Aspirin in primary prevention

Although the benefits of aspirin in the secondary prevention of cardiovascular disease (CVD) are clear, there has been ongoing uncertainty about low-dose aspirin for primary prevention, with NICE and SIGN guidelines not recommending its use. The American Diabetes Association position statement, however, states that low-dose aspirin (75–162 mg/day) is reasonable for those with diabetes who are at increased CVD risk (10-year CVD event risk >10%) and who are not at increased risk of bleeding (Pignone et al, 2010). It does not recommend low-dose aspirin for those whose 10-year CVD risk is <5% but suggests considering it for those with diabetes and a risk between 5–10%.

Previously, a meta-analysis of 11 randomised controlled trials of aspirin in primary prevention, involving more than 1 million people with generally low CVD risk, demonstrated a 22% reduction in non-fatal myocardial infarction (MI) and a 6% reduction in mortality; however, there was a 33% increase in haemorrhagic stroke and a 59% increase in gastrointestinal bleeds (Guirguis-Blake et al, 2016), supporting the UK stance.

The recent publication of a plethora of papers on aspirin and primary prevention suggested it would be useful to revisit this topic. The four studies, whose names all confusingly begin with A, were designed to explore the benefits and risk of aspirin for primary prevention in populations at different levels of cardiovascular risk. ASPREE (McNeil et al, 2018a; 2018b; 2018c) looked at disability-free survival, mortality and CVD risk with low-dose aspirin in older people; ARRIVE (Gaziano et al, 2018) aimed to study aspirin use in those at moderate CVD risk (10-year risk 20–30%); and ASCEND (ASCEND Study Collaborative Group, 2018) and ACCEPT-D (study not yet published) evaluated the risks and benefits in the higher-risk population with diabetes. All of these studies used a standard dose of aspirin 100 mg daily.

Since the ASPREE study excluded people with CVD or significant disability at enrolment, and recruited people aged 70 years and over (65 years and over in black and Hispanic people), participants were likely to be at low CVD risk. The primary endpoint was a composite of death, dementia and persistent physical disability, with secondary endpoints of major haemorrhage and CVD (fatal CVD, non-fatal MI, fatal or non-fatal stroke, or hospitalisation for heart failure).

There was no difference in CVD outcomes between the treatment and placebo groups (hazard ratio [HR], 0.95; 95% confidence interval [CI], 0.83–1.08), but there was a significantly higher rate of major haemorrhage (HR, 1.38; 95% CI, 1.18–1.62) in the treatment group (McNeil et al, 2018a). There was no difference in disability-free survival between the groups (McNeil et al, 2018b). There was a small, just significant, increase in mortality in the aspirin-treated group (HR, 1.14; 95% CI, 1.01–1.29; McNeil et al, 2018c). This was mainly attributable to increased risk of death from a variety of cancers (HR, 1.31; 95% CI, 1.10–1.56), and translated to 1.6 excess deaths per 1000 people treated. Previously it was proposed that long-term, low-dose aspirin may decrease the risk of colon cancer (Rothwell et al, 2011), so this new finding will require further study before it changes our practice.

ARRIVE (Gaziano et al, 2018) was a double-blind, placebo-controlled, randomised controlled trial of more than 12 500 men aged ≥55 years and women aged ≥60 years deemed to have moderate CVD risk; the study excluded those with diabetes or a history of gastrointestinal or other bleeding. In the intention-to-treat analysis, over a median follow-up of 60 months, the primary endpoint of time to first occurrence of CV death, MI, unstable angina, stroke or transient ischaemic attack (TIA) was not significantly different between the treatment and placebo groups (HR, 0.96; 95% CI, 0.81–1.13), but there was an approximate doubling of gastrointestinal bleeds (mainly mild; HR, 2.11; 95% CI, 1.36–3.28). The per protocol analysis demonstrated

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a non-significant reduction in fatal or non-fatal MI but no reduction in mortality, resulting in a reduced HR for the primary endpoint to 0.81 (95% CI, 0.64–1.02).

On publication, the authors concluded their population was actually at significantly lower risk than their scoring predicted, resulting in low numbers of events. As a result, the primary endpoint was altered to include unstable angina and TIA, and the duration of the study was extended. An associated editorial concluded that this study again looked at those with low CVD risk and could, therefore, not inform our management of those with moderate CVD risk, as was planned (Capodanno and Angiolillo, 2018). The editorial also raised the issue of whether doses of aspirin should be individualised based on body weight.

In secondary prevention, the ANDAMAN study is looking at once-daily versus twice-daily aspirin, and ADAPTABLE is comparing high-dose versus low-dose aspirin. These studies are ongoing.

The publication of the long-awaited ASCEND trial (ASCEND Study Collaborative Group, 2018) prompted us to invite Colin Kenny to review the evidence base for low-dose aspirin in people with diabetes in our *Studies That Changed Clinical Practice* series. To complement this, *Table 1* provides a summary of the new papers on aspirin for primary prevention in those with and without diabetes, which I hope will help clarify the exclusions, primary and secondary endpoints and, ultimately, the risks and benefits identified in each of the studies.

In this issue

I was reflecting with our medical students recently on the depth of learning available from rigorously scrutinising our decision-making in even straightforward consultations, and the value of applying our diabetes knowledge to managing specific patients. This set me thinking again about how we might share case-based discussion in the *Journal*. Many months ago, our Editorial Board shared their ideas too, and in this issue we begin a new series learning from clinical cases. To help us manage our first case, we have invited experienced primary care clinicians Gwen Hall, Nigel Campbell and Patrick Holmes to provide their unique perspectives on specific aspects of management. "Rory" is diagnosed with type 2 diabetes during admission with an MI – a common scenario which often results, as here, in a shell-shocked patient attending surgery dismayed at their collection of discharge medications and in denial about their health problems. I hope you will make the time to think about how you and your team might manage Rory, before reading the clinicians' perspectives and our key messages distilled from the case. As with most of the people we see, there is no one correct management plan, but we hope that readers will gain insight or a nugget of new learning from applying your knowledge and reading how colleagues manage Rory. Tell us what works and how we could make this new series more useful, and if you would like us to feature a challenging case that you have managed then send it to us at dpc@omniamed.com.

Also in this issue, Mike Kirby reminds us about the latest testosterone deficiency guidelines from the British Society for Sexual Medicine; Chris Askew, Chief Executive of Diabetes UK, outlines the benefits of their Primary Care Network; and David Morris tackles the definition and diagnosis of steroid-induced hyperglycaemia and diabetes. We continue our series on the diabetes multidisciplinary team, with Jen Bateman helping us understand the role of psychologists in diabetes care, while Mohammad Abdool, Kamlesh Khunti and Sam Seidu share South Asian diet resources in our *Tools to Support Practice* series. We hope there is something of interest for everyone.

NICE updated the PH38 public health guideline, *Type 2 diabetes: prevention in people at high risk*, in 2017, so we have updated our NHS Wales-funded e-learning module, and this is our linked module for this issue. The flier allows you to identify whether completing the module would be useful for you or your team. Successfully completing the self-assessment provides a certificate to upload into your appraisal folder.

Finally, we are excited to share that Colin Kenny, founder member of the Primary Care Diabetes Society and previous Editor-in-Chief of this Journal, has been awarded a well-deserved British Empire Medal for his services to diabetes care in Northern Ireland. We pay tribute here.

This month I have attended the European Association for the Study of Diabetes conference in Berlin, and I will share breaking news stories from that in our next issue. I look forward to meeting up with some of you at the PCDS Scotland conference later this month, and at the PCDS National conference in November, and I hope you will share with me your ideas for topics we should cover in future issues of the *Journal*. Both conferences promise to be excellent, so make space in your diary and book your place today! ■

ASCEND Study Collaborative Group (2018) Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med* 26 Aug [Epub ahead of print]. doi: 10.1056/NEJMoa1804988

Capodanno D, Angiolillo DJ (2018) Aspirin for primary prevention of cardiovascular disease. *Lancet* **392**: 988–90

Cook NR, Lee IM, Zhang SM et al (2013) Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of a randomized trial. *Ann Intern Med* **159**: 77–85

Gaziano JM, Brotons C, Coppolecchia R et al; ARRIVE Executive Committee (2018) Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet* **392**: 1036–46

Guirguis-Blake JM, Evans CV, Senger CA et al (2016) Aspirin for the primary prevention of cardiovascular events: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med* **164**: 804–13

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McNeil JJ, Woods RL, Nelson MR et al; ASPREE Investigator Group (2018b) Effect of aspirin on disability-free survival in the healthy elderly. *N Engl J Med* 16 Sep [Epub ahead of print]. doi: 10.1056/NEJMoa1800722

McNeil JJ, Nelson MR, Woods RL et al; ASPREE Investigator Group (2018c) Effect of aspirin on all-cause mortality in the healthy elderly. *N Engl J Med* 16 Sep [Epub ahead of print]. doi: 10.1056/NEJMoa1803955

Pignone M, Alberts MJ, Colwell JA et al (2010) Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. *Diabetes Care* **33**: 1395–402

Rothwell PM, Fowkes FG, Belch JF et al (2011) Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *Lancet* **377**: 31–41

Table 1. Summary of the findings on aspirin for primary prevention from three recently published studies.

Study name	*n*	Inclusions	Key exclusions	Primary outcome	Results (intention to treat)	Secondary outcome(s)	Results	Duration	Comments
ARRIVE (Gaziano et al, 2018)	12 546; RCT placebo-controlled; 100 mg aspirin	Men ≥55 years and women ≥60 years at moderate risk (10-year CVD risk of 20–30%)	• High risk of GI or other bleeding • Previous CVD event • Other need for aspirin or anticoagulation • Diabetes	• Composite of CV death, first MI, unstable angina, stroke or TIA • Haemorrhagic events and other adverse events	4.29 vs 4.48% (HR, 0.96 [95% CI, 0.81–1.13; *P*=0.60]) GI bleeding (mostly mild) 0.97 vs 0.46% (HR, 2.11 [95% CI, 1.36–3.28; *P*=0.007]) Serious adverse events 20.19% vs 20.89%	Composite of time to CV death, MI or stroke; time to each component individually; time to first occurrence of unstable angina, TIA or any death. (Cancer data reported elsewhere.)	All non-significant	60 months median	"The event rate was much lower than expected... making the study more representative of a low-risk population. The role of aspirin... among patients at moderate risk could therefore not be addressed."
ASCEND (ASCEND Study Collaborative Group (2018)	15 480; RCT placebo-controlled; 100 mg aspirin	Diabetes and no evidence of existing CVD	Evidence of CVD	• First serious vascular event (CV death, MI, stroke, TIA), excluding intracranial haemorrhage Primary safety outcome: • First major bleeding event (intracranial haemorrhage, sight-threatening retinal bleed, GI bleed or other bleed)	8.5% vs 9.6% (HR, 0.88 [95% CI, 0.79–0.97; *P*=0.01]) 4.1 vs 3.2% excess GI bleeds (HR, 1.29 [95% CI, 1.09–1.52; *P*=0.003])	• GI tract cancer • All cancers	2% in both groups 11.6% vs 11.5% (NS)	7.4 years	"Absolute benefits were counterbalanced by the bleeding hazard."
ASPREE (McNeil et al (2018a; 2018b; 2018c)	19 114; RCT placebo-controlled; 100 mg aspirin	Healthy, community-dwelling elderly men and women ≥70 years (≥65 years black and Hispanic)	• Adherence <80% in 4-week run-in • Dementia, high risk of bleeding, aspirin contraindication	Disability-free survival (composite of death, dementia or persisting disability)	21.5 vs 21.2 events/1000 patient-years (HR, 1.01 [95% CI, 0.92–1.11; *P*=0.79])	• Major haemorrhage • Death • Fatal or non-fatal CVD • Fatal or non-fatal CVD • Dementia • Persisting disability • Mild cognitive impairment • Depression	8.6 vs 6.2 events/1000 patient-years (HR, 1.38 [95% CI, 1.18–1.62; *P*<0.001]) 12.7 vs 11.1 events/1000 patient-years (HR, 1.14 [95% CI, 1.01–1.29]) 3.1% vs 2.3% (HR,1.31 [95% CI, 1.10–1.56]) 10.7 vs 11.3 events/1000 patient-years (HR, 0.95 [95% CI, 0.83–1.08])	4.7 years	"Daily use of aspirin did not provide a benefit with regards to the primary end-point of disability-free survival among older adults." "Higher all-cause mortality among those treated with aspirin, attributed primarily to cancer-related death... this result was unexpected and should be interpreted with caution."

CI=confidence interval; CVD=cardiovascular disease; GI=gastrointestinal; HR=hazard ratio; MI=myocardial infarction; NS=not significant; RCT=randomised controlled trial; TIA=transient ischaemic attack.