

Cardiovascular Catalyst:

accelerate your understanding of
cardiovascular risk factors and
their management

Presented by the Australian Atherosclerosis Society and the
High Blood Pressure Research Council of Australia, Sydney, 2014



Hypertension, lipids and diabetes

Garry Jennings and Richard O'Brien

Management of resistant hypertension

George Mangos and Karin Jandeleit-Dahm

Treatment options in type 2 diabetes

Neale Cohen

Managing type 2 diabetes in patients with comorbid renal disease

Merlin Thomas

Familial hypercholesterolaemia

What is it? Why does it matter? What can we do?

Gerald Watts and David Sullivan

Treatment inertia in the management of hypertension

Chris Reid and Len Arnolda

What will be the catalyst for achieving LDL goals?

Stephen Nicholls and Anthony Pisaniello

Retinopathy

Anthony Keech and Stephen Ong

Absolute risk and the individual with high cholesterol and/or high blood pressure

Mark Nelson and Rob Grenfell

(Mis)perceptions in dyslipidaemia

Alberto Zambon

Abbott provided an unrestricted educational grant and had no influence on the content.

Want to know more about any of the presentations? Video recordings of the complete talks are available at www.athero.org.au. From the home page, simply click on Cardiovascular Catalyst 2014 and then select the relevant presentation.

Hypertension, lipids and diabetes

Professor Garry Jennings¹ and Associate Professor Richard O'Brien²

¹Director, Baker IDI Heart and Diabetes Institute, Melbourne

²Clinical Dean, Austin Clinical School, University of Melbourne

Management of a young to middle aged patient with 'minor' elevations of cardiovascular risk factors needs to take into account both short-term interventions and long-term risks of morbidity and mortality. Using a hypothetical patient at the ages of 36, 46 and 56 years, Garry Jennings and Richard O'Brien illustrated the important issues to consider.

At 36 years

JG is a non-smoker who works in IT developing games. He is 178 cm tall, weighs 83 kg, has a waist circumference of 100 cm, BP 145/86 mmHg and heart rate 84/min. A physical examination is otherwise normal. His fasting cholesterol is 6.4 mmol/L, HDL 1.0 mmol/L, triglycerides 3.2 mmol/L and glucose 5.2 mmol/L. Using standard Australian risk charts, even with his risk factors, the 5 year cardiovascular risk for a 36 year old is likely to be low (5-9%). However, it should be noted that waist circumference is not included in standard risk charts and allowance should also be made for issues such as ethnicity and family history.

Initial management involves modification of risk factors – increased physical activity (including regular periods of standing for persons with sedentary jobs), diet and reduced sodium intake (checking salt content of processed foods, including bread and cereals, which provide 85% of the salt in a typical diet). Effective lifestyle changes at this point are important, as lifestyle modification later in life has lesser long-term effect.

Lifetime risk calculators are now available on-line and this calculation shows JG to have a 50% lifetime risk of cardiovascular disease (up to age 80). This would be reduced to 5% if his risk factors were fixed and this difference may be a strong motivator to act now.

At 46 years

JG remains well. His weight is 86 kg, waist circumference 104 cm, BP 150/87 mmHg, cholesterol 6.5 mmol/L, HDL 0.9 mmol/L, triglycerides 3.3 mmol/L and glucose 5.7 mmol/L. Despite several years for lifestyle intervention, increasing age, together with his risk factors mean that his cardiovascular risk is now moderate and some drug treatment is now required. Statin therapy would be first line treatment, as the evidence that these agents significantly reduce cardiovascular risk is very strong.

Screening for diabetes is appropriate in individuals who have suggestive symptoms, two or more risk factors, or a fasting or random blood glucose >5.5 mmol/L. A blood glucose >5.5 mmol/L should prompt a glucose tolerance test. Lifestyle modifications are important in preventing diabetes. Physical exercise and a weight loss of 5% will result in a halving of the risk of diabetes. Metformin can achieve a 40% reduction in the risk of diabetes at 5 years.

At 56 years

JG has hypertension diagnosed for the first time (BP 164/94 mmHg). His fasting glucose is now 7.6 mmol/L (two readings) and his HbA1c 7.2%. On atorvastatin 10 mg, his cholesterol is 4.9 mmol/L, HDL 0.9 mmol/L, triglycerides 2.6 mmol/L and LDL 2.8 mmol/L. In this situation (low HDL and high triglycerides), fenofibrate may be appropriate, with the FIELD study showing a 27% reduction in cardiovascular risk in this patient group). He now has a diagnosis of diabetes. JG's progress to this point shows the difficulty of meeting recommended targets (see Table 1).

Table 1. Treating to target

Variable	At target	Variable	At target
HbA1c ≤7.0%	45.8%	TC <4 mmol/L	19.2%
BP <130/85 mmHg	26.8%	TG <2 mmol/L	61.9%
BMI ≤25%	14.1%	HDL ≥1.0 mmol/L	83.0%
Ex-smoker	88.5%	LDL ≤2.5 mmol/L	45.6%

Australian experience from a large cohort study shows that many people are not meeting recommended targets¹

Management of resistant hypertension

Associate Professor George Mangos¹ and Professor Karin Jandeleit-Dahm²

¹St George and Sutherland Clinical School, University of NSW

²Head, Diabetes Complications Division, Baker IDI Heart and Diabetes Institute, Melbourne

Treatment resistant hypertension (TRHT) is defined as failure to reach a target blood pressure, defined as an office blood pressure of 140/90 mmHg, using three or more agents including a diuretic, assuring adherence and using maximum tolerated doses.

Two subclasses are increasingly identified - controlled resistant hypertension (patients fulfilling criteria for TRHT but controlled on 4 or more agents) and refractory hypertension (patients who remain hypertensive despite maximal doses of 4 or more agents). It is important to recognise a further group – those with pseudo-resistant hypertension (not allowing 3-5 minutes to rest before measuring BP, not taking 2-3 readings, incorrect cuff size, permitting smoking, permitting caffeine).

Based on US and European data, approximately 12% of patients with hypertension have treatment resistant hypertension, using the above criteria. However, studies in Europe and Australia using ambulatory blood pressure monitoring (ABPM) reveal that at least one-third of this group actually have blood pressure control. ABPM is therefore a very useful tool to evaluate these patients, minimising unnecessary drug exposure and the potential for adverse effects.

Management of patients with treatment resistant hypertension

1. **Does the patient really have resistant HT?** ABPM may show that up to one third of patients with apparent resistant HT actually have controlled BP (office or white coat effect).
2. **Is the patient adhering to treatment?**
3. **Don't forget to ask about lifestyle factors in patients with resistant HT** – salt intake, sleep hygiene, alcohol, physical activity, diet, weight – to name the commonest issues.
4. **Consider 'hidden' sodium and water** ('normal' or high sodium intake) and ensure diuretic is used in such patients.
5. **Preferred therapeutic combinations: ACEi or ARB + CCB + diuretic.**
6. **Avoid the combined use of ACEi and ARBs** – the combination has been shown to increase adverse events, including hyperkalaemia and renal failure, without any benefit.
7. **Spironolactone may be a useful addition to a three-drug regimen in patients with TRHT** – used at low doses and with caution (monitor potassium and renal function).
8. **The Symplicity HT-3 study in 2014 on Renal Sympathetic Nerve Ablation was negative leading to re-evaluation of this therapy.**

Challenges in resistant hypertension

Usefulness of old drugs: beta-blockers, methyl dopa, spironolactone

The place of new drugs: aldosterone synthase inhibitors, endothelin antagonists, neutral endopeptidase/angiotensin II type 1 (NEP/ARB) blockers

Interventional management strategies: baroreflex activation, renal sympathetic denervation

Treatment options in type 2 diabetes

Associate Professor Neale Cohen

General Manager Diabetes Service,
Baker IDI Heart and Diabetes Institute, Melbourne

There is considerable scope for improvement in the treatment of patients with type 2 diabetes. In Australia, only 50% achieve target levels of control, not least because diabetes is a difficult disease to treat.

HbA1c

It is generally agreed that the HbA1c target in diabetes is 7%. However, this is not the case for several groups. In the aging population and those with limited life expectancy, comorbidities, or at risk of severe hypoglycaemia, the target will be higher, while for younger patients who are fit and well, the target should be lower.

Treatment options

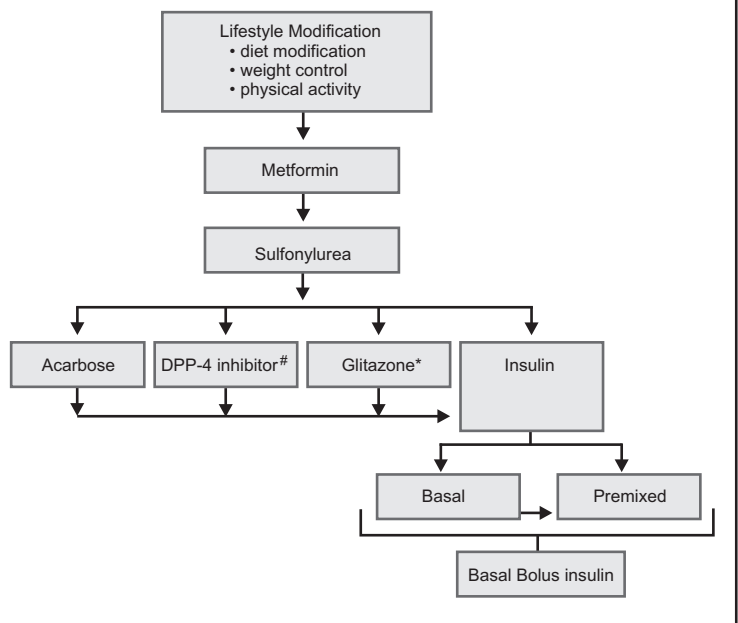
Current management for type 2 diabetes in Australia is shown in Figure 1. While this strategy includes multiple treatment options, at this time, only metformin has been shown, in randomised controlled trials, to lower cardiovascular risk. There are many other outcome studies in progress and their results are awaited with interest.

Impact of impaired renal function on choice of medication

As many patients with type 2 diabetes have impaired renal function, dosage adjustment of oral glucose lowering drugs is important. Metformin is contraindicated in patients with creatinine clearance <60 mL/min. Table 1, which lists agents that should be avoided in patients with significant renal impairment, shows that management becomes more challenging as renal function declines. The gliptins linagliptin and sitagliptin are ideal agents in such patients.

As treatment benefit with the new sodium glucose co-transporter 2 (SGLT2) inhibitor dapagliflozin is dependent on kidney function, this agent is contraindicated in patients with creatinine clearance <60 mL/min.

Figure 1. Management Algorithm for Blood Glucose Control in Type 2 Diabetes in Australia*



The algorithm includes only therapeutic agents available through the PBS. If HbA1c >7% consider intensifying treatment provided hypoglycaemia is not a problem. #Authorised only as dual therapy with metformin or sulfonylurea where combination metformin and sulfonylurea is contraindicated or not tolerated. *Rosiglitazone is not authorised for triple therapy or for use with insulin (from February 1, 2009), but is approved only as dual therapy with metformin or sulfonylurea where combination metformin and sulfonylurea is contraindicated or not tolerated.

Table 1. Oral glucose lowering drugs: dose adjustments in the setting of declining renal function**

CKD - Renal Function Stage (based on eGFR mL/min/1.73 m ²)				
	Stages 1 + 2 (>60)	Stages 3a + 3b (60-30)	Stage 4 (30-15)	Stage 5 (<15/dialysis)
Rosiglitazone				
Linagliptin				
Sitagliptin		DR	DR	DR
Pioglitazone				Avoid if on dialysis
Gliclazide			Avoid	Avoid
Glimepiride			Avoid	Avoid
Acarbose			Avoid	Avoid
Metformin		DR	Avoid	Avoid
Saxagliptin		DR	DR	Avoid
Vildagliptin		DR	DR	Avoid

Blue boxes indicate no dosage adjustment is required. DR = Dose reduction; **Data taken from respective Product Information.

Managing type 2 diabetes in patients with comorbid renal disease

Professor Merlin Thomas

NHMRC Senior Research Fellow, Baker IDI Heart and Diabetes Institute, Melbourne

Every second case of new diabetes seen by a general practitioner over the next 10 years will involve a patient over 65 years old. What problems does increasing age pose for management of type 2 diabetes?

Based on AusDiab data, 17-18% of 70 year old adults will have an eGFR <60 mL/min. In patients with diabetes, the proportion is slightly higher (around 20%). In younger individuals (40-50 years) diabetes is the major cause of renal impairment; however, in the majority of elderly (70-80 years) patients with diabetes, renal impairment is related to age, not diabetic nephropathy.²

“An eGFR <60 mL/min is a sign of frailty and if something else is superimposed – diabetes, hypertension, heart failure – things go wrong.”

Treatment issues related to renal impairment

Metformin

Dosage adjustment of metformin is important in the presence of renal impairment. As metformin has almost identical pharmacokinetic characteristics to creatinine, every time creatinine is doubled, metformin exposure increases by a factor of 2 as well. For an elderly patient with an eGFR of 50, a dose of 500-750 mg metformin is equivalent to 2g in a normal setting. For such a patient, the risks increase with dehydration, sepsis, or acidosis and the ability to reverse acidosis is decreased. GI upset can easily cause dehydration and a GFR of 50 can rapidly fall to 30. This would further elevate metformin levels, increasing the risk of additional GI upset and a risk of a spiralling down of GFR and increasing risk of acidosis. In such patients, the metformin dosage needs to be reduced significantly and renal function monitored, or metformin ceased.

Sulfonylureas

These agents also have varying problems in renal disease. Glibenclamide is cleared by the kidney and can accumulate in renal impairment, increasing the risk of hypoglycaemia. Glipizide is preferable, as it is not cleared by the kidney, although it is not without risk in these patients.

What HbA1c levels are appropriate targets?

In patients with an eGFR <60 mL/min there is a correlation between HbA1c and mortality.³ However, this disappears below an HbA1c of 8, so in patients with comorbidity and frailty, a softer target may be appropriate. However, this should not lessen attempts at intensive glucose control, as this will reduce the risk of overt nephropathy and keep people off dialysis. HbA1c values become less reliable as kidney function declines.

In patients with end-stage renal disease (ESRD), hypoglycaemia is much more common. If eGFR is <60 mL/min, a patient has a 10-fold greater risk of hypoglycaemia compared with those with eGFR >60 mL/min.

The value of other treatment options

The benefits of lowering blood pressure are more acute in patients with chronic kidney disease (CKD). Volume reduction is usually necessary to achieve adequate blood pressure reduction. However, thiazides may be ineffective in patients with low eGFR and cautious use of a loop diuretic may be required.

Statins are valuable treatment tools in this patient group. In patients with CKD not receiving dialysis, statins have been shown to reduce all-cause and cardiovascular mortality, with the risk of heart attack or stroke reduced by 20-25%. Statins have not been shown to be effective in patients on dialysis.

Familial hypercholesterolaemia

What is it? Why does it matter? What can we do?

Winthrop Professor Gerald Watts¹ and Associate Professor David Sullivan²

¹Deputy Head of School, Dept Medicine & Pharmacol, UWA, ²Senior Staff Specialist, Royal Prince Alfred Hospital, NSW

Familial hypercholesterolaemia (FH) is due to a mutation in the LDL receptor. Cholesterol is typically above 7 mmol/L and the condition causes premature coronary heart disease and death. It comes in two forms – heterozygous and homozygous FH – in the heterozygous form cholesterol is above 7 mmol/L, while in the homozygous form, cholesterol is above 12 mmol/L.

FH is an inherited condition, which can usually be traced over several generations. Its prevalence (1 in 200) is poorly recognised, it is under-detected and under-diagnosed (90% of FH is undiagnosed). Therapies for FH are sub-optimal and there is a lack of coordinated care.

The importance of screening

Targeted screening should be directed at all adults with premature CHD and a personal/family history of hypercholesterolaemia. Screening of children is important where parents have elevated LDL and there is relevant family history. If there is heterozygous FH in a parent, then children should be screened at 5-10 years; if the homozygous form is suspected (both parents have family history), then screening by the age of 2 years is appropriate. If a genetic mutation is identified in a parent, then genetic testing of a child is warranted. Cascade screening, starting with first degree relatives of the index case is a highly effective method.

Treatment options for FH

A heart healthy diet is very important. Drug therapy will be based on statins, with or without ezetimibe. Drug combinations, involving bile acid sequestrants, niacin, probucol, or fibrates may be required to further reduce LDL cholesterol. Hepatic aminotransferases, creatine kinase, glucose and creatinine should all be monitored.

Lipoprotein apheresis may be appropriate for severe cases. Women of childbearing age should receive pre-pregnancy counselling.

Management objectives in adults

Correct unhealthy lifestyles and non-cholesterol risk factors

Initially, aim for at least 50% reduction in LDL cholesterol, followed by further reduction of LDL cholesterol <2.5 mmol/L (no other CVD risk factors), or <1.8 mmol/L (with CVD or other risk factors).

Treatment of children

As with adults, a heart healthy diet is important. Statins should be considered at age 8-10 years, depending on LDL cholesterol. Treatment should ideally start before age 18 years.

Organisation of care

Effective management requires a multidisciplinary approach integrated with primary care. Lower complexity patients should be managed in general practice.

Looking for FH

- 1) Take the time to record a full family history of first (and, where relevant, second) degree relatives.
- 2) Grade likelihood of FH with a validated clinical instrument such as the Dutch Lipid Clinic Score (www.athero.org.au/fh/lipidscore).
- 3) Children whose parents have high cholesterol with or without a family history of CHD should be screened for FH.
- 4) FH should be detected by a combination of approaches to screening, including opportunistic, targeted and cascade strategies.
- 5) DNA testing can be very useful in detecting new cases of FH, but it is not essential.
- 6) The main objective of the care of FH is early detection and treatment with cholesterol lowering agents to prevent development of CHD.

Treatment inertia in the management of hypertension

Professor Chris Reid¹ and Professor Len Arnold²

¹Associate Director CCRE Therapeutics, Monash University, Victoria

²Director of Cardiology, Canberra Hospital, Australian National University, ACT

In an ideal world, patients with hypertension would comply with lifestyle advice and antihypertensive agents would be used singly or in combination to achieve and maintain blood pressure goals. Unfortunately, one of the greatest challenges to hypertension management is that this scenario is not realised and treatments fall short of expectations.

The evidence-treatment gap

An enormous amount of work has been done on population studies and clinical trials demonstrating the benefits of blood pressure lowering, but getting this implemented in practice is a big challenge. Two significant problems are patient compliance with treatment and the presence of resistant hypertension in many patients. A third is treatment inertia – things that the doctor can do to maintain, sustain and attain optimal levels of blood pressure that have been shown to reduce vascular events.

Blood pressure goals

Some blood pressure goals can be difficult to achieve, especially the more stringent goals for patients with renal disease, CHD, diabetes, stroke, or end-organ damage. In addition, there is a potential for confusion when blood pressure goals change over time. Data from AusDiab show that 60% of patients with treated hypertension have blood pressure values above the normal range (35% mildly elevated, 17% moderately elevated and 7% severely elevated).

Blood pressure targets are important, as raised blood pressure (BP) is a major risk factor for CV disease (CHD, kidney disease, heart failure, death). For people aged 40-70 years, each increment of 20mmHg (systolic) or 10mmHg (diastolic) doubles the risk of CV disease. BP targets should be regarded as maximum values.

However, more stringent targets may not necessarily produce better outcomes. Data from the ACCORD study, which randomised patients with type 2 diabetes to BP targets of 120 mmHg (systolic) or 140 mmHg (systolic), showed no significant difference in primary outcome (nonfatal MI, nonfatal stroke, death from CV causes) between the two groups when followed for 8 years.⁴ Data such as these are leading to modification of BP targets in some international guideline documents and they are also under review in Australia.

Australian data from general practice show that treatment inertia is most likely to occur in patients who at the highest risk of future events (older patients, patients with a history of CVD or diabetes and patients on combination therapy). As these patients are likely to have the greatest benefit from achieving BP targets, finding ways to address this issue is of great importance.

Selecting the right drug combination

ACE inhibitor + beta blocker

Although there is less than an additive effect on BP, this is a good combination in heart failure.

ACE inhibitor + calcium channel blocker (CCB) or thiazide diuretic

These combinations have been compared in a large randomised study. Both were effective in lowering BP, but there were significantly fewer events (combination endpoint of CV death, nonfatal MI, nonfatal stroke, CV hospitalisations) in the group randomised to ACE inhibitor + CCB.

ACE inhibitor + ARB

Not recommended. There is not much additional effect on blood pressure, no benefit in end points and some risk in progression of renal disease.

What will be the catalyst for achieving LDL goals?

Professor Stephen Nicholls¹ and Dr Anthony Pisaniello²

¹Heart Health Theme Leader, South Australian Health & Medical Research Institute, SA

²South Australian Health & Medical Research Institute, SA

The benefits of intervention with statins to lower LDL-cholesterol (LDL) have been shown repeatedly, both through lowering of cardiovascular morbidity and mortality and reduction in disease progression. Within these studies, the lower the level of LDL achieved, the greater the benefit. In studies of disease progression, LDL <1.8 mmol/L has actually promoted disease regression.

However, fewer than 50% of patients with coronary artery disease achieve an LDL target level of <2.6mmol/L and fewer than 15% achieve an LDL <1.8mmol/L. Even in very high risk CAD patients, for whom more intensive treatment is warranted, only 25% reach the target LDL of <1.8mmol/L.⁵

While the benefits of statins have been clearly demonstrated, patients are still at residual risk of cardiovascular events. Results show that, even in the most effective statin trials, where patients have greater levels of drug adherence and medical treatment is optimised (compared with the real world), at least 55% of the events in actively treated patients still occurred. This means that other treatments to complement the use of statins are still required. It should be remembered that statin therapy requires 6 weeks to achieve maximum lipid lowering effects.

Issues with statin use

Muscle symptoms. Around 10% of patients on statins may complain of muscle aches and pains at some point during their treatment; however, the incidence of myopathy is very low and difficult to separate from background levels.

New onset diabetes. The best evidence shows statin therapy to be associated with a small increased risk of type 2 diabetes, although some studies have shown no change or even a protective effect. The evidence is greater with more potent agents. However, it is likely that many affected individuals had pre-diabetes and the demonstrated strong cardiovascular benefits of statins in patients with diabetes outweigh the risks associated with any increased progression to type 2 diabetes.

Disease progression and management

Even when LDL levels are lowered to <1.8mmol/L, about 25% of patients with atherosclerotic cardiovascular disease continue to show progression. In general, these patients are characterised by diabetes, inadequate blood pressure control, low HDL cholesterol and elevated apolipoprotein B. This underscores the multifactorial nature of the disease and the need for global treatment of risk factors.

The involvement of apolipoprotein B also suggests a discord between LDL levels and particle based measures, whereby two patients may have the same LDL levels, but have very different particle sizes and numbers. This has very significant implications for cardiovascular risk, as patients with greater numbers of small dense LDL particles have greater disease risk and therefore require more aggressive treatment (eg, statins + ezetimide). Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) inhibitors, which enhance hepatic absorption of LDL particles, may also be useful in these patients, with studies showing an additive effect to statins and impressive efficacy in statin-intolerant patients.

Elevated triglycerides are now accepted as an independent risk factor that needs to be considered. Treatment options for these patients include higher doses of statins, fibrates and high dose (2-4 g/day) fish oil. Weight loss is also beneficial, with a 5-10% loss being associated with a 20% reduction in triglycerides. Implementation of a Mediterranean-style diet may lead to a further 10-15% lowering and an increase in marine polyunsaturated fatty acids an additional 5-10% reduction. Improved glycaemic control will also lead to reduced triglyceride levels. Increasing HDL levels is also beneficial. Statins and fibrates can raise HDL, as can diet and exercise.

Retinopathy

Professor Anthony Keech¹ and Dr Stephen Ong²

¹Professor in Medicine, Cardiology and Epidemiology, University of Sydney, NHMRC Clinical Trials Centre, NSW

²Consultant Ophthalmologist, Retinal Units Liverpool and Westmead Hospitals, NSW

Approximately half of all people with type 2 diabetes have retinopathy after 10 years of the disease. All are treated to control HbA1c levels and the majority are now treated with ACEI/ARB therapy for the benefits they offer to the kidney and the eye. At present, any further treatment for retinopathy involves referral to an ophthalmologist, often for laser therapy. While statins are an important element in diabetes management, they have not been shown to have any effect on diabetic retinopathy.

Clinical trial results

In the 1960s, a small study of clofibrate demonstrated a significant reduction in retinopathy with clofibrate compared with placebo. This encouraged the inclusion of retinopathy measurements in the FIELD study, a 10,000 patient study designed to investigate the effects of fenofibrate or placebo (added to conventional therapy, which did not include a statin), on the prevention of coronary heart disease in people with type 2 diabetes. As well as tracking all patients for the need for laser therapy, an eye substudy, involving serial retinal photographs in just over 1,000 individuals, was undertaken.

In 2007, a paper from the FIELD investigators reported on the first results related to retinopathy, in which fenofibrate was shown to reduce need for laser therapy to prevent sight-threatening retinopathy by 31% over a 5 year period.⁶ Benefits were apparent within 6-8 months of commencing therapy. In the eye substudy, the results were even more dramatic – a 79% reduction in the number of patients requiring laser treatment in the fenofibrate group. There was also an 80% reduction in progression of retinopathy based on photographic evidence.

More recently, results from the ACCORD study showed that progression of diabetic retinopathy in patients treated with simvastatin + fenofibrate was reduced by 40% compared with patients treated with simvastatin + placebo.⁷

Animal studies in type 1 diabetes models suggest that the beneficial effect of fenofibrate may be due to a reduction in retinal vascular permeability and leukocyte infiltration, as well as direct anti-angiogenesis effects (synthesis of vascular endothelial growth factor (VEGF) is switched off in retinal endothelial cells).

The ophthalmologist's view

All patients with type 1 diabetes and 50% of those with type 2 diabetes will develop diabetic retinopathy (DR). By the time that many patients with diabetic retinopathy see a specialist ophthalmologist they have already lost quite a lot of vision and may even be blind.

DR is defined as microvascular damage to capillaries within the retina and/or choroid. It can be caused by any stress to the microvascular circulation and is often asymptomatic in the early stages. Clinical features include microaneurysms, haemorrhages, hard exudates, cotton wool spots and neovascularisation. Macular oedema can occur at any stage. Retinopathy is a complex interplay between endothelial dysfunction, cellular metabolic dysfunction and disintegration of the vessel walls.

DR is the most common microvascular complication of diabetes and is the leading cause of blindness in the 20-60 year age group. After 15 years of diabetes, approximately 2% of people become blind and about 10% have severe visual impairment.

The major risk factors for DR include duration of diabetes, elevation of HbA1c and hypertension; dyslipidaemia, ethnic origin (Pacific Islanders and South Asians have higher risk), pregnancy and renal disease are additional risk factors.

Treatment for all patients includes optimal management of diabetes, hypertension and dyslipidaemia. Fenofibrate can slow progression of retinopathy and reduce the need for laser treatment. For those with non-proliferative DR, watchful waiting is appropriate. In patients with proliferative DR, treatment may include laser therapy and intravitreal anti-VEGF agents.

Absolute risk and the individual with high cholesterol and/or high blood pressure

Professor Mark Nelson¹ and Dr Rob Grenfell²

¹Professorial Research Fellow, Menzies Research Institute, Chair of General Practice, University of Tasmania. ²National Heart Foundation of Australia, Vic

Why take an absolute risk rather than individual risk factor approach?

An absolute risk approach best identifies who has covert CVD and therefore who is most likely to benefit from drug therapy.

Absolute risk looks at the probability of a cardiovascular disease (CVD) event over a 5 year period. This approach looks at the whole person and all their major determinants of risk, rather than individual risk factors that a person might have (e.g., isolated elevated blood pressure or cholesterol). Drug therapy is best given to those with high absolute CVD risk irrespective of individual risk factor levels because, being at the highest stroke and heart attack risk, they will have more events avoided and therefore have a lower number needed to treat. This approach also avoids CVD risk remaining unrecognised in the setting of other diseases. For example, in diabetes, management of the condition as hyperglycaemia (something that does not contribute substantially to CVD risk) may lead to neglect of the management of risk factors that do (e.g., blood pressure and cholesterol) in a disease that has a CVD event rate of 60-70%.

To estimate absolute risk reliably one needs to use a risk calculator unless there is a clinical determined high risk. These patients include those who are known to have CVD and those with chronic kidney disease (CKD). CKD confers a 19% increase in the risks of a CV event.

The Australian absolute cardiovascular risk calculator (<http://www.cvdcheck.org.au>)

The risk calculator uses information on gender, age, systolic blood pressure, smoking status, diabetes, and total and HDL cholesterol (Figure 1). LVH is also included as a measure of target organ damage. Using the risk calculator provides a figure for the risk of a CVD event over the next 5 years.

Australian absolute cardiovascular disease risk calculator

Enter patient information below:

Sex Male Female

Age years

Systolic blood pressure mmHg

Smoking status Yes No

Total cholesterol mmol/L

HDL cholesterol mmol/L

Diabetes Yes No

ECG LVH Yes No Unknown

Your heart and stroke risk score is **11%**

This means you are at moderate (medium) risk of getting cardiovascular disease in the next 5 years.

Click here if you would like to have a look at the information on this website that helps explain what your risk score means.

The next step is to talk to your doctor about what steps you can take to lower your chance of getting cardiovascular disease.

Please note: the absolute risk calculator score is only a guide to your heart and stroke risk score. Print out this page and take it to your doctor for further information on your personal risk. [Risk guidelines and resources](#)

An initiative of the National Vascular Disease Prevention Alliance

Diabetes Australia KIDNEY HEALTH AUSTRALIA Heart Foundation strokefoundation

Copyright © 2012 National Vascular Disease Prevention Alliance (NVDPA) | Disclaimer

Figure 1. The Australian absolute cardiovascular disease risk calculator

Patients are classified as low risk (<10% green), moderate risk (10-15% amber), or high risk (>15% red). For patients at low risk, lifestyle advice is the appropriate management option; medium risk warrants lifestyle advice and possibly drug treatment, while high risk requires immediate drug treatment. For Aboriginal and Torres Strait Islander people, 5% should be added to the calculated score.

Persons at moderate risk may need to be reclassified to high risk if other risk factors are at play, e.g., the individual is obese or comes from a high risk population such as the Indian subcontinent. Communicating risk to patients is critical. Colour coding is helpful and converting percent risk to odds may also be useful. The fact that a 20% risk represents a 1 in 5 chance of having a heart attack or stroke or dying from said over the next 5 years may be more convincing!

Advantages of using absolute CVD risk

- Recognises that BP and lipid levels represent a continuum of risk
- More cost effective
- Avoids medicalisation of the low risk population and identifies those most likely to have covert CVD, avoiding costly additional investigations
- Drugs can be initiated at a level above the ideal rather than an arbitrary cut point
- Attention is paid to CVD risk which otherwise might be subsumed within a particular chronic disease management strategy (e.g., diabetes).

(Mis)perceptions in dyslipidaemia

Professor Alberto Zambon

Professor of Medicine, Clinica Medica I, University of Padua, Italy

Professor Zambon addressed a number of important issues in lipid management, including several in which clinical opinion may not accord with evidence from clinical trials.

1. The priority of dyslipidaemia treatment is LDL-C management

While there is increasing appreciation of the importance of HDL and triglycerides (TG), reduction of LDL remains the primary goal of lipid management. Meta-analysis of major statin trials shows that, for every 1 mmol/L reduction in LDL there is at least a 20% reduction in major cardiovascular events.⁸

2. LDL targets, therapeutic adherence and achievement of clinical goals

Recent changes to US guidelines have moved away from numerical targets for lipid levels, focusing instead on intensity of therapy, an approach taken in several large trials of lipid lowering, in which patients were randomised to 'intensive' or 'moderate' doses of statin therapy. In these, the intensive treatment group achieved greater reduction in CV events and greater reduction in LDL levels (1.8 mmol/L), compared with the moderate group (2.6 mmol/L).

However, Australia, New Zealand and Europe currently retain specific target LDL levels. This approach is supported by clinical data showing that patients given a specific lipid target were more likely to continue their medication than those who were not.

3. Significance of elevated TG and/or low HDL when LDL is on target

The belief that elevated TG and/or low HDL is not significant if LDL is on target is common in some regions; however, this is not supported by clinical data. Data from the PROVE IT-TIMI 22 study clearly demonstrated that, in patients treated with statins after acute coronary syndrome, reaching LDL target alone did not achieve maximum risk reduction if TG levels were raised.⁹ Similar data are available to demonstrate additional risk reduction in patients with higher HDL levels. In addition, the ACCORD study in patients with diabetes showed that, in patients who had achieved an LDL of 2.0 mmol/L on simvastatin, fatal and non-fatal CV events were lowest in patients with the lowest TG and highest HDL levels (10.1%) and highest in those with both elevated TG and low HDL (17.3%).¹⁰

4. The value of measuring non-HDL cholesterol

In normal patients, LDL is the main atherogenic lipoprotein and levels of IDL and VLDL are fairly low. However, in patients with diabetes, concentrations of IDL and VLDL are significant. In these patients, non-HDL cholesterol is a secondary target and it could soon become the major target for treatment. It is the closest marker for the measurement of apoB levels. A 2012 meta-analysis of more than 62,000 patients in statin trials showed that, in patients who reached the target LDL of 1.8 mmol/L, those with an elevated level of non-HDL cholesterol (>2.6 mmol/L) had a 32% greater risk of major CV events than those with a level <2.6 mmol/L.¹¹

5. Fibrates in combination with statin therapy: efficacy and safety concerns

While benefits have not been shown for patients with normal HDL and TG levels, the ACCORD study has shown that, in patients with low HDL and high TG, the addition of fenofibrate to a statin results in a significant 31% relative risk reduction of CVD compared with treatment with statin alone. As well as macrovascular benefits, fenofibrate has been shown to reduce the progression of diabetic retinopathy in patients with type 2 diabetes and existing diabetic retinopathy. These effects on microvascular disease are achieved independently of effects on HDL and TG and may be due to a reduction in retinal vascular permeability and leukocyte infiltration, as well as direct anti-angiogenesis effects.

Some concern has been raised about the safety of combined use of a statin and a fibrate. In the case of fenofibrate, no significant increase in rhabdomyolysis or myopathy has been observed with combination therapy. Unlike gemfibrozil, fenofibrate has no significant effect on C_{max} or half-life of statins when used in combination.¹² Patients treated with fenofibrate + statin may show an increase in serum creatinine; however, creatinine levels return to normal approximately 8 weeks after cessation of therapy. Further, GFR was better preserved in patients on fenofibrate than on placebo.

References

1. Chittleborough CR, Baldock KL, Phillips PJ, Taylor AW. *Diabetes Res Clin Pract.* 2010 Jun;88(3):322-7.
2. Thomas MC, Maclsaac RJ, Jerums G, *et al.* *Diabetes Care.* 2009 Aug;32(8):1497-502.
3. Shurraw S, Hemmelgarn B, Lin M, Majumdar SR, *et al.* *Arch Intern Med.* 2011 Nov 28;171(21):1920-7.
4. ACCORD Study Group. *N Engl J Med.* 2010 Apr 29;362(17):1575-85.
5. Jones PH, Nair R, Thakker KM. *J Am Heart Assoc.* 2012 Dec;1(6):e001800. doi: 10.1161/JAHA.112.001800. Epub 2012 Dec.19.
6. Keech AC, Mitchell P, Summanen PA *et al.* *Lancet* 2007; 370: 1687-97.
7. The ACCORD Study Group and ACCORD Eye Study Group. *N Engl J Med* 2010; 363: 233-44.
8. Cholesterol Treatment Trialists' (CTT) Collaborators. *The Lancet* 2005; 366: 1267-78.
9. Miller M, Cannon CP, Murphy SA *et al.* *J Am Coll Cardiol* 2008; 51: 724-30.
10. ACCORD Study Group. *N Eng J Med* 2010; 362: 1563-74.
11. Boekholdt SM, Arsenault BJ, Mora S *et al.* *JAMA* 2012; 307(12): 1302-9.
12. Bergman AJ, Murphy G, Burke J *et al.* *J Clin Pharmacol* 2004; 44(9): 1054-62.

Presenters



Garry Jennings and Richard O'Brien
Hypertension, lipids and diabetes



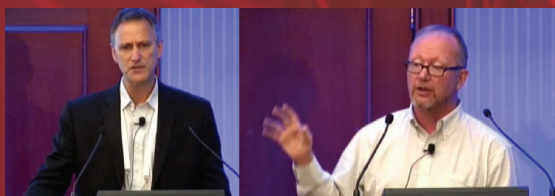
Stephen Nicholls and Anthony Pisaniello
What will be the catalyst for achieving LDL goals?



George Mangos and Karin Jandeleit-Dahm
Management of resistant hypertension



Tony Keech and Stephen Ong
Retinopathy



Neale Cohen and Merlin Thomas
*Treatment options in type 2 diabetes
Managing type 2 diabetes in patients
with comorbid renal disease*



Mark Nelson and Rob Grenfell
*Absolute risk and the individual with high
cholesterol and/or high blood pressure*



Gerald Watts and David Sullivan
*Familial hypercholesterolaemia (FH). What is it?
Why does it matter? What can we do?*



Alberto Zambon
(Mis)perceptions in dyslipidaemia



Chris Reid and Len Arnolda
*Treatment inertia in the management
of hypertension*

**Presented by the Australian Atherosclerosis Society and the
High Blood Pressure Research Council of Australia, Sydney, 2014**