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Cardioprotective aspirin in type 2 diabetes

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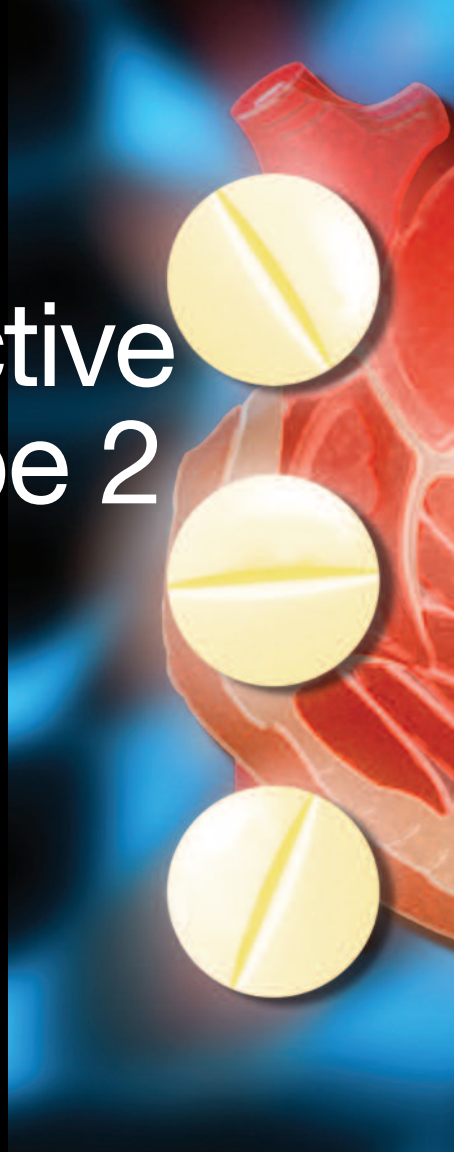

There is strong evidence supporting the use of low-dose aspirin in the secondary prevention of cardiovascular events in patients with type 2 diabetes but the evidence is less robust in primary prevention. Also, aspirin use can be associated with serious gastrointestinal haemorrhage.

Key points

- Cardioprotective doses of aspirin may prevent and/or delay cardiovascular events in patients with or without diabetes but can be associated with serious gastrointestinal (GI) haemorrhage.
- The current recommendation is that low-dose aspirin be considered for both primary and secondary prevention of cardiovascular events in people with type 2 diabetes. This may change when the results are known of a trial of low-dose aspirin in patients with type 2 diabetes but no known coronary heart disease.
- Patients at higher risk of GI bleeding include the biologically old, those who have a past history of an upper GI bleed, *Helicobacter pylori* infection or type 2 diabetes and those taking certain medications.
- In patients at high risk for an upper GI bleed, *H. pylori* testing and treatment should be considered prior to starting aspirin.

Cardiovascular disease is the major cause of the excess mortality, morbidity and healthcare costs associated with type 2 diabetes. Cardioprotective doses of aspirin may prevent and/or delay cardiovascular events but are associated with significant side effects, including serious gastrointestinal (GI) haemorrhage. This article uses a case-based approach to discuss this topic and provides guidance to identify patients at high risk of GI haemorrhage and opportunities to reduce this risk.

THE CASE

Ann is new to the practice and was identified as having diabetes in the tests arranged at her first visit two weeks ago. She is 68 years old, a little overweight (158 cm, 70 kg; body mass index [BMI] 28 kg/m^2), a nonsmoker, a rare social drinker and a keen bushwalker. Her ABCss of diabetes care (glycosylated haemoglobin [A_{1c}], blood pressure, cholesterol, smoking and salicylates) are shown in Table 1.

Ann is not keen on taking drugs but when she came to the practice she was taking citalopram 20 mg/day for depression, omeprazole 20 mg/day for past indigestion, intermittent ibuprofen 400 mg for hip pain and a range of health foods. She was initially reluctant to take hypoglycaemic medication but has now accepted her need for metformin 850 mg/day.

SHOULD ANN TAKE A CARDIOPROTECTIVE DOSE OF ASPIRIN?

There are two general approaches to the use of cardioprotective doses of aspirin (75 to 150 mg/day) in patients with type 2 diabetes: one is based on a history of a cardiovascular

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TABLE 1. ANN'S ABCss OF DIABETES

Factor	Ann's value	Target value
• A_{1c}	8.2%	<7.0%
• Blood pressure	124/70 mmHg	<130/80 mmHg
• Cholesterol	4.6 mmol/L	<4 mmol/L
– HDL cholesterol	1.1 mmol/L	>1 mmol/L
– LDL cholesterol	3.1 mmol/L	<2.5 mmol/L
• smoking	Nonsmoker	0
• salicylates	0	75 to 150 mg/day

event (secondary prevention) and the other on cardiovascular risk (primary prevention).

Ann has no history of a cardiovascular event but her five-year risk is more than 15% according to the Australian absolute cardiovascular disease risk calculator (www.cvdcheck.org.au). Reviewing her electrocardiogram might identify an unrecognised myocardial infarction (MI); these are common in older women with diabetes.

Supporters of secondary prevention consider that although there is strong evidence for net benefit over harm for cardioprotective aspirin in secondary prevention, the evidence for primary prevention is not robust. Supporters for primary prevention point out that type 2 diabetes is considered by many as a coronary risk equivalent, people with type 2 diabetes and no past history of MI having the same cardiovascular risk as those without diabetes but with a history of MI.[1]

A prospective randomised controlled trial of cardioprotective aspirin is in progress in subjects with type 2 diabetes but no history of coronary heart disease (see the website www.heartfoundation.org.au/information-for-professionals/Clinical-Information/Pages/coronary-heart-disease.aspx). This trial is powered to provide evidence of net benefit over harm. Until the results of the trial are available the recommendation is that, unless there are contraindications, low-dose aspirin should be considered for cardioprotection in people with type 2 diabetes.[2]

IS ANN AT SPECIAL RISK OF SIDE EFFECTS FROM ASPIRIN?

Aspirin, a platelet aggregation inhibitor, is generally well tolerated and the most common side effect (dyspepsia) is often a nuisance rather than a danger (see the box on page 46). However, the other common side effects of haemorrhage, allergy and asthma can be life threatening, especially in older, frailer people with multiple comorbidities. If Ann were allergic to aspirin or had aspirin-associated asthma, she would probably know by now, being in her late sixties. Nevertheless, patients should be monitored for atopic symptoms after aspirin therapy is initiated.

The major side effect to worry about in Ann is serious haemorrhage. Her blood pressure is not ideal but is not in the range threatening cerebral haemorrhage. She does, however, have several factors making her more likely to have an upper GI haemorrhage (see the box on page 46).[3,4] The relative risk of upper GI haemorrhage is almost tripled in patients taking cardioprotective doses of aspirin

SIDE EFFECTS OF ASPIRIN*

- Dyspepsia
- Gastritis/peptic ulcer disease
- Haemorrhage
  - gastrointestinal
  - CNS
  - other
- Allergy/asthma

* Less common side effects include dizziness, tinnitus and urate level abnormalities.

(relative risk, 2.6; 95% confidence interval, 2.2 to 3.1) and this is increased to six times in those taking cardioprotective aspirin with another NSAID.[5]

Ann does take another NSAID (ibuprofen), albeit intermittently. She also takes a selective serotonin reuptake inhibitor (SSRI; citalopram), a class of drugs that can predispose patients to bleeding through inhibition of platelet aggregation.[6] Additionally, Ann may well have *Helicobacter pylori* infection and/or be taking complementary medications, further increasing her risk of serious GI haemorrhage.

HOW CAN ANN'S RISK OF ASPIRIN-ASSOCIATED GI HAEMORRHAGE BE REDUCED?

Steps to take in reducing the risk of GI haemorrhage associated with cardioprotective aspirin therapy include avoiding the use of prescribed and nonprescribed medications that could pose a risk when taken with aspirin.

In Ann's case, a Home Medicines Review should be arranged to determine the prescribed and nonprescribed medications she is taking and whether any pose a risk if she starts aspirin. The next step is to phase out the use of the SSRI and intermittent NSAID if possible. If Ann finds her NSAID indispensable to her mobility then the lowest risk, lowest dose and shortest effective course should be used. It may be possible that Ann can phase it out later, possibly substituting paracetamol, specific complementary medications such as high-dose fish oil or glucosamine, or other interventions, such as acupuncture combined with strengthening exercises supervised by a physiotherapist. Ann may be able to phase out her SSRI with professional support.

Ann is of an age when *H. pylori* infection is quite likely (anti-*H. pylori* IgG antibodies have been detected in 40% of people aged over 60 years).[7] However, she is not in a higher risk ethnic group (Middle Eastern, Asian, Eastern European and possibly Aboriginal).[8] She also has several medical factors that predispose her to an upper GI bleed (see the box on this page). Testing and treating her for *H. pylori* infection would reduce the GI risks from the NSAID prescribed for her arthritis and/or from the cardioprotective aspirin. It is interesting to consider whether her past use of the NSAID has already presented a GI 'challenge', placing her in a lower risk group. Indeed, it is often noted that naïve NSAID users are at greatest risk for GI bleeding. The reduction of GI bleeding rates with time relative to the duration of NSAID therapy, however, seems to be fairly minor and should not be a reassurance that a patient will never have problems.[9]

The current regional guidelines, the 'Second Asia–Pacific Consensus Guidelines for *Helicobacter pylori* infection', endorse the testing and treating of *H. pylori* prior to starting aspirin in patients at high risk for ulcer and ulcer-related complications (age over 60 years, and especially over 75, and/or significant comorbidity; see the box on this page).[10] The guidelines also note the association between long-term proton pump inhibitor use and advanced pathological stages of *H. pylori* gastritis, providing another potential indication to test and treat.[10]

Given Ann's past history of dyspepsia, long-term proton pump inhibitor use, age and comorbidities, the decision was made to test and treat for *H. pylori* prior to starting aspirin. It is important to note that she has not had any recent dyspepsia, which would have required further specific investigation.

PATIENT GROUPS AT HIGH RISK OF GASTROINTESTINAL BLEEDING[3]

- The 'old' old (biological age over 75 years)
- Those on anticoagulant/antiplatelet therapy
- Those with a past history of an upper gastrointestinal bleed
- Those with *Helicobacter pylori* infection
- Those with type 2 diabetes
- Those taking certain medications:
  - NSAIDs
  - Selective serotonin uptake inhibitors
  - Some complementary medications (including fish oil, gingko extract)[4]

Noninvasive (i.e. nonendoscopic) tests for *H. pylori* infection are serology, the urea breath test and faecal antigen (Table 2).[11-13] The authors' noninvasive test of choice is the urea breath test, which may be used for both initial testing as well as confirmation of eradication after treatment.[10,11] Although this test is not as convenient as serology (antiacidity therapy must be stopped for two weeks before testing), its major advantage is that it tests for active infection. *H. pylori* antibody levels can remain elevated long after the infection has been eradicated and, therefore, testing for them cannot be used to assess whether the *H. pylori* infection is active, past exposure has occurred or if eradication has taken place.

In general, the more convenient serology tests may be reasonable for initial

testing in the preventative, asymptomatic setting. However, in patients at higher risk of adverse outcomes, such as a past history of bleeding, the more sensitive urea breath test is preferred. There is less experience with the faecal antigen test in Australia but it is another option for assessing patients for current infection.

In Ann's case, the urea breath test and serology are both reasonable options for initial testing for *H. pylori* infection. Acceptability, access and Ann's wishes will guide the choice. The urea breath test, however, is required to check whether treatment was successful.

Ann should understand that testing for *H. pylori* infection is only worthwhile if she would accept treatment (a proton pump inhibitor and two of clarithromycin, amoxycillin and metronidazole) for a positive test result. Thus Ann should be counselled regarding the treatment schedule and potential side effects prior to testing. As she is in the patient group at high risk of upper GI side effects, it is appropriate to retest her after eradication treatment to check that the treatment has been effective. As noted above, the urea breath test is the best and most acceptable test to check for eradication.[10] Prior to rechecking, Ann needs to have stopped taking a proton pump inhibitor and antibiotics for two weeks and four weeks, respectively.

SUMMARY

Cardioprotective doses of aspirin may prevent and/or delay cardiovascular events but can be associated with serious GI haemorrhage. It is important to identify patients at high risk and to reduce that risk so these patients can more safely take cardioprotective aspirin.

Although there is strong evidence for net benefit over harm with the use of aspirin in the secondary prevention of cardiovascular events, the evidence for primary prevention is less robust. However, the cardiovascular risk in people with type 2 diabetes is considered by many to be equivalent to a history of a cardiovascular event. Until results from ongoing prospective randomised controlled trials are available, it is recommended that unless there are contraindications, low-dose aspirin be considered for cardioprotection in people with type 2 diabetes.

Patients at higher risk of GI bleeding include the biologically old, those with a past history of an upper GI bleed, *H. pylori* infection or type 2 diabetes, and those taking certain medications. The GP should review the medications annually and phase out unnecessary medications to reduce confusion and unnecessary risks. For patients taking many medications and where the GP feels this is indicated, a Home Medicines Review can identify the prescription and nonprescription medications being taken and whether any pose a specific risk if taken with aspirin.

H. pylori infection is relatively common in older Australians and testing for this infection should be discussed with those patients at high risk for an upper GI bleed prior to their starting cardioprotective aspirin.[10] Treatment of *H. pylori* infection prior to aspirin or NSAID therapy should be offered to those patients most likely to benefit.[10] Patients treated for *H. pylori* infection should appreciate the importance of completing the medication schedule and have eradication confirmed following treatment. MT

TABLE 2. NONINVASIVE TESTS FOR *HELICOBACTER PYLORI*[11-13]

Test	Test characteristics	
	Sensitivity	Specificity
Serology*	85%	79%
Urea breath test†	95%	>95%
Faecal antigen†	93%	95%

* Not suitable for retesting after treatment.
† No proton pump inhibitor or antibiotics for two weeks or four weeks beforehand, respectively.

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A list of references is available on request to the editorial office.

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