

## Crucial primary care involvement in the ASPREE trial: implications for future research

James P Sheppard, Chris C Butler

Although aspirin medications prevent subsequent cardiovascular events,(1) meta-analyses of randomised trials have found that, overall, they do more harm than good when used for primary prevention.(2) The recently published ASPREE trial(3-5) confirmed that this holds true for older people without cardiovascular disease, dementia or physical disability. This well conducted trial, the largest undertaken in Australia, compared low dose aspirin to placebo in 19,114 participants and found no benefit over placebo in terms of disability-free survival,(5) cardiovascular disease(4) or fatal cancer.(3) However, there was evidence of harm, with an increased risk of death and bleeding in participants allocated to aspirin.(3, 4)

These results confirm the recommendations of previous clinical guidelines(6, 7) which counsel caution when considering aspirin prescription for primary prevention. The study also highlights the importance of recruiting a population representative of those for whom the intervention would be targeted to in routine care. In ASPREE, event rates for cardiovascular disease were 11.3 per 1000 patient-years, only around half what had been anticipated in the original trial protocol (22.3 per 1000 patient-years), which was based on previous prevention trials conducted predominantly in secondary care. These lower than anticipated event rates resulted in a less precise estimate of the treatment effect, and suggest that any potentially observed reduction in cardiovascular disease risk would likely translate to a very small absolute risk reduction in a primary care setting. This is critical when considering the relative benefits and harms of treatment and emphasises why it is important to recruit a representative population.

Pragmatic, primary care based trials are often perceived challenging, due to the complex nature of general practice. In this month's issue of *MJA*, xx and colleagues describe the approaches taken by investigators in Australia to engage GPs and recruit patients from primary care into ASPREE; the 2,717 participating GPs randomised 16,035 participants. To encourage recruitment, ASPREE investigators reimbursed GPs, included them as investigators and used local population data to target specific areas with high numbers of older patients. Of interest was the suggestion that GPs were motivated by their interest in the research question, which suggests that engaging them early in the research process may be important in identifying relevant and important questions. GPs based in areas of higher socio-economic status were more likely to recruit participants in the study and this may reflect differences in practices which are well organised and adequately funded compared to those in need of investment serving more socially deprived areas.

In the UK, investment in the Clinical Research Network (CRN) standing infrastructure has addressed a number of the challenges faced by the ASPREE trial investigators. This network enables large scale clinical studies to be rolled out across regions of the UK, using a single portal for approval processes and a standardised approach for engaging and working with individual practices. Local CRN facilitators build on ongoing relationships with local GP investigators to introduce studies, help with electronic health record searches, and often provide help with recruitment and follow up tasks. The network is supported by national funding and works through provision of nurses/facilitators and direct payments to GPs involved in consenting participants. In some respects, the ASPREE investigators had to create their own CRN capability and build up considerable research enthusiasm

in primary care. Establishment of an analogous national CRN in Australia could ensure the dividend of such investment continues to be reaped even once an individual trial is complete.

A further step would be to embed trials like ASPREE into routine care by maximising existing electronic records and systems to alert clinicians to potential trial participants and for follow-up. Incorporating these capabilities into the establishment of ongoing 'platform' trials would allow real world estimates of effectiveness to be fed back more or less in real time.<sup>(8)</sup> Such trials are based on a master protocol which allows the evaluation of many interventions simultaneously and in series. Analysis is ongoing rather than a single event that is performed once a predefined sample size has been reached, and it uses the data already accumulated for the assessment of current and subsequently introduced interventions. Such an approach holds much promise, but is yet to be realised in primary care due to technical and regulatory barriers.<sup>(9)</sup>

The ASPREE study reminds us of the need to refine the methods and establish ongoing infrastructure for primary care patients to be more routinely included in large scale clinical trials. Such an infrastructure will enable critical information such as was generated by ASPREE to be constantly updated and associated questions answered more efficiently.

### **Competing interests**

No relevant disclosures.

### **Funding sources**

JS receives funding from the Wellcome Trust/Royal Society via a Sir Henry Dale Fellowship (ref: 211182/Z/18/Z).

### **Acknowledgements**

None.

**Word count:** 749

### **References**

1. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009;373(9678):1849-60.
2. Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Erqou S, Sattar N, et al. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. *Arch Intern Med*. 2012;172(3):209-16.

3. McNeil JJ, Nelson MR, Woods RL, Lockery JE, Wolfe R, Reid CM, et al. Effect of Aspirin on All-Cause Mortality in the Healthy Elderly. *N Engl J Med*. 2018;379(16):1519-28.
4. McNeil JJ, Wolfe R, Woods RL, Tonkin AM, Donnan GA, Nelson MR, et al. Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly. *N Engl J Med*. 2018;379(16):1509-18.
5. McNeil JJ, Woods RL, Nelson MR, Reid CM, Kirpach B, Wolfe R, et al. Effect of Aspirin on Disability-free Survival in the Healthy Elderly. *N Engl J Med*. 2018;379(16):1499-508.
6. Nelson MR, Doust JA. Primary prevention of cardiovascular disease: new guidelines, technologies and therapies. *Med J Aust*. 2013;198(11):606-10.
7. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37(29):2315-81.
8. Butler CC, Connor JT, Lewis RJ, Broglio K, Saville BR, Cook J, et al. Answering patient-centred questions efficiently: response-adaptive platform trials in primary care. *Br J Gen Pract*. 2018;68(671):294-5.
9. Gulliford MC, van Staa TP, McDermott L, McCann G, Charlton J, Dregan A. Cluster randomized trials utilizing primary care electronic health records: methodological issues in design, conduct, and analysis (eCRT Study). *Trials*. 2014;15:220.