ABCss: s is for salicylates

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The case studies in this series focus on the ABCss of diabetes care (A_{1c}, blood pressure, cholesterol, smoking, salicylates), how to get them closer to target and how to keep them there.

Case scenario

'*I never thought this would happen – I've turned 60!*'

Sally has had type 2 diabetes for 12 years. Several family members have or have had the condition, including her mother (who died suddenly at age 58 years), a sister and two of her three daughters.

Sally has never mentioned her personal risk and has not been very conscientious about her health care. Over the years there have been many missed and cancelled appointments and gaps in prescription medication. Not surprisingly, some of her ABCss are off target, namely her glycosylated haemoglobin (A_{1c}) and blood pressure (Table).

On the other hand, she has always been concerned about her cholesterol and has conscientiously taken her statin (atorvastatin [Lipitor] 20 mg per day). Her total and LDL cholesterol levels have been on target over the last few years (Table 1).[1]

Sally has no microalbuminuria and she has never smoked. She is obese (160 cm, 80 kg; BMI, 31.3 kg/m^2), and rarely walks further than she has to. She says she likes a glass or two of white wine at dinner and enjoys being with her five grandchildren.

Her hypoglycaemic medication includes metformin 850 mg insulin [Humulin NPH]) 30 to 40 units at bedtime, depending on her test results. Intermittently she takes medication for her blood pressure (fosinopril/hydrochlorothiazide [Monoplus] 10/12.5 mg per day and atenolol 50 mg per day), as well as celecoxib (Celebrex) 20 mg per day. She visits the local health food store regularly and takes echinacea, ginkgo biloba and a range of vitamin and mineral preparations.

She is visiting you today because she wants to discuss her cardiovascular risk and improve her self-care. 'Turning 60 was a bit of a wake up call. I don't want to be like my mother and not see my grandchildren grow up'.

Questions

- What is Sally's risk of a cardiovascular event in the next five years?
- For Sally, which cardiovascular events are likely to be reduced by low dose aspirin, and by how much?
- Does the dose and formulation of aspirin affect its action?
- Could Sally be resistant to the action of aspirin and how might she tell?
- One week after Sally begins aspirin therapy she returns complaining that she has had a bad nosebleed and is bruising very easily. She is worried that she might have a dangerous bleed. What advice should she be given?

Future risk of a cardiovascular event

In type 2 diabetes the major contribution to adverse outcomes for the person (in terms of mortality) and for the community (in terms of cost) is cardiovascular disease. Figure 1 shows the cost to the United States healthcare system of the main diabetes complications.[2] Cardiovascular disease costs seven times as much as the next ranking complication (foot problems partly associated with peripheral vascular disease) and twenty times as much as eye disease, which is the most recognised complication of diabetes in the community.

Table. Sally's ABCss values

Factor	Sally's value	Target value
A_{1c}	7.5 to 9.0% (last visit, 8.2%)	<7.0%
Blood pressure	130 to 150/90 to 95 mmHg (last visit, 142/90 mmHg)	<130/80 mmHg
Cholesterol		
– total	3.8 mmol/L	<4 mmol/L
– LDL cholesterol	2.1 mmol/L	<2.5 mmol/L
– HDL cholesterol	0.8 mmol/L	>1 mmol/L
– triglycerides*	1.8 mmol/L	<1.5 mmol/L
Smoking	0 (never)	0
Salicylates	0	75 to 150 mg/day

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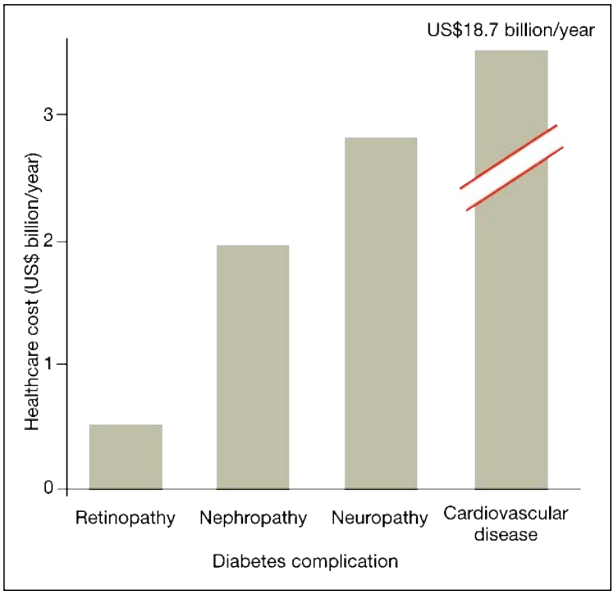

Figure 1. The cost of cardiovascular disease in diabetes outweighs that of any other complications.[2]

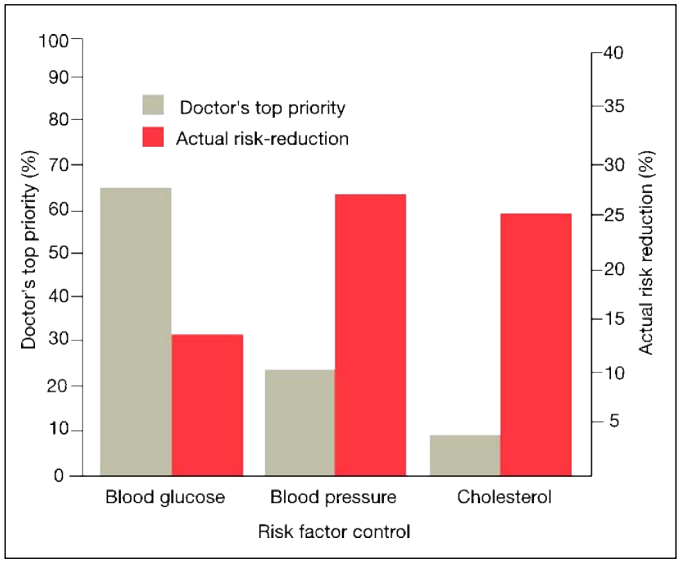

Figure 2. Controlling blood pressure and cholesterol gives greater reduction in risk for cardiovascular disease than controlling glycaemia (2001 meta-analysis data).[3]

For cardiovascular disease, albuminuria or decreased glomerular filtration rate (GFR) is a major risk factor, and often an indicator of existing vascular damage. Fortunately, Sally does not have this (her plasma creatinine is 75 µmol/L and her report shows her estimated GFR is >60 mL/min/1.73m^2). She also does not have the next ranking risk factor – smoking habit. Among the classical medical risk factors of diabetes, doctors (and patients) often overestimate the importance of glycaemic control (A_{1c}) and underestimate the importance of blood pressure (B) and cholesterol (C) control in contributing to cardiovascular risk (Figure 2).[3] Sally's cholesterol is under control so the priority is her hypertension.

Using the National Prescribing Service's version of the New Zealand Risk calculator and Sally's age, blood pressure, diabetes status and lipid levels, Sally's cardiovascular risk is approximately 10 to 15% over the next five years. However, given that she has the two additional risk factors of strong family history and obesity, this is likely to be an underestimate, and hence it is appropriate to move her into the next higher CV risk level (15 to 20%), which falls into the high risk category (>15%). (The National Prescribing Service's version of the New Zealand Cardiovascular Risk Calculator is promoted by the National Heart Foundation and is available at www.racp.edu.au/bp/resources/EBM_cardio.pdf and www.nps. org.au/site.php?page=1&content=/resources/content/hpro_cv_risk_calcu.html.)

Action to be taken

Step 1. Review Sally's lifestyle and see if she might be able to 'Eat less/more healthily, walk/exercise more' to reduce or at least not increase her weight.

Step 2. Assess Sally's blood pressure when she is taking her blood pressure medications, perhaps using self-blood pressure monitoring to give a better indicator of the 24-hour profile.

Sally also needs education and encouragement to improve adherence with her medications, particularly those for her blood pressure. It is important to ask why she only takes her blood pressure medication intermittently, whereas she takes the statin regularly. Explore her beliefs in this regard and ask if she experiences adverse effects from her blood pressure medications.

Step 3. Consider moving to the next level of intervention and/or consulting with a colleague.

Aspirin and cardiovascular event risk reduction

There is some controversy about aspirin's effects in high and low risk groups but the consensus seems to be that it is more effective in women when considering cerebrovascular disease and in men when considering myocardial infarction. A useful mnemonic is: women are from Venus when considering cerebroVascular disease, and men from Mars for Myocardial infarction. For men, the data for risk reduction with aspirin in type 2 diabetes mostly comes from analyses of diabetes cohorts in larger studies – for example, in the Hypertension Optimal Treatment (HOT) trial aspirin was associated with a relative risk reduction in myocardial infarction of approximately 40% at all

levels of blood pressure.[4] For women, the largest relevant study is the Women's Health Study (WHS), which showed a relative risk reduction of approximately 20% for all types of stroke, but no significant reduction in coronary events.[5]

Why aspirin seems to affect different cardiovascular events in women than in men is not fully known. It may be that the findings of the WHS reflect the fact that most women in this study were at low or low/moderate risk of cardiovascular disease at baseline, and that the dose of aspirin was lower than that currently used and previously studied (i.e. 100 mg on alternate days was used in the WHS, compared with 75 mg every day in the HOT trial). When the highest risk group in the WHS was analysed separately (women aged 65 years or older), there was a significant reduction in both coronary and cerebrovascular events.

There are many ideas but little convincing data on differences between men and women. Women may be different to men in their response to aspirin, but it is not clear if this difference is real or whether it is associated with a different pathophysiology of vascular disease or with a differential effect of aspirin on this pathophysiology.

For men and women, the action to take is the same: tackle the modifiable contributors. The modifiable risk factors for cardiovascular disease for both genders are the same – the ABCss. Some of these are more relevant to one circulation than another and some more relevant to one sex, but they all contribute to the overall risk of cardiovascular events in men and women with type 2 diabetes.

Sally's mother is reported to have had a sudden death, most likely a coronary event, but, like Sally, she was also at risk of a cerebrovascular event.

For Sally, commencing aspirin and modifying the other modifiable risk factors is appropriate to reduce her risk of future coronary, cerebrovascular and peripheral vascular events.

Aspirin dose and formulation

The sparse data available suggest that once a threshold dose of aspirin is reached, the cardiovascular protection remains constant but the risk of major gastrointestinal haemorrhage increases (because of the local gastric effects of aspirin). Doses of 75 to 150 mg aspirin per day are generally recommended as meeting this threshold for men and women.

Regarding formulations, there is some evidence that enteric coated aspirin (Astrix 100, Cartia) decreases gastric upset, but it does not appear to reduce the risk of gastrointestinal bleeding.[6]

There may be advantages in people taking special aspirin formulations in terms of adherence and also for contact with pharmacists who can provide advice on potentially interacting medications or problems with aspirin therapy.

Sally could take each day half a tablet of supermarket-strength aspirin – 150 mg per day, at a cost of about 2 cents per day – or one tablet of one of the branded low dose formulations (Astrix 100, Astrix Tablets, Cardiprin 100, Cartia, DBL Aspirin) – 100 mg per day, at about 13 to 17 cents per day. Perhaps Sally could make her own decision based on information about the potential benefits of special formulations and their extra cost.

Aspirin resistance

Controversy continues about 'resistance to' or 'failure of' aspirin and the other (coronary cerebral, peripheral) antiplatelet agents such as clopidogrel (Iscover, Plavix).[6,7]

Certainly aspirin 'resistance' can be shown in some patients in terms of a reduction or absence of expected laboratory measures of platelet activation and aggregation. It is also true that cardiovascular events do occur in people taking antiplatelet agents, but this may not mean 'resistance'. It often means that risk is reduced but not eliminated. A person who has a cardiovascular event on antiplatelet therapy may have had one earlier or the event may have been more severe had they not been on therapy.

If 'resistance' to the clinical effects of aspirin really exists, at present there is no clinically useful test to identify this. Even if there were, there is no evidence that increasing the aspirin dose or switching to another antiplatelet agent in these patients would be appropriate.

Bleeding on antiplatelet therapy

A response to Sally's bleeding while taking aspirin could be, 'That shows the aspirin is working'. This could perhaps be followed by further positive comments such as, 'If nosebleeds continue to be a problem, an ENT doctor probably can fix it' and 'Have you noticed how much easier it is to do your blood glucose tests?'

Concern about bleeding on antiplatelet therapy is quite appropriate for patients and their doctors. Patients are worried about the intrusion of bleeding affecting their lives, such as bruising and nosebleeds. Doctors are concerned about the risk of bleeding, particularly neurologists and gastroenterologists. For neurologists, the consensus is that above the high risk threshold of cardiovascular ischaemic events (15% over five years), the antiischaemic benefits of aspirin outweigh the risk of cerebral haemorrhage. For gastroenterologists, the situation is more complex. Frequently, patients are taking an NSAID – in Sally's case, celecoxib. They may also have a concomitant *Helicobacter pylori* infection. Both of these increase a patient's risk of a gastrointestinal haemorrhage, and this risk would be further potentiated and the haemorrhage worsened by aspirin. Sally is also predisposed to peptic ulceration and its complications by her age and her diabetes. The ginkgo biloba she is taking also has antiplatelet effects and would increase her risk of haemorrhage.

The potential additive effect of an NSAID is easily assessed if not easily addressed. Patients should be advised about the risk of NSAIDs and the effective alternatives. Physiotherapists and organisations such as Arthritis Australia (www.arthritisaustralia.com.au, freecall 1800 111 101) and Osteoporosis Australia (www.osteoporosis.org.au, freecall 1800 242 141) offer education about alternative ways to deal with musculoskeletal discomfort.

As far as the COX-2 'selectivity' of some NSAIDs is concerned, the potential lesser haemorrhagic risk compared with nonselective agents no longer applies with concomitant aspirin.[8]

If Sally finds her NSAID is indispensable then she may want to change from celecoxib to an equally effective agent (e.g. diclofenac) and to start a gastroprotective agent such as proton pump inhibitor or prostaglandin agonist (misoprostol [Cytotec]), with the advantage of lower cost for the NSAID. However, you would need to consider PBS restrictions and the lack of evidence for these agents in this setting.

It may be worth considering testing for *H. pylori* in patients like Sally who have significant risks for NSAID-induced gastrointestinal toxicity. Sally may also be prepared to forego the unproven benefits but definite risk of ginkgo biloba.

Key points

- Cardiovascular protection is usually the main priority for patients with type 2 diabetes.
- Cardiovascular protective doses of aspirin should be considered for those patients with type 2 diabetes whose cardiovascular risk exceeds 15% over five years.
- Aspirin doses in the range of 75 to 150 mg per day and the various low dose formulations that are available provide appropriate cardiovascular protection.
- Aspirin resistance may occur but, at present, this resistance is not easily identified or addressed.
- The major risks of bleeding are cerebral and gastrointestinal. The benefits in terms of reduction of ischaemic cardiovascular events exceeds haemorrhagic risk once the five-year risk of ischaemic events exceeds 15%. MT

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

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