The type 2 tablet

Evidence based medication for type 2 diabetes

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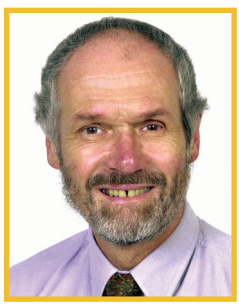
BACKGROUND Diabesity - the association of type 2 diabetes and obesity – is a major public health problem worldwide and is increasing dramatically in Australia. The abnormalities associated with diabetes, the 'type 2 diabetes syndrome' are cardiovascular risk factors and increased cardiovascular events. The full implications of type 2 diabetes syndrome may not be fully appreciated and opportunities for effective interventions may be being missed.
OBJECTIVE This article aims to review the cardiovascular risk associated with type 2 diabetes syndrome and to summarise the evidence supporting wider use of medications that target the different components of type 2 diabetes syndrome.
DISCUSSION The cardiovascular benefits of metformin, the ACE inhibitors, aspirin and the statins have been shown in prospective controlled trials and the beneficial effects of these medications are additive. There is a case for these medications to be considered for those with type 2 diabetes (and an opportunity for the pharmaceutical industry to provide the 'type 2 tablet' containing all four medications).



The rapidly spreading worldwide epidemic of 'diabesity' and the 'type 2 diabetes syndrome' (otherwise known as syndrome X, the metabolic syndrome, the insulin resistance syndrome, the deadly quartet), is associated with major risk factors for vascular disease. Over the past 20 years prevalence of the syndrome has increased dramatically in Australia (*Figure 1*) so that we now rank second to the United States among developed countries.

The type 2 diabetes syndrome is associated with high risk of vascular events. For example, people with diabetes have the same risk of a heart attack as those without diabetes who have a known history[1] (*Figure 2*). More than 70% of people with diabetes die from a cardiovascular event and many others suffer considerable short and long term cardiovascular morbidity. The microvascular complications make type 2

Case history

John is 60 years of age and has had type 2 diabetes for 15 years. He is overweight (BMI: 27.2 kg/m^2), inactive, a nonsmoker and has no past or family history of cardiovascular disease. He has laser treated retinopathy and microalbuminuria. His BP is 140/70, total cholesterol 5.0 mmol/L, HbA1c 8%.His medication includes maximum doses of two oral hypoglycaemic agents, a thiazide diuretic, beta blocker and naproxen.

What is his annual risk of a cardiovascular event?

John has four fixed risk factors (diabetes, male sex, one decade after the age of 50 years and microalbuminuria) and three modifiable risk factors (systolic BP 10 mm, total cholesterol 1 mmol/L above target). His annual risk of a cardiovascular event is 0.25x2[6]=16%, ie. a five year risk of 68% (1–0.84[5])*.

How could his risk be reduced?

John could reduce his risk by walking 150 minutes per week, and starting aspirin, a statin and an ACE.** These four risk reducers would reduce his annual risk of a cardiovascular event to 16%x0.754=16%x0.3=5%, ie. a 10 year risk of 23% (1–0.95[5])†

* Each year he has an 84% (0.84) chance of survival to the end of the year (100–16%)
** He should also stop his NSAID which may be contributing to hypertension and put him at risk of the 'triple whammy'
† Each year he has a 95% (0.95) chance of survival to the end of the year (100–5)%.

diabetes a major contributor to end stage renal failure (exceeding the contribution from type 1 diabetes), preventable blindness and loss of limbs.

The individual components of the type 2 diabetes syndrome contribute to both macro and microvascular complications but to different degrees. Microvascular disease is predominantly associated with hyperglycaemia and hypertension and macrovascular disease with hypertension, dyslipidaemia and cigarette smoking.

Over the past 10 years management has moved from a focus on 'sugar' to a more comprehensive approach. Healthy lifestyle is still fundamental with major messages being 'eat less, walk more', and 'QUIT'. Medications now target all components of the syndrome and diabetes monitoring has expanded to include regular checks on lifestyle, medication, risk factors and complications.

In clinical practice the syndrome is recognised when diabetes is diagnosed and the patient is seen to be at risk of microvascular complications. This prompts the review of lifestyle, promotion of healthy lifestyle, activity and weight, and where necessary, medication to control blood glucose. However, the full implications of type 2 diabetes syndrome, particularly for cardiovascular risk, may not be appreciated and opportunities to improve short and long term health outcomes may be missed.

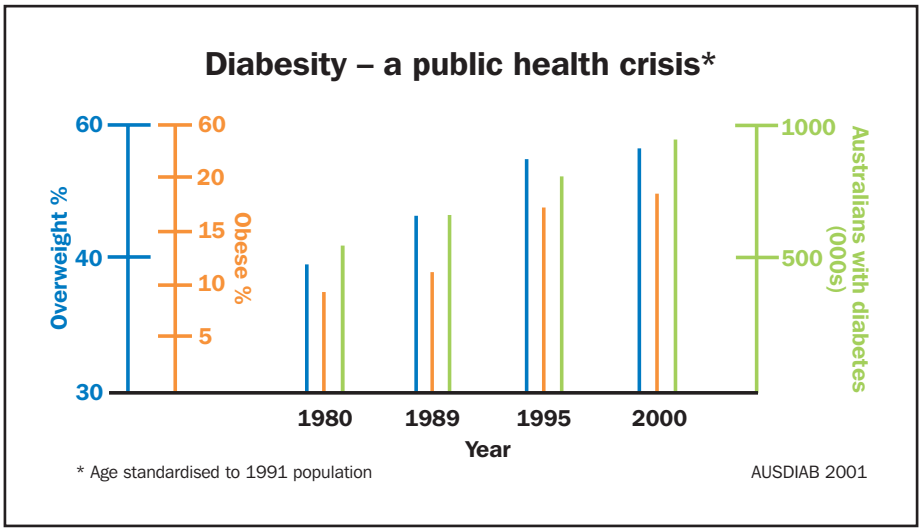


Figure 1. Diabesity epidemic

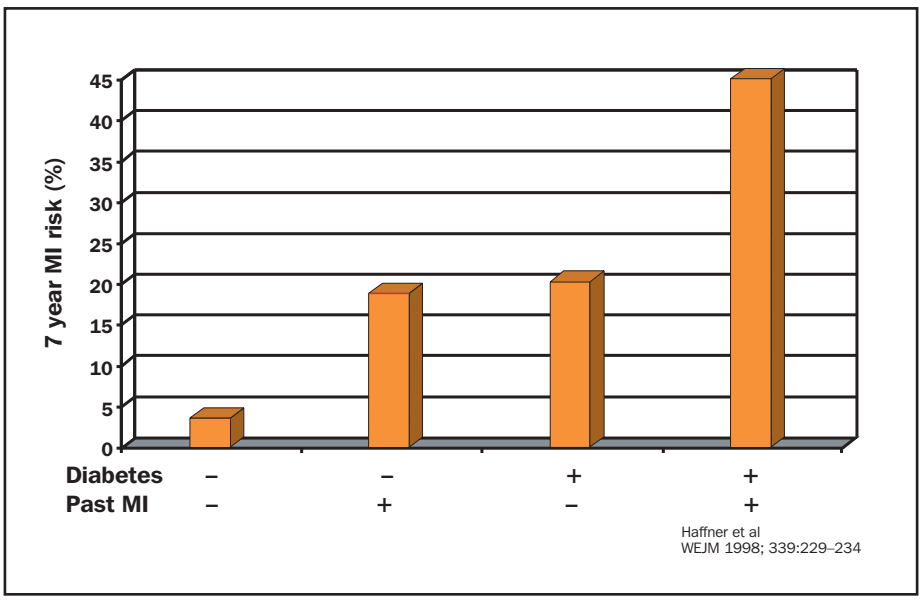


Figure 2. MI risk

The 'type 2 tablet'

There is now evidence that medications treating all components of the type 2 syndrome reduce diabetic complications. The ideal 'type 2 tablet' is not yet available but would include four medications (*Figure 3*) that are currently under utilised in Australian clinical practice.

Metformin

When medication is required for glycaemic control, metformin is generally considered the oral hypoglycaemic of first choice[2] but its special benefits may not be fully appreciated. Metformin is the only hypoglycaemic agent that was shown to reduce macrovascular complications in outcome trials. In the United Kingdom Prospective Diabetes Study,[3] compared with conventional treatment, intensive treatment of overweight patients with metformin reduced the risk of macrovascular events by 30% (*Figure 4*).[3]

Moreover, metformin targets central obesity which is the hallmark of the type 2 syndrome. Most studies show a weight loss of 2–3 kg in the first six months[4] whereas other oral hypoglycaemic agents are weight neutral (eg. acarbose) or are associated with increased weight

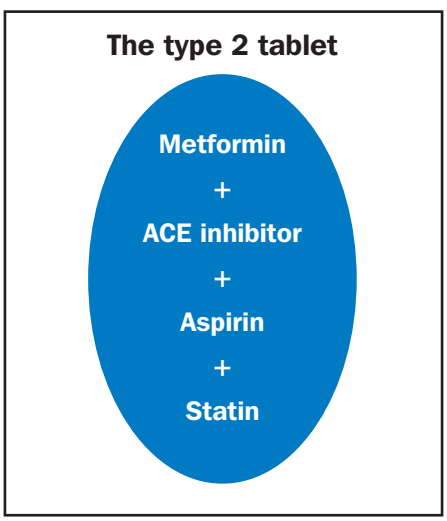


Figure 3. Type 2 tablet

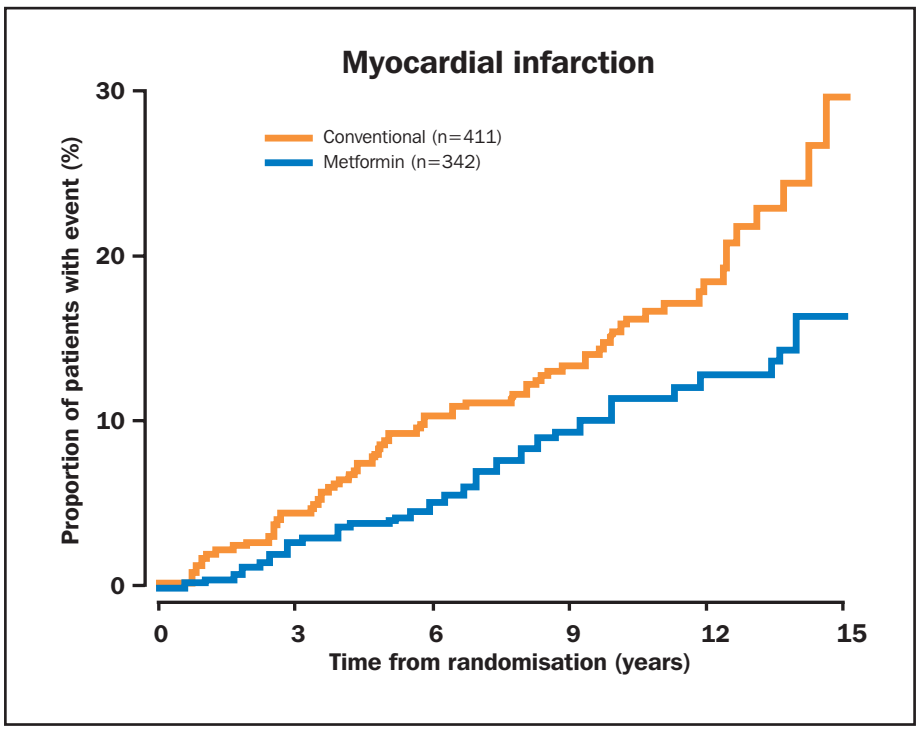


Figure 4. Metformin and MI (UKPDS)

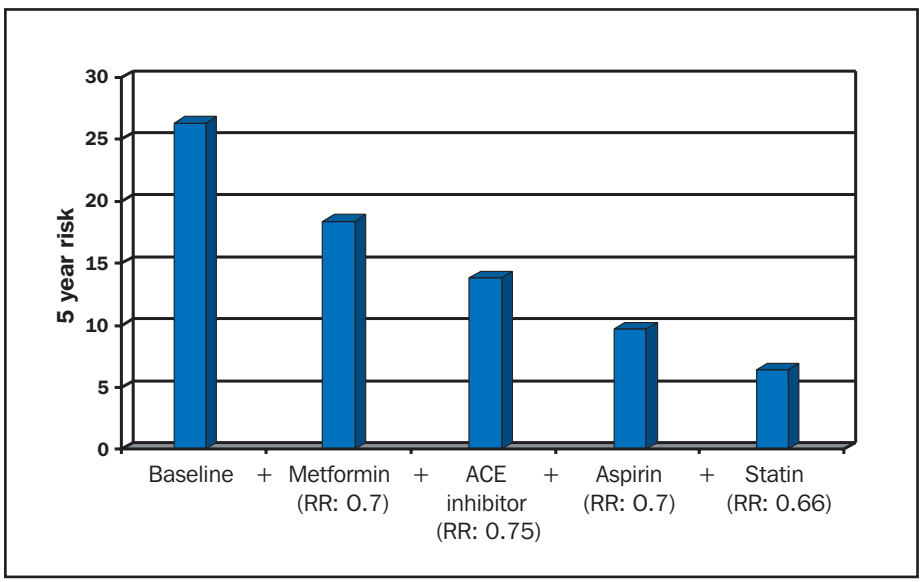


Figure 5. Totting up the tablets

(eg. sulphonylureas, glitazones). Metformin also improves the lipid profile with triglyceride decreases of 10–50%.[5] Decreases in LDL and total cholesterol and a slight increase in the HDL cholesterol have also been observed.[5,6]

Finally, metformin may also reduce the prothrombotic tendency by reducing platelet density and aggregability and increasing fibrinolytic activity.[7]

Angiotensin converting enzyme (ACE) inhibitors

The HOPE study included patients with diabetes who were 55 years of age or older and had at least one other cardiovascular risk factor (hypertension, elevated total cholesterol, low HDL cholesterol, cigarette smoking or documented microalbuminuria).[8,9] After a follow up of 4.5 years, ramipril significantly decreased the risk of cardiovascular events by 25% when adjustments were made for changes in systolic and diastolic blood pressure. It has been suggested that the cardiovascular benefits of ramipril over and above blood pressure reduction may be due to the protective effect of ACE inhibitors on the arterial wall.[9] Angiotensin converting enzyme inhibitors also reduce the onset and progression of diabetic nephropathy (eg. by 24% in the HOPE study).[9,10] The angiotensin 2 receptor antagonists have also been shown to reduce the progression of microalbuminuria, macroalbuminuria and end stage renal failure in patients with type 2 diabetes and hypertension.

The HOPE study makes a case for an ACE inhibitor for the vast majority of Australian patients with type 2 diabetes (because most will fulfill the HOPE criteria of being over the age of 55 years and have at least one other cardiovascular risk factor).

Statins

The HMG CoA reductase inhibitors ('statins') have been shown to reduce the incidence of cardiovascular disease in a number of secondary prevention studies.[11–13] More recently the Heart Protection Study (HPS) has shown the benefit of a statin (simvastatin 40 mg/day) as primary prevention.[14] Nearly 6000 patients with diabetes aged 40–80 years of age and with a base line total cholesterol of >3.5 mmol/L were randomised to simvastatin 40 mg at night or matching placebo, for five years. Approximately 4000 of the 6000 patients with diabetes had no pre-existing coronary heart disease. The average 1 mmol/L decrease in total cholesterol in this group was associated with a 34% risk reduction for cardiovascular events in those who took medication as prescribed. Treating 21 patients for 5.3 years prevented one cardiovascular event.[14]

The HPS suggests that most Australians with type 2 diabetes could significantly reduce their risk of cardiovascular events by taking a statin (since

Table 1. Cardiovascular risk factors

Fixed	Modifiable
Male sex	Lifestyle
Each decade after 50 years of age	Smoking habit
Type 2 diabetes	Inactivity
Previous cardiovascular event	Obesity
Family history of cardiovascular event before 60 years of age	**Medical**
	Each 10 mmHg systolic BP above 130
	Each mmol/L total cholesterol above 4
	Not being on an ACE inhibitor or low dose aspirin if high risk*

* Someone with type 2 diabetes and one or more other risk factor(s)

Table 2. Rating and reducing cardiovascular risk

The baseline annual risk of a cardiovascular event with no risk factors is 0.25% and risk calculation is fairly straightforward.

Epidemiologically risk roughly doubles with each risk factor but the effect of interventions is less; roughly decreasing risk by 25% per risk factor*. For example, epidemiologically a decrease of 1 mmol/L of total cholesterol is associated with the halving of risk but only reduced by 25% if the same decrease is induced by medical intervention.

* Some risk factors and interventions are associated with larger or smaller effects but doubling for each risk factor and 25% reduction for each intervention seem reasonable 'guesstimates'

most fulfill the entry criteria for being 40–80 years of age and having a total cholesterol >3.5 mmol/L).

Aspirin

Meta analyses of large trials involving patients with diabetes support the use of low dose aspirin as secondary prevention if no contraindications exist.[15–16]

In primary prevention, the US Physicians Health study showed that in male practitioners with diabetes, aspirin

Spot check

There is evidence that all people with diabetes aged 55-80 years should be offered an ACE inhibitor, a statin and aspirin if there are no contraindications, they have at least one other cardiovascular risk factor and their total cholesterol exceeds 3.5 mmol/L. Metformin should be prescribed if a hypoglycaemic agent is required. Most will, therefore, be eligible for the 'type 2 tablet'.

significantly reduced the five year risk of myocardial infarction from 10.0% (placebo) to 4.0% (aspirin).[17] The HOT study showed that aspirin (75 mg/day) reduced the risk of myocardial infarction in patients with diabetes and hypertension.[18]

The American Diabetes Association recommends the routine use of aspirin for virtually all patients with type 2 diabetes unless there are specific contraindications such as allergy, active peptic ulcer, bleeding diathesis or active liver disease.[19]

The Australian Therapeutic Guidelines: Endocrinology, recommend that because of a 20-fold increased risk of cardiovascular disease, patients with diabetes and microalbuminuria should receive aspirin even in the absence of clinical large vessel disease. These guidelines also recommend that because all people with diabetes over 50 years of age have a cardiovascular risk equivalent to a person with coronary heart disease, they should receive aspirin.[20]

Totting up the tablets

In general, risk reductions are multiplicative – tackling two different risk factors, each of which reduces risk by 30% (RR: 0.7) reduces overall risk by approximately 50% (RR: 0.7x0.7=0.49).

Three examples

The HPS showed that the benefits of simvastatin were independent of and in addition to concomitant therapy with ACE inhibitors or aspirin.[14] The UKPDS showed that the benefits of controlling blood glucose and blood pressure were independent and additive. The HOPE study showed that the benefit of ramipril was independent of effects on blood pressure.

'Totting up the tablets' the potential benefits of the 'type 2 tablet' are considerable with a relative risk reduction of approximately 75% (*Figure 5*) absolute five year risk reduction of 20% and the need to treat five patients for five years to prevent one cardiovascular event. Cardiovascular risk factors are shown in *Table 1*. *Table 2* shows methods of calculating cardiovascular risks.

In some cases there will be an absolute or relative contraindication or a patient will not be willing, able to afford or to tolerate one or more components. However, the whole 'type 2 tablet' should be considered for all patients with type 2 diabetes.

Type 2 tablet targets

Patients can understand the 'ABCs of diabetes care' and the idea of targets (*Table 3*). Recent trials have shown that generally lower is better (UKPDS,[21] HOT,[18] HPS,[14]) and there is a general consensus on the absolute target values (*Table 3*).

To achieve these targets, lifestyle change and multiple medications may be necessary. Even if patients are willing and able to make the changes and adhere to

Table 3. The ABCs of diabetes care

Risk factor	Target
HbA1c	<7%
Blood pressure mmHg*	<130/85
Cholesterol	<4mmol/L**
Salicylates	aspirin 75–150 mg/day[22]
Smoking	QUIT

* <125/75 mmHg if proteinuria exists
** Corresponding to LDL cholesterol <2.5 mmol/L

the medication schedule, achieving ideal targets may not be possible because of side effects. Usually an acceptable compromise between ideal and achievable can be reached. The situation can be reviewed later when new individualised targets can be set. Actively involving patients in setting and monitoring their ABCs has been shown to improve risk factor control. Patients should be encouraged to 'know their numbers'. Monitors for blood glucose and blood pressure are affordable and can provide doctor and patient with a more realistic picture of risk factor control than the occasional measurement in the surgery. Remember any progress toward targets is beneficial even if targets are not met.

Lifestyle targets, as well as medical risk factor targets, should be discussed and agreed. Most patients can appreciate the potential value of regularly recording and reviewing lifestyle change and many do the measurements already. Keeping a lifestyle diary need not be a great burden (weight/waist, food intake and activity level, eg. with a pedometer or by duration). Reviewing the medical and lifestyle diaries provides an opportunity to identify and discuss successes and problems. Specialist allied health professionals (diabetes nurse, dietitian, physiotherapist, podiatrist) or others involved in the extensive healthy lifestyle industry may be able to help.

Type 2 tablet troubles – 'dangerous drugs and diabetes'[23]

The components of the type 2 tablet are no exception to the adage that drugs can be dangerous as well as therapeutic. Sometimes there are contraindications, side effects or drug interactions that prevent their use (*Table 4*).

The situation may change with time, metformin may have been appropriate 10 years ago when it was started but has now become dangerous as renal function has deteriorated. A new medication may be prescribed, the risk of a drug interaction overlooked and an avoidable disaster occurs (eg. acute renal failure when an

Table 4. Type 2 tablet troubles

Tablet	Contraindications	Major side effects	Common major drug interactions
Metformin	• Severe renal impairment • Severe liver impairment • Hypoxic risk* • Pregnancy	• Gastrointestinal (nausea, diarrhoea, abdominal pain) • Lactic acidosis	• Drugs causing renal impairment
ACE inhibitors	• PHx angio oedema with ACE inhibitor • Bilateral renal artery stenosis • Severe renovascular disease	• Cough • Renal impairment • Hyperkalaemia • Angio oedema	• 'The triple whammy', diuretic, NSAID/COX2 inhibitor and ACE inhibitor
Statins	• Pregnancy • Active liver disease	• Myalgia • Myopathy • Hepatitis	• Cytochrome 450 inducers/inhibitors** • Gemfibrozil • Warfarin
Aspirin	• Active peptic ulceration • Allergy • Bleeding disorders • Active liver disease	• GI discomfort • GI bleeding • Haemorrhagic stroke	• Anticoagulant/platelet therapy • Other NSAIDs

* Eg. Previous hospital admission for cardiac or respiratory failure
** CYP3A4 inhibitors (eg. erythromycin, clarithromycin, ketoconazole, grapefruit juice, diltiazem, verapamil, some antidepressants) may particularly interact with simvastatin and atorvastatin. CYP2C9 inhibitors (eg. some SSRIs) may particularly interact with fluvastatin

NSAID is added to an ACE inhibitor, rhabdomyolysis when a fibrate is added to a statin). However, the major trouble patients usually have with the type 2 tablet is adherence which is also the commonest cause of drug failure. After all there is usually no symptomatic benefit from therapy, medications are expensive, a nuisance and easily forgotten. Those of us who take (or are supposed to take) regular medication know how easy it is to miss a tablet or to be unsure whether it was taken or not. Use combined and long acting once daily formulations where possible and limit medication taking occasions (eg. to breakfast and with the evening meal). Monitor adherence. Ask questions which encourage honesty, eg. 'How many times a week do you think you've missed your medication?' Rather than: 'You don't miss any medications do you?' Stress the benefits and that, 'the tablets can only work if you take them'. Note when a repeat prescription is due. Consider a home medication review (eligible for a specific Medicare rebate) by a pharmacist who can visit the patient at home, review the suitability of the medication, check the potential problems and discuss self management techniques (eg. blood glucose monitoring, insulin administration). The pharmacist's report may identify opportunities to stop unnecessary or potentially dangerous medication and to simplify schedules. Follow up visits can be arranged if needed.

Conflict of interest: none declared.

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