

Should aspirin be used for the primary prevention of cardiovascular disease in people with diabetes?

Timothy ME Davis, Brett A Sillars and Wendy A Davis

TO THE EDITOR: The ASPREE (ASPIrin in Reducing Events in the Elderly) study may provide useful data on the benefits and risks of aspirin therapy in patients aged ≥ 70 years, as described by Woods and colleagues.¹ However, the decision to allow general practitioner co-investigators to “help decide whether the patient is a suitable candidate for the placebo-controlled trial” introduces a source of selection bias that may limit the generalisability of the results. Without pre-specified objective selection criteria, it is likely that primary-prevention patients assessed by GP co-investigators as being at high vascular risk will be excluded because the GPs believe they should be taking antiplatelet agents. Similarly, those at low risk may be thought inappropriate participants because the risks of random allocation to this therapy might outweigh the perceived benefits, as has been shown in previous meta-analyses.^{2,3} ASPREE may end up with a disproportionate number of intermediate-risk patients.

In the case of diabetes, a recent observational study from our group highlighted patients with diabetes and retinopathy and those taking a sulfonylurea as being at increased risk of complicated peptic ulcer disease.⁴ By contrast, we did not find that aspirin use, positive serological results for *Helicobacter pylori*, or the interaction of these two factors predicted complicated peptic ulcer disease. If GP co-investigators were aware of these findings, they might also influence the screening and recruitment of patients with diabetes to ASPREE.

According to the trial registration details (ISRCTN83772183), patients with diabetes were eligible for recruitment to ASPREE from late February 2009, even though the trial started 6 years ago.⁵ Given this delayed eligibility, the fact that a substantial proportion of patients with diabetes older than 70 years will already have vascular disease, and the expected total sample size of 19 000,¹ the trial might include fewer than 1000 patients with diabetes and thus have insufficient statistical power to assess the risks and benefits of aspirin for primary prevention in this important subgroup.

We question why subjective assessment forms part of patient selection for a potentially important study such as ASPREE, and also

what steps the investigators are taking to determine whether the sample they recruit is representative. In addition, details of planned statistical analyses involving diabetic participants in this non-superiority trial would be reassuring.

Timothy ME Davis, Professor of Medicine
Brett A Sillars, PhD Student

Wendy A Davis, Research Fellow

School of Medicine and Pharmacology, University of Western Australia, Fremantle Hospital, Fremantle, WA.

tdavis@cyllene.uwa.edu.au

- 1 Woods RL, Tonkin AM, Nelson MR, et al. Should aspirin be used for the primary prevention of cardiovascular disease in people with diabetes [editorial]? *Med J Aust* 2009; 190: 614-615.
- 2 Hayden M, Pignone M, Phillips C, Mulrow C. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the US Preventive Services Task Force. *Ann Intern Med* 2002; 136: 161-172.
- 3 Baigent C, Blackwell L, Collins 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: 1849-1860.
- 4 Schimke K, Chubb SA, Davis WA, et al. Antiplatelet therapy, *Helicobacter pylori* infection and complicated peptic ulcer disease in diabetes: the Fremantle Diabetes Study. *Diabet Med* 2009; 26: 70-75.
- 5 International Standard Randomised Controlled Trial Number Register. ASPirin in Reducing Events in the Elderly. <http://www.controlled-trials.com/ISRCTN83772183/> (accessed Aug 2009). □

Robyn L Woods, Mark R Nelson,
Andrew M Tonkin and Christopher M Reid

IN REPLY: Recruitment to clinical trials through general practice is representative of the population, as a high proportion of all Australians regularly attend their general practitioners.¹ GP co-investigators are appropriate to decide whether their patients are suitable for the ASPREE (ASPIrin in Reducing Events in the Elderly) study because their assessment includes objective inclusion and exclusion criteria that must be satisfied before enrolment in the study (clinical trial registration number ISRCTN83772183),² as well as patient-specific potential risks with using aspirin, and known medical factors likely to influence patient survival during the trial. These include the risk of complicated peptic ulcer disease in patients with diabetes treated with a sulfonylurea.³ GP co-investigators support participation in ASPREE by eligible patients because of aspirin's therapeutic equipoise for primary prevention in older patients⁴ and in those with diabetes.⁵

Because of age alone, ASPREE participants will be at least at intermediate risk of cardiovascular disease and also at increased risk of bleeding. Determining the aspirin balance

underpins the importance of collecting more data in older people, who have been under-represented in previous primary prevention trials.

ASPREE is a superiority trial with pre-specified subgroup analyses, including for the subgroup with diabetes.² The study is powered to address the primary question reliably in the total cohort rather than subgroups. To date, fewer than 500 participants have been randomly allocated, with recruitment slowed subject to National Institutes of Health funding deliberations. Recruitment will be reinvigorated in late 2009, and will continue to include people with diabetes.

Robyn L Woods, Senior Research Fellow¹

Mark R Nelson, Professor²

Andrew M Tonkin, Professor¹

Christopher M Reid, Associate Professor¹

¹ Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC.

² Menzies Research Institute, University of Tasmania, Hobart, TAS.

robyn.woods@med.monash.edu.au

1 Knox SA, Harrison CM, Britt HC, Henderson JV. Estimating prevalence of common chronic morbidities in Australia. *Med J Aust* 2008; 189: 66-70.

2 Monash University. Medicine, Nursing and Health Sciences. ASPREE (ASpirin in Reducing Events in the Elderly). A placebo controlled trial of low dose aspirin in the elderly. <http://www.med.monash.edu.au/epidemiology/cardiore/aspree.html> (accessed Jul 2009).

3 Schimke K, Chubb SA, Davis WA, et al. Antiplatelet therapy, *Helicobacter pylori* infection and complicated peptic ulcer disease in diabetes: the Fremantle Diabetes Study. *Diabet Med* 2009; 26: 70-75.

4 Nelson MR, Reid CM, Ames DA, et al. Feasibility of conducting a primary prevention trial of low-dose aspirin for major adverse cardiovascular events in older people in Australia: results from the ASPIrin in Reducing Events in the Elderly (ASPREE) pilot study. *Med J Aust* 2008; 189: 105-109.

5 Woods RL, Tonkin AM, Nelson MR, et al. Should aspirin be used for the primary prevention of cardiovascular disease in people with diabetes [editorial]? *Med J Aust* 2009; 190: 614-615. □