Aspirin for cardiovascular disease prevention

Joseph Hung, for the Medical Issues Committee of the National Heart Foundation of Australia

ABSTRACT

Secondary prevention

- Aspirin provides benefit in nearly all groups of patients with clinical manifestations of coronary heart disease. This includes patients with evolving acute myocardial infarction or after recovery from myocardial infarction, with unstable or stable angina, and those who undergo coronary artery bypass grafting or coronary angioplasty.
- Aspirin provides benefit in patients with peripheral arterial disease. This includes patients with acute or previous history of ischaemic stroke or transient ischaemic attack, those with lower limb arterial insufficiency, and those who undergo grafting or angioplasty of peripheral arterial vessels.

Primary prevention

- People without symptoms but at increased risk of a coronary heart disease event (> 1% annual risk) may reduce this risk by taking low-dose aspirin. However, the decision to take aspirin requires detailed consideration of individual cardiovascular risk and the potential benefit versus harm of treatment, particularly bleeding.
- Aspirin should only be used to prevent a cardiovascular event in association with an overall program of lifestyle measures including healthy eating, cessation of smoking, control of blood pressure and regular physical activity.

Aspirin for prevention

- Prevention benefits of aspirin in heart disease can be achieved with doses as low as 75–150 mg daily.
- Unwanted effects of aspirin include stomach upsets, activation of peptic ulcers, an increased tendency to bruising, allergic reactions and increased risk of major gastrointestinal and other bleeding, including intracranial haemorrhage. In general, the risk of bleeding increases with increasing dose of aspirin and when it is used in combination with non-steroidal anti-inflammatory drugs or oral anticoagulants.

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RANDOMISED CONTROLLED TRIALS have proven that antiplatelet therapy (mainly with aspirin) is effective in reducing the risk of non-fatal myocardial infarction, non-fatal stroke or vascular death among patients with established arterial disease.[1] When used for secondary prevention, the benefit from aspirin substantially outweighs possible harm of therapy (E1) (for an explanation of level-of evidence codes, see Box 1). Recent controlled trials have also indicated a favourable risk–benefit ratio for aspirin in primary prevention among persons who are at higher risk of coronary heart disease (CHD) and who are not at increased risk of bleeding complications (E1).[3] An accurate assessment of individual cardiovascular risk is necessary when considering use of aspirin for primary prevention. Box 2 outlines definite and possible indications for aspirin prophylaxis based on the current clinical trial evidence. However, this position statement does not consider the potential use of aspirin in prophylaxis of venous thromboembolism.

Aspirin for secondary prevention

An updated systematic overview of randomised controlled trials of antiplatelet therapy involving nearly 144 000 patients at high risk of occlusive vascular events has been reported by the Antithrombotic Trialists' Collaboration.[1] Information was available on serious vascular events comprising non-fatal myocardial infarction, non-fatal stroke, or vascular death. Overall, 7705 serious vascular events (10.7%) were recorded among 71 912 high-risk patients allocated to antiplatelet therapy (mainly aspirin alone) versus 9502 (13.2%) among 72 139 patients allocated to "control treatment" over periods of 1 to 29 months. Antiplatelet treatment produced an overall absolute risk reduction (ARR) of 2.5% in serious vascular events, without an increase in non-vascular mortality (E1).[1] This translates to an absolute benefit of 25 fewer serious vascular events per 1000 patients treated. Box 3 shows separate benefits for non-fatal myocardial infarction, stroke, vascular death, and all serious vascular events (expressed as events prevented per 1000 patients treated) for different categories of high-risk patients. Aspirin at doses of 75–150 mg was at least as effective as higher daily doses (E1).[1] However, the efficacy of doses lower than 75 mg daily has not been established.

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Suspected or evolving myocardial infarction

Data are available on about 19 000 patients, nearly all of whom were in the ISIS-2 (Second International Study of Infarct Survival) trial, in which patients were randomly allocated to treatment with aspirin, streptokinase, both, or placebo within the first 24 hours of suspected or evolving myocardial infarction.[4] Aspirin treatment comprised half a tablet (162.5 mg), chewed then swallowed. The reduction in deaths by 23% with aspirin alone (ARR, 2.4%) was equivalent to that seen with streptokinase (E2). Further, the benefit of aspirin was independent of streptokinase, and their combination reduced vascular mortality by 49% (ARR,

5.2%) at 1 month (E2). In absolute terms, aspirin given for acute myocardial infarction could prevent 38 major vascular events per 1000 patients treated for 1 month, with most benefit in preventing vascular deaths (23 prevented per 1000 patients treated) (E1).

Patients with prior myocardial infarction

In 15 trials involving about 19 000 patients who survived myocardial infarction, antiplatelet therapy (mainly aspirin alone) reduced the risk of a major vascular event by 25% after 2 years of treatment (E1). In absolute terms, aspirin given to 1000 patients with a history of myocardial infarction over 2 years will prevent 36 major vascular events, mostly non-fatal reinfarctions (18 prevented per 1000 treated) and vascular deaths (14 prevented per 1000 treated) (E1).

Suspected acute ischaemic stroke

Two recent large trials included about 40 000 patients with suspected acute ischaemic stroke who were allocated to treatment with 160–300 mg aspirin daily, versus control (E2).[5] Aspirin treatment for a mean duration of 3 weeks produced a significant 11% reduction in risk of serious vascular events. The resulting absolute reduction of 9 fewer serious vascular events per 1000 patients treated reflects mostly non-fatal stroke recurrence (4 fewer per 1000) and vascular deaths (5 fewer per 1000) (E2). Antiplatelet therapy produced an absolute excess of 1.9 (standard error [SE] of the difference, 1.0) haemorrhagic strokes per 1000 patients. This was more than counterbalanced by an absolute reduction of 6.9 (1.4) fewer ischaemic strokes per 1000 patients treated (E2).

History of stroke or transient cerebral ischaemic attacks

Aspirin, alone and in combination with dipyridamole, has been studied in 21 trials, which included about 18 000 patients with a history of cerebrovascular disease. The results of these trials suggest that antiplatelet therapy for a mean duration of 29 months can significantly reduce the rate of major vascular events by 22% (E1). Treating 1000 patients with a history of cerebrovascular disease for this duration will prevent about 36 vascular events, mostly non-fatal stroke recurrence (25 fewer per 1000 treated), and some non-fatal myocardial infarction (5 fewer per 1000) (E1).

Other high risk categories

Other high risk groups include patients with other manifestations of coronary artery disease (unstable or stable angina, or those who have had coronary artery bypass grafting or coronary angioplasty), peripheral arterial disease (intermittent claudication, peripheral artery grafting or angioplasty), those at high risk of systemic embolism (atrial fibrillation, cardiac valve surgery), or those with other high risk conditions (haemodialysis, carotid artery disease, diabetes).[1] Antiplatelet therapy produced similar proportional reductions in serious vascular events among these high-risk patients (E1).[1]

Among over 15 000 patients with coronary artery disease, there were independently significant benefits among patients with unstable angina (ARR, 5.3%), those having coronary angioplasty (ARR, 2.8%), and those with stable angina (ARR, 4.2%) (E1).[1] Early use of aspirin after coronary artery bypass grafting was safe, and reduced the risk of death and ischaemic complications ($E3_2$).[6] In addition, aspirin therapy in patients undergoing vascular grafting or angioplasty reduced the risk of early (within 6 months) graft or arterial occlusion by an average of 34% (93 occlusions prevented per 1000 patients treated) (E1).[7] Among over 13 000 patients with peripheral arterial disease, there was an overall reduction of 23% in serious vascular events (ARR, 1.5%), with similar benefits among patients with intermittent claudication, those undergoing peripheral intervention, and those requiring haemodialysis (E1).[1]

1: Level-of-evidence codes

Evidence for the statements made in this article is graded according to the NHMRC system[2] for assessing the level of evidence.

- E1 Level I: Evidence obtained from a systematic review of all relevant randomised controlled trials.
- E2 Level II: Evidence obtained from at least one properly designed randomised controlled trial.
- $E3_1$ Level III-1: Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
- $E3_2$ Level III-2: Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case–control studies, or interrupted time series with a parallel control group.
- $E3_3$ Level III-3: Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
- E4 Level IV: Evidence obtained from case-series, either post-test, or pre-test and post-test.

2: Aspirin for cardiovascular disease prevention

Proven indications:
- Acute or previous history of myocardial infarction
- Stable or unstable angina
- Acute or previous history of an ischaemic stroke or transient ischaemic attack
- Coronary artery bypass or coronary angioplasty
- Peripheral arterial disease and peripheral grafting or angioplasty.

Possible indications:
- Prevention in higher risk patients without cardiovascular disease
- Non-valvular atrial fibrillation
- Prophylaxis of venous thromboembolism

Absolute and relative contraindications:
- Active or recent gastrointestinal bleeding
- Active or recent peptic ulceration
- History of intracranial haemorrhage
- Uncontrolled hypertension
- History of aspirin intolerance or allergy

Aspirin in primary prevention

Although the benefit of aspirin in secondary prevention is well established, its net beneficial effect in persons without known cardiovascular disease is less certain. Because of a generally lower baseline risk, there will be less absolute benefit from aspirin in primary prevention for the same relative risk reduction.[8-12] On the other hand, the adverse effects of aspirin appear unrelated to thrombotic risk, and hence there will be a lower ratio of benefit to risk for aspirin in primary, compared with secondary, prevention. Although the major effect of aspirin is thought to be in inhibiting thrombosis, benefits were observed in the Physicians' Health Study, particularly in those with elevated high-sensitivity C-reactive protein levels, raising the possibility of an anti-inflammatory mechanism.[13]

The United States Preventive Services Task Force has recently performed a systematic overview of five primary prevention trials of aspirin and examined "thresholds" of CHD risk at which aspirin may have a net beneficial effect.[3] The characteristics of the five randomised trials, which had a total of more than 50 000 participants, are shown in Box 4. Low-dose aspirin (< 162 mg per day) was used in four of the five trials, and treatment duration ranged from 3–7 years. Most participants were middle-aged men, and only two trials (Hypertension Optimal Treatment[11] and Primary Prevention Project[12]) included women. The annual risk of CHD events was below 1.0% in all but one trial.

Overall, aspirin produced a significant reduction in the risk of combined non-fatal and fatal CHD events (ARR, 0.5%).[3] This represented a proportional CHD risk reduction of 28% (odds ratio [OR], 0.72; 95% CI, 0.60–0.87)(E1).[3] However, aspirin increased the risk of haemorrhagic stroke (OR, 1.4; 95% CI, 0.9–2.0) and major gastrointestinal bleeding (OR, 1.7; 95% CI, 1.4–2.1) (E1).[3] Total strokes and all-cause mortality were not significantly affected.[3] Whether being female or very elderly, or having diabetes mellitus or hypertension, modifies the effect of aspirin remains unclear because of the limited data on these subgroups. The Women's Health Study, a primary prevention trial that will test low-dose aspirin in about 40 000 patients, is expected to clarify the risks and benefits among women.[14]

As shown in Box 5, based on modelling at different coronary risk thresholds, the US Preventive Services Task Force suggested that aspirin prophylaxis should have a net beneficial effect only among individuals with a greater than 1% annual risk of CHD (E1). For 1000 people with a 5% risk of a CHD event over 5 years, aspirin would prevent 6–20 myocardial infarctions, but cause 0–2 haemorrhagic strokes and 2–4 major gastrointestinal bleeding events. Conversely, for 1000 people with a CHD risk of 1% over 5 years, aspirin would prevent only 1–4 myocardial infarctions for the same number of major bleeding events. In line with this, the recent American Heart Association guidelines for primary prevention recommend that low-dose aspirin should be considered in people who are at higher CHD risk, especially those with a 10-year risk of CHD of more than 10%, but who are not at increased risk of gastrointestinal bleeding or haemorrhagic stroke.[15]

Thus, the decision to recommend aspirin for primary prevention requires assessment of an individual's absolute risk for CHD (risk calculators are available at www.med-decisions.com/ or www.absoluterisk.com/), and the judgement of the clinician concerning risk and benefit in the particular patient. Furthermore, aspirin prophylaxis should only be used in addition to the control of cardiovascular risk factors, including dietary and lifestyle changes, smoking cessation and control of blood pressure. A case history is given in Box 6 to illustrate the risk assessment and management issues associated with use of aspirin for primary prevention.

Other possible indications for aspirin

Non-valvular atrial fibrillation

In three primary prevention and three secondary prevention trials of people with atrial fibrillation, aspirin reduced the

3: Effect of antiplatelet therapy on vascular events in five main high risk categories: meta-analysis of 195 trials involving about 144 000 patients*

Category of trial	No. of trials	Events prevented per 1000 patients treated (SE) [*P*]			
		Non-fatal MI	Non-fatal stroke	Vascular death	Serious vascular event†
Acute MI (mean treatment duration 1 month)	15	13 (2) [< 0.001]	2 (1) [0.02]	23 (4) [< 0.001]	38 (5) [< 0.001]
Previous MI (mean treatment duration 2 years)	12	18 (3) [< 0.001]	5 (1) [0.002]	14 (4) [< 0.001]	36 (5) [< 0.001]
Acute ischaemic stroke (mean treatment duration 3 weeks)	7	NA	4 (2) [0.003]	5 (2) [0.05]	9 (3) [< 0.001]
Previous ischaemic stroke or TIA (mean treatment duration 3 years)	21	6 (2) [< 0.001]	25 (5) [< 0.001]	7 (4) [0.04]	36 (6) [< 0.001]
Other high risk groups‡	140	NA	NA	NA	22 (3) [< 0.001]

* Table contains data adapted from the report of Antithrombotic Trialists' Collaboration.[1] † Serious vascular events are non-fatal myocardial infarction, stroke or vascular death. ‡ Other high risk groups include patients with coronary artery disease (unstable or stable angina, coronary artery bypass, coronary angioplasty), peripheral arterial disease (intermittent claudication, peripheral grafting, peripheral angioplasty), high risk of embolism (atrial fibrillation, cardiac valve surgery), or other high risk conditions (haemodialysis, diabetes, carotid artery disease).
SE = standard error of the difference. MI = myocardial infarction. TIA = transient ischaemic attack. NA = not available.

incidence of stroke by 22% (95% CI, 2%–38%) (E1).[16] However, in three trials examining the relative benefits and risks of warfarin and aspirin, it was found that warfarin about halved the risk of stroke compared with aspirin (E1).[16] Thus, aspirin should be preferred to warfarin only in low-risk patients with atrial fibrillation (age < 65 years and no other risk factor for thromboembolism).

Prosthetic heart valves

Antiplatelet agents alone do not confer protection against systemic embolism in patients with mechanical valve prostheses, whereas warfarin is highly effective (E1).[17] However, in patients with mechanical heart valves, low-dose aspirin added to oral anticoagulants (target INR [international normalised ratio], 2.0–3.5), has been shown to reduce the risk of thromboembolic events (OR, 0.41; 95% CI, 0.29–0.58) and mortality (OR, 0.49; 95% CI, 0.35–0.67), but with a slightly increased risk of major bleeding (E1).[18] The combination of low-dose aspirin and warfarin may be particularly useful in patients with prosthetic valves who have CHD or have had systemic embolism despite adequate anticoagulation (E2).[17] Data are insufficient to recommend dipyridamole over low-dose aspirin in combination with warfarin in these patients.[17]

Adverse effects of aspirin

Aspirin is associated with a dose-dependent increase in upper gastrointestinal (GI) symptoms, upper GI bleeding, and intracranial haemorrhage (E1). Aspirin in doses up to 325 mg daily will increase the risk of major GI bleeding by a factor of 1.5– 2.0 times (E1).[19] There is no evidence that the risk of GI bleeding is different for plain, enteric-coated or buffered aspirin ($E3_1$).[20] The absolute excess risk of a major GI bleed is about four patients per 1000 receiving aspirin for 1 year.[19] Aspirin also leads to an increased risk of haemorrhagic stroke, but the absolute excess risk is small (about one per 2500 aspirin users per year[21]).

Definite or relative contraindications to aspirin

Because of its effect on bleeding, aspirin should generally be avoided in patients taking oral anticoagulants, except in those with a very high risk of thromboembolism, in whom reduction of risk substantially outweighs the potential hazard of combined administration. Aspirin should be used cautiously in people taking other non-steroidal anti-inflammatory drugs, as concomitant administration increases the risk of GI toxicity and may lessen the benefit of aspirin.[22]

4: Baseline characteristics of study populations in primary prevention trials

Variable	British male doctors[8]	Physicians' Health Study[9]	Thrombosis prevention trial[10]	Hypertension Optimal Treatment[11]	Primary Prevention Project[12]
Year	1988	1989	1998	1998	2001
Location	UK	US	UK	Worldwide	Italy
No. of patients (women)	5139 (0)	22 071 (0)	2540 (0)	18 790 (8831)	4495 (2583)
Participants included	Male physicians	Male physicians	Men at high risk for heart disease	Diastolic BP of 100–115 mmHg	> 1 major risk factor for CHD
Mean age (range)	NA; 53% > 60 years	53 years (40–84)	57.5 years (45–69)	61.5 years (50–80)	NA; 69% > 60 years
Daily aspirin dose	500 mg	162.5 mg	75 mg	75 mg	100 mg
Treatment duration (years)	5.8	5	6.8	3.8	3.6
Annual risk of CHD event among control participants	0.89%	0.48%	1.24%	0.36%	0.43%

BP = blood pressure. CHD = coronary heart disease. NA = not available.

5: Estimated benefits and harm of aspirin therapy for patients at different levels of risk for coronary heart disease*

Outcome	Patient risk categories (estimated 5-year risk for CHD events at baseline) 1%	3%	5%
Effect on all-cause mortality	No change	No change	No change
No. (95% CI) of CHD events avoided	3 (1–4)	8 (4–12)	14 (6–20)
No. of ischaemic strokes avoided	0	0	0
No. (95% CI) of haemorrhagic strokes precipitated	1 (0–2)	1 (0–2)	1 (0–2)
No. (95% CI) of major gastrointestinal bleeding events precipitated	3 (2–4)	3 (2–4)	3 (2–4)
Benefit-to-risk ratio	0.75	2.0	3.5

Table adapted from US Preventive Services Task Force Report.[3]
*Estimates based on 1000 patients receiving aspirin for 5 years and a relative risk reduction of 28% for coronary heart disease (CHD) events in those who received aspirin. The following caveats apply to these estimates: (i) reduction in risk may be smaller in women, but data are limited; (ii) for elderly people, absolute risk for haemorrhagic stroke and gastrointestinal bleeding may be two to three times higher in patients receiving aspirin, but aspirin may provide benefit by reducing ischaemic stroke, the incidence of which rises with age; (iii) patients at high risk, such as those with diabetes, may derive greater benefit from aspirin, including a reduction in ischaemic stroke and all-cause mortality, because their risk is similar to that of patients with known CHD.

Aspirin is also contraindicated in patients with active erosive gastritis or peptic ulceration, previous intracranial haemorrhage, or uncontrolled hypertension, and in the few people with known hypersensitivity to aspirin (Box 2). Aspirin should be withdrawn 5–7 days before major surgery, except where the continuing antithrombotic benefits of aspirin substantially outweigh the potential risk of perioperative bleeding. Hence, patients should be considered on an individual basis. For most dental procedures, it is unnecessary to withdraw aspirin.

Alternatives and adjuncts to aspirin

Evidence exists mainly for clopidogrel as an effective oral antiplatelet agent that can be used as an alternative or in addition to aspirin.[20] In the CAPRIE (clopidogrel versus aspirin in patients at risk of ischaemic events) trial, among 19 185 patients with a history of myocardial infarction, stroke, or peripheral arterial disease, treated over 1.9 years, clopidogrel reduced serious vascular events by 8.7% (95% CI, 0.3%–16.5%) compared with aspirin.[23] The overall safety profile of clopidogrel was at least as good as that of aspirin.[23] The recent CURE trial has also provided evidence that in patients with unstable angina, including those who undergo coronary angioplasty, clopidogrel produces additional benefits when combined with aspirin.[24] Therefore clopidogrel is a suitable alternative when aspirin is contraindicated, and should be considered in combination with aspirin for patients who have recurrent cardiac or cerebral ischaemic events while taking aspirin (E2).

Dipyridamole by itself is not a clinically effective antiplatelet agent.[20] Overall, trials comparing dipyridamole plus aspirin with aspirin alone did not find a significant further reduction in risk of serious vascular events (E1).[1] However, one secondary prevention trial found that the combination of modified-release dipyridamole with aspirin reduced the risk of non-fatal stroke recurrence by 15% compared with aspirin alone (E2).[1]

Short-term intravenous infusion of glycoprotein IIb/IIIa antagonists, added to aspirin, has been proven to reduce the risk of major vascular events, mainly in patients undergoing percutaneous coronary intervention and in a high-risk subgroup of patients with acute coronary syndromes (E1).[1]

Warfarin at doses that maintain a therapeutic INR (2.0–4.0) is also effective for secondary prophylaxis after myocardial infarction, although it carries a greater risk of bleeding complications than does aspirin (E2).[25] A recent randomised trial from Norway involving 3630 patients showed that, for secondary prevention after myocardial infarction, warfarin (INR 2.0–2.5) combined with aspirin (75 mg daily) was superior to aspirin alone (160 mg daily) for reducing a composite endpoint of death, non-fatal myocardial reinfarction, or ischaemic stroke. A combination of warfarin and aspirin was associated with an ARR of 5.0%, and warfarin alone with an ARR of 3.3%, for the composite endpoint.[26] However, the beneficial effect of warfarin, alone and in combination with aspirin, was restricted principally to non-fatal events, and was offset by a significantly higher risk of

6: Case history — considerations for aspirin in primary prevention

History: A 55 year-old asymptomatic company executive attends for a cardiovascular health check. He is worried because of a family history of premature coronary heart disease (CHD). He is also concerned that he has been unable to give up smoking because of "work stress", and because he likes "rich" foods and has a generally sedentary lifestyle. He has no history of peptic ulceration, bleeding problems, or aspirin intolerance.

Investigations: The patient is overweight (body mass index [BMI], 27 kg/m^2), and his resting supine blood pressure is 160/90 mmHg, confirmed over several visits. His cholesterol levels are: fasting total cholesterol, 5.8 mmol/L; and high-density lipoprotein [HDL]-cholesterol, 1.16 mmol/L; and his total cholesterol/HDL ratio is 5.0. His fasting blood glucose level and 12-lead electrocardiogram (ECG) are normal.

Management: Aspirin prophylaxis in the absence of contraindications may be beneficial in people with a higher risk of developing CHD (> 1% annual risk). A middle-aged man without diabetes would need to have several risk factors before his CHD risk exceeds this level. However, there is often clustering of risk factors or risk behaviours as illustrated by this case. Using the Framingham Risk Assessment Tool (www.med-decisions.com/) this man is estimated to have a 21% 10-year risk of myocardial infarction or coronary death. By comparison, the estimated 10-year risk in a woman of the same age and with the same risk factors is 9%, a level of risk that would not justify aspirin treatment. A caveat is that the available risk tools tend to underestimate CHD risk in those with ECG evidence of left ventricular hypertrophy or a family history of premature CHD.

In this patient's case, initial emphasis should be on help with smoking cessation, as this would more than halve his 10-year risk of a CHD event. His risk could be further improved by reducing his weight, blood pressure and cholesterol levels through dietary and lifestyle modifications, and with drug treatment if necessary. Aspirin prophylaxis should only be considered if, despite his best efforts, he continues to have a high CHD risk and he understands that aspirin treatment has potential risks as well as benefits. Also, his hypertension should be adequately controlled before commencing aspirin prophylaxis.

Background and evidence basis of recommendations

The National Heart Foundation of Australia (NHFA) Position Statement on Aspirin for Cardiovascular Prevention was prepared by Joseph Hung on behalf of the Medical Issues Committee of the NHFA. The draft statement was circulated for comment to the Medical Issues Committee members, who have clinical, research and policy expertise in relation to cardiology, general medicine, general practice and epidemiology. Comments were incorporated into the final document, which was ratified by the Heart Foundation's Cardiovascular Health Advisory Committee.

The following members of the Medical Issues Committee reviewed and commented on the draft position statement on behalf of the NHFA, before it being ratified by the Cardiovascular Health Advisory Committee and the National Board of the NHFA:

Associate Professor Con Aroney, Cardiologist, and Chair, Medical Issues Committee;
Dr Andrew Boyden, NHFA Medical Affairs Manager;
Associate Professor Gerard Carroll, Rural Physician;
Dr David Hunt, Cardiologist; and
Professor Andrew Tonkin, Cardiologist, and Director, Health, Medical and Scientific Affairs of the NHFA.

Evidence in this Position Statement is graded according to the National Health and Medical Research Council system for assessing the level of evidence[2] (see Box 1).

bleeding.[26] Similar results were obtained with the combination of low-dose aspirin and moderate intensity anticoagulation therapy, compared with low-dose aspirin, in the ASPECT-2 trial, which examined secondary prevention in 999 patients after acute coronary syndromes.[27] Because of justifiable concerns regarding oral anticoagulation, the use of warfarin, alone or in combination with aspirin, is recommended primarily in survivors of myocardial infarction at high risk of systemic thromboembolism, such as those with associated atrial fibrillation, mural thrombosis, congestive heart failure, or previous embolism (E4).[25]

Competing interests

None identified.

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