The aspirin controversy in primary prevention

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Purpose of review
Apparently conflicting meta-analysis results have led to renewed debate about the role of aspirin for the primary prevention of cardiovascular disease. We review the results of meta-analyses comparing aspirin with placebo or no aspirin for the primary prevention of cardiovascular disease and critically evaluate whether aspirin provides a net benefit.

Recent findings
The results of four independently conducted meta-analyses between 2009 and 2012 involving between 95 000 and 102 621 individuals at low risk of cardiovascular disease are consistent with the results of the 2002 Antithrombotic Trialists' Collaboration meta-analysis, which found that aspirin reduces cardiovascular events primarily by reducing nonfatal myocardial infarction (MI). There is no convincing evidence that aspirin reduces cardiovascular mortality, but estimates from all of the meta-analyses suggest a modest reduction in all-cause mortality. Aspirin reduces ischaemic stroke but increases haemorrhagic stroke and major bleeding.

Summary
The meta-analysis results consistently indicate that, in individuals at low risk for cardiovascular disease, aspirin reduces the risk of MI at the cost of an increase in major bleeding and produces a modest nominally significant reduction in total mortality. These results suggest that recommendations for primary prevention with aspirin should be individualized, taking into account the balance between benefits and risks and individual values and preferences.

Keywords
aspirin, cardiovascular disease, myocardial infarction, primary prevention, stroke

INTRODUCTION

Aspirin has gained widespread acceptance as the cornerstone of cardiovascular disease prevention. Its role in patients with established cardiovascular disease (secondary prevention) is well established, with strong evidence for a survival advantage. However, the role of aspirin in primary prevention is less certain, with recently updated meta-analyses [1–4] producing apparently conflicting results. This uncertainty is reflected by differences between guidelines and other expert groups in their recommendations for the use of aspirin (Table 1). The most recent guidelines from the American College of Chest Physicians (ACCP) [5▪], American Heart Association (AHA) [6], US Preventive Services Task Force [7] and European Society of Cardiology (ESC) [8] recommend the selective use of aspirin for primary prevention in older patients and in those otherwise deemed to be at higher risk. However, the Antithrombotic Trialists' Collaboration (ATTC) [1] and others [9] have expressed uncertainty about the benefit of aspirin for primary prevention [1] or recommend against its use for this indication [9].

To better understand the uncertainty about the role of aspirin for primary prevention and the possible reasons for disagreement, we critically examine the results of the recent meta-analyses comparing aspirin with placebo or no aspirin for the primary prevention of cardiovascular disease and evaluate whether aspirin provides a net benefit when used for this indication.

LITERATURE SEARCH

We searched the Medline database for the past 5 years (January 2007 to March 2012) to identify

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KEY POINTS

- When used for the primary prevention of cardiovascular disease, aspirin produces a nominally significant 6% reduction in all-cause mortality without reducing cardiovascular mortality.
- When used for the primary prevention of cardiovascular disease, aspirin reduces nonfatal myocardial infarction.
- When used for the primary prevention of cardiovascular disease, aspirin does not provide a net benefit in stroke.
- When used for the primary prevention of cardiovascular disease, aspirin increases major and intracranial bleeding.

randomized controlled trials and meta-analyses of randomized controlled trials of aspirin in the primary prevention of cardiovascular disease using the search terms aspirin, cardiovascular disease, myocardial infarction (MI), stroke, randomized controlled trial, meta-analysis, primary prevention and guidelines. Further searches were made using the bibliographies of the published journal articles to identify other studies or articles that might be relevant.

RESULTS

We identified four meta-analyses [1–4] published over the past 3 years that have pooled data from randomized trials of aspirin for the primary prevention of cardiovascular disease (Tables 2 and 3). No additional randomized trials of aspirin in primary prevention were identified since the publication of the most recent meta-analysis.

The 2009 meta-analysis by the ATTC [1] pooled data from the first six aspirin primary prevention trials: the British Doctors' Trial (BDT) [10], Physicians' Health Study (PHS) [11], Women's Health Study (WHS) [12], Hypertension Optimal Trial (HOT) [13], Thrombosis Prevention Trial (TPT) [14] and the Primary Prevention Project (PPP) [15]. The three meta-analyses [2–4] published since the 2009 ATTC meta-analysis pooled data from the same six trials as well as from three more recent trials: The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Trial (JPAD) [16] and The Prevention of Progression of Arterial Disease and Diabetes Trial (POPADAD) [17], which were performed exclusively in diabetes, and Aspirin for Asymptomatic Atherosclerosis (AAA) trial [18], which recruited individuals with abnormal ankle: brachial index.

META-ANALYSIS METHODS

The 2009 ATTC meta-analysis was based on individual participant data, which allowed detailed exploration of the effects of aspirin compared with placebo according to baseline risk of cardiovascular disease and in key subgroups.

The meta-analyses by Bartolucci *et al.* [2], Seshasai *et al.* [3] and Raju *et al.* [4] pooled tabular data from the same nine randomized controlled trials but included slightly different numbers of participants: 100 038, 102 621 and 100 076 in Bartolucci *et al.* [2], Seshasai *et al.* [3] and Raju *et al.* [4], respectively. Seshasai *et al.* included 2545 warfarin-treated patients from the TPT [14], whereas the other two meta-analyses excluded these patients. Bartolucci *et al.* excluded 60 patients from the AAA trial [18] for reasons that are unclear; these patients were included by Seshasai and Raju. Bartolucci *et al.* and Seshasai *et al.* reported the pooled treatment effect using the odds ratio, whereas Raju *et al.* reported relative risk (RR); the impact of this difference is, however, likely to be minimal because the odds ratio approximates the relative risk when event rates are low. All meta-analyses pooled data for all-cause and cardiovascular mortality as well as for MI and stroke, but only the ATTC, Seshasai *et al.* and Raju *et al.* reported estimates for major, nontrivial and gastrointestinal bleeding, and only Seshasai *et al.* reported the effect of aspirin on cancer mortality.

META-ANALYSIS FINDINGS: ALL-CAUSE AND CARDIOVASCULAR MORTALITY

The 2009 ATTC meta-analysis included 95 000 individuals followed for 660 000 person years, during which there were 3435 total deaths and 1256 vascular deaths. Aspirin compared with placebo or control did not reduce all-cause mortality [0.50 versus 0.53%, RR 0.95, 95% confidence interval (CI) 0.88–1.02], cardiovascular mortality (0.19 versus 0.19%, RR 0.97, 95% CI 0.87–1.09, $P = 0.7$), nonvascular mortality (0.27 versus 0.30%, RR 0.93, 95% CI 0.85–1.02) or deaths of unknown cause (0.04 versus 0.04%, RR 0.96, 95% CI 0.7–1.3).

The meta-analyses by Bartolucci *et al.*, Seshasai *et al.* and Raju *et al.* each suggested a reduction in total mortality which was nominally statistically significant in two [3,4] of the three meta-analyses [Seshasai *et al.*: odds ratio (OR) 0.94, 95% CI 0.88–1.00; Raju *et al.*: RR 0.94, 95% CI 0.88–1.00] (Table 4). The pooled estimates suggesting a reduction in all-cause mortality are consistent with the estimates obtained from eight of the nine included studies which had a point estimate in favour of aspirin for total mortality. The reduction

Table 1. Guidelines for aspirin use in individuals without established cardiovascular disease

Guideline or expert group (year)	Recommendation, interpretation	Strength of recommendation/ level of evidence[a]	Interpretation of recommendation	
			Strength of recommendation	Level of evidence
ACCP [5▪] (2012)	For persons aged 50 years or older without symptomatic cardiovascular disease, we suggest low-dose aspirin 75–100 mg daily over no aspirin therapy	Grade 2B	2 – Weak recommendation	B – Recommendation supported by RCTs with important limitations or strong evidence from observational studies
AHA/ASA [6] (2011)	The use of aspirin for cardiovascular (including but not specific to stroke) prophylaxis is recommended for persons whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (a 10-year risk of cardiovascular events of 6–10%).	Class I; Level of Evidence A	Class I – Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective	A – Data derived from multiple RCTs or meta-analyses
	Aspirin (81 mg daily or 100 mg every other day) can be useful for the prevention of a first stroke amongst women whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment.	Class IIa; Level of Evidence B	Class II – Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/ efficacy of a procedure or treatment. IIa–The weight of evidence or opinion is in favour of the procedure or treatment	B – Data derived from a single randomized trial or nonrandomized studies
	Aspirin is not useful for preventing a first stroke in persons at low risk.	Class III; Level of Evidence A	Class III – conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful	A – data derived from multiple RCTs or meta-analyses
	Aspirin is not useful for preventing a first stroke in persons with diabetes or diabetes plus asymptomatic peripheral artery disease (defined as an ankle brachial pressure index<0.99) in the absence of other established CVD.	Class III; Level of Evidence B	Class III – Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful	B – Data derived from a single randomized trial or nonrandomized studies
USPSTF [7] (2009)	Encourage men aged 45–79 years to use aspirin when the potential benefit of a reduction in myocardial infarction outweighs the potential harm of an increase in gastrointestinal haemorrhage.	A recommendation	A – The USPSTF recommends the service. There is high certainty that the net benefit is substantial	
	Encourage women aged 55–79 years to use aspirin when the potential benefit of a reduction in ischaemic stroke outweighs the potential harm of an increase in gastrointestinal haemorrhage.	A recommendation		
	Do not encourage aspirin use for cardiovascular disease prevention in women younger than 55 years and in men younger than 45 years.	D recommendation	D – The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits	

(*Continued*)

Table 1 (*Continued*)

Guideline or expert group (year)	Recommendation, interpretation	Strength of recommendation/ level of evidence[a]	Interpretation of recommendation	
			Strength of recommendation	Level of evidence
ATTC [1] (2009)	In primary prevention without previous disease, aspirin is of uncertain net value as the reduction in occlusive events needs to be weighed against any increase in major bleeds.	–	–	–
ESC JTF [8] (2007)	In asymptomatic individuals, aspirin should only be considered when the 10-year risk of CVD mortality is markedly increased and the BP is controlled.	–	–	–

ACCP, American College of Chest Physicians; AHA/ASA, American Heart Association/American Stroke Association; ATTC, Antithrombotic Trialists' Collaboration; ESC, European Society of Cardiology Joint Task Force; RCTs, randomized controlled trials; USPSTF, US Preventive Services Task Force.
[a]According to group.

in all-cause mortality was not explained by an effect on cardiovascular mortality, which was not significantly reduced. A recent report by Rothwell *et al.* [19▪] suggests that aspirin reduces cancer deaths; this may in part explain the reduction in all-cause mortality. The analyses by Seshasai *et al.* also suggested that aspirin reduces cancer mortality, although this effect was not statistically significant (OR 0.93, 95% CI 0.84–1.03).

MYOCARDIAL INFARCTION

The three meta-analyses that reported separately on nonfatal and total MI [1–3] demonstrated that aspirin reduced nonfatal MI by 19–23%. Aspirin compared with placebo or no aspirin was associated with a consistent pattern of reduced total MI in all four meta-analyses, although this was statistically significant only in the ATTC meta-analysis.

STROKE

Results for stroke also did not change significantly from the earlier findings of the ATTC, with each of the more recent three meta-analyses reconfirming no net benefit in stroke. Aspirin reduced ischaemic stroke [4], but the accompanying increase in haemorrhagic stroke negated this benefit [4].

MAJOR CARDIOVASCULAR EVENTS

All four meta-analyses demonstrated that aspirin reduces major cardiovascular events when used for primary prevention. The ATTC meta-analysis showed a 12% reduction in MI, stroke and vascular death (0.51 versus 0.57%, RR 0.88, 95% CI 0.82–0.94, $P = 0.0001$), which is similar to the proportional effect of aspirin compared with placebo or no aspirin in a meta-analysis of secondary prevention trials [1]. Similar estimates for major cardiovascular events were reported by Bartolucci *et al.*, Seshasai *et al.* and Raju *et al.*

BLEEDING

Aspirin increases major bleeding, gastrointestinal bleeding and haemorrhagic stroke. This has been a consistent finding in the three meta-analyses that reported bleeding outcomes [1,3,4], despite variability in the definition of bleeding across the studies (Table 5). The ATTC showed that aspirin increased major gastrointestinal and other extracranial bleeds by about 54%, and that fatal haemorrhagic strokes outnumbered fatal ischaemic strokes (82 versus 53). Raju *et al.* reported that aspirin increased gastrointestinal bleeding by 37%, major bleeding by 66% and haemorrhagic stroke by 36%. Seshasai *et al.* reported that aspirin increased nontrivial bleeding by 31% and total bleeding by 70%. Bartolucci *et al.* reported proportions of participants with gastrointestinal bleeding in the nine individual trials but did not pool the data.

NET BENEFIT

Simply adding the total number of events in patients treated with aspirin compared with placebo or no aspirin may provide misleading estimates of net clinical benefit because this approach does not take into account the different values that individuals may place on thrombotic and bleeding events. On the basis of patient population included in the

Table 2. Comparison of the four meta-analyses of aspirin in primary prevention

Meta-analysis	Number of RCT	Number of participants	Measure of association	Thrombotic outcomes	Bleeding outcomes
ATTC [1] (2009)	6	95 000	Relative risk	Serious vascular event (MI, stroke, death from vascular cause); major coronary event (MI, coronary or sudden death); any stroke, all-cause death	Major gastrointestinal and extracranial bleed, intracerebral haemorrhage
Raju *et al.* [4] (2011)	9	100 076	Relative risk	All-cause and cardiovascular mortality, major cardiovascular events, MI, stroke (total, ischaemic)	Haemorrhagic stroke, major and gastrointestinal bleeding
Bartolucci *et al.* [2] (2011)	9	100 038	Odds ratio	Total CHD, nonfatal MI, total cardiovascular events, stroke, cardiovascular mortality and all-cause mortality	-
Seshasai *et al.* [3] (2012)	9	102 621	Odds ratio	Mortality: all-cause, cancer, noncancer nonvascular, CVD, nonCVD; cardiovascular events, stroke, total CHD, fatal and nonfatal MI	Total bleeds, nontrivial bleeding
Comment	ATTC pooled individual patient data; other meta-analyses pooled tabular data	Raju *et al.* and Bartolucci *et al.* excluded warfarin arm of TPT	Odds ratio approximates relative risk when event rates are low (e.g. <10%)	Seshasai reported cancer and noncancer mortality	Bartolucci did not pool bleeding data

CHD, coronary heart disease; CVD, cardiovascular disease; TPT, Thrombosis Prevention Trial.

Table 3. Randomized controlled trials of aspirin in primary prevention

Trial (year of publication)	Participating countries	Design	Participants, *n*	Male (%)	Mean age (years)	% Elderly	Other risk factors	Mean follow-up (years)	Aspirin dose
BDT [10] 1988	UK	Open	5139	100	n/a	14% >70 years	[b]	6	300–500 mg/day
PHS [11] 1989	USA	Blinded	22 071	100	n/a	7% >70 years	–	5	325 mg alternate day
HOT [13] 1998	Europe, Asia, North America, South America	Blinded	18 790	53	61.5	32% >65 years	Hypertension[b]	3.8	75 mg/day
TPT [14] 1998	UK	Blinded	2540[c]	100	57.3	n/a	–	6.4	75 mg/day
PPP [15] 2001	Italy	Open	4495	42	64.4	50% >65 years	–	3.6	100 mg/day
WHS [12] 2005	USA	Blinded	39 876	0	54.6	10% >65 years	–	10.1	100 mg alternate day
AAA [18] 2008	Scotland	Blinded	3350	28	62.0	n/a	ABI ≤0.95	8.2	100 mg
JPAD [16] 2008	Japan	Open	2539	55	64.5	54% >65 years	Diabetes	4.4[a]	81 or 100 mg/day
POPADAD [17] 2008	Scotland	Blinded	1276	44	60.3	52% >60 years	Diabetes	6.7[a]	100 mg/day

AAA, Aspirin for Asymptomatic Atherosclerosis trial; ABI, ankle brachial index; BDT, British Doctors' Trial; HOT, Hypertension Optimal Treatment study; JPAD, Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes trial; PHS, Physicians' Health Study; POPADAD, Prevention Of Progression of Arterial Disease And Diabetes trial; PPP, Primary Prevention Project; TPT, Thrombosis Prevention Trial; WHS, Women's Health Study.
[a]Median.
[b]Studies included small proportion (<5%) of participants with preexisting cardiovascular disease.
[c]Excludes participants on warfarin.

Table 4. Results of the recent meta-analyses of aspirin for the primary prevention of cardiovascular disease: mortality and thrombotic outcomes

Author (year of publication)	Number of participants[a] (number of studies)	Results (aspirin versus placebo)							
		Overall mortality	CV mortality	Major CV events[b]	All CHD	Nonfatal MI	Stroke	Ischaemic stroke	NNT major CV events
ATTC [1] (2009)	95 000 (6)	0.95 (0.88–1.02)	0.97 (0.87–1.09)	0.88 (0.82–0.94)	0.82 (0.75–0.90)	0.77 (0.67–0.89)	0.95 (0.85–1.06)	0.86 (0.74–1.00)	–
Raju *et al.* [4] (2011)	100 076 (9)	0.94 (0.88–1.00)	0.96 (0.84–1.09)	0.88 (0.83–0.94)	0.83 (0.69–1.00)	n/a[c]	0.93 (0.82–1.05)	0.86 (0.75–0.98)	314
Bartolucci *et al.* [2] (2011)	100 038 (9)	0.95 (0.88–1.01)	0.96 (0.80–1.14)	0.87 (0.80–0.93)	0.85 (0.69–1.06)	0.81 (0.67–0.99)	0.92 (0.83–1.02)	n/a	–
Seshasai *et al.* [3] (2012)	102 621 (9)	0.94 (0.88–1.00)	0.99 (0.85–1.15)	0.90 (0.85–0.96)	0.86 (0.74–1.01)	0.80 (0.67–0.96)	0.94 (0.84–1.06)	n/a	384

CHD, coronary heart disease; CV, cardiovascular; MI, myocardial infarction; n/a, not available; NNT, number needed to treat.
[a]Refers to total number of participants; some of the analyses were limited to fewer participants according to data availability (data separating ischaemic and haemorrhagic stroke were not available from HOT.
[b]Major cardiovascular events includes a composite of cardiovascular death, MI and stroke.
[c]Not reported separately in publication.

Table 5. Results of the recent meta-analyses of aspirin for the primary prevention of cardiovascular disease: bleeding outcomes

Author (year of publication)	Number of participants[a] (number of studies)	Results (aspirin versus placebo)		
		Haemorrhagic stroke	Major bleeding	NNH major bleeding
ATTC [1] 2009	95 000 (6)	1.32 (0.91–1.91)	1.54 (1.30–1.82)	–
Raju *et al.* [4] 2011	100 076 (9)	1.36 (1.01–1.82)	1.66 (1.41–1.95)	300 (109 gastrointestinal[b])
Bartolucci *et al.* [2] 2011	100 038 (9)	n/a	n/a	–
Seshasai *et al.* [3] 2012	102 621 (9)	n/a	1.31 (1.14–1.50)	109

NNH, number needed to harm.
[a]Some of the analyses were limited to fewer participants according to data availability, e.g. BDT did not report gastrointestinal bleeding, HOT did not provide separate data on ischaemic and haemorrhagic stroke.
[b]Raju *et al.* reported major and gastrointestinal bleeding separately; Seshasai *et al.* reported all nontrivial bleeding combined.

aspirin primary prevention trials, 314–384 individuals would need to take aspirin for an average of 6.9 years to prevent one major cardiovascular event, at the cost of about three gastrointestinal or nontrivial bleeds [3,4].

SUMMARY

The results of the recent meta-analyses of randomized controlled trials of aspirin for the primary prevention of cardiovascular disease demonstrate the following:

(1) Aspirin produces a nominally significant 6% reduction in all-cause mortality.
(2) Aspirin does not significantly reduce cardiovascular mortality or cancer mortality but pooled estimates for both these outcomes are in favour of aspirin, thereby explaining the reduction in all-cause mortality.
(3) Aspirin reduces major cardiovascular events, defined as the composite, cardiovascular death, MI and stroke, by 10–13%.
(4) Aspirin reduces nonfatal MI by 19–23%.
(5) Aspirin does not reduce stroke; it reduces ischaemic stroke by 14% but increases haemorrhagic stroke by 32–36%; thus, there is no overall reduction in stroke.
(6) Aspirin increases major bleeding by 31–66% and gastrointestinal bleeding by 37%.

All the four meta-analyses produced consistent results, despite slightly different designs and patient numbers.

IMPLICATIONS FOR CLINICAL PRACTICE: WHO SHOULD RECEIVE ASPIRIN FOR PRIMARY PREVENTION

Calculations reported in the ATTC meta-analysis [1] indicate a 0.2% reduction in cardiovascular death, nonfatal MI or stroke for individuals with a 5-year cardiovascular risk of less than 5%. It is unclear whether the magnitude of this benefit outweighs the 0.1% increase in bleeding. The reduction in cardiovascular events in individuals with a 5-year cardiovascular risk of more than 10% is 2%, a 10-fold greater benefit than in those with a 5-year risk of less than 5%. The 2% absolute reduction in cardiovascular events clearly outweighs the 1% increase in bleeding with aspirin in this higher-risk population.

The challenge for clinicians is in defining the threshold at which the benefits of aspirin outweigh the risks in individual patients. Guidelines have attempted to define this threshold using age, sex and cardiovascular risk factors, but the threshold for a particular individual will also be influenced by their values and preferences concerning the trade-off between thrombotic and bleeding events.

Most trials of aspirin for the primary prevention of cardiovascular disease were performed prior to the routine use of other effective secondary prevention strategies such as angiotensin converting enzyme (ACE) inhibitors and statins. Consequently, the risk of cardiovascular events may be lower, and the absolute benefits of aspirin may be even smaller, in contemporary primary prevention populations, although this will vary by region. The vast majority of cardiovascular deaths occur in low-income and middle-income countries (http://www.who.int/mediacentre/factsheets/fs317/en/index.html, accessed 2 February 2012), where ACE inhibitors and statins are less widely used; in these settings, the benefits of aspirin when used for the primary prevention of cardiovascular disease may be greater than in high-income countries.

MAXIMIZING BENEFIT AND MINIMIZING RISK

To ensure the optimal balance between benefits and risk requires careful individualization of aspirin

therapy and a high level of compliance in those who are treated. Thus, individuals at low risk of cardiovascular risk and those at high risk of bleeding complications (e.g. recent gastrointestinal bleeding) may not be suitable for aspirin. Individuals may be less compliant if they feel that there is little to be gained from taking aspirin for primary prevention. Primary prevention studies have reported aspirin adherence rates ranging from 50 to 93%. Sanchez *et al.* [20] demonstrated that only 31% of individuals in the USA at increased risk (10-year risk 6–9.9%) and 44% of those at high risk (10-year risk $\geq$10%) of cardiovascular disease are taking aspirin for primary prevention. Careful education and engagement of individuals in decision making might improve the use of aspirin for primary prevention. Minor gastrointestinal symptoms may lead to reduced compliance or discontinuation [21] but may be ameliorated by the concomitant use of a proton pump inhibitor.

DOSE OF ASPIRIN

The efficacy of aspirin for the prevention of cardiovascular events is dose-independent, but the risk of gastrointestinal bleeding increases with increasing doses of aspirin. Thus, aspirin should be used at the lowest proven effective dose, generally $\leq$100 mg/day. Although there was clear evidence of benefit of alternate daily aspirin dosing in the PHS [11] and WHS [12], we recommend that aspirin be given once daily because this regimen has been most widely tested. Alternate daily treatment is associated with substantial day-to-day variability in the inhibition of platelet function [22] and may have contributed to the lack of an MI benefit in the WHS.

CONCLUSION

Meta-analyses of the randomized controlled trials of aspirin in primary prevention consistently demonstrate that aspirin compared with placebo or no aspirin prevents major cardiovascular events, predominantly MI, at the cost of an increase in bleeding and with no reduction in stroke. An overall modest survival benefit appears to be explained by numerical reductions in cardiovascular and cancer mortality, although neither of the latter outcomes is significantly reduced. The absolute benefit of aspirin is expected to be higher for those at higher levels of cardiovascular risk.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 562).

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