial trial of long-term aspirin therapy for the primary or secondary prevention of cardiac events has ever confirmed this reduction in mortality. No long-term trial after myocardial infarction has ever even studied doses <300 mg/d.

The results of meta-analyses have been driven by the ludicrously positive results of some small trials and the absence of small negative trials. This most likely reflects reporting and publication bias, which renders meta-analysis an intrinsically unreliable form of evidence that should be relegated to a method of confirming the results of an adequately powered, definitive trial or for generating hypotheses. Journal editors, unaware of their biases and the damage they might do, are only too willing to publish small implausibly positive results but reluctant to publish negative results unless they are definitive. There is abundant evidence that most coronary events do not provoke symptoms leading to medical attention, and there is some evidence that aspirin may increase the proportion of concealed events. Accounting for why some studies show fewer nonfatal vascular events in patients assigned to aspirin but no reduction in disability or death. Indeed, an increase in sudden death was observed in the US Physician’s Trial. Thus, the evidence that long-term aspirin reduces cardiovascular morbidity or mortality is a statistical illusion and clinical delusion. This does not mean to say that we know that aspirin is ineffective, merely that there is neither adequate evidence for safety nor efficacy.

This issue of Circulation: Heart Failure, Bermingham et al12 assert that aspirin has proven benefit in patients with established ischemic heart disease (IHD). This statement cannot be substantiated by a balanced view of the evidence; nor can the authors’ unreferenced suggestions that aspirin is effective in patients with diabetes mellitus13 or atrial fibrillation.

In an observational study, including propensity analysis, Bermingham et al12 report that aspirin 75 mg/d, given to 828 outpatients with chronic heart failure, was associated with a 30% reduction in hospitalizations for heart failure and a 42% reduction in mortality compared either with 503 patients not taking aspirin or 64 patients taking higher doses of aspirin. Median follow-up was 2 years, with some patients followed for up to 12 years, during which 358 patients had 21 hospitalization for heart failure and 464 died; the cause of death was not provided. The observed associations were not explained by other measured variables nor eliminated by the propensity analysis. If true, this suggests that aspirin 75 mg/d has a larger effect on mortality than observed with any other pharmacological agent for heart failure and greater than either an implantable cardiac defibrillator or cardiac resynchronization therapy. It is implausible, although not impossible, that aspirin truly has an effect of this size.

Could the result reflect differences in the population treated that were either unobserved or not adjusted for? Perhaps higher risk patients did not receive aspirin? Scrutiny of the data reveals that patients who were not taking aspirin were slightly younger, less likely to have ischemic heart disease and tended to have lower plasma concentrations of natriuretic peptides; all factors associated with lower risk. Surprisingly, although aspirin is meant to exert its effects on atherosclerotic disease, the association between aspirin and reduced mortality was consistently stronger among patients who had less evidence of vascular disease. However, of those not taking aspirin, 66% were taking warfarin compared with 31% of those on low-dose aspirin, a difference that was not corrected by the propensity analysis. Most but not all of the warfarin use could be attributed to the presence of atrial fibrillation. Indeed, the strongest association between low-dose aspirin and reduced mortality was among patients with atrial fibrillation, most of whom also seemed to be taking warfarin. Perhaps it is the combination of aspirin and warfarin that is of interest rather than aspirin alone? Interestingly, a large outcome study of low-dose rivaroxaban added to background aspirin <100 mg/d has just started (Cardiovascular Outcome Modification, Measurement AND Evaluation of Rivaroxaban in patients with Heart Failure [COMMANDER-HF]), based on the observation that low-dose rivaroxaban had striking effects of mortality among patients with an acute coronary event complicated by heart failure. This study
will provide evidence for the safety and efficacy of rivaroxaban but not the need to coprescribe aspirin.

The use of aspirin in cardiovascular medicine is based mainly on meta-analyses of questionable validity because of reporting and publication bias and on the theoretical construct that both atherosclerosis and vascular events are closely linked to thrombosis that might be prevented by aspirin. However, there is considerable evidence that atherosclerotic plaque growth and rupture are related to hemorrhage from fragile capillary in-growth from the vasa vasora; a concept that hardly encourages the use of aspirin. Perhaps both theoretical concepts hold some truth, in which case aspirin may do harm and good in equal measure in the long term, rendering it clinically useless. Aspirin is not harmless. Even low doses of aspirin may have an adverse effect on renal function, and aspirin might be responsible for the epidemic of iron deficiency in the heart failure population, which is linked to an adverse prognosis.

There is no doubt that Bermingham et al have identified a strong association between aspirin use and outcome in their population using robust and appropriate analytic techniques. The data and the analyses are what they are. However, their interpretation and that of the media of these data are at fault. The authors rightly conclude that more trials of low-dose aspirin are required, although they failed to explicitly state the need for randomization. Unfortunately, just such a study being performed in the United Kingdom has had its funding withdrawn because of administrative delays. Only 87 patients were randomized to aspirin 75 mg/d or clopidogrel 75 mg/d. After 6 months, most trends were in favor of clopidogrel (abstract submitted). The authors should be chided for stating in their conclusions that their analysis shows either a significant reduction in risk or benefit with aspirin. These terms imply that aspirin has changed something. All their analysis shows is an association that may reflect prescribing bias, unmeasured confounders, or chance rather than drug effect. It is time to take the hope, hype, and bias out of the aspirin story. There is no robust evidence of a cardiovascular benefit with aspirin except for short-term use in the immediate aftermath of a myocardial infarction. There is plenty of evidence from randomized controlled trials that patients withdrawn from aspirin do just as well or better than those who continue on it; a finding supported by the current analysis. This analysis by Bermingham et al should be a call to arms to perform placebo-controlled trials of low-dose aspirin not only in patients with heart failure but for many other cardiovascular problems where it is the current fashion to recommend aspirin. If low-dose aspirin does reduce mortality by 42%, then the trials would not have to be large or long. To quote Einstein, “In theory, theory and practice are the same. In practice, they are not.” When will the speculation over the benefits of aspirin be replaced by some facts?

Disclosures
Dr Cleland is a National Institute of Health Research (UK) Senior Investigator.

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