MedicineToday
The Peer Reviewed Journal of Clinical Practice

A to Z of diabetes

Reprint Collection

Formerly **MODERN MEDICINE**

This supplement is sponsored as an educational service by **GlaxoSmithKline**

Reprint Collection –
A to Z of diabetes
July 2007

ISSN 1443-430X
MANAGING EDITOR
Kate Murchison BSc(Hons)
DEPUTY MANAGING EDITOR
Brad McLean BN, GradDip(Journalism)
CONSULTANT MEDICAL EDITORS
Chris Pokorny FRACP
John Dearin FRACGP, DipGer, DipRehabMed, MBioEth
ASSISTANT EDITORS
Aleta van Kerkhoff MSc, GCertPopH, ELS
Julia Smith BSc(Hons)
Marie Lofthouse BSc(Hons)
MEDICAL WRITERS
Audra Barclay MB BS, BSc(Med)
Helen Francombe BSc(Hons)
EDITORIAL ASSISTANT
Judith Steele
ART DIRECTION
Kirk Palmer Design
PRODUCTION/DESIGN MANAGER
Maria Marmora
SALES & MARKETING DIRECTOR
Mark Danderson
SALES & MARKETING CO-ORDINATOR
Prue Anderson
ACCOUNTS MANAGER
Pauline Burnard
CIRCULATION/SUBSCRIPTIONS
Jenny Passlow
PUBLISHER/EDITORIAL DIRECTOR
Judy Passlow
PUBLISHER/MANAGING DIRECTOR
Tony Scott
SYDNEY OFFICE
Level 1, 57 Grosvenor Street,
Neutral Bay, NSW 2089
POSTAL ADDRESS
PO Box 1473,
Neutral Bay, NSW 2089
TELEPHONE (02) 9908 8577
FACSIMILE (02) 9908 7488
EMAIL
Editorial enquiries
katemurchison@medicinetoday.com.au
Production enquiries
mariamarmora@medicinetoday.com.au
Advertising sales enquiries
markdanderson@medicinetoday.com.au
prueanderson@medicinetoday.com.au
General enquiries
reception@medicinetoday.com.au

Medicine Today is a journal of continuing medical education and review, written and refereed by doctors for GPs and specialists. The editorial objective is to provide authoritative clinical information that is useful and relevant to doctors in their day-to-day practice and to expand their medical knowledge. Editorial content is selected by the Editors, with advice from the Editorial Board of Consultants, with a view to providing readers with a broad spectrum of opinion on a wide range of subjects.
Opinions expressed are those of the original authors and do not necessarily reflect those of the Editors, the Editorial Board or the Publisher.
Medicine Today is published on the 1st day of each month by Medicine Today Pty Ltd (ACN 089 519 264).

Printed by Hannanprint Victoria,
504 Princes Highway,
Noble Park, VIC 3174.

SUBSCRIPTION RATES
Add 10% GST to all listed prices.

Standard	$175.00 per year, $300.00 for two years
Medical students	$75.00 per year, $130.00 for two years
RMO/Intern introductory offer	$90.00 per year $170.00 for two years
NZ, PNG, Fiji (Pacific region)	$205.00
Asia	$250.00
Rest of the World	$305.00
Back issues	$15.00 each $8.00 medical students $22.00 overseas

MedicineToday

The Peer Reviewed Journal of Clinical Practice

© ERIK DREYER/STONE/GETTY IMAGES

COVER

PAGE 5

PAGE 21

The articles in this reprint collection were originally published in *Medicine Today,* July 2006 to February 2007. This collection has been sponsored by an unrestricted educational grant from GlaxoSmithKline. The opinions expressed in the articles are those of the authors and not necessarily those of GlaxoSmithKline. Some products and/or indications mentioned may not be approved for use in Australia. Please review Product Information, available from the manufacturer, before prescribing any agent mentioned in these articles.

The ABCss of diabetes care

Target the ABCss of type 2 diabetes to delay the complications that can ruin peoples' lives.

PAT J. PHILLIPS MB BS, MA(Oxon), FRACP, MRACMA, GradDipHealthEcon(UNE)

Type 2 diabetes is much more than 'just a touch of sugar'. Think of type 2 diabetes as an extension of the metabolic syndrome and as travelling in the same 'bad company', i.e. with hypertension, dyslipidaemia and prothrombosis. Abnormal glucose metabolism due to insulin resistance or glucose intolerance is only one part of the deadly quartet of the metabolic syndrome. Tackling type 2 diabetes means tackling all four components associated with the syndrome.

The ABCss

Think of the mnemonic 'ABCss' as a way of remembering the five major goals in managing a person with type 2 diabetes:

A = controlling A_{1c} (glycosylated haemoglobin); target <7%
B = controlling blood pressure; target <130/80 mmHg
C = controlling cholesterol; target <4 mmol/L
s = quitting smoking
s = taking salicylates (75 to 150 mg/day).

The ABCss are also useful for teaching patients the importance of knowing about their diabetes, remembering their numbers and working with the diabetes care team to get closer to target.

The STENO-2 trial showed how effective 'trying harder' can be. Compared with 'conventional therapy', which in Scandinavia is at least as good as in Australia, 'intensive therapy' halved cardiovascular events and progression from microalbuminuria to nephropathy over seven years.[1] The number needed to treat was impressive – treating five patients for seven years can prevent one cardiovascular event and one progression to nephropathy.

Patients and doctors should appreciate that type 2 diabetes is a progressive disease. Usually the underlying metabolic disorder worsens with time because insulin resistance increases and insulin secretion decreases. Treatment must also progress. Patients and doctors must 'try harder'.

Remember that moving closer to targets can have dramatic effects even if the targets are not achieved. For example, the absolute benefit from decreasing the A_{1c} from 10% to 9% is much more than that achieved from decreasing from 8% to 7%. The same applies to blood pressure and cholesterol. The further the risk factor is from the target value, the greater the benefit of intervention.

There is a case for the medications that target the deadly quartet to become part of routine treatment – a diabetes polypill, the 'type 2 tablet'. Metformin has been used even before the onset of clinical diabetes to prevent progression of impaired glucose tolerance. ACE inhibitors (ramipril and perindopril) and statins (simvastatin and atorvastatin) have been shown to reduce cardiovascular events in patients with type 2 diabetes regardless of whether they have hypertension or hypercholesterolaemia. Cardioprotective doses of aspirin are recommended for those at high risk of cardiovascular events; most people with type 2 diabetes are in that category.

Many doctors believe that type 2 diabetes is a coronary equivalent and would agree that the 'type 2 tablet' should be considered for most patients. Perhaps the steps should be to get the ABCss as close to target as you can and then ask yourself if there is a reason not to prescribe any component of the 'type 2 tablet' that is not already prescribed.

The PBS appears to endorse this approach: ACE inhibitors and statins are subsidised for most patients with type 2 diabetes. Metformin is accepted as the first line oral hypoglycaemic agent and aspirin is affordable and acceptable to most patients.

There is now a serious attempt to put all the ingredients into one 'type 2 tablet'. The ingredients are off-patent and the diabetes polypill would make life easier for patients and doctors: a once- or twice-daily pill for the patient and one script for the doctor.

The issue of stopping smoking has been difficult for both patients and doctors. However, there are established and successful approaches, programs and resources for quitting smoking. The five 'A's (ask, assess, advise, assist, arrange), pharmacotherapy (nicotine replacement therapy and/or bupropion) and the support of the QUIT program has quadrupled the success of an unassisted QUIT program from 4% to 20%. Adopt the five 'A's as part of your professional practice and organise your general practice to support the quitters. You'll find that pessimistic thoughts that 'it never works' change to 'let's do it'.

Risk factors for cardiovascular and diabetes

There is another mnemonic related to type 2 diabetes. The main cardiovascular and diabetes risk factors may be represented by WXYZ, where:

W = the weight/waist factor
X = the metabolic problems (syndrome X or the metabolic syndrome) associated with central overweight
Y = why a particular person develops the metabolic syndrome (the 'F' words – forty, family, fat)
Z = sleep apnoea, not getting enough zzzs.

Look for the WXYZs in your patients and intervene to slow progression to cardiovascular events and diabetes. MT

Dr Phillips is Senior Director, Endocrinology, North Western Adelaide Health Service, The Queen Elizabeth Hospital, Woodville, SA.

Reference

1. Goede P, Vedel P, Larsen N, et al. N Engl J Med 2003; 348: 383-393.

MedicineToday PEER REVIEWED ARTICLE MedicineToday 2006; 7(7): 39-42

Type 2 diabetes
not just a touch of sugar

Type 2 diabetes is more often than not associated with other cardiovascular risk factors; hence it is better considered a syndrome than simply a biochemical diagnosis.

PAT J. PHILLIPS
MB BS, MA(Oxon), FRACP, MRACMA, GradDipHealthEcon(UNE)

Dr Phillips is Senior Director, Endocrinology, North Western Adelaide Health Service, The Queen Elizabeth Hospital, Woodville, SA.

Type 2 diabetes is diagnosed according to blood glucose biochemistry, but nearly all patients with type 2 diabetes have at least one of the following associated features:

- central overweight (or 'overwaist')
- hypertension
- dyslipidaemia
- a prothrombotic tendency.

For the purposes of prevention and treatment, it is useful to view type 2 diabetes as a syndrome so that all risk factors for cardiovascular events can be assessed and managed. Taking this approach, there is overlap with features of the metabolic syndrome. Some experts would see the metabolic syndrome as a precursor or early stage of type 2 diabetes.

Progression of glycaemia

Impaired glucose metabolism is very common. About one in four adult Australians have abnormal glucose metabolism: 4% have diagnosed diabetes, 4% have undiagnosed diabetes, and 16% have impaired glucose tolerance or impaired fasting glucose (so-called 'pre-diabetes').[1] But all 24% have the same condition – just at different stages of its development.

As we age, our insulin resistance increases and our capacity to secrete enough insulin to overcome this resistance decreases (Figure). For a while, our pancreatic beta cells meet the challenge, but at some stage they may not and blood glucose will start climbing. Initially, the blood glucose may still be in the normal range, just higher than it was earlier in life. Then it might move into the range for impaired glucose tolerance and, finally, into the range for diabetes (Table).[2]

When impaired glucose metabolism progresses and diabetes is diagnosed, this may seem like a clear endpoint. However, type 2 diabetes continues to progress: insulin resistance increases, insulin capacity decreases, and the metabolic mess continues to worsen.

Progression beyond glycaemia

As age increases and blood glucose metabolism is increasingly impaired, other progressive changes

IN SUMMARY

- **About one in four adult Australians have abnormal glucose metabolism: 4% have diagnosed diabetes, 4% have undiagnosed diabetes, and 16% have impaired glucose tolerance or impaired fasting glucose.**
- **Nearly all patients with type 2 diabetes have at least one of the following associated features: central overweight, hypertension, dyslipidaemia and/or a prothrombotic tendency.**
- **A healthy lifestyle can slow the progression of impaired glucose tolerance to diabetes.**
- **In the beginning, type 2 diabetes is often controllable by lifestyle change alone, but as the disorder progresses so should treatment.**
- **Interventions can make a difference at all stages of the development and progression of type 2 diabetes.**

are also occurring. It is useful to consider the ABCss when managing patients with type 2 diabetes:

- A_{1c} (glycosylated haemoglobin)
- Blood pressure
- Cholesterol
- Smoking
- Salicylates.

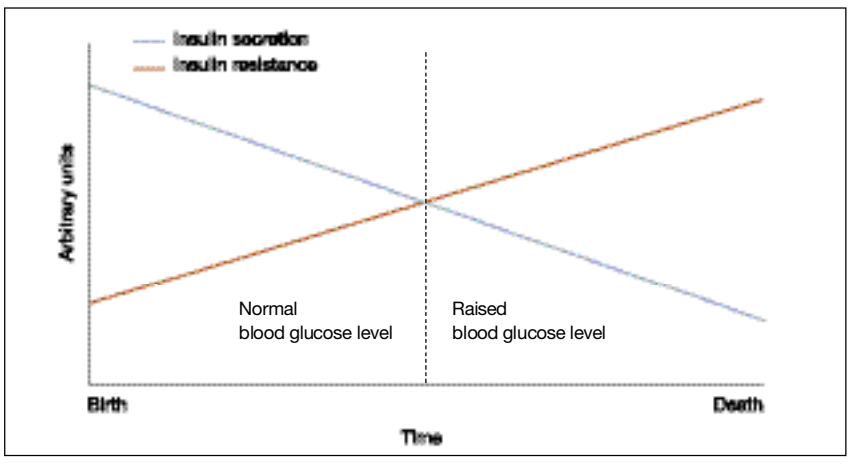


Figure. With increasing age, insulin resistance increases and insulin secretion decreases. Initially the blood glucose level is normal but when the lines intersect the blood glucose level progressively rises.

A_{1c}

Type 2 diabetes is said to often be controllable by lifestyle change alone. This is true – in the beginning – but as the disorder progresses so should treatment. Over time, oral hypoglycaemic agents are needed, then increasing doses and additional oral agents, and then insulin. In the United Kingdom Prospective Diabetes Study (UKPDS), 50% of participants required insulin within six years of diagnosis to maintain $A_{1c} \leq 7\%$.[3] Even with increasing treatment, overall blood glucose tends to rise over time. The UKPDS showed that A_{1c} increased by 1% each seven years despite 'intensive treatment'.[4]

Blood pressure

Initially, blood pressure increases but remains within the normal range, which is arbitrarily defined as <130/80 mmHg in people with diabetes[2] and <140/90 mmHg in others. Some young people with type 2 diabetes have systolic blood pressure below 100 mmHg; their blood pressure will take longer to increase into the 'abnormal' range, but their risk will be progressively increasing before this.

In the past, increasing blood glucose and blood pressure were accepted to be part of normal ageing. (Remember the old 'rule' that the upper limit of normal systolic blood pressure was 100 plus your age?) But blood pressure (like blood glucose) doesn't have to increase with age – for example, it often doesn't in those members of our indigenous population who maintain their traditional lifestyle and don't adopt an unhealthy one with overweight/overwaist and underactivity.

When 'hypertension' is diagnosed, blood pressure has already been increasing for years. Initially, it may be controlled with lifestyle modification, but then medication is needed and then more and more medication is needed. In the UKPDS, blood pressure was held constant (unlike blood glucose, which increased), but increasing medication was required to achieve this.[5]

Cholesterol

Dyslipidaemia is progressive and the associated cardiovascular risk also increases progressively. Interventions have been shown to be effective in reducing cardiovascular risk – two statins (simvastatin and atorvastatin) have been shown to reduce the risk of cardiovascular events by 25 to 40% in people with type 2 diabetes, one other cardiovascular risk factor and total cholesterol over 3.5 mmol/L (i.e. almost all people with type 2 diabetes).[6,7]

Smoking and salicylates

Quitting smoking is the best health decision any smoker can make – especially a smoker who has the high cardiovascular risk associated with the syndrome of type 2 diabetes.

Taking an aspirin a day does keep heart attacks away.[8]

Progressive syndrome, progressive risk

All clinical features associated with type 2 diabetes tend to progress, and so does the risk of further health problems. Even within the 'normal range' for cardiovascular events, there is an increase with increasing risk factors. Cardiovascular events among patients with impaired glucose tolerance are less frequent than among patients with diabetes, but more frequent than for the general population. Risk increases as impairment of glucose metabolism worsens.

Rates of cardiovascular events increase with time after a diagnosis of diabetes is made. This is partly because of time itself (getting older), but cardiovascular events also increase because risk factors are associated with progressive tissue damage and often the risk factors themselves get progressively worse.

Prevention

The progression of type 2 diabetes and associated features as well as the increasing cardiovascular risk is all a bit depressing. If it is inevitable, why shouldn't patients move on and enjoy the life they have rather than spending time restricting their lifestyle, taking pills, seeing health professionals and having tests?

The 'F factors' predisposing to type 2 diabetes are known: Forty, Family history and Fat (some also add Fitness). We can't change our age or genes, but our risk of diabetes can be greatly reduced if we change our fatness (and fitness) through healthy lifestyle behaviours. Results from the Diabetes Prevention Program, a randomised trial of 3234 people with impaired glucose tolerance, have shown that adopting a healthy lifestyle can delay progression of glycaemia.[9] Over an average follow up of almost three years, the absolute risk of progression to diabetes was reduced by 60% in those receiving a lifestyle modification program and by 30% in those receiving metformin (850 mg twice daily), compared with those receiving conventional treatment. The number needed to treat to prevent one person from developing diabetes in the next three years was five for the lifestyle program and ten for metformin.

We now know that interventions can make a difference at all stages of the development and progression of type 2 diabetes. Children of parents with type 2 diabetes don't have to gain as much weight as they do now. Early diagnosis of diabetes allows interventions to slow progression of cardiovascular risk factors. When complications occur, such as microalbuminuria, multiple interventions have been shown to greatly reduce the risk of macro- and microvascular events.[10]

Final comments

Our role as health professionals and educators is to identify people who can improve their future health and give them the information and opportunity to do so. We can work with them to integrate their chosen interventions into their daily routine so they can get on with their lives.

Perhaps the most important step is for us to convince ourselves of the value of identifying features associated with type 2 diabetes at all stages of development. We may need to change some of our beliefs that were formed before we knew interventions can make a difference. But once we are convinced, we can choose the level of intervention we wish to practise. Then we can incorporate these interventions into our daily professional work and get on with our jobs. MT

Table. Oral glucose tolerance test results[2]*

	Preprandial glucose (mmol/L)	Postprandial glucose (mmol/L)	Comments
Normal	<6.1	<7.8	No excess macro- or microvascular risk
Impaired fasting glucose	6.1 to 6.9	–	Excess macrovascular risk
Impaired glucose tolerance	–	7.8 to 11.0	
Diabetes	>6.9	>11.0	Excess macro- and microvascular risk

* Plasma glucose before (fasting) and two hours after a 75 g glucose load.

References

1. Dunstan D, Zimmet P, Welborn T, et al, on behalf of the AusDiab Steering Committee. Diabesity and associated disorders in Australia 2000: the accelerating epidemic. Melbourne: International Diabetes Institute; 2001.
2. Harris P, Joyner B, Mann L, Phillips P, Snowdon T, Webster C. Diabetes management in general practice 2005/6. 11th ed. Canberra: Diabetes Australia and RACGP; 2005.
3. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study Group. JAMA 1999; 281: 2005-2012.
4. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) . Lancet 1998; 352: 854-865 [erratum in: Lancet 1998; 352: 1558].
5. Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000; 321: 412-419.
6. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360: 7-22.
7. Colhoun HM, Betteridge DJ, Durrington PN, et al; CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004; 364: 685-696.
8. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients . BMJ 2002; 324: 71-86 [erratum in: BMJ 2002; 324: 141].
9. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346: 393-403.
10. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003; 348: 383-393.

DECLARATION OF INTEREST: Dr Phillips has received research and travel grants, acted on advisory boards and been involved with clinical trials and seminars sponsored by a range of pharmaceutical companies. He does not think that these associations have influenced the content of this article.

MedicineToday 2006; 7(10): 69-73

ABCss: A is for A_{1c}

PAT PHILLIPS MB BS, MA(Oxon), FRACP, MRACMA, GradDipHealthEcon(UNE)

This, the first in a series of case studies focusing on the ABCss of diabetes care (A_{1c}, blood pressure, cholesterol, smoking, salicylates), discusses how to get glycosylated haemoglobin (A_{1c}) closer to target and keep it there.

Case scenario

Arnold is 67 years old and has had type 2 diabetes for the past eight years. He has a strong family history of diabetes (both parents and one sister) and, with a weight of 91 kg and a height of 1.82 m, is overweight (BMI, 27.5 kg/m^2). Following the rough guide formula, healthy weight = height (cm) – 100, a healthy weight for Arnold would be about 82 kg.

Arnold is taking glimepiride 4 mg/day and metformin 1 g twice daily. His plasma creatinine of 0.11 mmol/L gives him a calculated creatinine clearance of 68 mL/min (creatinine clearance = 1.25[(140 – age) x healthy weight] ÷ plasma creatinine in μmol/L; for Arnold, 1.25 x [(140-67) x 82] ÷ 110). This is greater than the glomerular filtration rate (GFR) value below which metformin dosage should generally be limited (i.e. a calculated GFR <60 mL/min) or probably stopped (a calculated GFR <30 mL/min).

He has had hypertension for the past 15 years, and this is currently moderately controlled (systolic blood pressure, 135 to 145 mmHg; target, <130 mmHg) on an ACE inhibitor/hydrochlorothiazide preparation. He has been taking prophylactic aspirin since the age of 60 years.

There is evidence of microvascular disease (background retinopathy and pins and needles in his feet and legs, especially at night), but no history of a cardiovascular event.

Dr Phillips is Senior Director, Endocrinology, North Western Adelaide Health Service, The Queen Elizabeth Hospital, Woodville, SA.

Arnold's glycosylated haemoglobin (A_{1c}) has been climbing over the past 18 months and is now 8.7% (ideal, <7%), and many of his capillary blood glucose values exceed 10 mmol/L.

Questions

- Regarding Arnold's hyperglycaemia, what else do you need to find out?
- What options are there to control Arnold's hyperglycaemia?
- How would you choose between these options?
- Four years later, the chosen combination of oral hypoglycaemic agents is not controlling his blood glucose. How will you suggest Arnold start insulin?

Before changing medication

Before changing Arnold's medication to better control his hyperglycaemia, it is worth finding out more about his medication and lifestyle, and also other medical conditions he may have that may be contributing to his hyperglycaemia.

Medication

Is Arnold taking his oral hypoglycaemic agents? In randomised controlled trials, ongoing participation requires adherence rates generally exceeding 80%. In the real world, adherence rates may be closer to 30%.

Is he taking other prescription or nonprescription medications that could cause hyperglycaemia? We know that patients often see more than one GP and take more nonprescription and/or complementary medications than prescription medications. Table 1 lists common medications likely to cause hyperglycaemia.

Table 1. Medications and medical conditions causing hyperglycaemia*

Medications
Oral contraceptive pill
Oral corticosteroids
Thiazides†
Beta blockers
Phenytoin
Glucosamine
Medical conditions
Urinary tract infection‡
Hyperthyroidism
Occult malignancy

* Not an exhaustive list.
† Equivalent to 50 mg hydrochlorothiazide.
‡ May be more common and asymptomatic in individuals with neuropathy.

Lifestyle

Is Arnold trying to 'Eat less, walk more', and is he succeeding? Has his weight/waist been growing or shrinking over the past two years?

It is unlikely that Arnold would be willing or able to make the sort of lifestyle changes that could bring his A_{1c} into the target range but the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes has shown that modest achievable lifestyle changes can bring the A_{1c} down by 0.5 to 1%.[1]

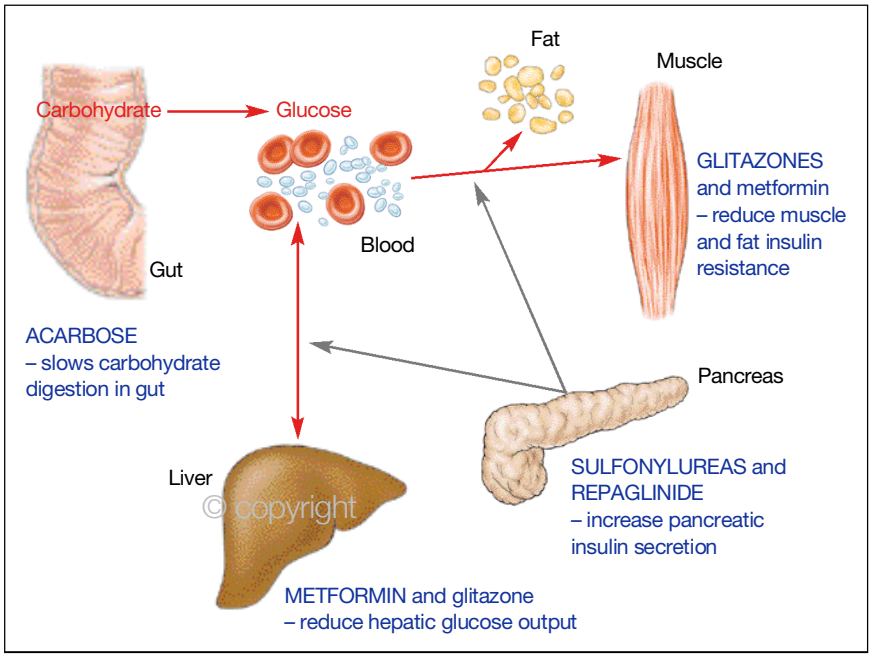
Medical matters

Has Arnold developed some secondary cause of hyperglycaemia? This may not be obvious but its treatment could help in the control of his glycaemia (Table 1).

Options for controlling hyperglycaemia

Apart from lifestyle changes, acarbose, glitazones and/or insulin might be useful in controlling Arnold's hyperglycaemia.

continued



ILLUSTRATIONS © C WIKOFF, 2002

Figure. Sites of action of oral hypoglycaemic agents.

There are five classes of oral hypoglycaemic agents, and they have different mechanisms of action (Figure):[2]

- acarbose (Glucobay) – slows carbohydrate digestion
- glitazones – reduce muscle and fat insulin resistance, and also reduce hepatic glucose output (but to a lesser degree than metformin)
- metformin – reduces hepatic glucose output, and also reduces muscle and fat insulin resistance (but to a lesser degree than glitazones)
- repaglinide (NovoNorm), a glitinide – is a short acting insulin secretagogue
- sulfonylureas – are long acting insulin secretagogues.

Each class can be added to the others with additive effects, with the exception of combining repaglinide and a sulfonylurea as they are both insulin secretagogues. Generally, metformin is tried first, followed by a sulfonylurea and then a glitazone.[3] Both acarbose and repaglinide may be useful to control postprandial glycaemia early in the course of diabetes.

On average, each class of oral hypoglycaemic agent will decrease A_{1c} by about 0.5 to 1.5%. Some patients may experience more or less effect because of the differing contributions of increased insulin resistance and decreased capacity for insulin secretion.

The use of basal and/or bolus insulin is a treatment option at any stage of type 2 diabetes but is usually resisted by both the patient and the doctor until all other agents have been tried. This psychological resistance to use therapeutic insulin and the patient's pathological insulin resistance both contribute to hyperglycaemia.

Choosing between options

The pros and cons of each class of oral hypoglycaemic agent are listed in Table 2.

Adding repaglinide to Arnold's medications will not help as he is already taking the sulfonylurea glimepiride (Amaryl, Aylide, Diapride, Dimirel).

We do not know Arnold's blood glucose profile but if his blood glucose values before meals were not far off the target value of 4 to 6 mmol/L and the problem was caused by postprandial glycaemia, adding acarbose could help. It would be started low, e.g. 25 mg before meals, and then increased slowly towards 50 or 100 mg before meals if tolerated. Arnold's A_{1c} of 8.7% suggests that his average blood glucose level exceeds 10 mmol/L (as a rough guide, blood glucose level = $2A_{1c} - 6$; for Arnold, 11.4 mmol/L) so it is unlikely that any of his blood glucose values, before or after meals, are on target. Thus, acarbose is not likely to improve control.

For Arnold, therefore, the main choice lies between using a glitazone or insulin.

In the UKPDS, 50% of participants required insulin within six years to maintain $A_{1c} \leq 7\%$.[4] In practice, however, patients and doctors usually delay longer than this. Arnold has had diabetes for almost nine years and his capacity to secrete insulin is likely to have decreased considerably since diagnosis. Insulin may well prove necessary in the short to medium term and it may be worth discussing this now so that Arnold is not disappointed or resistant when insulin is needed.

The choice of glitazone is largely driven by the prescribing indications. Compared to each other, rosiglitazone (Avandia) has less potential for medication interactions and pioglitazone (Actos) may have more beneficial effects on the lipid profile. However, rosiglitazone can be prescribed as ongoing triple therapy (with metformin and a sulfonylurea) whereas, at present, the PBS indication for pioglitazone is more limited.

It will take two to three months for either rosiglitazone or pioglitazone to have maximal therapeutic effect. However, if the glitazone is going to work, some effect is usually seen in the first few weeks.

The major risk with both glitazones is the accumulation of extracellular fluid. Arnold has no history of cardiovascular events but should be advised to seek medical attention if he develops oedema. He should also be made aware that NSAIDs

Table 2. Pros and cons of oral hypoglycaemic agents

Oral hypoglycaemic agent or class	Pros	Cons	Overall usage*
Acarbose	No hypoglycaemia† Weight neutral	Gastrointestinal side effects Less A_{1c} reduction	1%
Glitazones	Increase insulin sensitivity No hypoglycaemia†	Increased subcutaneous fat or fluid	–
Glitinides	Increase meal time insulin secretion	Hypoglycaemia risk	–
Metformin	Increase insulin sensitivity No hypoglycaemia† Weight loss or neutral	Gastrointestinal side effects Lactic acidosis risk	76%
Sulfonylureas	Increase insulin secretion	Hypoglycaemia risk Weight gain	47%

* Overall usage (mono and combination therapy) in the 2005 National Prescribing Service clinical audit of 1733 GPs and 34,576 patients with type 2 diabetes (personal communication).
† Unless insulin or an insulin secretagogue is coadministered.

(prescription and over-the-counter) or a high sodium intake (e.g. Chinese food) could precipitate dangerous fluid accumulation.

Starting insulin

The 'keep it safe and simple' (KISS) principle will apply when it comes to the time for Arnold to start using insulin.

Reassure Arnold that insulin therapy is safe and simple, that the injections do not hurt and that all patients with diabetes feel better once they have started insulin and control of their glycaemia has improved (in fact, many patients say they wish they had taken the step much earlier). The new insulin injection devices make the process of injecting insulin much easier and the practice nurse or diabetes nurse educator could show Arnold the range of devices available and how to use them. The nurse could also stress to Arnold the importance of continuing the 'Eat less, walk more' program to prevent the weight gain associated with better glycaemic control due to the decreased loss of glucose in the urine.

Arnold should continue taking the oral hypoglycaemic agents while insulin is initiated. If he stops taking one or more of them, his blood glucose control will get worse, not better.

Insulin therapy should be started with a 10 U night time (bed time) basal dose of the intermediate acting insulin isophane insulin (human), also known as NPH insulin (Humulin NPH, Protaphane).[3] The long acting insulin analogue insulin glargine [Lantus] has recently become listed on the PBS for type 2 diabetes and may be used as the basal insulin instead. A dose of 10 U is a small dose and will probably not make much difference to the blood glucose level; on the other hand,

Table 3. Insulin titration*

Start with 10 units of isophane insulin at bedtime.
Adjust the dose twice weekly, to reach the target fasting blood glucose of <6 mmol/L, using the regimen below:

Mean fasting glucose over preceding 2 days (mmol/L)	Insulin increase (U/day)
>10	8
8 to 10.0	6
7 to 7.9	4
6 to 6.9	2

- Do not increase insulin dosage if the blood glucose level is <4 mmol/L at any time in the preceding week.
- The insulin dose may be decreased (small decreases of 2 to 4 units) if there is severe hypoglycaemia (requiring assistance) or the blood glucose level is <3.0 mmol/L in the preceding week.

*Derived from reference 5 (*Diabetes Care* 2003; 26: 3080-3086).

it is not going to cause hypoglycaemia. Having reassured Arnold that insulin is safe, the last thing you want is a hypo on day one or two.

Although premixed insulins are widely used to start insulin therapy in patients with type 2 diabetes, the main requirement is for basal insulin replacement. The quick acting component is usually not necessary at this stage, and may cause hypoglycaemia and/or weight gain.

Initially, follow a patient's blood glucose level before breakfast and review the insulin dose every two to three days. This can be done either by phone or in conjunction with the practice nurse or diabetes nurse educator using an agreed protocol, such as the insulin titration given in Table 3.[5]

When the before breakfast blood glucose is at the desired target (e.g. 80% between 4 and 6 mmol/L), change to reviewing the blood glucose before the evening meal. If this is on target, the other blood glucose values through the day are also likely to be on target. Measuring the A_{1c} will confirm this. If the evening blood glucose is not on target, add morning basal insulin (10 U) before breakfast and repeat the titration process.

Once the before breakfast and evening blood glucose values are on target, consider stopping one or more of the oral hypoglycaemic agents. If blood glucose levels were to increase, the oral agent could be restarted or the insulin therapy increased. With regard to Arnold stopping taking these agents:

- Arnold's beta cells are probably not making much insulin and he is already being given exogenous insulin, so stopping the sulfonylurea may not make much difference to his blood glucose control
- if fluid retention and increased extracellular fluid are a concern, the glitazone could be phased out as these effects are caused by both the glitazones and insulin
- Arnold's renal function will deteriorate as he gets older (GFR decreases by about 1 mL/min/year), and a metformin dose that was appropriate 10 to 15 years ago will become excessive; starting insulin may provide the opportunity of proactively reducing the metformin dose (e.g. from 1 g to 850 mg or 500 mg tablets) or simplifying the schedule (e.g. from a thrice daily to a twice daily schedule).

In the more distant future, Arnold may need a rapid or short acting bolus insulin before one or more meals to control postprandial glycaemia. However, ensure that the basal blood glucose levels before breakfast and before the evening meal are on target, and always adjust the basal insulin before adding or adjusting the bolus insulin.

Key points

- Before changing a patient's oral hypoglycaemic agent therapy, review his or her medication, lifestyle and medical issues that can affect blood glucose control.
- Each of the five classes of oral hypoglycaemic agent have pros and cons. Generally, the sequence of prescribing these is metformin, sulfonylurea, glitazone. Acarbose and repaglinide may be useful to control postprandial glycaemia early in the course of diabetes.
- The KISS principle makes starting insulin more acceptable to the patient and practical for the doctor. First get the fasting glucose on target using bed time basal insulin, then review evening glycaemia and, if necessary, add morning basal insulin.
- Once the patient's blood glucose is on target, consider stopping one or more of the oral hypoglycaemic agents.
- When adjusting insulin, always adjust the basal insulin to get the fasting and evening glucose on target before adding or changing preprandial bolus (rapid or short acting acting) insulin. MT

References

1. United Kingdom Prospective Diabetes Study Group (UKPDS). Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in people with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837-853.

2. Phillips P. Tablet tips for type 2 diabetes. Curr Ther 1996; 37: 26-32.

3. Harris P, Mann L, Phillips P, Snowdon T, Webster C. Diabetes management in general practice 2006/7. 12th ed. Canberra: Diabetes Australia. 2006. Available online at www.racgp.org.au (accessed September 2006).

4. Wright A, Burden AC, Paisey RB, Cull CA, Holman RR; UKPDS Study Group. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). Diabetes Care 2002: 25: 330-336.

5. Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomised addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003; 26: 3038-3086.

DECLARATION OF INTEREST: Dr Phillips has received research and travel grants, acted on advisory boards and been involved with clinical trials and seminars sponsored by a range of pharmaceutical companies. He does not think that these associations have influenced the content of this article.

MedicineToday 2006; 7(11): 57-61

ABCss: B is for blood pressure

PAT PHILLIPS MB BS, MA(Oxon), FRACP, MRACMA, GradDipHealthEcon(UNE)

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

Bob is 64 years old and has had type 2 diabetes for 11 years. His weight is 82 kg and his height is 1.82 m, which means he is overweight (BMI, 25.9 kg/m^2); his weight has been steady over the last few years. He walks for 20 to 30 minutes several times a week with his wife and an ageing Labrador and enjoys 'a few beers' on weekends. His father died suddenly of a heart attack at the age of 66 years, and Bob is well aware of his own coronary risk.

Four of Bob's ABCss are pretty good. He is close to target with his glycosylated haemoglobin level (A_{1c}) of 7.6% (target, <7%) and his cholesterol is 3.1 mmol/L (target, <4.0 mmol/L). He quit smoking at the age of 60 years and started taking prophylactic aspirin when he was diagnosed with diabetes.

It is Bob's blood pressure that is the problem. Despite taking an ACE inhibitor and a selective beta blocker each day and a diuretic (frusemide) three days a week (on Monday, Wednesday and Friday), his systolic blood pressure consistently exceeds 150 mmHg. His other medications include:

- metformin (850 mg three times daily)
- glipizide (10 mg twice daily)
- pantoprazole (20 mg once daily, at night)
- diclofenac (50 mg twice daily)
- vitamin E (10 mg once daily)
- a multivitamin supplement (once daily, with breakfast).

Questions

- Considering that Bob's other ABCss are pretty good, how important is his elevated blood pressure?
- Are there potentially correctable contributors to his hypertension?
- What further management options are available?

Hypertension in patients with diabetes

It is easy for patients with diabetes to focus solely on glycaemic goals – for many, diabetes is 'sugar'. Doctors also may overrate the importance of controlling blood glucose and underrate the importance of controlling other complication risk factors. In a survey of American doctors, glucose lowering was found to be the most commonly assigned top priority in diabetes management, whereas in fact both blood pressure lowering and cholesterol lowering are associated with greater reductions in risk for cardiovascular outcomes in the medium term (Figure).[1] The HOT and UKPDS studies have shown the importance of blood pressure control, with reduced rates of both cardiovascular and microvascular events being associated with lower blood pressure.[2,3]

Having diabetes puts any patient into a high risk category for cardiovascular events,[4] but Bob has several additional risk factors (Table 1). We don't know if he

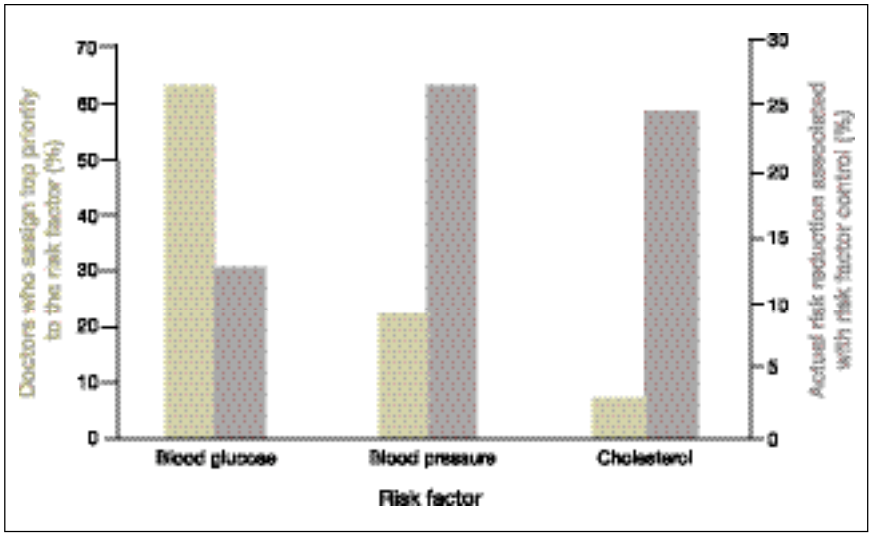


Figure. Ranking risks in diabetes management – doctors' perception and reality. Doctors' ranking of the top priorities in diabetes management are shown (left-hand axis) along with actual risk reductions for cardiovascular outcomes in the medium term (right-hand axis).[1]

Dr Phillips is Senior Director, Endocrinology, North Western Adelaide Health Service, The Queen Elizabeth Hospital, Woodville, SA.

Table 1. Risk factors for cardiovascular complications

Nonmodifiable

Past history of cardiovascular events
Family history of cardiovascular events prior to age 60 years
Age (every extra decade past 50 years is equivalent to an additional risk factor)
Menopausal status

Modifiable

Lifestyle

Smoking
Low level of physical activity
High intake of fat and/or energy

Medical

Microalbuminuria
Hypertension
Dyslipidaemia
Dysglycaemia

has microalbuminuria or left ventricular hypertrophy but it would be important to find out – the presence of either would make controlling his blood pressure even more important. Microalbuminuria is an indicator of endothelial damage throughout the cardiovascular system, not just in the kidney, and, if present, would be a treatment target itself. Left ventricular hypertrophy would indicate damage of other end organs (particularly the eyes and kidneys) as well as the heart, and it would be useful to arrange an ECG to identify this. A baseline ECG would also be useful in case Bob later presents with symptoms that might be an atypical presentation of a myocardial infarct. Remember that autonomic neuropathy may mean an infarct does not present with crushing chest pain but with much more nonspecific symptoms (e.g. weakness, vague discomfort, nausea and shortness of breath).

Blood pressure is an important risk factor in any patient with diabetes, but it becomes even more important as coronary risk increases and when there is evidence of end organ damage. In fact, Bob did have confirmed microalbuminuria (albumin:creatinine ratios, 8.1 and 6.4 mg/mmol; normal range for men <2.5 mg/mmol). He is, therefore, at very high risk for coronary events.

Potentially correctable contributors to hypertension

Adherence, adherence, adherence

Generally in clinical trials, participants are required to take at least 80% of the prescribed medication, otherwise they are excluded. In the real world, the rule of thirds often applies:

- one-third of patients don't take the medication at all
- one-third don't take it as prescribed
- one-third do take it as prescribed.

Checking medication adherence is part of a diabetes review. This may be done informally, using an approach such as, 'Most people find it hard to take all their medication, how often do you miss yours?' This type of questioning makes it easier for a nonadherent patient to tell you the truth. A more formal approach may involve reviewing the frequency of prescription or involving a pharmacist in a Home Medications Review.

Bob's medication schedule should be simplified by reducing the number of medications he is taking and/or the medication-taking occasions. He is supposedly taking 10 medications – 13 tablets on four days a week and 14 tablets on the other three days. The chances are that he is missing some of his pills.

Measures that could be considered for Bob include:

- using a combination ACE inhibitor and diuretic preparation
- switching to extended release metformin with a twice daily dosing schedule (1 g twice daily)
- switching to a once daily sulfonylurea (e.g. modified release gliclazide [Diamicron MR] or glimepiride [Amaryl, Aylide, Diapride, Dimirel])
- improving his sleep position to prevent reflux so he can stop taking the proton pump inhibitor.

Bob is also taking medications that have been shown not to help (vitamin E and the multivitamin supplement). Perhaps he could stop taking the tablets that don't work and try harder to take those that do.

Misleading hypertension

Don't forget that the blood pressure readings you obtain may be misleading or nonrepresentative. Not many of us measure blood pressure as carefully as we could – that is, using a correctly sized cuff and a calibrated sphygmomanometer in an unhurried environment after giving the patient adequate time to relax. Given that Bob is (correctly) concerned about his blood pressure, he would be a prime candidate for white coat hypertension. Either a 24-hour ambulatory blood pressure recording or home monitoring would show if the surgery readings are misleading.

Diabetes can also be associated with calcified arteries, which are not compressible. A heavily calcified aortic arch on chest x-ray might prompt you to check that the brachial artery is compressible.

Correctable hypertension

Together, the NSAID, ACE inhibitor and diuretic make a 'triple whammy' that is putting Bob at high risk of acute renal failure.[5] Stopping the NSAID will reduce his renal risk and it may also help control his blood pressure. Even though he is not very overweight, sleep apnoea should be considered. It would be useful to check his neck size (>42 cm would identify him as being at high risk) and to ask about night time snoring and daytime naps to determine if a sleep study is warranted. Treating sleep apnoea can have dramatic effects on blood pressure, and it could have other benefits for Bob (as well as sleep benefits for his wife).

Table 2. The pros and cons of 'add on' hypotensive agents*

	Pros	Cons
Alpha blockers	No metabolic effects	Increased risk of cardiac failure and coronary events Postural hypertension
Angiotensin receptor antagonists†	Indicated if micro- or macroalbuminuria is present Same advantages as ACE inhibitors if ACE inhibitor not used	First dose hypotension Decreased glomerular filtration Hyperkalaemia Cough and angioedema (rarely)
Calcium channel blockers‡		
– centrally acting (diltiazem, verapamil)	–	Risk of heart block Constipation Oesophageal reflux
– vasodilating (dihydropyridines)	–	Peripheral oedema Flushing Headache
Sympatholytics	–	Postural hypotension Depression

* Modified from reference 9.
† ACE inhibitors and angiotensin receptor antagonists are contraindicated in pregnancy and may not be wise choices in women of childbearing potential who are not using reliable contraception. Advice from an obstetrics specialist may be helpful.
‡ All calcium channel blockers have the full range of side effects but gastrointestinal effects and heart block are more common with the centrally acting agents and vasodilating effects with the dihydropyridines. The risk of heart block is increased if a beta blocker is being taken.

Bob may be prepared to consider lifestyle changes. By eating less and walking more, cutting back on his beer consumption and losing a few kilograms, he could reduce his systolic blood pressure by 5 to 10 mmHg.[6] Either a 24-hour urinary sodium measurement would tell you whether he (or more likely his wife) should be advised to 'sack the salt' – both from the kitchen and the table – and to check food labels for low salt products.[6] The recommended salt intake is less than 100 mmol/day (equivalent to 2300 mg/day of sodium), but the average Australian intake is over 200 mmol/day.[7]

Secondary causes

Secondary causes of hypertension include coarctation of the aorta and renal artery stenosis as well as adrenal diseases (Cushing's syndrome, hyperaldosteronism, phaeochromocytoma) and renal disease. Recreational drugs should also be remembered.

Secondary causes should be considered when hypertension starts in a younger or elderly patient or when it is resistant to therapy, accelerating or severe (e.g. over 180/115 mmHg). In Bob's case, it would be useful to check that his blood pressure is the same in both arms, and to look for an abdominal bruit or hypokalaemic alkalosis. If a secondary cause is suspected, discussion with a specialist would help determine if further investigation is appropriate.

Further management options

In the RACGP guidelines *Diabetes Management in General Practice*, the suggested medication steps for reducing blood pressure to target (that is, <130/80 mmHg; <125/75 mmHg if proteinuria is greater than 1 g/day) are to start with an ACE inhibitor (or an angiotensin receptor antagonist if an ACE inhibitor is not tolerated), then to add a diuretic, and then a beta blocker.[8] Bob is already taking all three of these, which is not unusual. In both the HOT and UKPDS studies quoted earlier, one-third or more of participants required three or more medications to manage their blood pressure.[2,3]

Assuming that maximum doses are already being prescribed, that Bob is taking his medications as instructed, that the blood pressure readings you are getting are correct and that Bob has modified his medication schedule and lifestyle as recommended, adding a fourth hypertensive agent could be considered. However, there are various pros and cons to consider (Table 2).[9]

Choosing a fourth medication is difficult because all additional hypotensive agents have significant disadvantages. The alpha blockers do not have metabolic effects but have been associated with excess risk of cardiac failure and coronary events.[10] Combining an angiotensin receptor antagonist with an ACE inhibitor is theoretically attractive because both

angiotensin production and its receptor are blocked; however, the combination does make hyperkalaemia a real risk.

Adding a centrally acting calcium channel blockers to a beta blocker makes heart block more likely – particularly if there is already some block (e.g. lengthening of PR interval >0.12 second). This is less likely with long acting peripheral calcium channel blockers, but there is the disadvantage of peripheral oedema, especially if autonomic neuropathy is present. (This is because autonomic neuropathy causes arteriovenous shunting, raising capillary and filtration pressure. Vasodilating calcium channel blockers also increase capillary and glomerular filtration pressure.) The sympatholytics often cause troublesome hypotension and may be associated with depression (especially if beta blockers are also being taken). Slow acting oral nitrate therapy and hydralazine are other options but are rarely used.

Once again, discussion with a specialist may help guide the treatment decision. Many would consider adding a long acting peripheral calcium channel blocker to be the next step, with precautions to prevent peripheral oedema (e.g. use of support stockings, especially in hot weather). Alternatives would include an angiotensin receptor antagonist (with monitoring for hyperkalaemia) or an alpha blocker (with monitoring for postural hypotension and worsening of heart failure).

Key points

- Blood pressure is an important risk factor for both micro- and macrovascular complications of type 2 diabetes.
- Microalbuminuria and left ventricular hypertrophy are markers of endothelial and end organ damage throughout the body.
- When blood pressure is difficult to control:
  - check adherence and consider reducing the number of medications and the number of occasions on which they are taken
  - consider home or ambulatory monitoring to define the 24-hour blood pressure profile
  - check for correctable causes of hypertension, particularly NSAIDs, sleep apnoea and lifestyle factors
  - consider secondary causes involving two arteries (aortic coarctation and renal artery stenosis), two organs (adrenal gland and kidney) and recreational drugs (e.g. cocaine).
- The medication steps suggested by the RACGP to achieve target blood pressure (<130/80 mmHg; <125/75 mmHg if proteinuria >1 g/day) are to start with an ACE inhibitor (or angiotensin receptor antagonist if an ACE inhibitor is not tolerated), then to add a diuretic and then a beta blocker. Selecting a fourth medication (if necessary) can be difficult – possible choices include a long acting peripheral calcium channel blocker, angiotensin receptor antagonist, alpha blocker and centrally acting sympatholytic. Discussion with a specialist colleague may be helpful. MT

References

1. Huang ES, Meigs JB, Singer DE. The effect of interventions to prevent cardiovascular disease in patients with type 2 diabetes mellitus. Am J Med 2001; 111: 633-642.
2. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the hypertension optimal treatment (HOT) randomised trial. Lancet 1998; 351: 1755-1762.
3. UK Prospective Diabetes Study (UKPDS) Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998; 317: 703-713.
4. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in non-diabetic subjects with and without myocardial infarction. N Engl J Med 1989; 339: 229-234.
5. Adverse Drug Reactions Advisory Committee (ADRAC). Beware the triple whammy! Aust Adv Drug Reactions Bull 2006; 25: 18.
6. Carapetis M, Phillips P. Eat less, walk more. Enjoyable eating for type 2 diabetes. Aust Fam Physician 2002; 31: 1065-1071.
7. Nutrient reference values for Australia and New Zealand including Recommended Dietary Intakes. Canberra: Commonwealth of Australia; 2006 (available at: http://www.nhmrc.gov.au/publications/synopses/n35syn.htm).
8. Harris P, Joyner B, Mann L, Phillips P, Snowden T, Webster C. Diabetes management in general practice 2006/7. 12th ed. Canberra: Diabetes Australia and RACGP; 2006.
9. Phillips PJ, Popplewell P, Wing L. Diabetes and hypertension – double trouble. Med Today 2003; 4(7): 32-45.
10. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). ALLHAT Collaborative Research Group. JAMA 2000; 283: 1967-1975.

DECLARATION OF INTEREST: Dr Phillips has received research and travel grants, acted on advisory boards and been involved with clinical trials and seminars sponsored by a range of pharmaceutical companies. He does not think these associations have influenced the content of this article.

MedicineToday 2006; 7(12): 65-70

ABCss: C is for cholesterol

PAT PHILLIPS MB BS, MA(Oxon), FRACP, MRACMA, GradDipHealthEcon(UNE)

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

Christine is 58 years old and has had type 2 diabetes for 11 years. The practice nurse has suggested a GP management plan because the Service Incentive Payment (SIP) cycle of the Commonwealth Government's National Integrated Diabetes Program has highlighted that Christine's ABCss are off target (see Table 1).

Christine has always had problems with her weight and has gained a further 5 kg since starting insulin a year ago. Her current weight is 83 kg, her height is 164 cm (BMI, 30.9 kg/m^2) and her waist circumference is 104 cm, which means she is obese (BMI >30 kg/m^2; waist circumference >88 cm). Christine is very concerned about her weight gain but has not been able to prevent a steady increase. Her physical activity is limited by pain in her knees and ankles, despite NSAID therapy. She continues to smoke, partly because last time she stopped she gained 4 kg in the next three months.

As far as complications are concerned, she had a course of laser therapy for maculopathy 18 months ago but has not required further intervention. Her albumin to creatinine ratio is currently 5.2 mg/mmol. She has been identified as being at a high risk of developing foot problems (as she has a loss of sensation in the distal half of her foot and weak pedal pulses).

Her medications include:

- metformin (850 mg twice daily)
- intermediate acting insulin (isophane insulin; 34 units at bedtime)
- lisinopril/hydrochlorothiazide (40/12.5 mg/day)
- celecoxib (50 mg/day)
- esomeprazole (40 mg/day)
- amitriptyline (25 mg at bedtime, for her night-time foot discomfort).

Questions

- What are Christine's risk factors for a cardiovascular event and what is her five-year risk of a myocardial infarction or stroke?
- To target her cholesterol, what SNAP recommendations (quit Smoking, better Nutrition, moderate Alcohol and more Physical activity) could be made and how successful might these be in lowering her cholesterol?
- If statin therapy were prescribed for Christine, would she be eligible for PBS subsidy of this treatment?
- Three months after Christine begins statin therapy (40 mg simvastatin daily) her cholesterol has decreased to 5.7 mmol/L. Is this what was expected? Should her cholesterol be more actively targeted?
- Two weeks after Christine's statin dose is doubled she complains of aching muscles, particularly in the shoulders and neck after she has been gardening. Statin myotoxicity is suspected. What other factors should be assessed?
- Assuming there are no contributing factors to her myalgia that could be changed, what other ways are there for managing her cholesterol?

Risk factors for a cardiovascular event

Christine has most of the risk factors for a cardiovascular event: she is nearly 60 years old, she has had type 2 diabetes for more than 10 years and all her ABCss are off target. She also has microalbuminuria and evidence of existing macrovascular disease (weak pulses).

There are several cardiovascular risk calculators for men and women with no history of cardiovascular disease. These include the National Prescribing Service's version of the New Zealand Cardiovascular Risk Calculator (www.nps.org.au/site.php?page=1&content=/resources/

Table 1. Christine's ABCss values

Factor	Christine's value	Target value
A_{1c}	7.6	<7.0%
Blood pressure	142/75 mmHg	<130/80 mmHg
Cholesterol*	7.4 mmol/L	<4 mmol/L
Smoking	15 cigarettes/day	0
Salicylates	0	75 to 150 mg/day

* Christine's value (target value): LDL cholesterol, 5.5 mmol/L (<2.5 mmol/L); HDL cholesterol, 1.1 mmol/L (>1 mmol/L); triglycerides, 1.6 mmol/L (<1.5 mmol/L).

Dr Phillips is Senior Director, Endocrinology, North Western Adelaide Health Service, The Queen Elizabeth Hospital, Woodville, SA.

Cholesterol lowering therapy: PBS eligibility criteria relevant to patients with diabetes, 1 October 2006[1*]

Statins and fibrates

Very high risk categories

Patients qualify for PBS subsidy of therapy with statins or fibrates regardless of their cholesterol level if they are identified as having in one of the following:

- symptomatic vascular disease (coronary heart disease, cerebral vascular disease, peripheral vascular disease)
- diabetes mellitus with microalbuminuria (defined as urinary albumin excretion rate above 20 μg/min or urinary albumin to creatinine ratio greater than 2.5 for males and 3.5 for females)
- diabetes mellitus in Aboriginal or Torres Strait Islander patients
- diabetes mellitus in patients aged 60 years or more
- familial hypercholesterolaemia (symptomatic before age of 55 years in two or more first degree relatives or before age of 45 years in one or more first degree relatives).

Other categories

Patients with diabetes mellitus who are not included in the above very high risk categories are required to have a total cholesterol level above 5.5 mmol/L to qualify for PBS subsidy of therapy with statins or fibrates.

Ezetimibe

Patients qualify for PBS subsidy of therapy with ezetimibe or ezetimibe plus simvastatin if, after three months of statin therapy and lifestyle change, their total cholesterol level:

- exceeds 4 mmol/L and they are in one of the above very high risk categories
- exceeds the initial level qualifying for statin or fibrate therapy.

The full PBS eligibility criteria additionally list lipid levels for other patients not identified as being in very high risk categories.

content/hpro_cv_risk_calcu.html), the UKPDS Risk Engine (www.dtu. ox.ac.uk/index.php?maindoc=/riskengine/index.php) and those included in medical desktop software. None is entirely satisfactory. For example, neither the New Zealand nor the UKPDS calculators consider microalbuminuria or antiplatelet therapy, although the latter does consider duration of diabetes, presence of atrial fibrillation, ethnicity and A_{1c} in addition to the age, gender, levels of blood pressure, cholesterol, smoking habit and presence of diabetes considered by the NPS version of the New Zealand calculator.

According to these risk engines, Christine's five-year risk of a cardiovascular event (a myocardial infarction or stroke) is greater than 15%. She is at even higher risk given the risk factors not considered by these tools.

Lifestyle changes to reduce cholesterol

Of the four SNAP recommendations to reduce behavioural risk factors that affect the health of the general population, three are applicable to Christine to help her reduce her cholesterol levels: quitting smoking, better nutrition and more physical activity. As is often the case, the three are linked. Christine is unlikely to seriously consider quitting smoking if she expects her weight to increase. Unless she can 'Eat less and walk more' – the key message for achieving a healthy lifestyle, the cornerstone of diabetes management – she is unlikely to lose much weight and also likely to gain weight if she stops smoking.

It may be appropriate to consider a Team Care Arrangement to involve a dietitian in her nutrition program and a physiotherapist or an exercise physiologist in her activity schedule. A diabetes educator could advise on the changes required in her hypoglycaemic medication as she increases her activity and decreases her weight.

The focus on lifestyle issues would be:

- eat less – less food, less total fat, less saturated and trans fats.
- walk more – every day, each week, every week.

Behaviours associated with successful weight loss and successful maintenance of that loss should be encouraged. The people who succeed keep track of their food intake and their activity (such as with a food diary and a pedometer), are guided as to the steps they should take, and are monitored and supported through those steps. Nursing and allied health colleagues can help: the practice nurse can review progress on each practice visit, the diabetes educator can provide specialised advice and the physiotherapist or exercise physiologist can advise on and supervise the activity program.

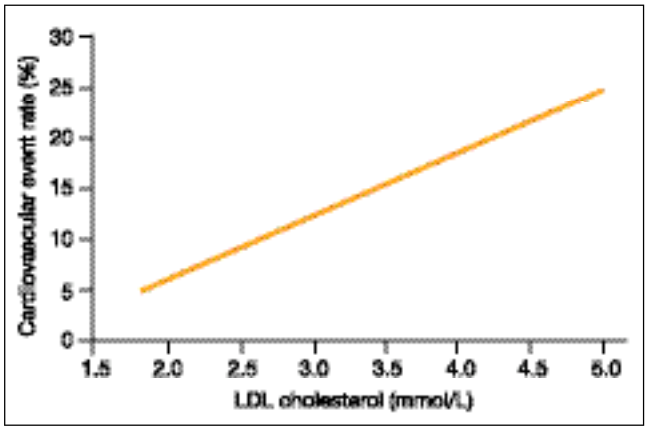
Successful lifestyle change will result in some weight loss, improvement in glycaemic control and perhaps reduction in hypoglycaemic medication. Weight loss and decreased total, saturated and trans fat intakes can be expected to reduce cholesterol by about 10% (in Christine's case, this would be from 7.4 to 6.7 mmol/L).

Christine's eligibility for subsidised statin therapy

Christine meets the most recent eligibility criteria for PBS subsidy of cholesterol-lowering therapy (introduced 1 October 2006), as having diabetes mellitus with an albumin to creatinine ratio of more than 3.5 mg/mmol (hers is 5.2 mg/mmol) puts her into a very high risk category (see the box on this page).[1] These new eligibility criteria allow patients in very high risk categories to have access to subsidised cholesterol lowering drugs regardless of their cholesterol levels.

As Christine is at very high risk of a cardiovascular event and is unlikely to reach targets with lifestyle changes alone, it may be worth starting both lifestyle changes and statin therapy at once, rather than waiting to see the effect of lifestyle changes alone. After all, Christine has been working hard to achieve a healthy lifestyle for years.

Both simvastatin and atorvastatin



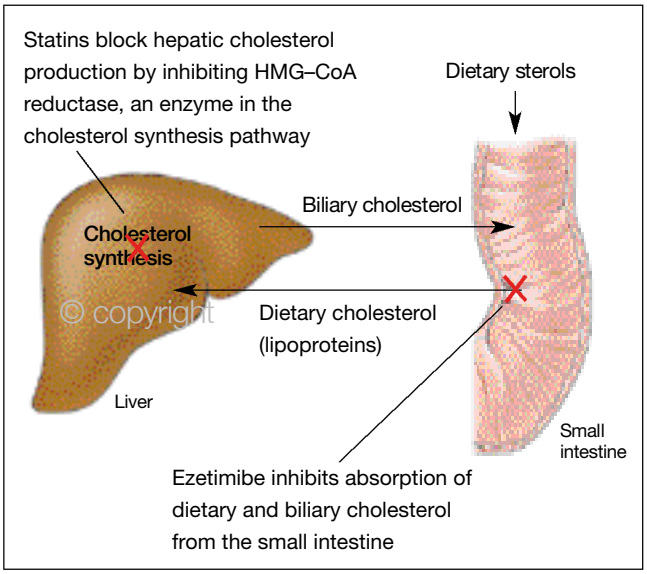


Figure 1 (above). Secondary prevention studies have shown that the lower the cholesterol level, the lower the risk of cardiovascular events.[4]
Figure 2 (right). Sites of action of statins and ezetimibe on cholesterol metabolism.

(Lipitor) have recently been shown to decrease coronary and cardiovascular events in people like Christine.[2,3] Although many patients are started on a statin at a dose of 5 or 10 mg daily, it should be remembered that the doses used in studies demonstrating the efficacy of simvastatin and atorvastatin were 40 mg and 10 mg daily, respectively.

Statin therapy

A decrease in Christine's cholesterol level to 5.7 mmol/L after three months' therapy with simvastatin 40 mg/day would be expected. A starting dose of 40 mg of simvastatin or 10 mg of atorvastatin daily is likely to decrease the total cholesterol by some 15 to 20%. Taking into account the 10% or so reduction in cholesterol level as a result of lifestyle changes (in Christine's case, from 7.4 to 6.7 mmol/L), this translates into a decrease in cholesterol of about 1 mmol/L due to the statin. As cardiovascular risk decreases with decreasing cholesterol levels (Figure 1),[4] Christine's risk could be further reduced since her new cholesterol level (5.7 mmol/l) is still above the target level (<4 mmol/L).

The next step is to check that Christine is actually taking the statin and will continue to take it. Her lifestyle should then be reviewed to see if she is able and/or willing to make further lifestyle change.

The final consideration would be to double Christine's statin dose. However, doubling the statin dose unfortunately does not double the cholesterol lowering effect but more than doubles the risk of side effects (myalgia, creatine kinase rises and abnormal liver function tests, for example).[5] For cholesterol lowering, the 'rule of 6s' applies – each dose doubling results in a further 6% decrease in cholesterol, rather than the initial 15 to 20% decrease being repeated.[6]

Statin myopathy

Christine's simvastatin dose is doubled to 80 mg daily and two weeks later she complains of aching muscles, particularly in the shoulders and neck after she had been gardening. Statin myotoxicity was suspected.

Checking her creatine kinase (CK) levels could be considered, but a normal CK does not mean that the statin is not affecting muscles. Also, an abnormal CK can be caused by factors other than statins.

It would, however, be useful to check whether there are other factors in Christine's case that might potentiate the muscle side effects of statins (Table 2).[7] If there are and if they could be changed, it might be possible to continue with the statin at the current dose rather than stopping it or reducing the dose to a level not associated with problems. Most of the factors potentially contributing to statin myopathy affect muscle themselves and are easy to remember and assess. Some of the medications are also easily remembered – for example, the fibrates because they may be coprescribed, and the mycins (macrolide-type antibiotics) and azoles (antifungal agents) because they commonly cause drug interactions. A desktop tool such as 'MIMS Interactive' or a pharmacist Home Medication Review can be useful sources of advice on potentially contributing medications.

Assuming none of these factors are relevant in Christine's case, it would be prudent to stop the statin, allow the muscle problem to abate and then resume the statin at the previous dose that did not cause problems. Of course, reducing the statin dose would mean that Christine's total and LDL cholesterol levels and her cardiovascular risk would increase.

Other medications

If there are no contributing factors to Christine's myalgia that could be changed,

continued

Table 2. Factors increasing statin myotoxicity

Major illness
- Severe infection
- Surgery
- Trauma
- Hypoxia
- Hypothermia
- Uncontrolled seizures

Chronic illness
- Debilitation or advanced age
- Chronic renal or liver failure

Endocrine and metabolic disorders
- Hypothyroidism
- Hyponatraemia
- Metabolic acidosis

Medications

Concurrent administration of other drugs utilising the cytochrome P450 enzyme system (CYP3A4 is the isoenzyme most often involved in drug metabolism)
- Fibrates (gemfibrozil more than fenofibrate)
- Macrolide antibiotics
- Azole antifungals
- Calcium channel blockers (such as verapamil and diltiazem)
- Antidepressants (such as fluoxetine and fluvoxamine)
- Warfarin
- Cyclosporin

Others
- Concomitant use of recreational drugs – e.g. ecstasy (a CYP2D6 substrate)
- Grapefruit juice (a CYP3A4 inhibitor)

another way to reduce her cholesterol would be to add a medication to reduce gastrointestinal cholesterol absorption to reinforce the statin effect on cholesterol synthesis. In the past, this has not been practical because the medications available (bile acid sequestrant resins) were unpalatable and long term adherence was unusual.

In August 2004, ezetemibe (Ezetrol) was added to the range of hypolipidaemic medications available on the PBS. Ezetimibe (Vytorin) is an oral, once daily medication that selectively binds to the cell surface receptor for cholesterol in the small intestine, reducing the absorption of both exogenous (dietary) and endogenous (biliary) cholesterol. Its mode of action is complementary to that of statins (Figure 2), and it is used concomitantly.

As Christine's total cholesterol level is still above the target level of 4 mmol/L after three months of statin therapy and lifestyle changes, she would be eligible for a PBS subsidised prescription of ezetimibe or the combination preparation simvastatin and ezetimibe.

Other medications that could be used to reduce Christine's total and LDL cholesterol are:
- bile acid sequestrants (colestipol [Colestid], cholestyramine [Questran Lite]) – however, as previously noted, these are unlikely to be acceptable to her
- nicotinic acid – but this is likely to increase Christine's blood glucose and has a range of other unpleasant side effects.

The fibrates and omega-3 fatty acids (fish oils) are not appropriate agents in Christine's case as they target triglycerides and HDL rather than LDL cholesterol.

Key points

- Calculation of five-year risk of cardiovascular events identifies patients in whom cholesterol lowering is a priority.
- Lifestyle change can be expected to reduce total cholesterol by about 10%.
- Recently introduced revised guidelines make most high risk Australians with diabetes eligible for PBS subsidised cholesterol lowering therapy.
- Statin therapy (such as simvastatin 40 mg daily or atorvastatin 10 mg daily) can be expected to reduce total cholesterol by 15 to 20% but, according to the 'rule of 6s', doubling the statin dose only reduces cholesterol by a further 6%.
- If statin therapy does not lower a patient's total cholesterol to the target level, consider the use of ezetimibe (10 mg daily) to block cholesterol absorption. MT

Acknowledgement

The author would like to thank the reviewers of this article for their helpful suggestions.

References

1. PBS-Eligibility criteria for lipid lowering drugs fact sheet. Australian Government Department of Health and Ageing. September 2006. www.health.gov.au/internet/wcms/Publishing.nsf/Content/lipid_eligibilitycriteria.htm
2. Collins R, Armitage J, Parish S, Sleigh P, Peto R; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003; 361: 2005-2016.
3. Colhoun HM, Betteridge DJ, Durrington PN, et al, CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004; 364: 685-696.
4. LaRosa JC, Grundy SM, Waters DD, et al, Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005; 352: 1425-1435.
5. Leitersdorf E. Cholesterol absorption inhibition: filling an unmet need in lipid-lowering management. Eur Heart J 2001; 3(Suppl E): E17-E23.
6. Knopp RH. Drug treatment of lipid disorders. N Engl J Med 1999; 341: 498-511.
7. Drug and Therapeutic Information Service (DATIS). Dyslipidaemia. Adelaide: DATIS; 2002. 62-66. ISBN: 0-7308-8626-3.

DECLARATION OF INTEREST: Dr Phillips has received research and travel grants, acted on advisory boards and been involved with clinical trials and seminars sponsored by a range of pharmaceutical companies. He does not think these associations have influenced the content of this article.

MedicineToday 2007; 8(1): 69-73

ABCss: s is for smoking

JOHN LITT MB BS

PAT PHILLIPS MB BS, MA(Oxon), FRACP, MRACMA, GradDipHealthEcon(UNE)

PHOTOLIBRARY

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

Sam is visiting the surgery because he has run out of his cholesterol tablets. However, he says, he has been taking his diabetes and blood pressure tablets so his blood pressure can be taken and his glycosylated haemoglobin (A_{1c}) checked while he is here.

As he takes off his coat so the sphygmomanometer cuff can be put on, you smell tobacco smoke. After measuring his blood pressure (which is a bit high at 156/82 mmHg), you ask Sam how many cigarettes he smokes each day. He looks a bit sheepish and tells you, 'about 10 to 15 a day, but I'm cutting back steadily'.

Although you do not have much time right now, you do not want to miss the opportunity to address Sam's smoking habit.

Questions

- How can you get smoking on the agenda without offending Sam?
- How could you best use one minute to assist Sam? And three minutes?
- How likely is Sam to respond to these interventions and try quitting?
- If Sam does decide to quit, is nicotine replacement therapy likely to help him? What other help is available to him?
- If Sam does quit, how likely is he to be a nonsmoker 12 months later? What factors might influence his continuing abstinence?

Dr Litt is Senior Lecturer, Department of General Practice, Flinders University, Flinders Medical Centre, Bedford Park. Dr Phillips is Senior Director, Endocrinology, North Western Adelaide Health Service, The Queen Elizabeth Hospital, Woodville, SA.

Getting smoking on the agenda

While most smokers do not object to being asked about their smoking, obtaining more than the basic information is usually not easy unless they can be reassured they will not be lectured about smoking. They expect to be 'harassed' and this tends to put them in a defensive frame of mind.

A few tips to bear in mind when raising the issue of smoking with a patient are discussed below and listed in Table 1.

Be alert for sensitivity

Sensitivity is the norm. Nevertheless, when the issue of smoking is raised sensitively and discussed nonjudgementally, patient satisfaction is often higher than when it is not discussed.[1-3]

Normalise enquiry

If everyone is being asked then patients are less likely to feel singled out. Asking everyone also increases the recognition of smoking status and can prompt patients to think about quitting.[4,5]

Understand the patient's perspective

Smoking may play an important role in the person's life. Many smokers see quitting like killing their best friend.[6] Quitting smoking involves many changes – for example, what to do when they are feeling stressed, how to keep their weight down, not joining their friends at smoko, losing the 'time out' that a cigarette may give. Understanding the issues and challenges for patients will help you to engage them in the quitting process. Remember that the number of significant others in a person's immediate family and friends who are smokers is a potent predictor of the likelihood of the person relapsing after quitting.[7]

Table 1. Asking a patient about smoking

Be alert for sensitivity
Normalise enquiry
Understand the patient's perspective
Separate information from the 'persuasive imperative'
Avoid dangerous assumptions
Establish and maintain common ground
Keep confrontation in reserve
Leave the door open

Table 2. The 5As approach to smoking cessation*

5As	If only 1 minute available	If more time available (about 3 minutes)
Ask	Identify and document smoking status routinely and review at least every 12 months: current, ex, or never smoker?	Explore smoking status further
Assess	Identify: • interest in quitting • barriers to quitting, e.g. what would be the hardest thing about quitting? • level of nicotine dependence – time to first cigarette in the morning (<30 mins), number smoked per day (>15 cigarettes), previous symptoms of withdrawal	Explore: • motivation and confidence • barriers to quitting • quitting history – what worked, what didn't work, what tipped him or her back? • high risk situations – which cigarette would be the hardest to give up, when might slips occur (even one puff greatly increases the risk of relapse)?
Advise	Provide brief, clear personalised and nonjudgemental advice to quit Set quit date	Address the three main domains – dependence, habit, triggers (especially negative emotions) Brainstorm solutions – provide options, explore what is likely to support his or her ability to quit Negotiate/advise how to deal with high risk situations
Assist	Offer a Quitbook and give the Quitline number (137 QUIT) Negotiate a separate smoking cessation orientated consultation	Enrol in an active call back program (12 weeks) Discuss/offer pharmacotherapy Develop a plan to deal with nicotine withdrawal, habit, negative moods, weight gain, stress, high risk situations
Arrange	Follow up (ideally in first seven days)	Recruit support (partner, family and friends)

* Based on the Quit SA website's resource for GPs:GP desk prompt -5As (www.quitsa.org.au/cms_resources/documents/resource_gpdeskprompt.pdf).

Separate information from the 'persuasive imperative'

Patients are very sensitive to judgements being made about their health-related behaviour.[8] While many doctors recognise this, it unfortunately does not stop us being somewhat judgemental.[8,9] Patients do need personalised information about the risks of smoking to them. Downplaying the risks, scepticism about the medical evidence, a sense of fatalism and inevitability, normalising the dangers of smoking because of the many other risks to health, and the belief that smoking is worth the probable health damage are all common beliefs that need to be countered with clear and accurate information.[10-12]

Three ingredients are necessary for a person to make a successful lifestyle behaviour change:

- concern about his or her current behaviour
- a belief that changing will be beneficial to him or her
- a perception that he or she will be able to change.

Avoid dangerous assumptions

Dangerous assumptions that doctors may make include:[13]

- the patient ought to change
- now is the right time
- my way is best.

Establish and maintain common ground

Ensuring agreement on what the problem is and respecting the patient's autonomy helps the communication process and improves health outcomes.[14] If you want to talk about a patient's smoking but he or she does not wish to discuss it, do not push the issue. Instead, address the patient's concerns and the reasons behind his or her reticence. Getting a patient's permission to discuss smoking and promising not to give a lecture are useful steps that provide a nonjudgemental signal to the patient.[15,16]

Keep confrontation in reserve

Although confrontation works occasionally, more often it provokes reactance, or resistance.[13,17] When patients react in this way to a personal threat, they become defensive and tend to dig in or harden their beliefs. Such a reaction can make it more difficult to raise the topic again as the patient expects to be confronted.

Leave the door open

If first you don't succeed, try again. Patients see their GP five times a year on average, so there will be further opportunities to

discuss smoking. Quitting smoking will only occasionally result from a single consultation, but one consultation can start the ball rolling.

Best use of time

The 5As

One straightforward option for spending a few minutes productively with Sam is to use the 5As – ask, assess, advise, assist and arrange. However, before doing so, ensure that Sam is prepared to talk about his smoking. The 5As approach is summarised in Table 2.

Ask. Ask Sam if he is interested in quitting.

Assess. Ask Sam how confident he is that he would succeed if he tries quitting. Get him to rate his chances on a 10-point scale where 10 is very confident and 0 is not confident at all. Then ask, 'What would need to happen to increase the score from 3 (or whatever low score he gives) to 9?' If he has an initial high score (say 8 or more), ask him 'Why is your confidence an 8 and not a 2?' This should give some insight into what is underpinning his confidence.

Remember that many heavy smokers believe that they can quit at any time so do not need to think about it until it is really necessary. A useful counter to this view is to tell patients that the more they smoke, the more likely they are to be dependent on nicotine and the more difficult it will be to quit. Also ask about whether they have ever quit for any period, and what happened when they did.

If you think Sam may be nicotine dependent, ask when he has his first cigarette of the day and the number he smokes each day. If he is having his first cigarette within 30 minutes of waking up and smoking more than 15 a day, he is likely to be nicotine dependent.

Advise. Provide Sam with brief, concise and nonjudgemental advice on how to quit. Mention the risks of smoking and the benefits of quitting.

Assist. Offer support and reassure Sam that he will not be lectured about his smoking. Refer him to the Quitline and outline the benefits of the Quitline active callback program. (The Quitline is the phone support service of the National Tobacco Campaign, a Federal, State and Territory health initiative, and is discussed in detail later.) Discuss pharmacotherapy if there is time.

Arrange. Offer Sam a follow up appointment for review of progress and pharmacotherapy. Enlist the support of his family and friends.

Other options

If Sam is very sensitive about his smoking (as many smokers are) and seems to overreact to questions, another option is to use the minute to outline an approach to managing his smoking. This would include an offer of practical help to quit, reassurance that he will not be given a lecture, acknowledgement of how difficult it is stop smoking and exploration of how he feels about quitting.

Many smokers erroneously believe that they should be able to quit smoking on their own and that asking for help is a sign of weakness. Remember that the unassisted quit rate is 3 to 5%,[18] and that GPs can increase this four to sixfold by using a range of proven strategies. These strategies include focusing on those smokers who express interest in quitting, arranging at least one follow up visit and getting the smoker to take some form of nicotine replacement therapy; each of these can double the success rate,[4,5] and collectively they can increase the likelihood of quitting significantly.

A further option is to encourage Sam to see your practice nurse who can talk to him about the steps involved in quitting (using the 5As approach).[19,20]

Likelihood of quitting smoking

Whether Sam is likely to respond to these interventions and try quitting depends to a great extent on how the message is delivered. There is good evidence that patient satisfaction in smokers is higher when doctors address smoking.[1,2] The challenge is to do it in a manner that is not too confronting. The moral imperative should be separated from the useful information that you can offer the patient. Externalise the patient's smoking through forming an alliance; for example, 'How can you and I work together on your smoking?'

Most surveys of smokers demonstrate that up to two-thirds of people using cigarettes are interested in quitting and health concerns are a potent stimulus for thinking about quitting.[21] The challenge is often the smokers' perceived confidence of success.[11,22] Some patients really want to quit but feel they can't, so they don't try. Many doctors mistakenly perceive this as lack of interest in quitting, when it may in reality reflect an inability to be able to quit despite interest.

Most smokers will make a serious quit attempt at least once a year. The secret to successful quitting is getting them to understand that quitting is more challenging without some form of help. A useful strategy is to liken quitting to participating in a triathlon. The latter requires three independent sets of skills: running, swimming and cycling. Quitting also involves three sets of skills:

- overcoming the physical dependence on nicotine
- dealing with the habit of smoking
- managing negative emotions, such as boredom, anxiety, anger and depression.

Using a medication like nicotine replacement will only help with nicotine withdrawal; it will not address the habit or help with the negative emotions. All the randomised controlled trials of pharmacotherapy in smoking cessation have involved some form of counselling, some quite intensive. Consequently, bupropion or some form of nicotine replacement should not be prescribed on its own. Varenicline, a selective $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, is a further alternative to assist smokers to quit but has not yet been released in Australia.[23-25] A recent 12-month follow up

Table 3. Quitting: what works, what doesn't and what might[27]

What works
- Counselling – individual, group, phone
- Follow up – visits, phone calls
- Pharmacotherapy – nicotine replacement therapy, bupropion

What doesn't
- Written materials alone
- Aversion therapy, acupuncture

What might
- Hypnotherapy

trial has reported that varenicline was superior to bupropion in reducing relapse rates.[26]

Strategies that work in quitting and those that do not are summarised in Table 3.[27]

Many smokers feel that quitting will just be a matter of not smoking anymore, without realising that smoking is playing a big role in their life (e.g. as a coping strategy, as a means of keeping their weight down and as time out from a stressful day).[11,12,28] It is important to show Sam that you are interested and that you will not tell him what to do.

Nicotine replacement therapy and other help

Most forms of pharmacotherapy double the success rate in smoking cessation.[29,30] Up to two-thirds of smokers are nicotine dependent so it is useful to determine whether the patient is nicotine dependent (see above, under 'Best use of time').[29,31]

Nicotine replacement therapy

Many smokers do not get good instructions about how to take the various forms of nicotine replacement therapy (patches: NicabateCQ, Nicorette Patch, QuitX Patch; lozenges: NicabateCQ Lozenges; chewing gums: Nicorette Chewing Gum, Nicotinell Chewing Gum, QuitX Chewing Gum; inhaler: Nicorette Inhaler; sublingual tablets: Nicorette Microtab). Often more than one form of nicotine replacement therapy is needed; for example, a nicotine patch plus some form of quicker delivery of nicotine in the morning to deal with early morning cravings.

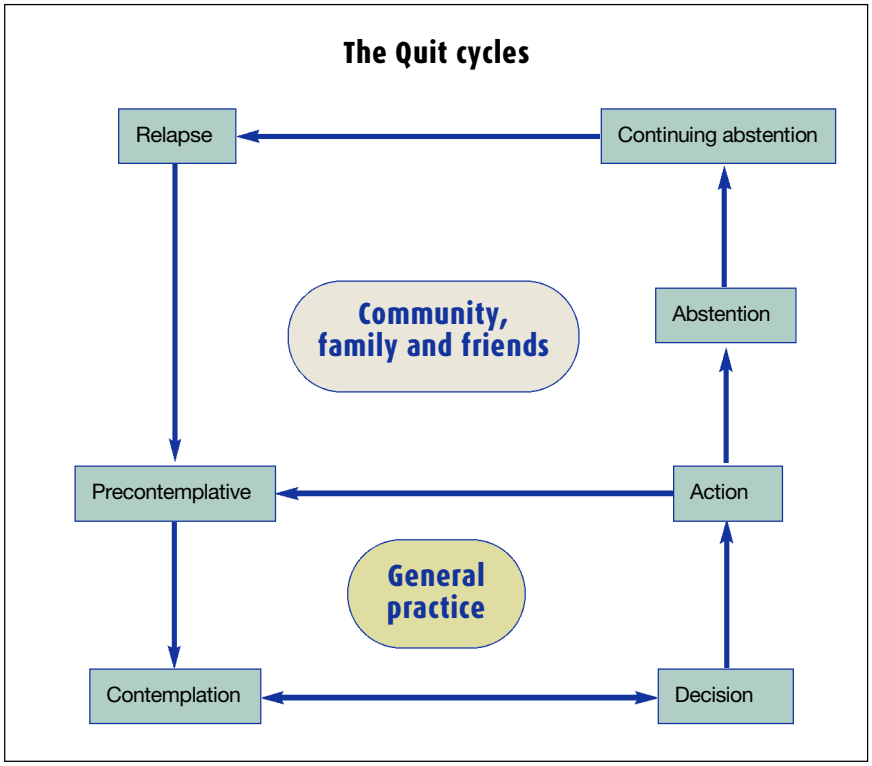


Figure. Long term smoking abstention is influenced by community factors.

Bupropion

An alternative therapy for nicotine dependence is bupropion sustained release (Clorprax, Zyban SR), a selective catecholamine (norepinephrine and dopamine) reuptake inhibitor initially developed for use as an antidepressant that has also been shown to act as a competitive $\alpha 3\beta 4$ nicotinic antagonist. Common side effects of bupropion include difficulty sleeping, dry mouth, headache, dizziness, anxiety and nausea. Bupropion sustained release is available as a PBS authority item once per year.

Increasingly, smokers are using a combination of bupropion and nicotine replacement therapy. Sam's employer may provide a subsidy that may help.

Quitline

The other key strategy is to refer Sam to the Quitline in his State or Territory, where Quitline counsellors provide advice and assistance to smokers who want to quit, including the offer of a copy of the self-help *Quit Book*, and the opportunity to enrol in an active callback program. This active Quitline phone follow up service operates in most States and Territories and is very effective.[32,33] The Quitline is answered 24 hours a day, but Quitline counsellors are only available during business hours and at certain times at weekends. An interpreter service is available.

Sam can contact the Quitline himself (phone number 137 QUIT) or you, his GP, can refer him by phone or fax and they will contact him. Fax referral forms are available on the Quitnow website

(www.quitnow. info.au), as are other resources, such as the *Quit Book* and *Smoking Cessation Guidelines for Australian General Practice*.

Less than 5% of the population of smokers have called the Quitline. There is a lot of scope for improvement, especially since many clinicians are not yet referring smokers for smoking cessation counselling.[34,35]

If Sam has a partner who smokes then it will be harder for him to quit. However, if the partner tries to quit at the same time, the success for both is doubled.[36,37]

Other therapies

Strategies such as hypnotherapy and acupuncture do not appear to be effective in smoking cessation. While they may work for some, in general the systematic reviews show no benefit.[4]

Likelihood of continuing abstinence

Twelve-month quit rates depend on the approach taken. In the absence of support, 3 to 7% of quitters will still be non-smokers. If Sam is enrolled in the Quitline active callback program and gets support and some form of pharmacotherapy from you, then his quit rate could be as high as 33% at 12 months.

It is important to remember that most of the factors influencing Sam's continuing abstention in the long term lie in the general community (Figure). The program set up for Sam can only influence his behaviour when the Quitline calls back, you send a letter of support or he returns for a visit.

Larger environmental factors, such as advertising, restrictions on smoking behaviour and cigarette prices, are powerful influences. There may also be direct factors influencing Sam's future behaviour, such as other smokers in his household or his circle of friends, enjoyable regular activities associated with smoking behaviour and the role of smoking in dealing with issues such as stress and weight management.

Internet resources for smoking cessation

Smoking cessation guidelines for Australian general practice
www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pubhlth-publicat-document- smoking_cessation-cnt.htm

Quitnow – Resources for health professionals
www.quitnow.info.au/internet/quitnow/publishing.nsf/content/health_professionals-lp

QUIT SA resources for health professionals
www.quitsa.org.au/aspx/quitsa_resources.aspx

5As – desk prompt (GPs Assisting Smokers Program)
www.quitsa.org.au/cms_resources/documents/resource_gpdeskprompt.pdf

Pharmacotherapy for smoking cessation
www.quitsa.org.au/cms_resources/documents/resource_gpcardbuproprion05.pdf
www.quitsa.org.au/cms_resources/documents/resource_gpNRTcard05.pdf

Sam's previous attempts to quit or to change another important lifestyle behaviour should be explored. What helped and what hindered? How did he maintain the positive and deal with the negative influences? How did he/could he recruit family and friends to be part of his long term support team? What will he do if he relapses (as many do)? Sam may need five to eight attempts at quitting before finally succeeding. Will he feel able to seek your help or advice from the Quitline?

It should be stressed to Sam that help will always be available and that you will work with him rather than judge or lecture him. Mention of ongoing abstinence should be added to the agenda of future consultations, such as 'Do you realise it is now two years since you stopped smoking. Pretty damn good!'

A final word

Referring to the analogy of quitting smoking and participating in a triathlon, Sam is the triathlete, and you and the other resources are his support team.

To start the process of quitting, Sam must answer 'Yes' to three questions about smoking as an issue in his life:

- Do I care? Yes, smoking is a life issue for me.
- Will it work? Yes, quitting will improve my life.
- Can I do it? Yes, with a program I can quit.

To help Sam succeed, you, his GP, need to establish:

- the routine of the '5As' as part of your usual practice
- the organisation within your practice to support quit attempts and ongoing abstention – for example, computerised prompts and using practice nurses to also provide counselling (see the RACGP *Putting Prevention into Practice* monograph for a summary of effective practice-based implementation strategies)[38]

A list of internet resources to assist GPs when encouraging smokers to quit is given in the box above. MT

References

1. Barzilai D, Goodwin M, Stange K. Does health habit counseling affect patient satisfaction? Prev Med 2001; 33: 595-599.
2. Solberg L, Boyle R, Davidson G, Magnan S. Patient satisfaction and discussion of smoking cessation during clinical visits. Mayo Clin Proc 2001; 76: 138.
3. Quinn VP, Stevens VJ, Hollis JF, et al.

Tobacco-cessation services and patient satisfaction in nine nonprofit HMOs. Am J Prev Med 2005; 29: 77-84.
4. Fiore M, Bailey W, Cohen S, et al. Treating tobacco use and dependence: clinical practice guideline. Rockville: US Department of Health and Human Services, Public Health Service; 2000.
5. Zwar N, Richmond R, Borland R, Stillman S, Cunningham M, Litt J. Smoking cessation guidelines for Australian general practice. Canberra: Commonwealth Department of Health and Ageing; 2004.
6. Carter S, Borland R, Chapman S. Finding the strength to kill your best friend: smokers talk about smoking and quitting. Sydney: Australian Smoking Cessation Consortium and GlaxoSmithKline Consumer Healthcare; 2001.
7. Ockene JK, Emmons KM, Mermelstein RJ, Perkins KA, Bonollo DS, Voorhees CC. Relapse and maintenance issues for smoking cessation. Health Psychol 2000; 19: 17-31.
8. Butler C, Pill R, Stott N. Qualitative study of patients' perceptions of doctors' advice to quit smoking: implications for opportunistic health promotion. BMJ 1998; 316: 1878-1881.
9. Coleman T, Cheater F, Murphy E. Qualitative study investigating the process of giving anti-smoking advice in general practice. Patient Educ Couns 2004; 52: 159-163.
10. Cummings K, Hyland A, Giovino G, Hastrup J, Bauer J, Bansal M. Are smokers adequately informed about the health risks of smoking and medicinal nicotine? Nicotine Tob Res 2004; 6: 333-340.
11. Weinstein ND, Slovic P, Gibson G. Accuracy and optimism in smokers' beliefs about quitting. Nicotine Tob Res 2004; 6(Suppl 3): S375-380.
12. Yong H, Borland R, Siahpush M. Quitting-related beliefs, intentions, and motivations of older smokers in four countries: findings from the International Tobacco Control Policy Evaluation Survey. Addict Behav 2005; 30: 777-788.
13. Rollnick S, Mason P, Butler C. Health behavior change. Edinburgh: Churchill Livingstone; 1999.
14. Rao J, Weinberger M, Kroenke K. Visit-specific expectations and patient-centred outcomes: literature review. Arch Fam Med 2000; 9: 1148-1155.
15. Litt J. Smoking and GPs: time to cough up: successful interventions in general practice. Aust Fam Physician 2005; 34: 425-429.
16. Zwar NA, Richmond RL. Role of the general practitioner in smoking cessation. Drug Alcohol Rev 2006; 25: 21-26.
17. Fogarty J. Reactance theory and patient non-compliance. Social Science Med 1997; 45: 1277-1288.
18. Zhu S, Melcer T, Sun J, et al. Smoking cessation with and without assistance: a population-based analysis. Am J Prev Med 2000; 18: 305-311.
19. Litt J, Stillman S, Oberklaid D, et al. Rationale, issues and feasibility of using a practice nurse to improve the provision of preventive care in the general practice setting, using smoking cessation as an example: a pilot study (final report to Tobacco Control Unit, Department of Human Services, Victoria). Melbourne: RACGP; 2004.
20. Rice V, Stead L. Nursing interventions for smoking cessation (Cochrane review). Cochrane Database Syst Rev 2004; (1): CD001188.
21. McCaul KD, Hockemeyer JR, Johnson RJ, Zetocha K, Quinlan K, Glasgow RE. Motivation to quit using cigarettes: a review. Addict Behav 2006; 31: 42-56.
22. Goldberg D, Hoffman A, Anel D. Understanding people who smoke and how they change: a foundation for smoking cessation in primary care, part 2. Dis Mon 2002; 48: 445-485.
23. Klesges RC, Johnson KC, Somes G. Varenicline for smoking cessation: definite promise, but no panacea. JAMA 2006; 296: 94-95.
24. Schroeder SA, Sox HC. Trials that matter: varenicline: a designer drug to help smokers quit. Ann Intern Med 2006; 145: 784-785.
25. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA 2006; 296: 56-63.
26. Gonzales D, Rennard SI, Nides M, Oncken C, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA 2006; 296: 47-55.
27. National Prescribing Service. Managing COPD and preventing progression: stopping smoking. NPS News 45; April 2006.
28. Hammond D, McDonald P, Fong G, Borland R. Do smokers know how to quit? Knowledge and perceived effectiveness of cessation assistance as predictors of cessation behaviour. Addiction 2004; 99: 1042-1048.
29. Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev 2004; (3): CD000146.
30. Henningfield J, Fant R, Buchhalter A, Stitzer M. Pharmacotherapy for nicotine dependence. CA Cancer J Clin 2005; 55: 281-299.
31. Cornuz J. Treating tobacco use and dependence in clinical practice. Expert Opin Pharmacother 2006; 7: 783-792.
32. Stead L, Perera R, Lancaster T. Telephone counselling for smoking cessation (Cochrane Review). Cochrane Database Syst Rev 2006; 3: CD002850.
33. Borland R, Segan CJ. The potential of quitlines to increase smoking cessation. Drug Alcohol Rev 2006; 25: 73-78.
34. Litt J, Pilotto L, Young R, et al. GPs Assisting Smokers Program (GASP II): Report for the six month post intervention period. Adelaide: Flinders University; 2005.
35. Meredith LS, Yano EM, Hickey SC, Sherman SE. Primary care provider attitudes are associated with smoking cessation counseling and referral. Med Care 2005; 43: 929-934.
36. Richmond RL, Kehoe LA, Webster IW. Multivariate models for predicting abstention following intervention to stop smoking by general practitioners. Addiction 1993; 88: 1127-1135.
37. Helgason A, Tomson T, Lund K, Galanti R, Ahnve S, Gilljam H. Factors related to abstinence in a telephone helpline for smoking cessation. Eur J Public Health 2004; 14: 306-310.
38. RACGP. Putting prevention into practice. Guidelines for the implementation of prevention in the general practice setting. (The green book.) 2nd ed. Melbourne: RACGP; 2006. www.racgp.org.au/guidelines/ greenbook (accessed Dec 2006).

DECLARATION OF INTEREST: Dr Litt: None.
Dr Phillips has received research and travel grants, acted on advisory boards and been involved with clinical trials and seminars sponsored by a range of pharmaceutical companies. He does not think these associations have influenced the content of this article.

MedicineToday 2007; 8(2): 55-58

ABCss: s is for salicylates

PAT PHILLIPS MB BS, MA(Oxon), FRACP, MRACMA, GradDipHealthEcon(UNE)
JODY BRADDON BPharm

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

Dr Phillips is Senior Director, Endocrinology, North Western Adelaide Health Service, The Queen Elizabeth Hospital, Woodville, SA. Ms Braddon is Clinical Pharmacist, Drug and Therapeutic Information Service (DATIS), Repatriation General Hospital, Daw Park, SA.

continued

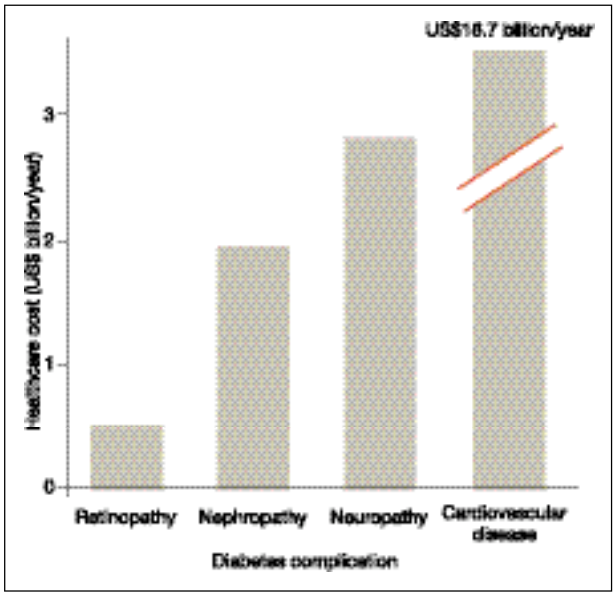


Figure 1. The cost of cardiovascular disease in diabetes outweighs that of any other complications.[2]

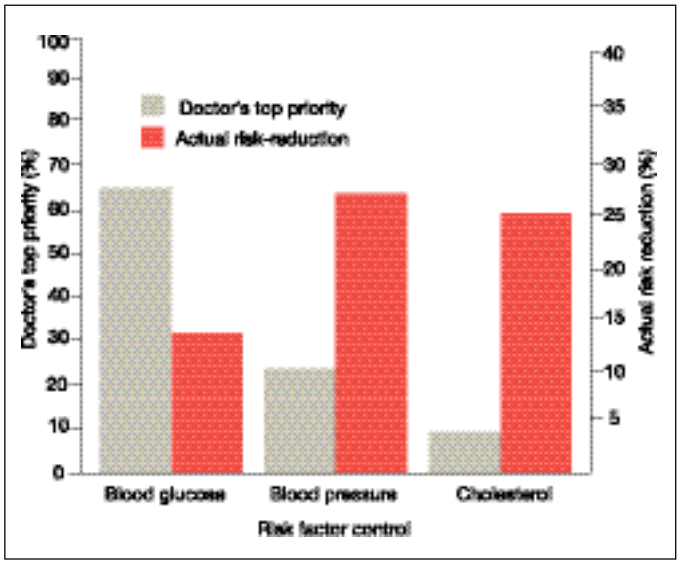


Figure 2. Controlling blood pressure and cholesterol gives greater reduction in risk for cardiovascular disease than controlling glycaemia (2001 meta-analysis data).[3]

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 anti-ischaemic 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

References

1. Heart Foundation of Australia. Hypertension management guide for doctors 2004. Available online: www.heartfoundation.com.au/downloads/hypertension_management_guide_2004.pdf.
2. Hogan P, Dall T, Nikolov P; American Diabetes Association. Economic costs of diabetes in the US in 2002. Diabetes Care 2003; 26: 917-932.
3. Huang ES, Meigs JB, Singer DE. The effect of interventions to prevent cardiovascular disease in patients with type 2 diabetes mellitus. Am J Med 2001; 111: 633-642.
4. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998; 351: 1755-1762.
5. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005; 352: 1293-1304.
6. Gailer J. DATIS review of antithrombotic therapy in general practice. Role in the prevention of cardiovascular disease. Drug & Therapeutics Information Service, Daw Park, SA. April 2005.
7. Eikelboom JW, Hankey GJ. Aspirin resistance: a new independent predictor of vascular events? J Am Coll Cardiol 2003; 41: 966-968.
8. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs non-steroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomised controlled trial. JAMA 2000; 284: 1247-1255.

DECLARATION OF INTEREST: Dr Phillips has received research and travel grants, acted on advisory boards and been involved with clinical trials and seminars sponsored by a range of pharmaceutical companies. He does not think these associations have influenced the content of this article. Ms Braddon: None.

MedicineToday PEER REVIEWED ARTICLE MedicineToday 2007; 8(2): 47-53

The WXYZ of cardiodiab risk

Early recognition of the risk factors for cardiovascular disease and diabetes enables control of the progression of these factors by lifestyle changes (weight loss and increased physical activity) and/or medication.

PAT PHILLIPS
MB BS, MA(Oxon), FRACP, MRACMA, GradDipHealthEcon(UNE)

Dr Phillips is Senior Director, Endocrinology, North Western Adelaide Health Service, The Queen Elizabeth Hospital, Woodville, SA.

In Australia we have accepted the importance of the ABCss of diabetes care (controlling glycosylated haemoglobin [A_{1c}], blood pressure [B] and cholesterol [C], quitting smoking [s] and taking salicylates [s]) when managing patients with diabetes. This article considers the risk factors for cardiovascular disease and diabetes, introducing the mnemonic WXYZ. It is important to recognise these cardiodiab risk factors and respond to them since their progression can be controlled by lifestyle changes, medication or both. As the post-World War II baby boomers move into their 60s and, for women, their size 16 clothes, the metabolic syndrome and 'diabesity' will become more and more common.

The mnemonic WXYZ

The main cardiovascular disease and diabetes risk factors are represented by the mnemonic WXYZ, where:

- W = the weight/waist factor, especially in women
- X = the metabolic problems (syndrome X, or metabolic syndrome) associated with central overweight
- Y = why a particular person develops the metabolic syndrome
- Z = sleep apnoea, not getting enough zzz's.

A case study of a woman in her forties is used in this article to discuss each of these cardiodiab risk factors in detail.

IN SUMMARY

- **W – each year our weight and waist get bigger, both as individuals and as a population. There are many factors but the 'big two' are high energy food and low energy lifestyle.**
- **X – syndrome X, or the metabolic syndrome, has three core components: overweight/waist, cardiovascular risk and abnormal glucose metabolism. Lifestyle change (eating less and walking more) can reverse, stop or slow the progression of these. Cardioprotective medications such as ACE inhibitors, statins or a low dose aspirin may be necessary depending on an individual's cardiovascular risk.**
- **Y – why people develop the metabolic syndrome is usually a consequence of the 'f' words (forty, family and fat). The modifiable risk factor (fatness) should be focused on sooner rather than later, but avoid 'blaming the victim' for his or her problem.**
- **Z – sleep apnoea, or not getting enough zzz's, often occurs with the other risk factors for cardiovascular diseases and diabetes, and may worsen both the W and X factors. Night-time sleep disturbance can worsen the metabolic profile and daytime tiredness can reduce motivation and capacity for lifestyle change.**

Table 1. Factors in increasing weight and waist measurements[2]

The 'big two'
Eating more
Walking less
Possible other factors
Not enough sleep
Climate control
Less smoking
Prenatal effects
Fat equals fecund
A little older
More medications
Pollution
Mature mums
Like marrying like

W – the weight/waist factor

Wendy

Wendy presents to you concerned about her weight. She had her 45th birthday last week and found that none of her party clothes fitted her. She is now size 16, a size she says she would have thought 'gross' when she was younger. She weighs 69 kg and her waist circumference is 90 cm. Looking back, she can track a steady weight gain from her trim size 10 and 50 kg when she was married 20 years ago. She no longer likes looking in the mirror, buying clothes or going out, and she has started wearing loose fitting dark clothes. She is very upset and would like your help.

Weight gain

Wendy is not alone. Australian women aged between 20 and 50 years are gaining about 0.6 kg each year, partly because they are getting older and partly because Australians of all ages are getting fatter (Figure 1).[1] Australian men are also getting heavier, gaining about 0.4 kg per year. This is the W factor for cardiodiab risk, and is assessed by waist circumference (>88 cm for women; >102 cm for men).

The obvious explanation for weight gain is the 'big two' of high energy food and low energy lifestyle – fast foods, television and computers, for example. While it is true that we live in an environment disposing towards obesity, where healthy lifestyle choices are the hard choices, there may be other systematic factors that also lead to weight gain. The most plausible alternatives, which are summarised in Table 1, are:[2]

- smoking less and sleeping less seem to predispose to weight gain – the QUIT campaign has been a great public health success but the price may have been a fatter Australia; also, we try to cram as much as we can into a day and compared to 1960 we now sleep 1.5 hours less each night
- heating and air conditioning in homes and workplaces have reduced the need for body energy expenditure to keep warm or cool
- heavier people tend to have more children and, as overweight has a strong genetic component in our society, overweight people tend to have overweight children
- some groups of people are fatter than others, such as older people and certain ethnic groups
- women are delaying having children, and older mothers seem to have fatter children
- people tend to be attracted to those who are like them, so a fat person is likely to marry another fat person, possibly amplifying increases in obesity from other causes (particularly genetics and the tendency of heavier people having more children)
- people are now exposed to more chemicals (pharmaceuticals and industrial/agricultural chemicals – many of the latter of which become environmental pollutants), and some of these can lead to weight gain.

Over the last 40 years our society has changed in many ways that make it more and more difficult to control the W factor.

X – metabolic problems

Wendy, three years later

Wendy is now 48 years old and presents for a health check as she is worried about her future health. She weighs 73 kg (height, 151 cm; BMI, 32 kg/m^2) and has a waist circumference of 94 cm. Examination confirms the central overweight but is otherwise unremarkable:

- blood pressure, 140/90 mmHg
- total cholesterol, 6.2 mmol/L; HDL cholesterol, 0.8 mmol/L; triglycerides 2.8 mmol/L; LDL cholesterol, 4.0 mmol/L
- fasting plasma glucose, 6.7 mmol/L.

With the exception of her fasting plasma glucose level, these values are outside the National Heart Foundation target ranges (i.e. blood pressure, <130/80 mmHg; total cholesterol, <4.0 mmol/L; HDL cholesterol, >1.0 mmol/L, triglycerides <1.5 mmol/L, LDL cholesterol, <2.5 mmol/L).[3]

You explain that these features indicate that something should be done about her weight as otherwise her health is going to worsen.

The metabolic syndrome

Wendy has syndrome X – more often known these days as the metabolic syndrome. There are many definitions but all contain three components: overweight/waist (central obesity), cardiovascular risk and abnormal glucose metabolism (Table 2). Within these components, blood glucose, blood pressure, blood fats and prothrombosis are the most important in clinical practice because they can be treated.

The major feature of the metabolic syndrome is the progressive nature of the overweight and associated problems. Wendy's fasting glucose is now in the impaired fasting glucose (prediabetes) range but has been rising for years (her

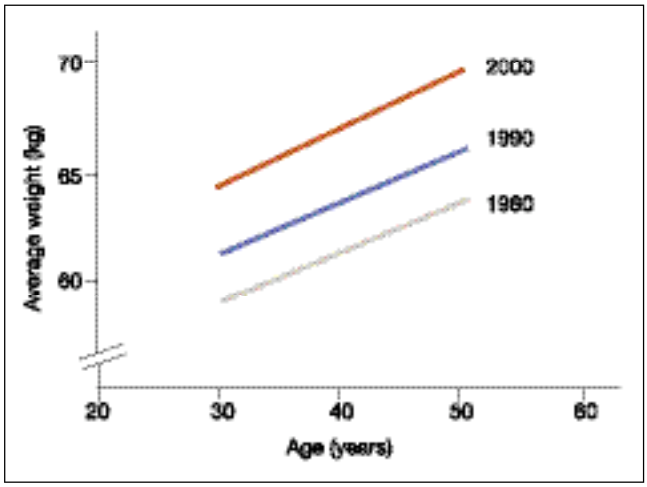


Figure 1 (above). The increase in the average weight of Australian women aged 20 to 50 years from 1980 to 2000.[1]

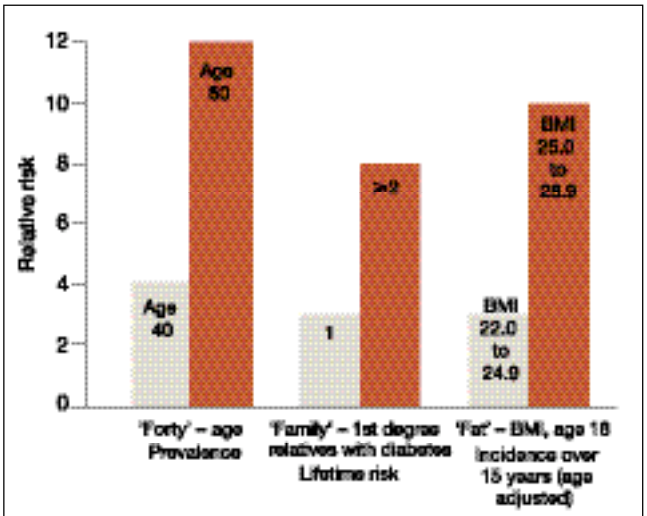


Figure 2 (right). The 'f' words (forty, family and fat) and diabetes risk. Data from the Nurses' Health Study showing the relative risks of diabetes increase progressively with increasing age over 40 years, having one and two or more first degree relatives with diabetes, and increasing BMI at age 18 years.[9]

Relative risk = 1 for:

Prevalence of diabetes at age 20 to 29 years of 1.6%

Lifetime risk of developing diabetes if no family history of diabetes of 10%

Incidence over 15 years for women with BMI below 22 kg/m^2 at 18 years of age

Data from the Nurses' Health Study, Ann Intern Med 1995; 122: 481-486.

fasting glucose level of 6.2 mmol/L is lower than that required to diagnose diabetes [≥7.0 mmol/L] but higher than the normal reference range [<6.1 mmol/L]). Based on the progression of glycaemia seen in the Diabetes Prevention Program,[4] Wendy's blood glucose level started rising in her twenties and will continue to rise into the diabetic range as she gets older. Similarly, her blood pressure and blood fats are clearly abnormally high now but have also been progressively increasing.

Epidemiological studies show that there is a continuum of cardiovascular risk with risk progressively increasing with increasing blood glucose, blood pressure and blood fat levels, even in the so-called normal range. Twenty years ago, Wendy's fasting glucose level was 3.0 mmol/L, her blood pressure was 110/70 mmHg and her blood fat levels were well within target values. Now they are not particularly abnormal for her age but they are much higher than when she was younger (and healthier). They are also likely to progress unless Wendy is able to make lifestyle changes and/or you are able to control the risk factors with medication.

If Wendy cannot change her lifestyle by eating less and walking more[5] or if her blood glucose, pressure and fats are still not on target, medication might help. The Diabetes Prevention Program showed that metformin could reduce the progression from prediabetes to diabetes by one-third and the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) study showed that rosiglitazone could do much the same.[4,6] However, in Australia, neither metformin nor rosiglitazone is available on the PBS to prevent diabetes. If you were to consider prescribing metformin or rosiglitazone (Avandia), or the combined rosiglitazone and metformin preparation (Avandamet), on a private script it would be wise to warn Wendy about the side effects of these medications (gastrointestinal upset with metformin, fluid retention with rosiglitazone). She should also be asked to sign an informed consent form for off label use if you do prescribe either of these medications.

Table 2. Features of the metabolic syndrome

Central obesity

Increased BMI

Increased waist circumference

Increased waist–hip ratio

Cardiovascular risk

Increased blood pressure

Abnormal triglycerides, HDL cholesterol

Prothrombosis

Microalbuminuria

Abnormal glucose metabolism

Impaired fasting glycaemia, impaired glucose tolerance or diabetes

Insulin resistance

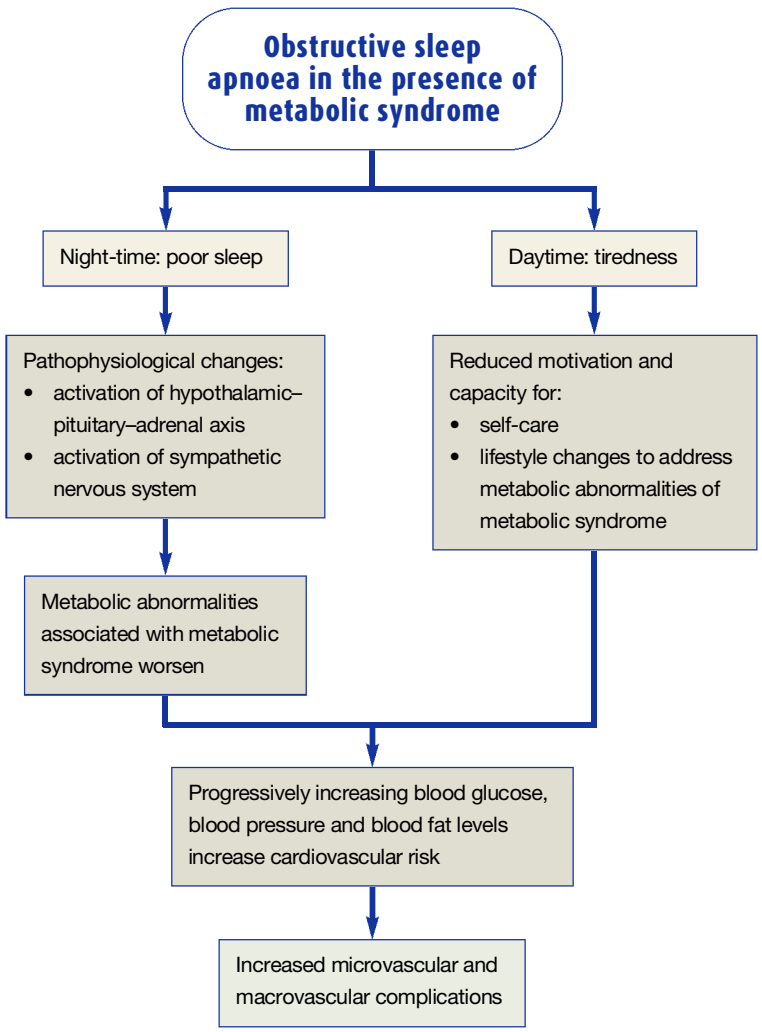
continued

Wendy's cardiovascular risk is considerable (10% over the next five years) because of her age, hypertension and dyslipidaemia, and her prediabetes would increase this further.

Irrespective of her other risk factors, Wendy might be wise to take an antihypertensive medication (such as an ACE inhibitor) and, when her hypertension is controlled, an antithrombotic medication (such as low dose aspirin). If prescribing aspirin, some doctors would consider testing for *Helicobacter pylori* and eradicating it if present to reduce the future risk of gastrointestinal haemorrhage.

Given Wendy's hypertension (blood pressure, 152/96 mmHg) and dyslipidaemia (total cholesterol, 6.2 mmol/L; HDL cholesterol, 0.8 mmol/L), she is eligible for a PBS subsidy for cholesterol lowering therapy (statins) according to the criteria introduced in October 2006 for patients with hypertension (i.e. total cholesterol >6.5 mmol/L or total cholesterol >5.5 mmol/L and HDL cholesterol <1 mmol/L).[7]

Obstructive sleep apnoea and cardiovascular risk



It is not current practice to prescribe the full 'type 2 tablet' (metformin, ACE inhibitor, statin and aspirin)[8] for people like Wendy with the metabolic syndrome. Three of the components seem appropriate in Wendy's case – ACE inhibitor, aspirin and a statin; metformin may be indicated in the near future.

Y – why me?

Wendy might be asking you or herself why she has the metabolic syndrome. In Australia, the 'f' words account for most cases of metabolic syndrome and its components:

- forty – age over 40 years
- family – history of type 2 diabetes in a first degree relative (father, mother, sibling, offspring)
- fat – overweight/waist.

When asked, most doctors will identify fatness as a major risk factor, and possibly also family; however, we may struggle to identify age as another major risk factor. This may lead us to feel that those with diabetes are responsible for their own diabetes, a possible extreme view being 'they are lazy gluttons who are suffering from their self-indulgence'. It is true that age and genes are fixed and that fatness is, to some degree, under the individual's control but most of the 60% of our population who are fat do not get diabetes, and many people who do get diabetes are no fatter than the rest of us. We should focus on the modifiable risk factor (fatness) sooner rather than later, and avoid 'blaming the victim' for his or her problem.

The Nurses' Health Study followed a cohort of women for 14 years and monitored the development of components of the metabolic syndrome such as diabetes.[9] As for many other chronic diseases, age emerged as a major risk factor with diabetes risk increasing 10-fold between the ages of 20 and 60 years (Figure 2). Not surprisingly genetic inheritance was also important, with the risk increasing two-fold with one first degree relative (mother, father, sibling, offspring) and threefold

with two or more who had developed diabetes. On top of these risk factors, increasing overweight further independently multiplied diabetes risk.

Wendy has two 'f' words (forty and fat) and is quite likely to have a family history as well. On questioning, Wendy says that her mother and her sister have type 2 diabetes, her father had gout and her sister's daughter developed gestational diabetes after ovulation induction because of infertility associated with polycystic ovary syndrome (another aspect of the metabolic syndrome).

Z – sleep apnoea

Wendy's sleep problems

Wendy presents again, this time concerned about her sleeping. Her husband John is with her and tells you that he has moved into another bedroom because Wendy's loud snoring is disturbing his sleep. Wendy is looking embarrassed and slightly annoyed. She says she can't help it and she doesn't think she sleeps well anyway. 'Even when I wake up, I'm tired. I'm so tired during the day that I drop off all the time. Once I went to sleep waiting for a traffic light to change and was woken up by the other cars beeping me!'

Sleep apnoea and lack of zzz's

Obstructive sleep apnoea is often associated with the other cardiodiab factors and can predispose to increasing weight and waist and to worsening of the metabolic abnormalities associated with syndrome X. Night-time sleep disturbance can worsen the metabolic profile and daytime sleepiness reduces motivation and capacity for lifestyle change (see the flowchart on page 34).

Obstructive sleep apnoea can cause considerable disturbance to sleep, with activation of both the hypothalamic–pituitary–adrenal axis and the sympathetic response. Disturbed sleep can lead to daytime sleepiness, which does not help motivation to participate in active social activities or to adhere to a lifestyle prescription of eating less and walking more.[5] The combination of nocturnal hormonal disturbance and daytime lethargy aggravates any innate tendency to weight/waist gain and to the associated adverse risk factor profile.

Neck circumference (more than 42 cm) or a high Epworth sleepiness score identifies patients who might warrant further investigation, such as a formal assessment at a sleep study centre. The Epworth sleepiness scale was developed to measure daytime sleepiness and has been shown to significantly distinguish normal subjects from patients with various conditions including obstructive sleep apnoea, narcolepsy and idiopathic hypersomnia.[10] An example of the self-administered questionnaire is given in the box on this page.

Wendy is very likely to have obstructive sleep apnoea, which might respond to continuous positive airway pressure (CPAP). However, she might have a different or additional problem, which could be addressed by a chin splint, ENT surgery or other procedure.

If CPAP is indicated and is successful, the results can be dramatic, including weight and waist loss, decreases in blood glucose, blood pressure and blood fat levels, and increases in physical and mental functioning and wellbeing.

Conclusion

Early recognition of the risk factors for cardiovascular disease and diabetes enables control of the progression of these factors by lifestyle changes (weight loss and increased physical activity), medication or both. The mnemonic WXYZ provides a useful approach when considering these cardiodiab risks. W represents

Epworth sleepiness scale*

How likely are you to doze off or fall asleep in the situations described below, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you haven't done some of these things recently, try to work out how they would affect you.

Use the following scale to choose the most appropriate number for each situation:

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Situation	Chance of dozing
Sitting and reading	……..
Watching TV	……..
Sitting inactive in a public place (e.g. a theatre or meeting)	……..
As a passenger in a car for an hour without a break	……..
Lying down to rest in the afternoon when circumstances permit	……..
Sitting and talking to someone	……..
Sitting quietly after a lunch without consuming alcohol	……..
In a car, while stopped for a few minutes in traffic	……..

Score:

0 to 10	Normal range
10 to 12	Borderline
12 to 24	Abnormal

* The Epworth sleepiness scale was developed by Dr Murray Johns, Melbourne (Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991; 14: 540-545).

overweight/waist; X, syndrome X, or the metabolic syndrome; Y, why a patient develops X; and Z, the lack of sleep (zzz's) due to the obstructive sleep apnoea that often occurs with the other cardiodiab risk factors and may worsen both the W and X factors. MT

References

1. Australian Institute of Health and Welfare (AIHW). Australia's Health 2006. Canberra: AIHW. AIHW Cat No. AUS 73; 2006.
2. Motluk A. The 10 roads to fatsville. New Sci 2006 (3 November); 2576: 34-38 (based on Keith SW, Redden DT, Katzmarzyk PT, et al. Putative contributors to the secular increase in obesity: exploring the roads less travelled. Int J Obesity 2006; 30: 1585-1594).
3. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand. Position statement on lipid management – 2005. Heart Lung Circ 2005; 14: 275-291.
4. Knowler WC, Barrett-Connor E, Fowler SE, et al; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346: 393-403.
5. Carapetis M, Phillips P. Eat less, walk more. Enjoyable eating for type 2 diabetes. Aust Fam Physician 2002; 31: 1065-1071.
6. DREAM Trial Investigators; Gerstein HC, Yusuf S, Bosch J, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 2006; 368: 1096-1105.
7. PBS-Eligibility criteria for lipid lowering drugs fact sheet. Australian Government Department of Health and Ageing. September 2006. www.health.gov.au/internet/wcms/Publishing.nsf/Content/lipid_eligibilitycriteria.htm (accessed January 2007).
8. Phillips P, Braddon J. The type 2 tablet. Evidence based medication for type 2 diabetes. Aust Fam Physician 2003; 32: 431-436.
9. Colditz G, Willet WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med 1995; 122: 481-486.
10. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991; 14: 540-545.

DECLARATION OF INTEREST: Dr Phillips has received research and travel grants, acted on advisory boards and been involved with clinical trials and seminars sponsored by a range of pharmaceutical companies. He does not think these associations have influenced the content of this article.

Focus on Avandamet

PAT PHILLIPS MB BS, MA(Oxon), FRACP, MRACMA, GradDipHealthEcon(UNE)

ANDREW LOWY BMedSc, MB BS, FRACP

Avandamet – a fixed dose combination therapy of rosiglitazone and metformin – is now available for treating patients with type 2 diabetes.

Type 2 diabetes accounts for over 90% of diabetes in Australia. Although glycaemic control can be improved with a healthy diet and physical activity, many patients find long term adherence to these lifestyle measures difficult. Oral hypoglycaemic medications and then insulin are usually required. In the UK Prospective Diabetes Study (UKPDS), most participants progressed steadily from lifestyle modification alone to tablets and then to insulin in order to keep their glycosylated haemoglobin (A_{1c}) on target; after nine years, most were taking oral hypoglycaemic medications and/or insulin (Figure 1).[1] Most patients with type 2 diabetes require multiple medications to keep their ABCss on target (the ABCss of diabetes care are listed in the Table). These medications are over and above those for coexisting medical conditions, such as arthritis, reflux, depression and insomnia.

Fixed dose combination therapy, in which pharmacological agents are coformulated in a single tablet or capsule, is increasingly being used to enhance patient adherence and gain the benefits of different medications. Common examples include the coformulation of either an ACE inhibitor or angiotensin receptor antagonist with a thiazide diuretic for the treatment of hypertension.

For glycaemic control in type 2 diabetes, a combination of metformin and glibenclamide (Glucovance) is already available. This article focuses on the new coformulation of metformin and rosiglitazone, which is marketed as Avandamet.

Metformin and glitazones

Metformin is a biguanide antihyperglycaemic agent. It has been used since the late 1950s and remains first line pharmacotherapy when glycaemic control is not achieved with lifestyle modification alone. Metformin lowers fasting and postprandial blood glucose by decreasing hepatic gluconeogenesis and glucose output.

Rosiglitazone and pioglitazone are thiazolidinediones ('glitazones'), which reduce insulin resistance in skeletal muscle, liver and adipose tissue. Glitazones stimulate an intracellular (nuclear) protein (the peroxisome proliferator activator receptor gamma) and reduce levels of circulating free fatty acids that otherwise increase insulin resistance in type 2 diabetes. By reducing insulin resistance, glitazones increase tissue response to insulin and increase glucose utilisation and fatty acid uptake.

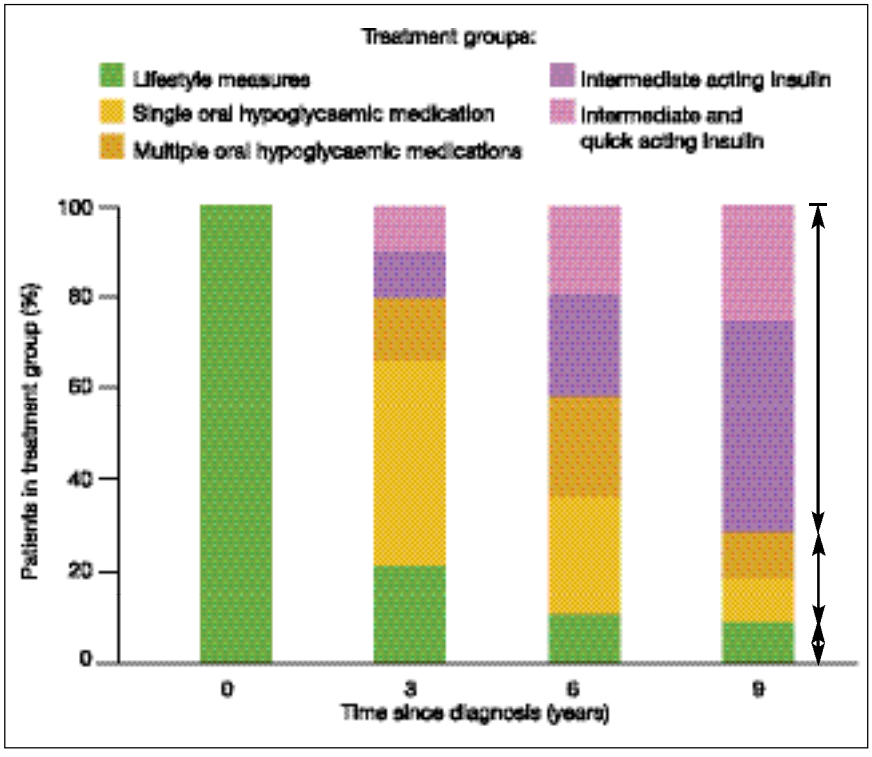


Figure 1. In UKPDS, a progressive increase in requirements for medication (oral hypoglycaemics and insulin) was demonstrated in the majority of patients with type 2 diabetes in order to maintain A_{1c} below 7%.[1] Arrows on the right-hand side of the graph indicate the proportion of patients using insulin, oral hypoglycaemic medications and lifestyle measures at nine years.

Dr Phillips is Senior Director, Endocrinology, North Western Adelaide Health Service, The Queen Elizabeth Hospital, Woodville, SA.

Dr Lowy is Endocrinologist and Clinical Pharmacologist, St Vincent's Clinic and Diabetes Centre, St Vincent's Hospital, Sydney, and Visiting Endocrinologist, The Sutherland Hospital, Caringbah, NSW.

Metformin and glitazones can be considered 'insulin sensitisers' (as opposed to sulfonylureas and glitinides, which stimulate insulin release from pancreatic beta cells). Their actions are shown in Figure 2.

At present, the recommended sequence for prescribing oral hypoglycaemic medication is to start with metformin (unless contraindicated by renal impairment, risk of hypoxia or side effects) and then to add a sulfonylurea (unless contraindicated by risk of hypoglycaemia or side effects) and then to consider triple therapy by adding rosiglitazone.[2] (Pioglitazone is not currently authorised for use in triple therapy.) However, if sulfonylureas or metformin cannot be used then either of the glitazones can be added as double therapy.[2]

Avandamet

Avandamet is approved in the USA, European Union and now Australia for use in patients with type 2 diabetes that is inadequately controlled by metformin in addition to a healthy lifestyle. However, the glitazones are only available on the PBS (authority required) as double therapy with metformin when:

- sulfonylureas are contraindicated
- there is documented intolerance to sulfonylureas, or
- use of sulfonylureas is not appropriate in the opinion of the prescriber.

Avandamet is also available on the PBS (authority required) for use in triple combination therapy with a sulfonylurea for patients with type 2 diabetes.

A fixed dose combination of rosiglitazone and metformin has been shown to be bioequivalent to the two separate components given concomitantly.[3] The fixed dose and free combination schedules were equally well tolerated in clinical trials, with the likelihood of adverse effects to metformin or rosiglitazone being similar in both groups. A retrospective analysis suggested that adherence is greater for the fixed dose combination than for the two separate medications.[4]

Table. The ABCss of diabetes care

Risk factor	Target
A_{1c} (glycosylated haemoglobin)	<7%
Blood pressure	<130/80 mmHg (<125/75 mmHg if proteinuria >1 g/day exists)
Cholesterol	<4 mmol/L (corresponding to LDL cholesterol <2.5 mmol/L)
smoking	Cessation
salicylates	Aspirin 75 to 150 mg/day

Starting treatment

Avandamet is available in four formulations of rosiglitazone/metformin: 2/500, 4/500, 2/1000 and 4/1000 (mg/mg). For patients who are already receiving metformin (with or without a sulfonylurea), Avandamet can be introduced at the same daily dose of metformin (up to 2000 mg), with up to 8 mg of rosiglitazone given in the same divided doses prescribed for metformin alone.

For patients who are already receiving rosiglitazone with a sulfonylurea, Avandamet can be introduced at the same daily dose of rosiglitazone, plus metformin 1000 mg/day (usually in two divided doses with the main meals). The dose of metformin may be increased further by changing the formulation of Avandamet (e.g. from 4/500 twice daily to 4/1000 twice daily). The dose of the rosiglitazone component of Avandamet could be doubled (e.g. from 2/1000 twice daily to 4/1000 twice daily) after six to eight weeks if significant improvement in glycaemic control is not achieved.

To switch from a schedule of rosiglitazone and metformin as separate tablets, the nearest daily dose of Avandamet should be used (up to a maximum of rosiglitazone 8 mg, metformin 2000 mg).

Precautions, contraindications and adverse reactions

The precautions and contraindications for Avandamet are the same as for the

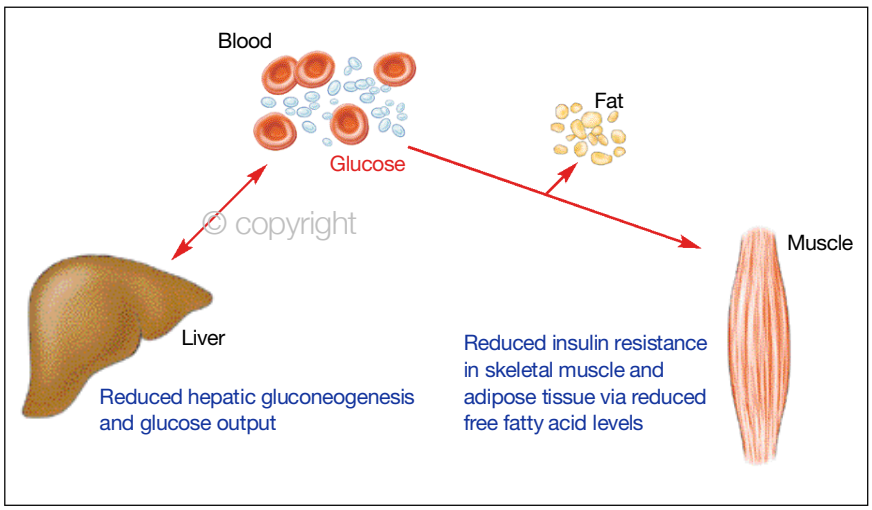


Figure 2. Actions of metformin and a glitazone such as rosiglitazone.

separate components. These include:

- metformin – renal impairment, risk of hypoxia
- rosiglitazone – congestive cardiac failure (especially New York Heart Association Class III and IV), active liver disease.

Avandamet should not be used in pregnancy, lactation or type 1 diabetes. It can be used in elderly patients, but they should be monitored regularly for adverse effects.

The adverse event profile for Avandamet is also similar to that of its components. For example:

- metformin – gastrointestinal upset
- rosiglitazone – fluid retention, possible exacerbation of heart failure and weight gain, although the latter may be less likely when coadministered with metformin.

Full lists of precautions, contraindications and potential adverse effects can be found in the product information leaflets.

Summary

- Avandamet combines two insulin sensitisers, rosiglitazone and metformin, in clinically appropriate dosage combinations.
- The doses of rosiglitazone and metformin in the combined preparation are bioequivalent to the same medication doses given separately at the same time.
- Adherence may be improved by using the combined preparation rather than the two medications separately.
- The same indications, contraindications and precautions apply to the combined preparation as to the two separate components. MT

References

1. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA 1999; 281: 2005-2012.
2. Harris P, Joyner B, Mann L, Phillips P, Snowden T, Webster C. Diabetes management in general practice 2006/7. 12th ed. Canberra: Diabetes Australia and RACGP; 2006.
3. Wellington K. Rosiglitazone/metformin. Drugs 2005; 65: 1581-1592.
4. Vanderpoel DR, Hussein MA, Watson-Heidari T, Perry A. Adherence to a fixed-dose combination of rosiglitazone maleate/metformin hydrochloride in subjects with type 2 diabetes mellitus: a retrospective database analysis. Clin Ther 2004; 26: 2066-2075.

DECLARATION OF INTEREST: Dr Phillips and Dr Lowy have received research and travel grants, acted on advisory boards and been involved with clinical trials and seminars sponsored by a range of pharmaceutical companies. They do not think these associations have influenced the content of this article.