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Case study 38: Management of ischaemic heart disease

## Targeting ischaemic heart disease: improving health outcomes with multiple medications

While deaths related to cardiovascular disease have declined in the last ten years, ischaemic heart disease (most commonly angina or myocardial infarction) remains the leading cause of sudden death and disability in Australia, and its prevalence is expected to rise with the ageing population.<sup>1,2</sup>

During 2001–2, there were an estimated 48 700 coronary events related to ischaemic heart disease: around half were fatal.<sup>1</sup> For people with previous myocardial infarction or stroke, mortality is about 5% per year without preventive treatment.<sup>1</sup> This *NPS News* looks at reducing the burden of ischaemic heart disease by modifying risk factors and improving the use of preventive medicines.<sup>1,2</sup>

### Reduce the burden by reducing the risks

Modifiable risk factors for ischaemic heart disease include smoking, elevated blood pressure and cholesterol, inactivity and obesity.<sup>1</sup> The good news is that the prevalence of smoking and elevated blood pressure is falling, however other risk factors, including diabetes, are on the increase.<sup>1</sup> Target risk factors with lifestyle interventions and drug treatments, particularly in those at greatest risk (see Box 1).<sup>1–4</sup> Manage multiple risk factors concurrently, as this can have an additive effect in reducing risk.<sup>3,4</sup>

Guidance on managing cardiovascular risk factors is available from the National Heart Foundation (NHF) website ([www.heartfoundation.com.au](http://www.heartfoundation.com.au), go to 'Health & Lifestyle'), the SNAP (Smoking, Nutrition, Alcohol and Physical activity) guide ([racgp.org.au/guidelines/snap](http://racgp.org.au/guidelines/snap)) and *NPS News* 39 'Reducing risk in type 2 diabetes' ([www.nps.org.au/healthpro](http://www.nps.org.au/healthpro), go to 'Newsletter Index').

#### Box 1: Lifestyle interventions and drug treatments shown to reduce the risk of cardiovascular morbidity and/or mortality from ischaemic heart disease<sup>1,3–7</sup>

Lifestyle interventions and drug treatments	Relative risk reduction (%)
Smoking cessation	50%
Regular physical activity*	50%
Reducing blood pressure†	15–25%
Reducing cholesterol with diet and statins‡	30–50%
Antiplatelet therapy with low-dose aspirin	25%
Beta-blockers post myocardial infarction	20–30%
ACE inhibitors post myocardial infarction	20–26%
Controlling blood glucose	14% <sup>§</sup>

\* Vigorous activity (e.g. swimming) that increases cardiovascular fitness confers greater benefit than moderate activity (e.g. brisk walking); aim for at least 30 minutes on most days of the week, gradually increasing the intensity of exercise.

† Aim for < 140/90 mmHg for age ≥ 65 years (< 130/85 mmHg for patients < 65 years; < 130/85 mmHg or 130/80 mmHg for those with diabetes; < 125/75 mmHg for those with proteinuria > 1 g/day).

‡ Restricting dietary fat (saturated fats and cholesterol) can reduce cholesterol levels by 5–15%.

§ For every 1% reduction in HbA<sub>1c</sub>.

## Which patients should, or should not, take aspirin?

### Low-dose aspirin is the antiplatelet drug of first choice

**Use aspirin 75–150 mg daily in all patients with ischaemic heart disease.**<sup>3,4,7</sup> Aspirin is effective, has an established safety profile and is inexpensive.<sup>7</sup> In a meta-analysis by the Antithrombotic Trialists' Collaboration, aspirin prevented 36 serious vascular events (myocardial infarction, stroke or vascular death) per 1000 high-risk patients (including those with ischaemic heart disease) treated for 2 years.<sup>6</sup> These benefits far outweighed the risks of major extracranial bleeding or haemorrhagic stroke (1–2 per 1000 patients treated over 1 year).<sup>6</sup>

### Managing patients who are intolerant of aspirin

Aspirin is contra-indicated in patients with a history of intracranial haemorrhage, active or recent peptic ulcer disease, aspirin allergy or bleeding disorder.<sup>5,8,9</sup> Assess symptoms in patients who claim to be allergic to aspirin as this may be intolerance that is not an allergy.<sup>10,11</sup> The symptoms of aspirin allergy include<sup>10,11</sup>:

- rhinorrhoea, bronchospasm and/or laryngospasm
- urticaria with or without angioedema
- anaphylaxis (e.g. hypotension, swelling, tachypnoea, laryngeal oedema, pruritus).

### Severe dyspepsia, upper gastrointestinal ulceration or bleeding are symptoms of aspirin intolerance.

<sup>3,5,8</sup> Patients with dyspepsia may tolerate aspirin when taken with food, at a lower dose, or as an enteric-coated formulation, however this will not reduce the risk of bleeding.<sup>5,12</sup> Where possible, avoid medications that can exacerbate gastrointestinal intolerance, such as NSAIDs and oral corticosteroids.<sup>5,13</sup>

Clopidogrel (Iscover, Plavix) may be used when patients have a contra-indication to or intolerance of aspirin.<sup>3–5,7,8</sup> It is as effective and well-tolerated as aspirin, but is less cost-effective.<sup>7</sup> It may also cause skin rashes, diarrhoea and, rarely, thrombotic thrombocytopenic purpura.<sup>5</sup>

In the CAPRIE study, the slight difference in the annual rate of serious vascular events (clopidogrel 5.3% vs aspirin 5.8%) was largely due to an effect in patients with intermittent claudication.<sup>14</sup> Two hundred patients would need to be treated for one year with clopidogrel instead of aspirin to prevent one vascular event. Aspirin and clopidogrel had similar rates of gastrointestinal bleeding (aspirin 2.7% vs clopidogrel 2.0%) and intracranial bleeding (0.5% vs 0.4%).<sup>14</sup>

Clopidogrel may be used for patients with recurrent vascular events while taking aspirin.<sup>3,4</sup> Check first that the patient has been compliant with aspirin treatment and has been taking the correct dose.<sup>6,15</sup> When clopidogrel is added to aspirin the risk of major bleeds increases<sup>3,4</sup>: in both the MATCH<sup>16</sup> and CURE trials<sup>17</sup>, the combination doubled the risk of major gastrointestinal bleeding compared to clopidogrel or aspirin alone.

## Symptom control with nitrates: balancing tolerance and intolerance

Controlling the symptoms of angina with nitrates (see Box 2 for preparations available in Australia) can be compromised by nitrate tolerance and side-effects.<sup>18</sup> Tolerance to the effects of nitrates can develop within 24 hours of frequent or continuous exposure by any route.<sup>3</sup> Ensure patients have a nitrate-free interval of 10–12 hours each day during a period when symptoms are least likely (e.g. overnight).<sup>3,5,18</sup>

Common side-effects with nitrates include headache, postural hypotension, flushing and syncope.<sup>3,5,18</sup> Slow upward titration of the dose, or reducing the dose, can help minimise side-effects.<sup>18,19</sup> Reassure the patient that headache and postural hypotension usually resolve after several days.<sup>18,19</sup> Taking oral nitrates with food may

reduce nausea, and changing application sites for patches can minimise skin irritation.<sup>19</sup>

### Consider once-daily nitrate preparations over those dosed more frequently

Poor compliance has been seen in patients with stable angina taking oral nitrates twice or three times daily: the afternoon dose was omitted or taken incorrectly in 50% of cases.<sup>19–21</sup> Oral nitrates once daily had better compliance and were preferred to other regimens by 90% of patients.<sup>20,22</sup> There is a lack of information on compliance with nitrate patches: they may offer ease of use, but the required nitrate-free interval may not be adhered to by some patients.<sup>23</sup>

## Box 2: Dosing frequencies of nitrate preparations for preventing angina<sup>3,5,19</sup>

Nitrate preparations	Recommended dosing regimen
Isosorbide mononitrate sustained-release oral tablets (Arsorb, Duride, Imdur Durules, Imtrate SR, Isomonit, Monodur)	Once daily at the same time every day (e.g. 8am) as the formulation allows for a nitrate-free interval
Glyceryl trinitrate transdermal patches (Minitran, Nitro-Dur, Transiderm-Nitro)	Apply morning or evening and remove patch for a 10–12 hour nitrate-free interval (e.g. on 8am, off 8pm)
Isosorbide dinitrate standard-release oral tablets (Isordil, Sorbidin)	Up to three times daily with a 10–12 hour nitrate-free interval between two doses (e.g. 8am, 12pm, 3pm)

## Keep medication regimens simple to aid compliance

Multiple medications are necessary to manage ischaemic heart disease. A recent case-control analysis found that people taking a combination of aspirin, statins and beta-blockers, with or without ACE inhibitors, had greater reductions in all-cause mortality compared to any of these treatments alone.<sup>24</sup>

Poor medication compliance has been identified in patients with ischaemic heart disease: compliance with statins or beta-blockers falls by 25–50% after 6 months to 2 years of treatment.<sup>25–29</sup> Strong predictors of noncompliance include age (> 75 years) and depression, which often co-exist with ischaemic heart disease.<sup>4,26,28</sup> Other predictors include dementia, social isolation or deprivation, recent myocardial infarction and multiple medications.<sup>26,28</sup>

Complex regimens of lifestyle modification and multiple medications are not easy to maintain and patients may overestimate their compliance.<sup>30</sup> Compliance is less likely when the treatment benefits are poorly understood, or where treatments do not control symptoms or prevent a serious vascular event.<sup>25,26</sup> Intolerable side-effects may also lead to noncompliance, particularly with beta-blockers.<sup>7</sup>

### Identify and regularly monitor patients for noncompliance by<sup>30</sup>:

- identifying those at risk of poor compliance early
- asking how many medications were missed during the previous week
- checking for poor responses to dose increments
- following up missed appointments.

### What strategies can help improve compliance to multiple medications?

Single strategies do not help most patients as noncompliance is usually caused by a number of factors (see Box 3).<sup>31</sup> A review of randomised controlled trials found that a multifaceted approach may improve medication compliance long-term (see Box 4, over).<sup>32</sup>

**As a starting point, simplify the dosage regimen by limiting the number of daily doses.** Reducing the number of daily doses can be an effective intervention in patients with hypertension and dyslipidaemia.<sup>32</sup> Where possible, time the doses with the patient's routine (e.g. meals).

### Drugs that treat co-existing conditions (e.g. hypertension) may improve compliance by minimising the number of medications.<sup>25–27,31</sup>

Guidance on drug classes that treat multiple conditions is available from the NPS sheet 'Choice of antihypertensive drugs in patients with co-existing conditions' ([www.nps.org.au/resources/Health\\_Professional\\_Tools/choicedrugsform.pdf](http://www.nps.org.au/resources/Health_Professional_Tools/choicedrugsform.pdf)) and the NHF 'Hypertension Management Guide for Doctors' ([www.heartfoundation.com.au/downloads/hypertension\\_management\\_guide\\_2004.pdf](http://www.heartfoundation.com.au/downloads/hypertension_management_guide_2004.pdf)).

### When a patient starts a multiple treatment regimen, organise a follow up appointment within two weeks for an early review of compliance.<sup>30</sup>

Contact patients who miss appointments or GP visits, as this can be a signal of poor compliance with healthcare.<sup>30</sup> When discussing the risks of not taking medicines, address the concerns of the patient first, as they may respond more positively to information that is tailored to them.<sup>33</sup>

## Box 3: Barriers to compliance

Common barriers to medication compliance <sup>4,25,26,29,30</sup>
Poor attitudes to taking medicines
Lack of insight into treatment benefits
Fear of adverse effects
Difficulty managing multiple daily doses
Anxiety or depression
Recent vascular event e.g. myocardial infarction
Missing appointments

## Box 4: Medication compliance: multiple strategies

### Multiple strategies that can improve medication compliance<sup>30,32,33</sup>

#### Regular patient review and reinforcement

- use cardiovascular risk calculators to convey risk and treatment benefits
- acknowledge patient's efforts with compliance
- contact patients who miss appointments or GP visits

#### Simplify medication regimens

- reduce dose frequency and/or coincide doses with events (e.g. meals)
- use controlled-release or combination products

#### Monitor treatment effects (e.g. cholesterol levels, blood pressure)

#### Provide verbal and written instructions, information materials

#### Provide reminder systems (e.g. dose administration aids, appointment cards)

#### Establish an ischaemic heart disease patient register and recall system for missed visits

#### Establish or seek out disease and social support groups

#### Seek assistance from other health professionals, relatives and/or carers

## Where can GPs get further support for patients with ischaemic heart disease?

Cardiac rehabilitation outpatient programs can help patients with myocardial infarction or stroke by improving medication use and reducing their risk of a further event.<sup>1</sup> Health professionals can find information at the Australian Cardiac Rehabilitation Association (ACRA) website ([www.acra.net.au](http://www.acra.net.au)).

GPs can help their patients with ischaemic heart disease to manage the many healthcare services they require by using an *Enhanced Primary Care* (EPC) plan. Information on EPC plans can be found at the Department of Health and Ageing website ([www.health.gov.au/internet/wcms/publishing.nsf/Content/Enhanced+Primary+Care+Program-1](http://www.health.gov.au/internet/wcms/publishing.nsf/Content/Enhanced+Primary+Care+Program-1)).

Patients having difficulty taking their medicines for ischaemic heart disease may benefit from a *Home Medicines Review* (HMR), where a pharmacist provides advice to the GP on the medicines issues of the patient being reviewed. Information on HMRs can be found at the Department of Health and Ageing website ([www.health.gov.au/internet/wcms/publishing.nsf/Content/health-epc-dmmr.htm](http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-epc-dmmr.htm)).

### Reviewers

Dr James Best, General Practitioner

A/Prof Nick Buckley, Clinical Pharmacologist, The Canberra Hospital

Ms Jan Donovan, Consumer

Dr Richard Abbott, General Practitioner

Dr John Dowden, *Australian Prescriber*

Ms Simone Rossi, *Australian Medicines Handbook*

Ms Susan Parker, Pfizer Australia

Any correspondence regarding content should be directed to the NPS. Declarations of interest have been sought from all reviewers.

### Expert Reviewer

Prof Peter Fletcher

Professor of Cardiovascular Medicine, Faculty of Health, School of Medical Practice and Population Health, University of Newcastle

Professor and Head of Cardiovascular Medicine, John Hunter Hospital, Newcastle

### References

1. Heart, stroke and vascular diseases: Australian facts 2004. AIHW Cat. No. CVD 27. Canberra: Australian Institute of Health and Welfare and National Heart Foundation of Australia (Cardiovascular Disease Series No. 22) May 2004.
2. The shifting burden of cardiovascular disease in Australia. Canberra: Access Economics Pty Limited and National Heart Foundation of Australia May 2005. [http://www.heartfoundation.com.au/media/nhfa\\_shifting\\_burden\\_cvd\\_0505.pdf](http://www.heartfoundation.com.au/media/nhfa_shifting_burden_cvd_0505.pdf) (accessed 4 May 2005).
3. Therapeutic Guidelines: Cardiovascular Version 4, 2003. North Melbourne: Therapeutic Guidelines Limited. Electronic version, April 2005.
4. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand. Reducing risk in heart disease 2004: Guidelines for preventing cardiovascular events in people with coronary heart disease. Canberra: National Heart Foundation of Australia. Revised March 2005. [http://www.heartfoundation.com.au/downloads/RRHID\\_fullguide\\_update\\_010405.pdf](http://www.heartfoundation.com.au/downloads/RRHID_fullguide_update_010405.pdf) (accessed 4 May 2005).
5. Australian Medicines Handbook 2005. Adelaide: Australian Medicines Handbook. Electronic version, January 2005.
6. Antithrombotic Trialists' Collaboration. BMJ 2002;324:71–86.
7. New Zealand Guidelines Group (NZGG). The assessment and management of cardiovascular risk evidence-based best practice guideline 2003. Wellington: NZGG December 2003. [http://www.nzgg.org.nz/guidelines/0035/CVD\\_Risk\\_Full.pdf](http://www.nzgg.org.nz/guidelines/0035/CVD_Risk_Full.pdf) (accessed 13 April 2005).
8. Hankey GJ, et al. Med J Aust 2003;178:568–74.
9. Hung J. Med J Aust 2003;179:147–52.
10. Gollapudi RR, et al. JAMA 2004;292:3017–23.
11. Ramanuja S, et al. Circulation 2004;110:e1–4.
12. Derry S, et al. BMJ 2000;321:1183–7.
13. Cryer B. N Engl J Med 2005;352:287–9.
14. CAPRIE Steering Committee. Lancet 1996;348:1329–39.
15. Sanderson S, et al. Ann Intern Med 2005;142:370–80.
16. Diener HC, et al. Lancet 2004;364:331–7.
17. CURE Investigators. N Engl J Med 2001;345:494–502.
18. Parker JD, et al. N Engl J Med 1998;338:520–31.
19. Shaw SV, et al. Formulary 1999;34:590–600.
20. Kardas P. Am J Cardiol 2004;94:213–6.
21. Straka RJ, et al. J Clin Pharmacol 1996;36:587–94.
22. Niemeyer MG, et al. Curr Ther Res 1996;57:927–36.
23. Brown RE, et al. J Clin Pharm Ther 1997;22:67–76.
24. Hippisley-Cox J, et al. BMJ 2005;330:1059–63.
25. Howell N, et al. Pharm J 2004;272:23–6.
26. Benner JS, et al. JAMA 2002;288:455–61.
27. Jackevicius CA, et al. JAMA 2002;288:462–7.
28. Butler J, et al. J Am Coll Cardiol 2002;40:1589–95.
29. Wei L, et al. Pharmacoepidemiol Drug Saf 2004;13:761–6.
30. Haynes RB, et al. JAMA 2002;288:2880–3.
31. Heidenreich PA. Am J Med 2004;117:130–2.
32. McDonald HP, et al. JAMA 2002;288:2868–79.
33. Alaszewski A. PLoS Med 2005;2:41.

*The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.*



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