What do Cardiology & Homoeopathy Have in Common?

Aspirin?

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Convictions are more dangerous enemies of truth than lies.

Friedrich Nietschze

The title of this article will upset many cardiologists and homoeopathists. However, there is as much evidence from randomized, placebo-controlled trials that use of long-term aspirin delivers cardiovascular benefits as there is for any homeopathic remedy and neither discipline knows what dose of aspirin is effective; presumably a "homeopathic dose" would be safe!. Is the current belief in aspirin just driven by publication-bias and an uncritical, semi-religious belief in inherited teachings? After all, aspirin is a non-steroidal anti-inflammatory drug (NSAID) and other agents of this class have caused concerns about increased cardiovascular risk. Why should aspirin be different?

In this edition of JACC-HF, the Warfarin Versus Aspirin in Reduced Ejection Fraction (WARCEF) trial investigators report that, compared to warfarin, aspirin does not increase the risk of hospitalization for heart failure (1). This result contrasts with those of two previous trials that showed an increase in such risk (2, 3). In WARCEF, 2305 patients with heart failure in sinus rhythm and with a left ventricular ejection fraction $\leq$35% were randomized to either adjusted-dose warfarin with target international normalized ratio of 2.75 (acceptable range: 2.0–3.5) or aspirin 325 mg daily in a double-blind, double-dummy design. As such, WARCEF was both the largest and most methodologically robust trial comparing warfarin and aspirin. These results allay some of the fears raised by previous trials that aspirin could increase the risk of congestion but provides no evidence that either warfarin or aspirin should be given routinely to patients with heart failure in sinus rhythm. What a great opportunity to reduce unhelpful polypharmacy!; not only of anti-thrombotic therapy but also of potentially harmful treatments given to reduce the risk of gastro-intestinal haemorrhage.

Aspirin is a non-specific cyclo-oxygenase inhibitor that blocks the production of a range of prostaglandins. Many prostaglandins are thought to have beneficial actions, including vasorelaxation, increases in glomerular filtration rate and reductions in adhesion of platelets to vessel walls, whilst others, such as thromboxane, increase platelet aggregation, providing a theory to support the supposed benefits of aspirin in patients with coronary artery disease. Aspirin is a 'nuclear' option, destroying indiscriminately both the benefits and risks conferred by prostaglandins. The balance of beneficial and harmful effects of aspirin is likely to vary according to the clinical setting. In the presence of ulcerated plaque, benefit may greatly outweigh risk. In the presence of stable plaque, the balance is less clear. Aspirin-induced haemorrhage into plaque, aggravated by inhibiting thromboxane, may de-stabilise it. In heart failure, prostacyclin may be an important counter-regulatory mechanism that causes vasorelaxation and reduces sodium retention thereby reducing the risk of worsening heart failure. This may be one mechanism by which ACE inhibitors exert benefit.

Few trials have randomised patients to receive anti-thrombotic or not in patients with heart failure. The largest of these (WASH) include only 279 patients but showed some evidence of harm with aspirin; warfarin was not obviously superior to receiving no anti-thrombotic treatment at all (2). There is a great deal of evidence that the benefits of ACE inhibitors are diminished in the presence of anti-platelet therapy (4), predominantly aspirin, for which there are at least four possible explanations; it may not be true and is just a chance finding in one of many retrospective analyses (unlikely given the strength of the interaction); aspirin may interfere with the beneficial effects of ACE inhibitors, which is biologically plausible; ACE inhibitors and aspirin may exert benefit through the same mechanism but this is not additive (also biologically plausible); alternatively, antiplatelet therapy may just be a surrogate for ischaemic heart disease and such patients derive less benefit from an ACEi. Further retrospective analyses are unlikely to resolve, with confidence,

which of these explanations is true. The evidence for an interaction between aspirin and other disease-modifying therapies for heart failure, including beta-blockers and mineralo-corticoid antagonists is less strong and subject to similar explanations (5).

The major evidence-gap is with placebo-controlled studies. There is a stronger evidence-base comparing different anti-thrombotic therapies in patients with heart failure. Randomized trials comparing aspirin and clopidogrel, an antiplatelet agent that does not inhibit cyclooxygenase, suggest that glomerular filtration rate and exercise capacity were greater and plasma concentrations of natriuretic peptides were lower on clopidogrel but no difference in morbidity or mortality was observed (6). Randomized trials of aspirin compared to warfarin, show that warfarin reduces the risk of stroke but increases major bleeding; overall mortality was similar on aspirin and warfarin (2, 3). The absolute reduction in stroke events was about one event for every 200 patient-years of follow-up; about 20% of strokes were fatal and only one third of survivors had moderate or severe persisting disability. The importance of occult or incident atrial fibrillation to strokes in patients with heart failure is uncertain. In summary, we have little evidence that one anti-thrombotic agent is superior to another and little evidence that any agent is superior to none.

So why do we use anti-thrombotic agents in heart failure? Cardiologists will generally respond that they are not treating the heart failure, they are treating the associated coronary artery disease. So what evidence is there that patients with coronary artery disease benefit from long-term aspirin? Surprisingly, at least to most cardiologists, no trial of long-term aspirin administration to patients with proven coronary disease has demonstrated a reduction in mortality. Of special relevance to patients with heart failure, all substantial, placebo-controlled, long-term trials of aspirin after a myocardial infraction have used >300mg/day. Indeed, these studies, conducted in the 1970's with high doses of aspirin, with or without dipyridamole, before the modern era of heart failure diagnosis and therapy, showed trends to a worse outcome in patients with heart failure if they were assigned

to aspirin (Figure 1A)(7, 8). The aspirin-advocate, now exasperated, desperate and confused, starts clutching for straws. What about the anti-platelet trialists meta-analysis! This is poor evidence. If an intervention requires a meta-analysis of large, individually-neutral clinical trials, then the benefit is unlikely to be clinically useful. Moreover, the results of the antiplatelet meta-analysis for patients after a myocardial infarction is driven by improbably large effects in smaller trials; larger trials were neutral or trended to harm (Figure 1B).

The aspirin-advocate, even more desperate by this time, exclaims "but these trials are old and used too high a dose of aspirin". I agree, but absence of evidence is a poor argument to do something – imagine the mess we would get into with this approach to care! The only substantial placebo-controlled trial of aspirin after myocardial infarction (The Second International Study of Infarct Survival; ISIS-2) may then be mentioned. This trial showed a benefit for patients assigned to aspirin for up to 10 years after the event. However, aspirin was only administered for 28 days; the study provides no support for long-term aspirin use. Perhaps a course of aspirin should be given after a myocardial infarction just as we might give a course of antibiotics for pneumonia? How did we get into the mess of giving life-long aspirin based on this evidence? Finally, the cardiologist might invoke the US Physicians study of healthy volunteers. After 100,000 participant-years of follow-up this study was stopped for futility, showing just one cardiovascular death difference between aspirin and placebo. Hardly a positive result! True, there was a reduction in non-fatal myocardial infarction but why this did not translate into a reduction in mortality has never been explained; perhaps an increase in aspirin-induced sudden death is the explanation? (5, 9)

If we are going to use aspirin for generations to come, we should know which doses are effective and safe. Unfortunately, dose-comparison studies are not very helpful because, if no aspirin is not known to be effective there is no reference-dose? In the acute setting, few new anti-platelet agents

have built on the design of the only positive trial (ISIS-2) and shown that long-term anti-platelet therapy is superior to short-term therapy. Recent reports of dual anti-platelet trials suggest that shorter courses of therapy may be superior to longer ones. Perhaps 28 days would suffice? This has enormous financial repercussions and is important for patients who complain about polypharmacy. Recently, it was announced that a study comparing low-dose rivaroxaban, aspirin and the combination was stopped because one or both rivaroxaban arms were superior to aspirin. If rivaroxaban monotherapy is not inferior to the combination then it might become the new gold-standard against which other treatments should be tested. The results of a large comparing low-dose rivaroxaban to placebo patients with HFrEF are keenly awaited (10), although unfortunately the study is conducted on a background of anti-platelet therapy.

In summary, research into anti-thrombotic therapy could be entering a golden-era after dark days of dogma. If we are uncertain, we can progress. If we are certain and we are wrong, we are in trouble. As Nietzsche said, “convictions are more dangerous enemies of truth than lies”.

Legends:

Figure 1A:
The Two Largest, Late-Initiation Long-Term Mortality Trials Comparing Aspirin (or Aspirin & Dipyridamole) to Placebo After Myocardial Infarction
NYHA = New York Heart Association Class I = asymptomatic; II-III = symptoms of heart failure on exertion
AMIS = Aspirin Myocardial Infarction Study
PARIS-II = Persantine-Aspirin ReInfarction Study. Part II.
Asasantin was a rather sinister proprietary name given to the combination of aspirin and dypridamole
RexR = Relative Excess Risk
RRR = Relative Risk Reduction

Figure 1B:
Long term trials of comparing placebo with anti-platelet agents initiated later after myocardial infarction. (see References 16 and 20 for relevant trials)
The X-axis shows the odds ratio for mortality – points to the right suggest benefit
The Y-axis shows the statistical weight of the study – the larger the number the greater the statistical weight
The point at the bottom of the graph showing a trend to harm represents the Acute Myocardial Infarction Study

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