BEST PRACTICE

30

AUGUST 2010

HbA$_{1c}$ targets
Statins
Alzheimer's disease
Diabetic retinopathy

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better medicine

This magazine is printed on an environmentally responsible paper managed under the environmental management system ISO 14001, produced using Certified ECF pulp sourced from Certified Sustainable & Legally Harvested Forests.

We would like to acknowledge the following people for their guidance and expertise in developing this edition:

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Dr Paul Drury, Auckland
Dr Rosemary Ikram, Christchurch
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Professor Norman Sharpe, Auckland
Associate Professor Mark Thomas, Auckland
Dr Richard Worrall, Auckland
Dr Neil Whittaker, GP Reviewer, Nelson

Best Practice Journal (BPJ)

ISSN 1177-5645

BPJ, Issue 30, August 2010

BPJ is published and owned by bpac^{nz} Ltd
Level 8, 10 George Street, Dunedin, New Zealand.

Bpac^{nz} Ltd is an independent organisation that promotes health care interventions which meet patients' needs and are evidence based, cost effective and suitable for the New Zealand context.

We develop and distribute evidence based resources which describe, facilitate and help overcome the barriers to best practice.

Bpac^{nz} Ltd is currently funded through contracts with PHARMAC and DHBNZ.

Bpac^{nz} Ltd has five shareholders: Procare Health, South Link Health, IPAC, the University of Otago and Pegasus Health.

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RESISTANCE TO ANTIMICROBIALS

– an increasing problem in our community

Contributed by **Dr Rosemary Ikram**, Clinical Microbiologist, MedLab South

Resistance to antimicrobials has provided continuing challenges in the treatment of infections since the first agents were used more than 70 years ago. Most antimicrobials are based on molecules that are produced by one organism to kill or inhibit the growth of other microorganisms. The organism producing the natural antimicrobial substance must also have a mechanism to avoid being killed or damaged itself. Resistance to antimicrobial agents can occur when the genes that are responsible for the "defence mechanism" in the original organism are transferred to other organisms, thus also rendering them resistant. Unfortunately this process has led to increasing resistance to most new antimicrobial agents within years of their introduction.

For many years the pharmaceutical industry has managed to stay ahead of the game by continually developing new antimicrobials. However, fewer new agents are now being developed, largely due to economic reasons – the short-term nature of an antibiotic course does not provide the returns associated with long-term medicines, and resistance means that the antimicrobial becomes obsolete within a short time period. Late in 2009, the Infectious Disease Society of America called for a worldwide commitment to achieve the development of ten new antibiotics within the next ten years (the 10 x 20 initiative). The World Health Organisation (WHO) has identified antimicrobial resistance as "one of the three greatest threats to human health". We may well be

The era of antibiotics is coming to a close. In just a couple of generations, what once appeared to be miracle medicines have been beaten into ineffectiveness by the bacteria they were designed to knock out. Once, scientists hailed the end of infectious diseases. Now, the post-antibiotic apocalypse is within sight. – *Sarah Boseley, The Guardian, UK.*

entering an age where, once again, it is not possible to successfully treat a range of infections caused by common bacterial pathogens.

In the past, antimicrobial resistance was largely limited to infections acquired in hospitals, but in recent years it has increasingly become a problem with infections acquired in the community, leading to the emergence of multiple drug resistant organisms. The WHO has recommended several interventions to reduce the spread of these organisms.

These interventions include educating people about:

- Basic hygiene measures to help prevent infection
- The need for rational use of antimicrobials
- The problems posed by antimicrobial resistant bacteria

Healthcare professionals should also be educated about resistant organisms, infection control and the benefits of restricting antimicrobial use to those who have definite indications for treatment.

Understanding the threat of multiple drug resistant organisms in New Zealand

From overseas surveillance studies it is apparent that many of the multiple drug resistant organisms are clonal i.e. have the same origin, and have been able to spread widely. As an example, most methicillin resistant *Staphylococcus aureus* (MRSA) isolates in New Zealand have originated from overseas. Extended spectrum beta lactamase (ESBL) producing *Klebsiella pneumoniae* was first recognised in Hawke's Bay and has now spread around the country – Hawke's Bay still had a high rate of this organism in surveillance performed in 2008. Many of these organisms have become widespread in the community as well as causing infections in healthcare settings.

The major factor responsible for this resistance problem is the misuse of antimicrobials, which includes inappropriate prescribing by healthcare professionals (wrong choice of agent, prescribing when an antimicrobial is not indicated,

inappropriate dose or duration of therapy) and lack of compliance by patients. Microbiologists have been talking for years about widespread resistance potentially occurring, but the reality is that it is happening now.

It is essential for everybody to contribute to the efforts to prevent antimicrobial resistance. Widespread emergence of multiple drug resistant organisms will impact on all healthcare sectors, leading to increasing morbidity and mortality, due to the difficulty of treating increasingly resistant bacteria.

What strategies could work? There needs to be a greater focus on educating the general public about increasing antimicrobial resistance and the fact that viral infections do not respond to antimicrobial treatment. There have been some programmes that have focused on these issues already e.g. PHARMAC's "Kick that Bug" Wise Use of Antibiotics campaign, but the messages need to be continually promoted, in a variety of changing ways to keep the issue in the forefront of everybody's mind.

The current situation of antimicrobial resistance in New Zealand could be used to strengthen the message and illustrate the consequences of antimicrobial misuse. To do this, comprehensive data are required. Surveillance is presently carried out through Environmental Science and Research (ESR) and is published on its website (**www.esr.cri.nz**). However this is national data and does not reflect the situation in some smaller centres, which may have clones of resistant bacteria, but the numbers are too small nationally to raise awareness. The spread of the ESBL producing *Klebsiella pneumoniae* from the Hawke's Bay is a good example of this.

Local information needs to be collected and analysed so that each area can determine what specific issues need to be addressed. For example, in South Canterbury a multidrug resistant *E.coli* has become more prevalent over the last two years. This area has the highest quinolone use in New Zealand, leading to antimicrobial resistance, and strategies are currently being developed to reduce this. In Christchurch, "MRSA USA 300" has emerged in at least a couple of residential care facilities, and without intervention will spread widely including into acute care hospitals.

Regional information needs to be used to inform healthcare professionals about the issues through local meetings and workshops. Resources, such as patient information

pamphlets, are required to assist in reducing unnecessary prescriptions. Targeted interventions can be developed to reduce the prescription of specific antimicrobials,which appear to be increasing local resistance.

Antimicrobial resistance in the community is becoming an increasing problem. Interventions must be implemented on a large scale to be successful and unfortunately this is not a simple process. The solutions for many of the issues of resistance also remain unclear. However, this is not a reason to ignore the problem and failure to respond effectively will only increase the prevalence of these potentially incurable infections in our communities.

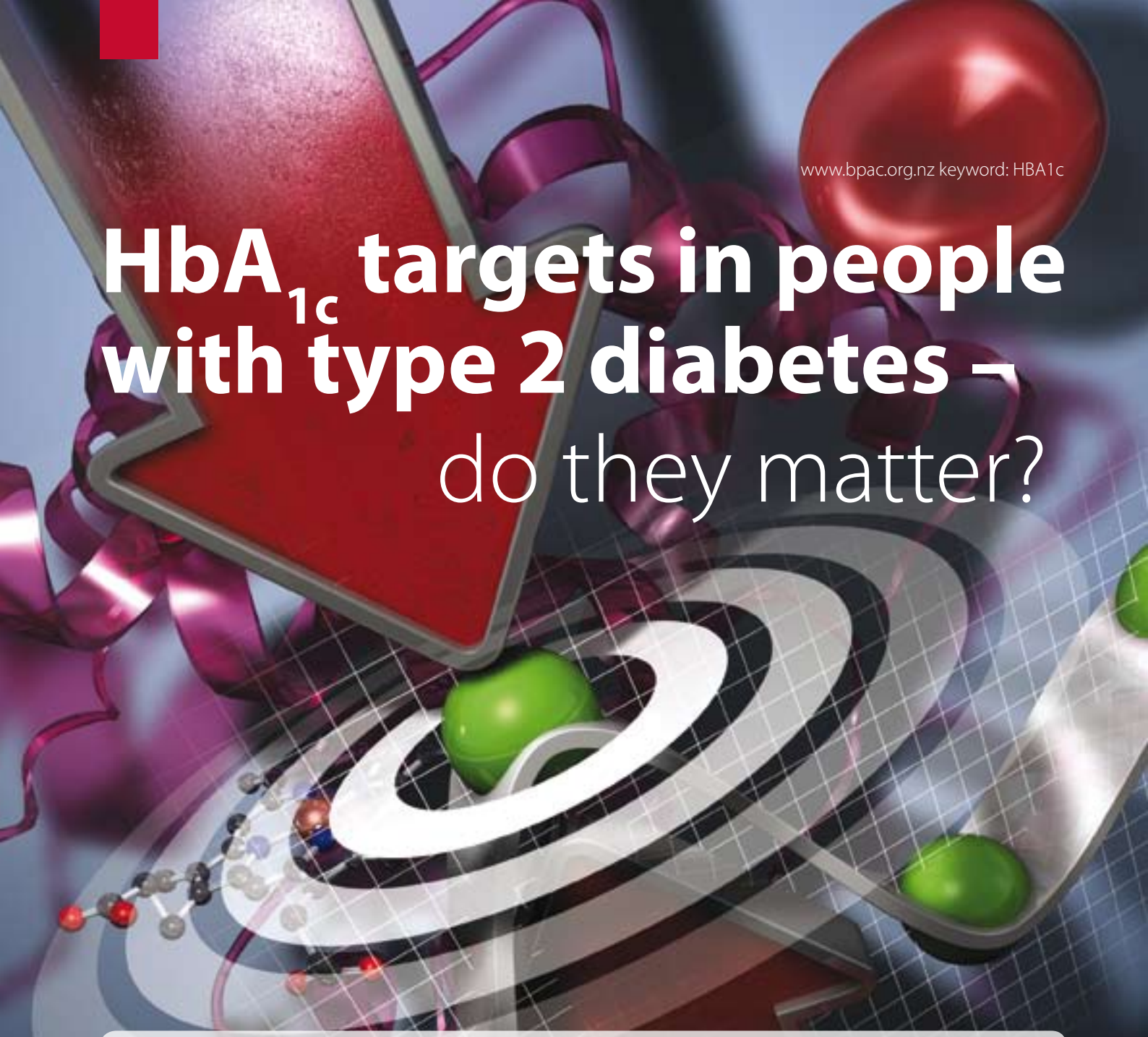
ACKNOWLEDGMENT Thank you to Associate **Professor Mark Thomas**, Infectious Disease Specialist, University of Auckland for expert guidance in developing this article.

This article is the first in a series devoted to understanding and addressing the problem of antimicrobial resistance in New Zealand. Subsequent articles will cover appropriate and rational use of antimicrobial agents, strategies to minimise the problem of resistance and an overview of antimicrobial use and resistance in New Zealand.

We challenge you to examine the use of antimicrobials in your practice and to consider ways in which you may contribute to reducing resistance in our communities.

Prescribers, please complete the accompanying questionnaire about antimicrobial use in primary care. This is also available online at: ***www.bpac.org.nz***

HbA_{1c} targets in people with type 2 diabetes – do they matter?



Key concepts:

- **A target HbA_{1c} should be negotiated individually, but a level of close to 7% (53 mmol/mol) seems to be an acceptable compromise for the majority of people with type 2 diabetes**
- Good glycaemic control reduces the risk of microvascular complications and may also reduce the risk of some macrovascular complications of type 2 diabetes
- Very intensive glycaemic control is associated with increased risks e.g. hypoglycaemia, weight gain and possibly increased risk of mortality
- Hyperglycaemia should not be treated in isolation when attempting to reduce cardiovascular risk
- Older people with longer duration of diabetes and who are at high cardiovascular risk may be at particular risk of harm from intensive control
- Early intervention is beneficial

The emphasis of most diabetes management guidelines was, until recently, "the lower the HbA_{1c} the better". The results of several major recent studies have generated much discussion in the literature about what a target HbA_{1c} should be, how tight intensive glycaemic control should be and which people are most likely to benefit from intensive control. Should this recent research alter the management of people with type 2 diabetes in primary care?

What is the current recommended HbA_{1c} target?

The current New Zealand guidelines for the management of type 2 diabetes, published in 2003, recommend that a target HbA_{1c} should be as close to physiological levels as possible.[1] The suggested level is preferably less than 7% or 53 mmol/mol (see below for unit conversion). In addition, the guidelines include the comment that "the lower the level of HbA_{1c}, the better".[1] Any sustained reduction in HbA_{1c} is felt to be worthwhile.

Comparison of HbA_{1c} units

Percentage units (%)	Molar units (mmol/mol)
6.0	42
6.5	48
7.0	53
7.5	59
8.0	64
8.5	69
9.0	75
9.5	80
10.0	86
10.5	91
11	97

See "Changes to laboratory reporting of HbA_{1c}" (Best Tests, Oct 2009) for further information and a method for converting between units.

What is intensive glycaemic control?

Intensive or tight glycaemic control is usually regarded as the management regimen required to achieve HbA_{1c} levels of below 6.5% or even 6.0% (48 or 42 mmol/mol). The medicines and lifestyle factors needed to reach these levels varies between clinical settings and also between research settings.

In the majority of recent clinical trials, patients randomised to intensive therapy were initiated on an oral agent that was increased or added to, if control was not achieved. Multiple agents, and often insulin, were required to achieve the target HbA_{1c}. Medicines were used that are either not available or funded in New Zealand. Standard treatment for the purposes of the trials, reflected management outlined in current local guidelines and was generally aimed at achieving a HbA_{1c} of about 1.0 – 1.5% higher than in the intensive group – usually around 7 to 8.5% (53 to 69 mmol/mol).

What are the benefits of intensive control?

There is clear evidence that intensive glycaemic control reduces the long-term risk of microvascular complications e.g. retinopathy, nephropathy and neuropathy, in people with type 2 diabetes, although it may take many years for these benefits to become apparent.[2, 3, 4]

It is less clear whether intensive glycaemic control, aimed at achieving a HbA_{1c} target of less than 6.5 or 6.0% (48 or 42 mmol/mol), can also reduce the risk of macrovascular complications, i.e. coronary artery disease, stroke and peripheral vascular disease, in people with type 2 diabetes.[5, 6]

What are the risks of intensive control?

The increased risks of intensive glycaemic control include hypoglycaemia, the possibility of hypoglycaemic unawareness, weight gain (particularly with insulin or sulphonylureas) and the potential short-term risk of worsening microvascular complications if the decrease in HbA_{1c} occurs rapidly. Patients may also find the demands of intensive glycaemic control difficult to manage. This may result in psychological stress, frustration and non-adherence especially if hypoglycaemia occurs.[7]

Results from some major trials have indicated that patients who had intensive glycaemic control were at an increased risk of death compared to patients in the standard treatment group and that there was no major reduction in microvascular complications.[5, 6]

A balance must be sought between the benefits and risks of intensive glycaemic control for the patient.

What are the current issues in the literature?

The Action in Diabetes and Vascular Disease (ADVANCE),[3] Action to Control Cardiovascular Risk in Diabetes (ACCORD)[5, 6] and Veterans Affairs Diabetes Trial (VDAT),[8] were three randomised controlled trials designed to assess the effects of intensive glycaemic control on cardiovascular outcomes. The results of these large, long-term studies have generated much debate and sparked further research.

Patients were randomly allocated to an intensive glucose lowering group or a control group with standard treatment. The HbA_{1c} targets in the intensive treatment groups were set at 6.0 to 6.5% (42 to 48 mmol/mol), which was considered to be as close to a physiological level as possible, and at 7.0 to 8.0% (53 to 64 mmol/mol) in the standard group.

Table 1 summarises some key characteristics of these trials and the overall effect on all cause mortality (primarily deaths due to cardiovascular causes).

The evidence from these three trials plus other studies is inconsistent in showing whether intensive glycaemic control has a beneficial effect on overall mortality. There was no significant change in cardiovascular or overall mortality for patients in the intensively treated groups in the ADVANCE and the VDAT trials.[3, 8] However, patients in the intensively treated group in the ACCORD study, showed statistically significant increases in both cardiovascular (35%) and overall (22%) mortality resulting in a decision to stop the trial early.[5] A trend towards increased mortality was also seen among patients in the intensively treated arm of the VDAT study although this was not statistically significant.[8, 9]

The initial results of the United Kingdom Prospective Diabetes Study (UKPDS) did not show any significant reduction in mortality in the group of patients treated with intensive glycaemic control. However after an additional ten years of follow-up there was a significant reduction in mortality in these patients, despite the intervention being withdrawn in the follow-up period.[2, 4]

Can the differences in results be explained?

Review of the major trials reveals that the characteristics of the selected patients and aspects of the design of the studies may help explain the differing results obtained.

Patients enrolled in the ACCORD, ADVANCE and VADT studies were:

- Older
- Had a longer history of diabetes at entry to the studies
- Had either a history of cardiovascular disease or multiple cardiovascular risk factors

In contrast, patients enrolled in the UKPDS study were younger, newly diagnosed with diabetes at entry and had lower cardiovascular risk.

Patients in the intensive glycaemic control group of the ACCORD study had the lowest HbA_{1c} target (<6.0% or 42 mmol/mol) and were subject to more rapid reduction

Table 1. Intensive glycaemic control in diabetes: study characteristics and results[3, 5, 8]

Study	Length of trial	No. of participants	Mean age of participants	Duration of diabetes at entry (median)	Baseline HbA_{1c}	Target HbA_{1c} (intensive group)	HbA_{1c} achieved (intensive group vs standard group)	All cause mortality (intensive group vs standard group)
ACCORD	3.5 years*	10,251	62	10 years	8.1%	<6.0%	6.4%† vs 7.5%	5.0 vs 4.0% (hazard ratio 1.22, P=0.04
ADVANCE	5 years (median)	11,140	66	8 years	7.2%	≤6.5%	6.5% vs 7.3%	8.9 vs 9.6% (hazard ratio 0.93, P=0.28)
VDAT	5.6 years (median)	1,791	60	12 years	9.4%	<6.0%	6.9% vs 8.4%	11.4 vs 10.5% (hazard ratio 1.07, P=0.62)

*mean, trial stopped early

† rapid reduction to this target

Mortality in the ACCORD study

The cause of the increased mortality observed in the intensively treated patients in the ACCORD study is not known. Several contributing factors have been proposed, including:[10, 11]

- Patient characteristics – patients were older, had a longer history of diabetes and had higher cardiovascular risk
- Study design – an aggressive regimen was used to lower HbA_{1c} within a short time frame and multiple medications were initiated to achieve the HbA_{1c} target, more so than in the ADVANCE trial
- Patient outcomes – patients in this study had higher rates of hypoglycaemia and higher weight gain (average of 3.5 kg)
- Medications used – glitazones (see below) were one of a number of medications prescribed to help achieve target HbA_{1c} levels.

There is evidence that glitazones (particularly rosiglitazone), as used in the ACCORD study, are associated with an increased risk of cardiovascular events and death.[12, 13] Glitazones are not recommended for use in people with heart failure (current or previous), ischaemic heart disease or peripheral vascular disease.[14, 15] There is also an increased risk of heart failure and cardiac ischaemia if a glitazone is used in combination with insulin. Specialist advice is recommended if a glitazone is being considered.

The ACCORD study also used some other newer medicines for glycaemic control, including dipeptidyl peptidase-4 inhibitors (DPP4) and glucagon-like peptide-1 (GLP-1), that are not currently funded in New Zealand.

in HbA_{1c}. Any available anti-diabetic medicines or combinations of up to five medicines were used to achieve these results. Intervention strategies in the other studies were less aggressive and fewer medicines were used to reduce glucose levels.

The length of the studies also varied. UKPDS trial results have now been reported for patients followed for ten years (median) while patients in the ADVANCE and VADT trials were followed for five years. Patients in the intensive glycaemic control group of the ACCORD study were followed for 3.5 years only, because this arm of the study was terminated early, due to the increase in mortality.

Do the results of the recent trials mean that guidelines for people with type 2 diabetes should be revised?

In light of conflicting evidence of the benefit of intensive glycaemic control on mortality, some researchers have suggested that guidelines may need to be revised to include a minimum value for HbA_{1c} rather than advocating "the lower, the better".[16]

A target HbA_{1c} should be negotiated individually, but a level of close to 7% (53 mmol/mol) seems to be an acceptable compromise for the majority of people with type 2 diabetes and this is consistent with the current New Zealand guideline.[1] Aiming for a HbA_{1c} below 6% appears unwise.[7] Intensive glycaemic control may do more harm than good for some people.

What do the results of the studies mean for people with type 2 diabetes?

Achieving good glycaemic control is beneficial for all people with type 2 diabetes, particularly for preventing microvascular complications. Macrovascular complications may also be reduced in the longer term i.e. after more than eight to ten years.

The key messages from the current evidence are that:

- Hyperglycaemia should not be treated in isolation

when attempting to reduce cardiovascular risk. Managing hypertension and lowering lipid levels may be easier to achieve and result in a more rapid improvement in outcomes than optimal glycaemic control.

- Early intervention is likely to be beneficial
- HbA_{1c} targets should be individualised – no one level will suit all people

Treat all cardiovascular risk factors

Achieving good glycaemic control is only one aspect of the overall treatment of diabetes, therefore hyperglycaemia should not be targeted in isolation.

All people with type 2 diabetes are at increased risk of cardiovascular disease. Preventing macrovascular complications relies on a comprehensive approach that assesses and targets all cardiovascular risk factors, e.g. blood pressure, lipids, smoking, weight, exercise and family history. The prevention of microvascular complications, e.g. retinopathy and nephropathy, also relies on management of other risk factors such as blood pressure.

Early intervention is important

The evidence suggests that intensive glycaemic control appears to be most beneficial for reducing the development of both microvascular and macrovascular complications in people who are younger, and are newly diagnosed with type 2 diabetes, and have low cardiovascular risk. However, in practice many newly diagnosed patients may already be at higher cardiovascular risk, as this can increase with "pre-diabetes".

Early initiation of intensive therapy to achieve a target HbA_{1c} of 6.0 to 6.5% (42 to 48 mmol/mol) is recommended for newly diagnosed patients with low cardiovascular risk, particularly if the anti-diabetic medication initiated is metformin and good glycaemic control can be achieved without the risk of hypoglycaemia.[3]

Steno-2 study shows mortality benefits after 13 years

The Steno-2 study investigated the effects of intensive management of multiple cardiovascular risk factors in patients with type 2 diabetes.[17] The multiple targets for treatment were a HbA_{1c} of < 6.5% (48 mmol/mol), fasting total cholesterol of < 4.5 mmol/L, fasting triglyceride level of < 1.7 mmol/L and a blood pressure of < 130/80 mmHg. In addition, patients received low dose aspirin, an ACE inhibitor (regardless of their blood pressure level), education and behavioural modification.

Results after the first eight years showed a reduction in microvascular complications only. However, after 13 years (approximately 7.5 years of treatment and 5.5 years of follow-up) there was a 20% decrease in the risk of death from any cause. N.B. Mortality curves only separated after the treatment period, very similar to the results seen in the UKPDS follow-up study.[4]

At the time of diagnosis with type 2 diabetes, patients should be given practical and motivational advice about lifestyle and diet. Consider also initiating metformin (see sidebar) rather than waiting for patients to fail to achieve their glycaemic target with lifestyle measures.

The benefits of early intervention may be explained by the "legacy effect" or "metabolic memory".[19, 20] This has been proposed as an important factor to consider when treating patients with type 2 diabetes, and may explain the improvement in macrovascular complications reported in studies with long term (greater than ten years) follow-up.[4, 17]

The "legacy effect" refers to the concept that intensive control initiated early in diabetes results in beneficial effects that persist for years and therefore reduces long term complications. Conversely, poor glycaemic control leads to the development of complications due to the chronic hyperglycaemic environment. Possible mechanisms for this include higher levels of free radical production and an increase in oxidative stress and endothelial dysfunction. The result is a complex and vicious cycle of damage which ultimately leads to complications of chronic diabetes. If intensive control is initiated after a period of poor glycaemic control it appears that the benefits for cardiovascular health are less, at least in the short term (approximately less than ten years).

Metformin is the initial medication of choice for people with type 2 diabetes

Metformin use is recommended because it:

- Does not cause weight gain
- Does not cause hypoglycaemia
- Reduces insulin resistance
- Reduces cardiovascular risk[2]
- Is low cost
- Has a long history of effectiveness and a good safety profile

For the majority of patients, these advantages outweigh the disadvantages which may include:[18]

- Gastrointestinal intolerance (5–20%)
- Lactic acidosis (very rare < 1/10,000, risk increases with renal insufficiency and age)
- A mild reduction in vitamin B12 and folate levels

See "Folate deficiency with metformin" (BPJ 16, Sep 2008) for further information.

Individualise targets

The evidence suggests that what is "good" glycaemic control for one person will not necessarily be the same for another person.

Body weight may influence both the focus of a diabetic treatment plan and the choice of medication if required, e.g. metformin when BMI is increased. People with diabetes who are overweight are at higher cardiovascular risk and require more intensive management of all cardiovascular disease risk factors.

A HbA_{1c} target of 6.0 to 6.5% (42 to 48 mmol/mol) may be appropriate and safe in a younger, newly diagnosed patient with low cardiovascular risk but an older patient with a longer history of diabetes who is at high cardiovascular risk, may be at risk of harm from intensive or tight control that aims for a target HbA_{1c} in this range.

Older patients are also likely to have a higher risk of co-morbidity, an increased risk of hypoglycaemia and an increased risk of drug-related adverse effects and interactions. A patient with existing macrovascular complications or who is at high risk of complications should have a less stringent HbA_{1c} target and the HbA_{1c} should be reduced to this target level more slowly.

Most researchers and specialist clinicians now advise that intensive glycaemic control to achieve a HbA_{1c} target of ≤ 6.0% (42 mmol/mol) should not be universally recommended.[21, 22]

ACKNOWLEDGMENT Thank you to **Dr Paul Drury**, Clinical Director, Auckland Diabetes Centre for expert guidance in developing this article.

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An update on STATINS

Key concepts

- The decision to initiate a statin should be based upon an individual's risk of CVD, the likely benefit of treatment and potential adverse effects
- Targets are generally not necessary in primary prevention, where any reduction in lipid levels results in a reduction in CVD risk
- In secondary prevention, lipid levels should be viewed as a guide to management rather than targets to achieve
- Simvastatin 20 – 40 mg is a reasonable starting dose for many people, although individual patient factors influence the choice of statin and intensity of treatment - people at highest CVD risk tend to benefit the most from higher doses or higher potency statins
- After initiating statin treatment, creatine kinase should be checked when there are unexplained muscular symptoms, however no other monitoring is routinely required
- Lipid-lowering agents other than statins may be considered for those who require additional lipid-lowering, when statins alone are not adequately controlling dyslipidaemia, or in cases of statin intolerance

Current recommendations for statin use in New Zealand and international guidelines

New evidence is continually emerging on the use of statins, particularly in relation to their role in primary prevention of cardiovascular disease (CVD), specific dose regimens and treatment targets. This information, both in the lay press and medical literature, prompts reflection on current cardiovascular guidelines and consideration of whether there is anything new that represents a significant shift from current practice for primary care clinicians.

New Zealand Guidelines Group cardiovascular guidelines

The New Zealand guidelines for the use of lipid lowering agents as part of CVD risk management recommend the following:[1]

- Treatment should be based on an individual's five-year CVD risk
- Statin treatment should be initiated for people with known CVD or at high CVD risk
- Starting doses:

  For people with a five-year CVD risk of 15 – 20%, simvastatin 20 mg (titrate if needed)

  For people with known CVD or a CVD risk > 20%, simvastatin 40 mg
- Lowering of LDL-cholesterol is the primary indicator of optimum lipid management. Targets include total cholesterol < 4.0 mmol/L and LDL-cholesterol < 2.0 mmol/L.
- If LDL-cholesterol targets are not met, options include increasing simvastatin to 80 mg, substituting simvastatin for atorvastatin or combining simvastatin with nicotinic acid or ezetimibe.

For full details of the New Zealand Guidelines Group (NZGG) Cardiovascular Guideline, visit: **www.nzgg.org.nz**

United Kingdom NICE cardiovascular guidelines

The National Institute for Health and Clinical Excellence (NICE) guidance on lipid modification is presented in terms of primary and secondary prevention and recommendations are based on the ten-year risk of CVD. The following recommendations are given:[2]

- Statin treatment for primary prevention is recommended when the CVD ten-year risk reaches 20%
- For both primary and secondary prevention the recommended initial dose for simvastatin is 40 mg

Comparison between Guidelines

A key difference between NZGG and NICE Guidelines is in the use of cholesterol targets. The NICE guidance recognises that more than half the patients will be unable to achieve traditional targets such as LDL-cholesterol < 2 mmol/L. Targets are now regarded as levels that can guide increases in dose or intensity of treatment in patients at greatest risk i.e. for secondary prevention. Measurement of lipid levels is considered unnecessary in lower risk patients i.e. for primary prevention.

It may appear that patients can be started on statin treatment at lower CVD risk in the United Kingdom. However recent risk/outcome data (which are still accumulating) indicate that CVD risk in New Zealand may be overestimated by up to 5%.[3] This means that a patient calculated to have a 15% five-year CVD risk, is more likely to have a risk closer to 10%. If it is assumed that a 10% five-year CVD risk is equivalent to a 20% ten-year CVD risk, then it can be concluded that New Zealand recommendations are similar to United Kingdom recommendations.

When should statin treatment be initiated?

New Zealand guidelines recommend the use of a statin in the primary prevention of cardiovascular disease when the five-year CVD risk reaches 15–20%.[1]

Increasingly people are being considered for statin treatment for primary prevention of CVD. The potential benefit of statins for primary prevention was highlighted by the landmark West of Scotland Coronary Prevention Study (WOSCOPS) which found a 31% reduction in coronary events with pravastatin compared with placebo.[4] A recent meta-analysis of primary prevention trials concluded that statins improve survival and reduce the risk of major cardiovascular and cerebrovascular events in people without established cardiovascular disease.[5]

Included in this analysis was the JUPITER trial (see sidebar) which has caused much subsequent debate. This trial demonstrated that rosuvastatin reduced the rate of adverse cardiovascular events in people with increased CVD risk.[6] However the patients included in the study had normal LDL-cholesterol levels to begin with and the CVD risk was defined by increased levels of high sensitivity CRP, a controversial surrogate marker of CVD risk.

Based on current evidence it may be appropriate to view lipid lowering treatment with statins as an intervention that can reduce relative cardiovascular risk (by approximately 20% to 30%) regardless of baseline LDL-cholesterol. The absolute benefit of treatment is proportional to the underlying absolute risk.[7]

Determining when the benefits of treatment outweigh its disadvantages (cost and adverse effects) requires estimation of the patient's underlying cardiovascular risk. Once a patient's cardiovascular risk is assessed, together with their doctor, they can decide whether a 20% to 30% relative risk reduction translates into an absolute risk reduction, large enough to be worth the cost and potential adverse effects of daily statin therapy.[7]

For example:

A 45-year-old non-smoking, non-diabetic, normotensive woman has a total cholesterol of 6.2 mmol/L and a HDL-cholesterol of 1.1 mmol/L. Her five-year risk of a cardiovascular event is assessed to be less than 2.5%. This could potentially be reduced by 0.5 to 0.75% if she were to be treated with a statin.

The GP and patient decide against the use of a statin as the absolute benefit of treatment is minimal (less than 1%) and does not warrant exposing the patient to the potential adverse effects of long-term statin therapy.

Acknowledging the limitations of CVD risk assessment

The calculation of CVD risk is limited by factors specific to individual patients. For example, using the charts in the New Zealand Cardiovascular Handbook may underestimate CVD risk for those who have:

- Total cholesterol ≥ 8 mmol/L
- Total cholesterol : HDL-cholesterol ratio ≥ 8
- Blood pressure consistently ≥ 170/100
- Diabetes with microalbuminuria for 10 years or with HbA_{1c} consistently ≥ 8%
- Family history of premature coronary heart disease or ischaemic stroke in a first-degree relative (father or brother < 55 years, mother or sister < 65 years)

And those who are:

- Māori, Pacific or from the Indian subcontinent
- Aged ≥ 75 years
- Aged < 35 years with known CVD risk factors
- Aged 20–34 years with diabetes
- Overweight
- High consumers of alcohol

For patients with these risk factors especially, lipid lowering drug treatment should be combined with advice on diet and lifestyle measures such as exercise, weight management, alcohol consumption and smoking cessation. Other risk factors should also be appropriately

addressed such as lowering raised blood pressure and managing diabetes.[1, 2]

For example:
A 52-year-old man has an estimated five-year CVD risk of 10–15% (calculated from the CVD risk tables). He reveals that he has a family history of premature coronary heart disease.

The GP decides that this patient should be moved up a risk category to >15% on the basis of his family history and therefore a statin is indicated.

How important are target lipid levels?

New Zealand guidelines recommend the following optimal lipid levels (targets) for people with known cardiovascular disease, cardiovascular risk > 15% or diabetes:[1]

Total cholesterol < 4.0 mmol/L
LDL cholesterol < 2.0 mmol/L
HDL cholesterol ≥ 1.0 mmol/L
Triglycerides < 1.7 mmol/L

The traditional view on lipid levels is "the lower, the better", which is technically correct from a disease-based point of view. However this view does not take into account how the treatment used to achieve this intervention will affect patient outcomes.[9]

Although specific target levels are recommended in New Zealand Guidelines, it is now widely agreed that it is not necessary to treat to target lipid levels in primary prevention of CVD. Many patients are unable to achieve target lipid levels, potentially leading to lack of motivation and non-compliance with treatment.[10]

The JUPITER Study

When results were first reported in 2008, the Justification for the use of statins in primary prevention: an intervention trial evaluating rosuvastatin (JUPITER) study was regarded by some as an important development in statin research. The results suggested that statins were beneficial in people with no history of CVD but assessed as being at increased CVD risk.[6] However, since this time the JUPITER study has received much criticism.

One of the most controversial aspects of JUPITER was that trial participants had no known CVD and had cholesterol levels within normal ranges but were designated to be at increased CVD risk due to elevated high sensitivity C-reactive protein (hsCRP) levels. The use of hsCRP as a surrogate marker for CVD risk is debatable.

The absolute effect size of the study was relatively modest – for every 1000 patients who received rosuvastatin for one year, roughly six fewer primary-endpoint events (first major cardiovascular event including unstable angina, myocardial infarction, stroke and arterial revascularisation) and three fewer deaths occurred. Therefore a large number of people with low-CVD risk would have to be treated in order for any benefit to be derived.

The JUPITER study was terminated early, after only 1.9 years, instead of the planned four years, due to strong evidence of benefit in the treatment group. Early termination for benefit can provide an inflated estimate of benefit and understate harm.[8] There was also no indication about the long-term safety of the very low LDL-levels which were achieved in the study.

The results of the JUPITER study were taken into account when the New Zealand Cardiovascular Guidelines Handbook was revised in 2009 by the New Zealand Guidelines Group. However the Group did not think it justified any change in practice.

Additional reasons for not using lipid level targets in primary prevention include:[10]

- Clinical trial evidence is based on using specific doses of specific medicines to treat people, rather than using medicines to achieve specific targets
- The majority of studies that recruited selected populations did not find statin therapy reduced LDL-cholesterol below 2 mmol/L
- Targets do not take into account the distribution of cholesterol levels in the population prior to commencement of treatment, nor differing responses or adherence to treatment
- The adoption of targets may encourage indiscriminate use of either high-dose statins or combination lipid therapy

Target lipid levels are appropriate for guiding treatment in secondary prevention and for people with conditions that carry very high risk, such as those with familial hypercholesterolaemia.

Which statin and what dose should be prescribed?

The New Zealand guidelines recommend the following starting doses:[1]

- For people with five-year CVD risk of 15–20% – simvastatin 20 mg (titrate if needed)
- For people with known CVD or CVD risk >20% – simvastatin 40 mg

Statins available in New Zealand

There are three statins currently listed on the Pharmaceutical Schedule in New Zealand – simvastatin, atorvastatin and pravastatin (refer to the Pharmaceutical Schedule for prescribing criteria). N.B. The access criteria for atorvastatin have recently been widened (see page 55).

At comparable doses, statins are therapeutically equivalent in reducing LDL-cholesterol.[11] The HDL-cholesterol elevating and triglyceride lowering effects are also similar among different statins at equivalent doses. While there are some pharmacokinetic differences between statins, choice can generally be guided by patient tolerability and cost. If high intensity statin treatment is indicated atorvastatin may be better tolerated than simvastatin.

Simvastatin

- Current guidelines, availability criteria and cost mean simvastatin is the most commonly prescribed statin in New Zealand

Atorvastatin

- Consider when more intensive statin therapy is required
- Can be used in people with impaired renal function as no dose adjustment is required

Pravastatin

- Has the lowest potential for drug interactions as it is not extensively metabolised by cytochrome P450 isoenzymes

Initiating a statin

For primary prevention, the starting dose of a statin ranges from 20 – 40 mg. Table 1 outlines some specific scenarios in which a different dose or type of statin may be more appropriate.

Tolerance to dose and adverse effects

Moderate to high doses of statins are often used to ensure maximum LDL-cholesterol reductions. However, it is important to remember that most of the effect of a statin occurs at less than the maximum dose.[12] For each doubling of the statin dose e.g. from 20 mg to 40 mg simvastatin, there is only a small, additional absolute reduction in cardiovascular events. In addition, higher doses are associated with greater adverse effects.

Table 1: Recommended statin doses

Situation	Prescribing solution
Primary prevention of CVD (CVD risk ≥ 15%)	Simvastatin 20 – 40 mg
Patient with known CVD	Simvastatin 40 mg
Simvastatin not tolerated	Reduce dose if appropriate OR trial atorvastatin
Patient with severe renal insufficiency (creatinine clearance less than 30 mL/min)	Simvastatin 10 mg (use doses above 10 mg with caution) OR Consider changing to atorvastatin (no dose adjustment required in impaired renal function)
Risk of drug interactions e.g. amiodarone, verapamil, diltiazem, warfarin or combination with other lipid lowering agents	Consider switching to pravastatin (less potential for interactions, special authority criteria apply)
Intensive therapy required e.g. familial hypercholesterolemia, very high CVD risk	The maximum dose of simvastatin is 80 mg, with an increased risk of adverse effects and interactions at this level Consider switching to atorvastatin

For those patients who are unable to tolerate higher doses, or if there is the potential for drug interactions, lower doses may be safer and still provide worthwhile benefits.

If a patient experiences adverse effects with one particular statin, the dose can be lowered or the patient can be switched to another statin.[12]

Adverse effects of statin therapy are usually minor (Table 2). Asymptomatic elevation of transaminase levels can occur. However for some patients, adverse effects are more severe, sometimes leading to discontinuation of treatment.

Statin intolerance

Statin intolerance is defined as "the presence of clinically significant adverse effects that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised".[10]

Table 2: Adverse effects related to statin use[10]

Common	Gastrointestinal disturbance (abdominal pain, constipation, flatulence, acid reflux) Headache Myalgia
Less common	Sleep disturbances, including insomnia and nightmares Memory loss Sexual dysfunction Depression
Rare	Serious muscular effects e.g. myopathy, rhabdomyolysis Peripheral neuropathy Interstitial lung disease Skin rashes and hair loss

Statin intolerance is common and is thought to affect approximately 5 to 10% of people taking statins.[10] A recent study found that a regimen of 2.5 mg simvastatin, taken every other day and titrated upward, was tolerated in more than 50% of previously statin intolerant patients, with satisfactory lipid lowering efficacy.[13] Studies have also shown that low dose atorvastatin is tolerated and efficacious in people with previous statin intolerance.[13]

What monitoring is required when prescribing a statin?

The New Zealand guidelines recommend that creatine kinase is checked in symptomatic patients taking statins. No other monitoring is routinely required.[1]

Before initiating a statin:

- Measure baseline liver enzymes (ALT only required). The risk to the liver from statin treatment is negligible. Statins should not be withheld in patients with mildly raised baseline levels. However, do not initiate a statin if the ALT level is three or more times the upper limit of normal.
- A baseline creatine kinase level is not necessary. Awareness of risk and monitoring for symptoms is more important.

Monitoring during statin treatment:[1]

- It is not necessary to routinely monitor liver function during treatment
- Monitoring of creatine kinase is not required in people who are asymptomatic. If there is unexplained muscle pain, tenderness or weakness, statin treatment should be stopped and creatine kinase levels checked.

For more information on monitoring, see "Liver Function Testing in primary care" (bpac^nz, July 2007).

Statin induced myopathy

The risk of myopathy in people using statins is usually related to the dose they are taking, with higher risk associated with higher doses. Elderly people and people taking combination lipid-lowering treatments are also at greater risk.

Other risk factors for statin induced myopathy include:[14]

- Underlying muscle disorders
- Past history of myopathy with any lipid-lowering drug
- Renal or liver impairment
- Multisystem diseases e.g. diabetes
- Untreated hypothyroidism
- Major surgery or trauma
- Co-prescription of drugs that inhibit cytochrome P450 (CYP3A4) e.g. fibrates, nicotinic acid, calcium channel blockers, ciclosporin, amiodarone, macrolide antibiotics, azole antifungals, protease inhibitors, warfarin
- Vigorous exercise
- Alcohol misuse
- Excessive consumption of grapefruit juice

Management

For muscle pain without an elevated creatine kinase level, reduce the dose of the statin or trial a different statin. If symptoms do not resolve, discontinuation of the statin may be required.

If there are symptoms and the creatine kinase level is elevated between three to ten times normal, reduce the dose of the statin and monitor symptoms and creatine kinase level weekly. If symptoms do not resolve or creatinine kinase levels do not return to normal, discontinuation of the statin may be required.

If there are symptoms and the creatine kinase level is elevated greater than ten times normal, the statin should be discontinued immediately.[1]

When should other lipid lowering agents be considered?

The New Zealand guidelines recommend that simvastatin is the first-line medicine of choice for lipid reduction.[1]

Evidence from clinical trials strongly supports the use of statins in preference to other lipid lowering agents. Statins reduce the risk of major coronary events, revascularisation rates and stroke, regardless of the initial lipid levels.[9] In contrast to statins, the evidence of benefit to patient outcomes for other treatments is variable, ranging from reasonable evidence for nicotinic acid to no supportive evidence for ezetimibe (of long-term reduction in morbidity and mortality).[9]

Combination lipid-lowering treatment should generally be supervised by a specialist due to the increased risk of serious adverse effects such as rhabdomyolysis. Monitoring of liver function and creatine kinase should also be considered.[15]

For patients who require intensive lipid lowering treatment, combination treatment is considered to be no more effective than high-dose statin monotherapy, for improving clinical outcomes.[16]

Nicotinic acid

Nicotinic acid (also known a niacin or vitamin B3) has a long history of use for treating lipid disorders. It is particularly useful for increasing HDL-cholesterol levels. Nicotinic acid can be used alone or in combination with other lipid lowering medicines.

The addition of nicotinic acid to statin treatment significantly increases HDL-cholesterol and leads to additional LDL-cholesterol lowering along with lowering triglycerides and lipoprotein (a).[17] Nicotinic acid increases HDL-cholesterol between 15% to 35%, compared to between 5% to 15% with statin treatment.[17]

There is some evidence that combination nicotinic acid and statin treatment has the potential to result in reductions in risk for adverse cardiovascular events. However, large-scale clinical outcome trials are needed to confirm this.[17]

There has been concern that nicotinic acid treatment may lead to worsening of glucose control in people with diabetes. Studies have shown that the use of nicotinic acid may increase fasting glucose levels, possibly requiring adjustment of the patient's antihyperglycaemic regimen.[17]

The use of nicotinic acid is often limited by poor tolerability. At standard doses (1.5 to 4.5 g/day), flushing occurs in 80% of patients and pruritus, paresthesias and nausea each occur in about 20%.[18] A combination product (Tredaptive) has now been developed, which combines extended release nicotinic acid (1000 mg) with a prostaglandin inhibitor laropiprant (20 mg). This combination has been shown to reduce flushing compared to placebo. Tredaptive is not funded and costs approximately $100 per month.

See. "Nicotinic acid/laropiprant (Tredaptive®) now available in New Zealand" (BPJ 24, Nov 2009) .

Bottom line: Nicotinic acid could be considered in combination with a statin for those who require additional lipid-lowering, when statins alone are not adequately controlling dyslipidaemia. It may also be used as monotherapy for people who are intolerant of statins.

Ezetimibe

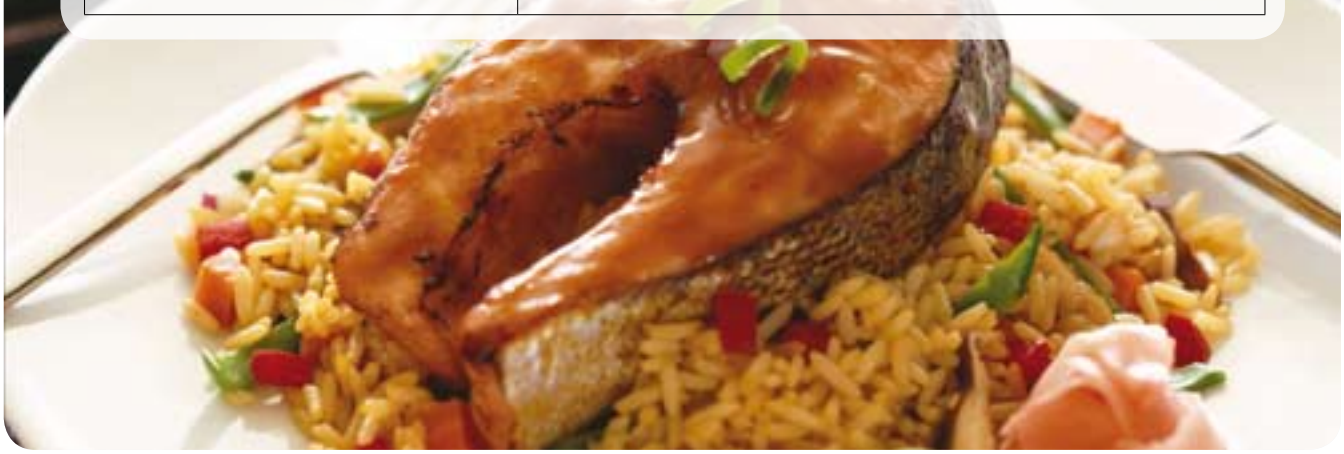
Ezetimibe is a cholesterol absorption inhibitor that reduces intestinal absorption of both dietary and biliary cholesterol.[19] The precise role of ezetimibe relative to other lipid lowering drugs is unclear. A recent trial found that ezetimibe in combination with a statin is less effective than nicotinic acid combined with a statin.[20] In addition the clinical benefits of ezetimibe, alone or in combination with a statin, on cardiovascular morbidity and mortality have not been established.[21]

Lifestyle interventions for lipid lowering

Lifestyle interventions, including dietary modification, exercise and weight management are an essential component for all people who require of lipid lowering,[22] and should accompany any pharmacological therapy.

Lifestyle advice should promote "healthy heart" foods and an active lifestyle. In general the following lifestyle advice can be discussed:[1]

Dietary advice "Small changes in eating habits can make a big difference"	Adopt a cardioprotective dietary pattern e.g. ▪ Consider adding plant sterol or stanol-fortified spreads ▪ Eat oily fish regularly ▪ Choose foods which are low in saturated fats and dietary cholesterol ▪ Choose fruits and/or vegetables at every meal and for most snacks ▪ Select whole grains, whole grain breads, or high fibre breakfast cereals in place of white bread and low fibre varieties Consider referral to a dietitian for a personalised eating plan
Physical activity "Look for ways to build physical activity into your day"	Complete a minimum of 30 minutes of moderate intensity physical activity e.g. brisk walking on most days of the week. This may be carried out all at once or accumulated in ten minute bouts during the day. People who are already doing this should increase the amount and intensity of their exercise if possible. Consider issuing a green prescription or referring to a local sports trust such as Push Play (**http://pushplay.sparc.org.nz**)



The recommended dose of ezetimibe is 10 mg per day and there is no additional benefit in using higher doses.[12]

Bottom line: Ezetimibe may be considered in combination with a low dose statin in patients who are not able to tolerate high doses of statins.[18] It may also be considered as an option for monotherapy for people who are intolerant to statins.

Fibrates

Fibrates are a class of medicines that are primarily used for the treatment of specific lipid abnormalities, such as hypertriglyceridaemia.[19] Fibrates currently available in New Zealand are bezofibrate and gemfibrozil (not subsidised). Fenofibrate is often used in clinical trials but is currently not registered in New Zealand.

Fibrates are known to reduce coronary risk, especially in people with type 2 diabetes or with features such as high triglycerides, low HDL-cholesterol and excessive weight. This benefit may relate in part to the HDL-cholesterol raising effects of these medicines. However, while fibrates increase the level of HDL-cholesterol in most patients, they are much less effective than statins in lowering LDL-cholesterol and may need to be given in combination with a statin. This combination is effective but has been associated with an increased risk of myopathy.[22]

Combination treatment with a statin and a fibrate should usually be initiated under specialist advice.[10]

Bottom line: A fibrate e.g. bezafibrate, may be considered in combination with a statin in people with high triglyceride levels or low HDL-cholesterol levels, that have not responded to statin treatment alone, bearing in mind the increased risk of myopathy with combination treatment.

Caution over the use of red yeast rice supplements

Red yeast rice, also known as chinese red rice, is a herbal medicine supplement which is promoted for use as a lipid-lowering agent. The active ingredients occur as a fermentation by-product of cooked rice on which red yeast has been grown. Supplements contain a naturally occurring form of the statin, lovastatin (mevinolin) along with several other mevinic acids and compounds such as sterols, isoflavones and monounsaturated fatty acids.[23]

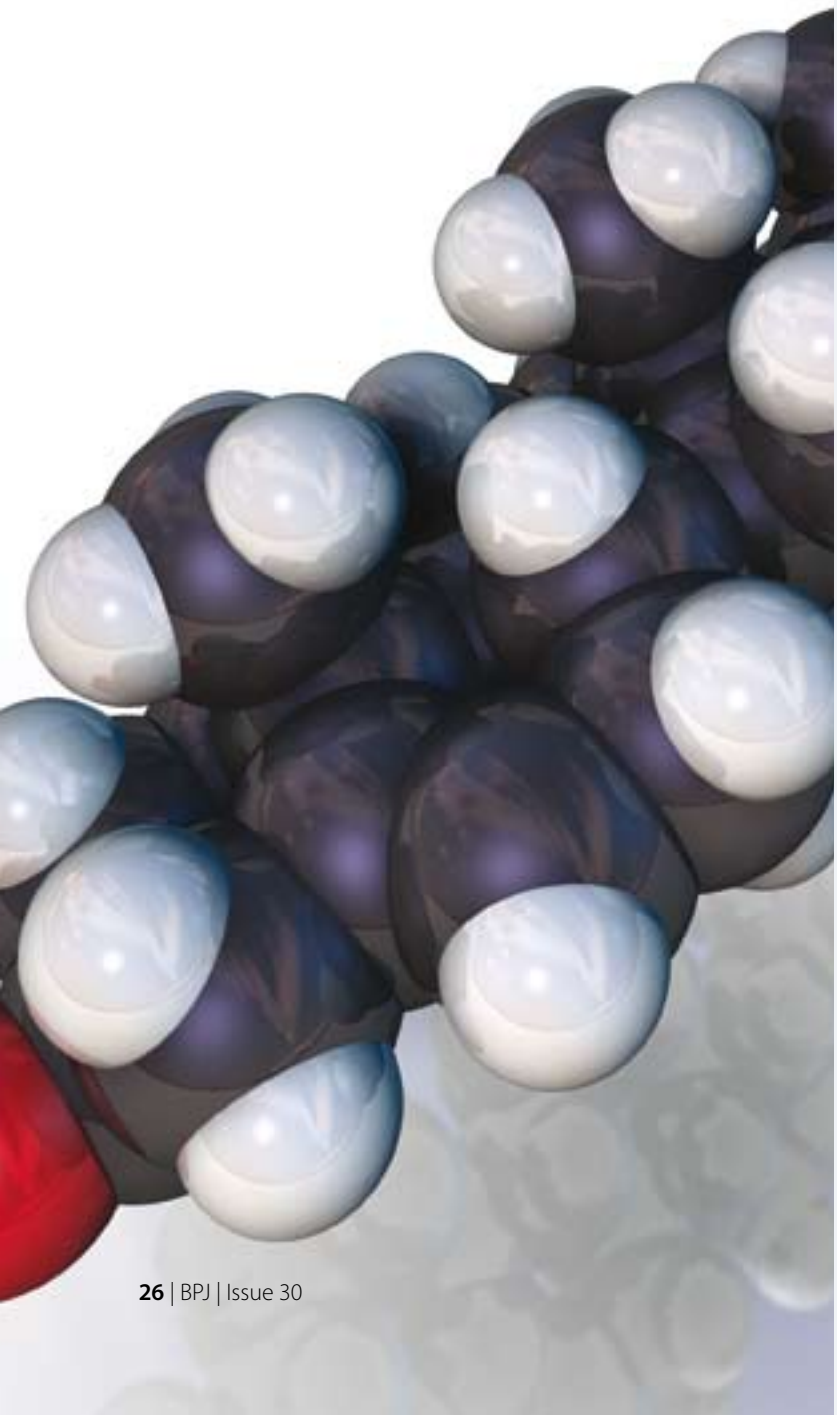
The lovastatin compound, mevinolin, is likely to make the greatest contribution to the cholesterol lowering effect of this supplement, however the other ingredients may contribute to an additive effect on cholesterol lowering. Supplements may contain from 0 to 5 mg of “statin-like” substances in each capsule or tablet.[23]

Because red yeast rice supplements may contain significant amounts of statin-like substances, they can potentially cause the same adverse effects as statins e.g. myopathy and raised liver enzymes. Red yeast rice is also likely to be subject to the same interactions as statins e.g. grapefruit juice and prescription medicines such as amiodarone, verapamil, diltiazem and warfarin. Red yeast rice supplements may act additively with prescription statins and other lipid lowering medicines.[23]

In the USA, the Food and Drug Administration (FDA) considers red yeast rice supplements that contain statins to be unapproved drugs. The general consensus is that the use of red yeast rice supplements should be avoided.

Red yeast rice supplements do not presently appear to be commonly available in New Zealand, however the product is readily accessible via the internet.

ACKNOWLEDGMENT Thank you to **Professor Norman Sharpe**, Medical Director, National Heart Foundation of New Zealand for expert guidance in developing this article.



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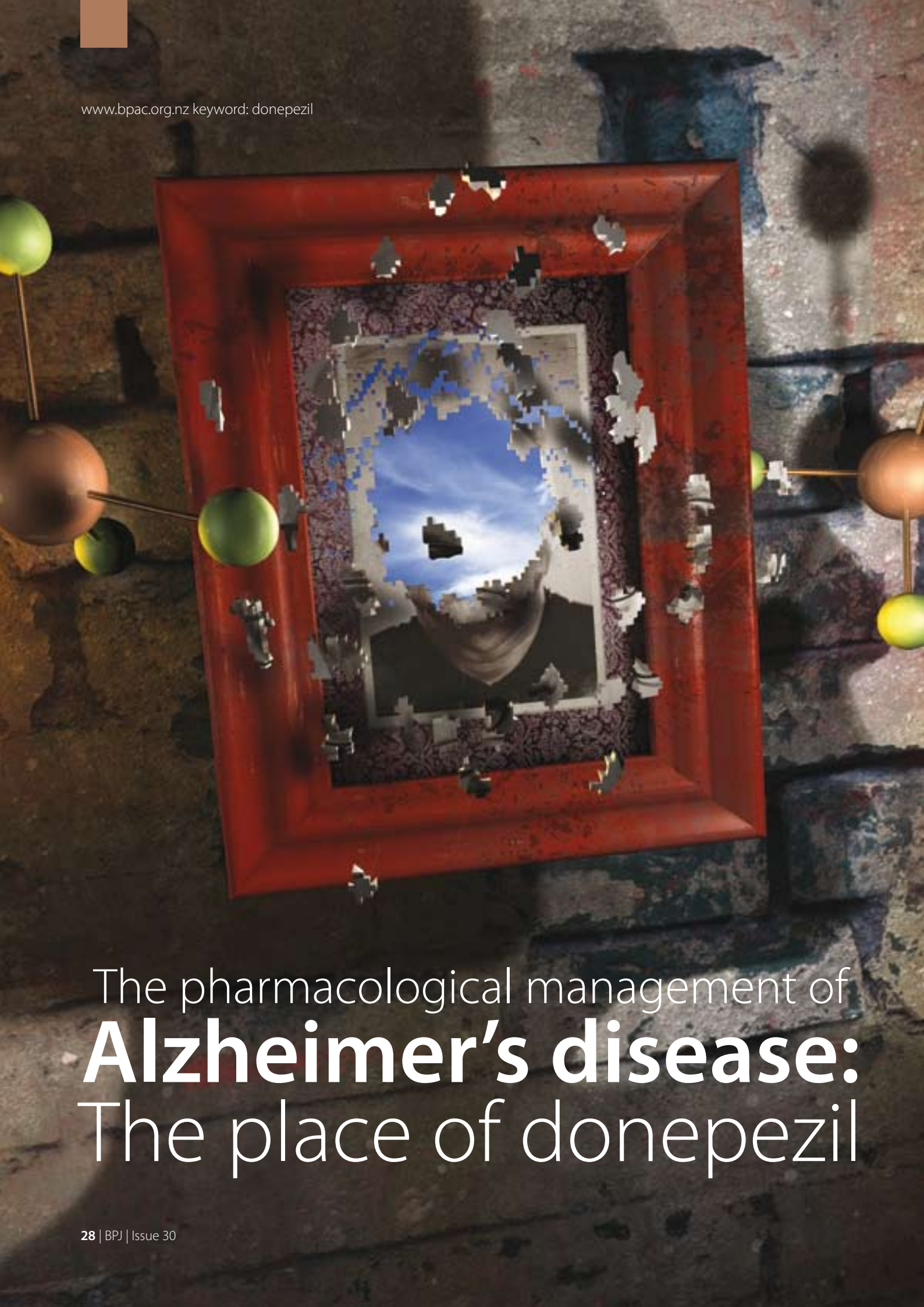
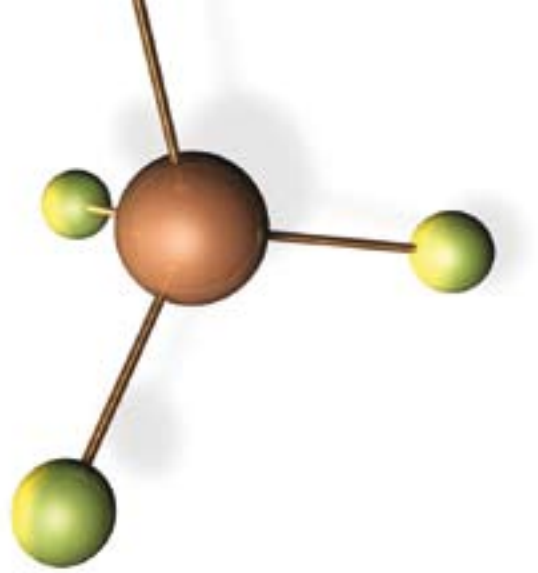


The pharmacological management of **Alzheimer's disease:** The place of donepezil



Donepezil to be funded for the treatment of Alzheimer's disease

As the world's population ages, the number of people affected by Alzheimer's disease, the most common form of dementia, will rise rapidly. There is currently no treatment available that can prevent the onset of Alzheimer's disease or its progression. Management is focused on symptomatic treatment using lifestyle, behavioural and pharmacological methods, where appropriate. The aim of treatment is to improve quality of life for both the person with Alzheimer's disease and their family.

PHARMAC recently announced that donepezil, a medicine used in the management of Alzheimer's disease, will be funded on the Pharmaceutical Schedule from November 1, 2010. The Donepezil-Rex brand (donepezil hydrochloride) will be available for prescription by any prescriber, and will not require Special Authority approval or specialist recommendation.

Donepezil is a specific and reversible inhibitor of acetylcholinesterase, registered in New Zealand for the symptomatic treatment of Alzheimer's disease and vascular dementia. Some guidelines recommend that donepezil (and other acetylcholinesterase inhibitors) only be used in

* The Mini Mental State Examination (MMSE) is a commonly used test of cognition. The MMSE is not specific for Alzheimer's disease and is confounded by age and education level. It should be used only as an aid to assessment and not as an explicit guide to treatment.

Key Concepts

- Management of Alzheimer's disease focuses on slowing the progression of symptoms through lifestyle, behavioural and sometimes pharmacological methods.
- Donepezil is an acetylcholinesterase inhibitor used in the management of Alzheimer's disease. From November 1, 2010, Donepezil-Rex will be funded on the Pharmaceutical Schedule, without the need for Special Authority.
- Donepezil and other acetylcholinesterase inhibitors treat the symptoms of Alzheimer's disease and in some people improve symptoms related to cognition, behaviour and function. They may delay the need for full-time institutional care. There is no evidence to suggest that they prevent the onset or the ultimate progression of Alzheimer's disease.
- Before prescribing donepezil GPs are advised to discuss this with a practitioner experienced in the treatment of dementia and in the use of acetylcholinesterase inhibitors.
- Patients using cognitive enhancers such as donepezil should be reviewed regularly for treatment response and adverse effects.

Cost-effectiveness of donepezil in Alzheimer's disease

Estimates of the cost-effectiveness of donepezil need to make several assumptions around the effects of treatment on progression to full-time care. The extent that acetylcholinesterase inhibitors delay rest home placement is uncertain, as the evidence is incomplete and ambiguous.

The AD2000 study, published in 2004, concluded that donepezil provided very minimal clinical benefits and was not cost-effective in people with mild or moderate disease.[7] However, due to low recruitment and methodological issues, many subsequent reviews or analyses have not incorporated the results of the AD2000 study.

In the National Institute for Clinical Excellence (NICE) guidelines from the United Kingdom it was concluded that donepezil and other acetylcholinesterase inhibitors are cost-effective, but only in people with moderate Alzheimer's disease, and this is the basis of their recommendation for the use of these medicines.[2] The main benefits are associated with assumed cost savings due to delayed full-time institutional dementia care and support.

There is also debate about the cost-effectiveness of donepezil in people with mild Alzheimer's disease, and whether there are benefits in starting acetylcholinesterase inhibitors, both on clinical and economic grounds. While the AD2000 trial did not report any benefits in people with mild disease, other more recent cost-effectiveness models for donepezil in mild to moderate Alzheimer's disease, support their use in the early stages of the disease.[6]

The lack of clarity regarding cost-effectiveness reinforces the need to regularly review and assess the response to donepezil and to stop treatment if it appears ineffective or is not tolerated.

moderate Alzheimer's disease (rated by a MMSE* score of 10 – 20).[1,2] However there is evidence that donepezil has a positive effect in some people with severe[3,4] and mild Alzheimer's disease.[5] In practice, donepezil may be used in any patient with Alzheimer's disease, ranging from the newly diagnosed to those with severe disease.

Donepezil is considered to be cost-effective in moderate Alzheimer's disease (see sidebar) and there are emerging views that cost effectiveness may also extend to patients with mild disease (MMSE 21 – 26) mainly due to assumed reduced costs related to institutionalisation and care.[6]

It is recommended, due to the complexity of Alzheimer's disease and dementia treatment in general, that only clinicians with experience in treating dementia should initiate therapy. In practice this may be difficult but it is advisable to discuss treatment with a specialist and to become familiar with local protocols and practices. GPs may work in conjunction with the care team to assess the response to therapy, as the GP is more likely to be familiar with the patient over a longer time period.

The use of acetylcholinesterase inhibitors in Alzheimer's disease

Alzheimer's disease is associated with a decrease in activity of the cholinergic system in the brain. Pharmacological treatments for Alzheimer's disease are based on inhibition of acetylcholinesterase, which increases the concentration of acetylcholine in the brain, resulting in increased cognitive function in some people. This class of drugs have also been shown to have some effect on other forms of dementia, including vascular dementia.[8]

There are currently three acetylcholinesterase inhibitors available and registered in New Zealand for the treatment of Alzheimer's disease – donepezil (Donepezil-Rex, Aricept, Donezil), galantamine (Reminyl) and rivastigmine (Exelon). Donepezil-Rex is the only acetylcholinesterase inhibitor that will be funded on the Pharmaceutical Schedule at this time.

Are acetylcholinesterase inhibitors effective?

Acetylcholinesterase inhibitors improve symptoms related to cognition, behaviour and function for some people with Alzheimer's disease.[5] However, there is no evidence to show that they slow the underlying progression of the disease.[1, 2] Minor improvements in daily activity scores and cognition test results have been observed such as an improvement of one to two points on the 30 point MMSE test. For some people with Alzheimer's disease this may mean that they have improved memory and ability to perform daily tasks, improved quality of life and reduced need for care.

The results of acetylcholinesterase inhibitor therapy are variable, but on average, patients may expect about six months of preserved cognitive function. Clinically relevant improvement has been measured (using cognitive tests) in approximately 39% of patients taking donepezil versus 22% taking a placebo.[2] Increasing the dose of the acetylcholinesterase inhibitor may result in a greater improvement for some patients, however adverse effects may become intolerable.[2,5]

Comparing donepezil to other non-funded acetylcholinesterase inhibitors

All three acetylcholinesterase inhibitors available in New Zealand are similarly effective in treating the symptoms of Alzheimer's disease and are associated with similar adverse effects. Lack of response to one drug does not necessarily mean that benefit will not be derived from another.

Galantamine

Like donepezil, galantamine is a selective inhibitor of acetylcholinesterase, however it also enhances the action of acetylcholine on nicotinic receptors. Nicotinic cholinergic receptors are thought to be important in regulating cognitive functions such as attention. Galantamine has a longer half-life than donepezil, which could mean that severe adverse effects persist for longer.[2] However, there have been no significant clinical differences demonstrated between the effect and tolerability of galantamine and donepezil.

Cognitive testing in Alzheimer's disease and its role in defining progression

Cognitive tests are used to monitor both the progression of Alzheimer's disease and the treatment effect of pharmacological agents. The two most commonly used tests in New Zealand are the Mini Mental State Examination (MMSE) and Addenbrooke's Cognitive Examination-Revised (ACE-R).

The MMSE is a brief test (approximately ten minutes) that can be used for screening for cognitive impairment and for estimating severity and progression of Alzheimer's disease and other forms of dementia. The maximum score on the MMSE test is 30. Age and education levels may influence scores. Scores above 20 can suggest mild cognitive impairment, scores between 11 and 20 suggest moderate cognitive impairment and scores of ten or below suggest severe cognitive impairment. These scores are suggested in the context that a patient has already been clinically diagnosed with Alzheimer's disease and a level of cognitive impairment is to be ascertained.

The ACE-R is a simple and effective test that can be administered by any clinician.[9] It has been suggested that it can detect dementia earlier than MMSE though neither test should be used as a means of diagnosing Alzheimer's disease. Both tests are useful in assessing patients and helping family and caregivers to understand disease progression.

An online copy of ACE-R can be found at several websites including: **www.stvincents.ie/dynamic/File/Addenbrookes_A_SVUH_MedEl_tool.pdf**

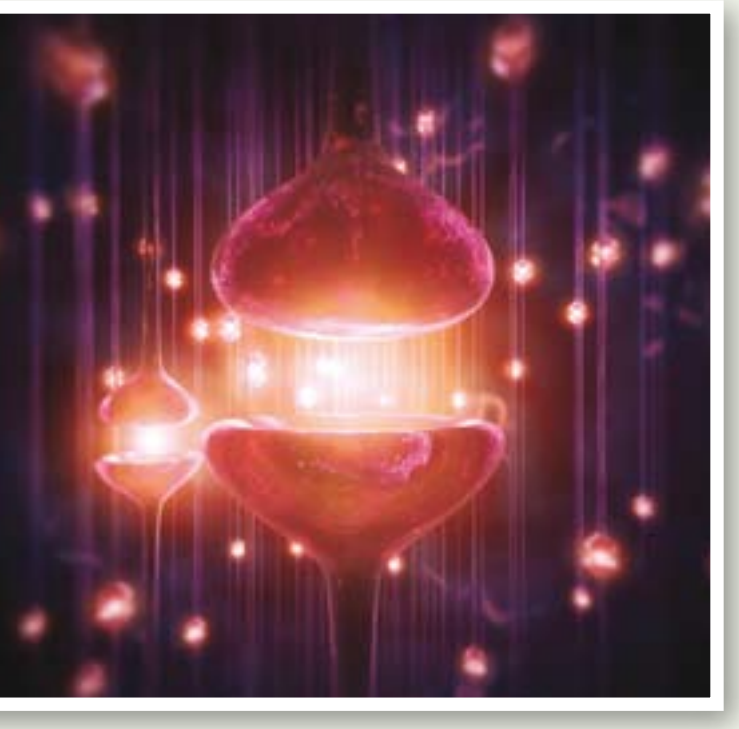
The Alzheimer's disease Assessment Scale-cognitive subscale (ADAS-cog) is used for measuring cognitive impairment and is frequently used as the outcome measure in clinical studies.

Memantine

Memantine is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist, which is also used for the symptomatic treatment of Alzheimer's disease.[10] It is thought that malfunction of glutaminergic neurotransmission at NMDA receptors may contribute to symptom expression and progression of Alzheimer's disease. Memantine partially blocks NMDA receptors, inhibiting over-stimulation by the excitatory neurotransmitter glutamate.[10] This action can result in a small symptomatic improvement in cognition, mood and the ability to perform daily tasks, similar to the functional gain observed in some people taking acetylcholinesterase inhibitors.

The adverse effects of memantine are usually mild and may include influenza-like symptoms, headaches, muscular pain and dizziness.

In general, it is considered that the limited evidence of benefit for memantine is outweighed by the economic costs involved with the treatment.[2, 11] Memantine is not currently funded in New Zealand.



Rivastigmine

Rivastigmine is less selective than donepezil and targets both acetylcholinesterase and butyl-cholinesterase inhibitors.[5] However this increased inhibition does not appear to result in a clinically different effect than donepezil. Clinical trials used to study rivastigmine have only lasted 24 weeks in duration, therefore it is unproven whether treatment gains would last longer than six months. Rivastigmine is available as a transdermal patch preparation, which may be preferable for people who have experienced intolerable adverse gastrointestinal effects with an oral acetylcholinesterase inhibitor.

Initiating donepezil and assessing treatment response

Clear treatment goals should be set before commencing an acetylcholinesterase inhibitor. As donepezil is the only acetylcholinesterase inhibitor that is to be funded, it is recommended to trial this medicine first. Other acetylcholinesterase inhibitors may be trialled if there is no response to donepezil, however this will depend on whether the cost of treatment is able to be met.

Individual response to donepezil can not be predicted. The duration of treatment should be for as long as the patient is seen to benefit. The benefits of continuing donepezil should be assessed through the use of periodic evaluations of the patient's overall and cognitive function.

Initiating donepezil

Practice points

- Before initiating donepezil in a person with Alzheimer's disease it is strongly recommended that a practitioner experienced in the treatment of dementia is consulted.
- Donepezil should not be considered unless a clear diagnosis of Alzheimer's disease has been made. There is no evidence that donepezil is beneficial in people with mild cognitive impairment or that it delays the progression to Alzheimer's Disease.[12]

- Clearly defined treatment aims should be set e.g. decreased carer burden and stress, increased time until long-term care is needed, stabilisation of memory or cognition, decline in specific behaviours.
- Once the decision has been made to prescribe donepezil, it is recommended that treatment is commenced at 5 mg/day (once daily dosing, usually taken at night). This dose should be maintained for at least one month before clinical response is assessed. Monitor for adverse effects.
- If tolerated the dose may be increased to 10 mg/day. Treatment response should be reassessed at three months and again at six months.
- Reduce the dose to 5 mg/day if adverse effects become intolerable or improved clinical benefit is not apparent.
- If no benefit is observed at either dose, donepezil should be discontinued.

Best Practice Tip: Some DHB areas have specialised "memory clinics" where patients with Alzheimer's disease can be diagnosed and treated and families can be supported in understanding the changes and challenges likely to take place after diagnosis. Contact your local DHB for details of this service.

Assessing response to treatment

It is important to explain to both the patient and their family that pharmacological therapy for Alzheimer's disease is largely symptomatic. Acetylcholinesterase inhibitors can improve quality of life and cognitive function in many patients, but these gains are only temporary. Family and caregivers are often involved in observing for treatment response and adverse effects.

Potential adverse effects should be discussed prior to treatment as they can affect the way treatment goals are set. For example, if the goal for therapy is to increase the quality of life then the extent of the adverse effects can play a large role in deciding if, and when, to cease therapy.

Cognitive improvement[2]

- Assess cognitive function and activities of daily living prior to starting treatment using cognitive tests such as MMSE or ACE-R and self-reported and family observation of behaviours
- Assess initial treatment response after one month
- After three months at the highest tolerated dose, assess cognitive response to therapy
- If cognitive test scores indicate improvement (or no deterioration) and there is evidence of functional or behavioural improvement, continue treatment
- Treatment for longer than six months should be based on clear response and adequate ability for monitoring of the patient

Adverse effects, precautions and drug interactions

Mild cholinergic adverse effects such as vomiting and nausea affect approximately 20% of people taking acetylcholinesterase inhibitors. Other adverse effects associated with donepezil may include fatigue, dizziness, headache, syncope, bradycardia, agitation, confusion, dyspepsia, increased sweating and tremor.

Adverse effects are dose dependent, usually of short duration, and resolve spontaneously or after dose reduction. Adverse effects may be minimised by initiating treatment at a low dose, i.e. 5 mg donepezil, and increasing the dose gradually, i.e. after one month.

N.B. Each acetylcholinesterase inhibitor has a slightly different adverse effect profile. Refer to the manufacturer's data sheets.

Precautions to the use of donepezil include: asthma, COPD, epilepsy or seizure disorder, urinary retention and a history of peptic ulcers.

As donepezil and other acetylcholinesterase inhibitors may cause bradycardia, particular caution is required in prescribing to people with significant bradycardia, sick sinus syndrome or other superventricular cardiac

Pharmacological treatments should be used as part of a wider management plan for Alzheimer's disease

Management of Alzheimer's disease involves treatment of cognitive, behavioural and psychological issues. Acetylcholinesterase inhibitors such as donepezil can have a beneficial effect on cognitive symptoms, patient function, behaviour and reduce the burden on caregivers, but they are not a cure. The wider management of patients with Alzheimer's disease includes educating patients, their caregivers and family on the nature of the disease and how to deal with the inevitable decline in the patient's cognitive function and their ability to care for themselves. The role of clinicians in this education process and in the overall management of the disease is important.

For more information about identifying early signs of cognitive decline in older people, see BPJ 23 (Sept 2009); "Having a Senior Moment".

conduction disturbances, such as sinoatrial or atrioventricular block.

Drug interactions

All acetylcholinesterase inhibitors have the potential to increase the risk of bradycardia with beta blockers, digoxin, amiodarone and calcium channel blockers. The actions of other anticholinergic drugs, e.g. oxybutinin and benztropine, may be antagonised.

Donepezil is metabolised in the liver but there appear to be few clinically significant drug interactions involving the cytochrome p450 system. There is a possibility that enzyme inhibitors, e.g. fluoxetine, paroxetine and erythromycin, may increase drug concentrations of donepezil, and enzyme inducers, e.g. phenytoin and carbamazepine, may reduce drug concentrations. However, such interactions do not appear to be clinically significant.

Discontinuing donepezil

Treatment with donepezil or any other acetylcholinesterase inhibitor should be discontinued if:

- Significant adverse effects occur
- There is poor adherence to the treatment regimen or monitoring requirements
- Treatment goals are not achieved or major deterioration in the patient's condition occurs

After donepezil is discontinued beneficial effects usually abate gradually. There is little evidence to suggest a rebound effect after abrupt cessation of donepezil, however in practice this is sometimes observed. Sudden loss of cognitive function is possible and patients should be supported and monitored prior to, and during, the cessation period.

ACKNOWLEDGMENT Thank you to **Dr Gary Cheung** and **Dr Richard Worrall**, Specialist Psychogeriatricians, Greenlane Clinical Centre, Auckland DHB for expert guidance in developing this article.

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What's up with the men folk?

A call for successful initiatives in getting men to attend general practice

The average life expectancy of males in New Zealand is four years less than females – 78.2 years versus 82.2 years. Life expectancy for Māori males is 8.6 years less than other males in New Zealand. Men are more likely to have cardiovascular disease, high cholesterol and higher rates of many common cancers, yet anecdotal reports suggest that they are much less likely than women, to attend general practice and talk to a GP or practice nurse about their health.

In Part One of our men's health series, we outline some national programmes and campaigns that promote men's health. In Part Two, we hope to bring you some insight, solutions and success stories from your primary care colleagues.

Men's health initiatives in New Zealand

One Heart Many Lives

One Heart Many Lives is a cardiovascular disease primary prevention programme, targeting Māori and Pacific men. It aims to raise both awareness of cardiovascular disease and its causes and decrease the level of cardiovascular risk among men. The main message is that the health of one person affects the lives of many others.

One Heart Many Lives is currently operating in Northland, Hawke's Bay, Whanganui, Taranaki and Lakes DHB. Each area adds unique characteristics to the national programme, making it their own.

www.oneheartmanylives.co.nz

Mana Tāne Ora o Aotearoa

Mana Tāne Ora o Aotearoa, the National Māori Men's Health Coalition, was formed to raise awareness of Māori men's health issues by profiling relevant health and social services targeting men's health.

Mana Tāne Ora o Aotearoa was established at the inaugural Māori men's health conference in 2009. The coalition is creating, developing and sharing innovative practices in Māori men's health, and expanding on successful models, programmes and services. It supports the sharing of successful practices and effective outcomes with the wider sector, providing a forum for information exchanges and facilitating research and best practice guidance.

www.taneora.co.nz

Movember

Movember is an international campaign that aims to raise funds and awareness for men's health. In New Zealand, Movember supports the Cancer Society (prostate cancer) and Mental Health Foundation (Out of the Blue depression campaign).

Men from around New Zealand can join the campaign and seek sponsorship from family, friends and colleagues, while they grow a moustache during the month of November.

Since 2006, more than 50,000 people have participated and $4 million has been raised in New Zealand.

http://nz.movember.com/

Men's Sheds

The Men's Sheds movement started in Australia to connect men with their communities and society, and is now growing throughout New Zealand.

Men's sheds offer a place for men to gather for friendship, to discuss health issues and to learn new skills. Men's sheds can help in addressing isolation, loneliness and depression.

www.menzshedaotearoa.org.nz

The Men's Health Challenge – Te Mātātaki Hauora Tāne

Men are more frequently diagnosed with cancer than women and also more likely to die from it. The Cancer Society of New Zealand has developed Te Mātātaki Hauora Tāne, a men's health challenge aimed at encouraging men, especially those aged over 50 years, to be more proactive about their health. Men are encouraged to complete a "scorecard" of health risk factors and make an appointment to see a health professional if they have identified two or more risks.

www.cancernz.org.nz/information/mens-health

Blue September

Blue September is a New Zealand campaign for the promotion of prostate cancer awareness. It encourages men to think about prostate cancer and to discuss it with their GP.

In New Zealand, around 2500 men are diagnosed with prostate cancer every year and 600 men die from it. Promoters of Blue September believe that this mortality rate can be halved by:

- Men taking responsibility for their health
- Men having regular health and prostate checks from at least age 40 years
- Early detection
- Early treatment

A Māori man's risk of dying of prostate cancer is double that of a non-Māori man. It is thought that an unwillingness to recognise the risks of prostate cancer and a reluctance to talk to their GP about it are significant factors in this disparity.

The Blue September campaign supports the Prostate Cancer Foundation of New Zealand.

www.blueseptember.org.nz

www.prostate.org.nz

Men's Health Week

Men's Health Week is an international campaign that was recently held for the first time in New Zealand in June 2010. It aims to encourage men to improve their lifestyle, wellbeing and all areas of their physical, mental, emotional and sexual health. It promotes awareness of important male specific preventable health issues, daily exercise and a regular health checkup.

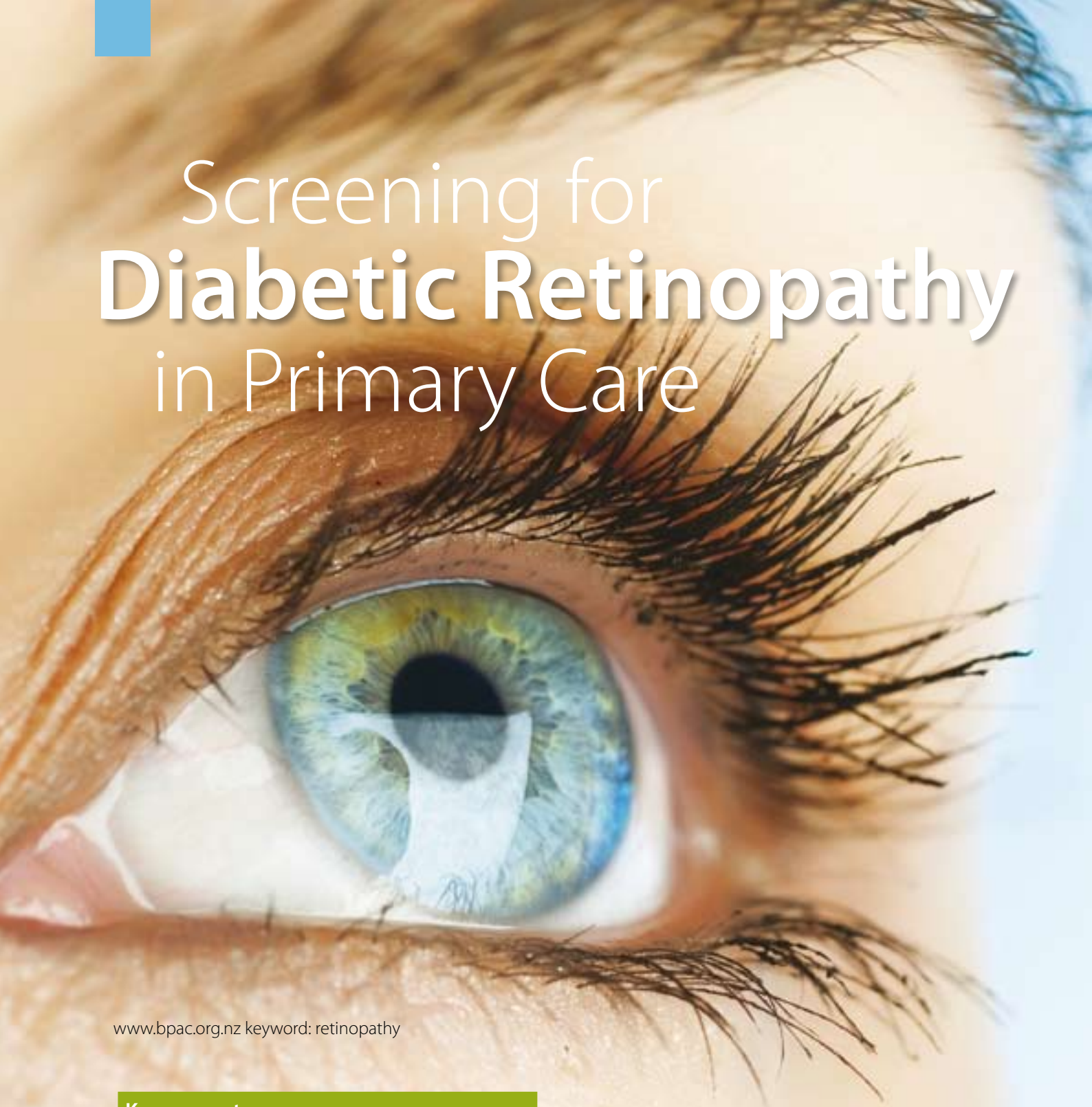
www.menshealthweek.co.nz

We would like to hear from you!

- Do men attend your practice less than women?
- What do you think are some of the reasons why men do not attend general practice?
- What initiatives could your practice adopt to encourage men to attend general practice?
- Is it a good idea to promote "men's health checks" to encourage males of all ages to attend general practice?
- Do you have a "success story" that you would like to share with others?

Please email: **editor@bpac.org.nz** or write to: Editor, Best Practice Journal, P.O. Box 6032, Dunedin

Screening for **Diabetic Retinopathy** in Primary Care



www.bpac.org.nz keyword: retinopathy

Key concepts

- Sight-threatening diabetic retinopathy is largely preventable through regular retinal screening and prompt treatment
- Retinal screening should be carried out at least every two years. More frequent screening regimens are indicated by clinical risk factors such as the duration of diabetes and the degree of pre-existing retinopathy.
- Primary care plays a critical role in ensuring that patients are referred for and attend retinal screening so they can be treated before there is visual deterioration
- Maintaining good glycaemic control, treating hypertension and managing lifestyle risk factors, especially smoking cessation, is also essential

"Get Checked" for diabetes complications

Approximately 5 – 7% of New Zealand adults have been diagnosed with type 1 or type 2 diabetes.[1] The actual number of people with diabetes is likely to be much higher than this. The self-reported prevalence of diabetes is two to three times higher among Pacific, Māori and Indo-Asian people.[1] Diabetes is a leading cause of blindness, end stage kidney failure and complications leading to lower limb amputation. It is a major risk factor for cardiovascular disease and early mortality.

Regular health checks are essential to reduce the frequency of complications from diabetes, as well as to minimise their impact. The "Get Checked" programme is a national initiative, offering free annual health reviews to people with diabetes, by their GP or practice nurse. The programme aims to promote early detection and intervention for problems associated with diabetes.

The "Get Checked" annual health review includes:

- A HbA_{1c} level
- Cardiovascular risk assessment, including blood pressure, lipid profile, height and weight
- Kidney function (microalbuminuria)
- Sensation and circulation of feet
- Retinal check (at least every two years)
- Follow-up plan for care

The annual check for people with diabetes is also a PHO Performance Programme (PPP) indicator.

> The PPP goal is for at least 80% of all people with diabetes enrolled in a practice to have had a full annual "Get Checked" review each year.

In 2009 53% of the estimated number of people with diabetes in New Zealand had an annual "Get Checked" review.[2] This is an improvement from the previous year (46%),[2] but this number still falls considerably short of the PPP target of greater than 80%.

Between 2008 and 2009 annual reviews in the high needs population (identified as Māori and Pacific peoples and those living in lower socioeconomic areas) improved from 52% to 57%.[2]

There is much variation throughout DHB regions and PHOs, with some areas achieving better results. Technical difficulties in data collection may contribute to lower figures in some areas.

Consider the barriers to achieving this goal and ways in which the practice can address this. People with diabetes who are not receiving an annual free review, are potentially at a greater risk of developing harm from complications, which could have been treated if detected early enough.

Diabetic retinopathy is one of the leading causes of blindness in New Zealand

Diabetic retinopathy has been, until recently, the leading cause of preventable adult blindness and vision

impairment in New Zealand. Factors such as advances in treating retinal damage and more effective screening are slowly decreasing the prevalence of diabetic retinopathy in some areas.

The exact incidence of diabetic retinopathy is unknown but it is estimated that 30% of people with diabetes have some degree of retinopathy, with 10% having sight-threatening retinopathy.[3] A New Zealand study of almost 12 000 people with diabetes, conducted between 2003 and 2005, found that almost one-third (32%) had some signs of diabetic retinopathy.[4] There was also evidence that Māori were accessing the retinal screening service at a lower rate than other ethnic groups.[4] As this study was based in one particular region of New Zealand (Wellington), incidence of diabetic retinopathy and disparities in accessing services, may be even greater in other areas. An earlier small study of almost 500 people with type 2 diabetes in South Auckland found that the prevalence of moderate to severe retinopathy was 4% in Europeans, 13% in Māori and 16% in Pacific peoples.[5]

The longer the duration of diabetes, the greater the prevalence of retinopathy. A large longitudinal study, based in the United Kingdom, found that the incidence of sight-threatening diabetic retinopathy after five years, in patients with diabetes (type 1 or 2) who had no signs of retinopathy at baseline, was 3.9%. In patients who initially had mild diabetic retinopathy, 15% had developed sight-threatening retinopathy by five years.[6]

Sight-threatening diabetic retinopathy is largely preventable, through regular retinal screening and prompt treatment. Primary care plays a critical role in ensuring that patients are referred for and attend retinal screening so they can be treated before avoidable loss of vision occurs.

Detecting and preventing diabetic retinopathy

Diabetic retinopathy is asymptomatic until it is at an advanced stage and then it is usually too late for effective treatment. Therefore early detection and prevention are imperative.

In primary care the two key responsibilities are:

- Referral for regular retinal screening at least every two years (and following-up on attendance and subsequent treatment if needed)
- Management of risk factors

Early detection of retinopathy with regular screening can save vision

The objectives of retinal screening in people with diabetes are to:[3]

1. Screen those with known diabetes for the onset of diabetic retinopathy
2. Identify those with early microvascular disease so primary care and diabetes teams can optimally manage risk factors such as glycaemic control and hypertension
3. Refer those with more significant retinopathy who are at risk of visual impairment for management and treatment by an ophthalmologist, before avoidable loss of vision occurs

N.B.: People with pre-diabetes (impaired glucose tolerance and impaired fasting glucose) do not require retinal screening and should not be referred.

Referral process for screening

- Make a referral to the local retinal screening provider
- Check with the patient at their next consultation, that they have been assigned an appointment time for retinal screening (or they have attended the appointment) and follow-up with the provider if this has not occurred
- Request and review a copy of the screening results, ensure that appropriate follow-up has occurred e.g. check that referral to an ophthalmologist has occurred if indicated, or make a note in the patient record that a more frequent screening interval has been recommended
- Place an automatic recall on the patient's notes for when screening is next due
- Follow-up patients who do not attend for screening, ask them what their difficulties in attending are, consider barriers to screening and how your practice may help address these

Each DHB has an individual arrangement with local providers for retinal screening (contact your local DHB if you are unfamiliar with referral options). Screening is usually performed by a suitably trained optometrist, photographic technician, ophthalmologist or other clinician. A designated ophthalmologist usually oversees each local retinal screening programme, to ensure consistency in grading of retinopathy.

Some areas may be under-resourced for the numbers of patients who require retinal screening. In some cases, if the public waiting list is too long, patients may be referred privately. A new study, soon to be published, suggests that the waiting time for referral to an ophthalmologist for moderate background retinopathy or mild maculopathy varies considerably throughout the country, but in most cases is less than the recommended referral time for this grade of disease (four to six months).[7]

Do not wait for signs and symptoms to occur

Early retinopathy is asymptomatic. Signs of blurred or fluctuating vision, spots or "floaters", if related to diabetic retinopathy, are most often associated with advanced disease.

People with diabetes who present with an acute impairment of vision from any cause should be referred for urgent review with an ophthalmologist/eye clinic.

Best practice tip: Retinal photo-screening for diabetic retinopathy does not constitute a full eye examination. Patients should still be regularly reviewed for other eye pathologies such as cataracts or glaucoma. Primary care clinicians can test visual acuity using an eye chart and pinhole. **As a general rule, if visual acuity improves with pinhole testing, then it is more likely that any reduction in visual acuity is due to a refractive error (and may require subsequent referral to an optometrist) rather than due to pathology in the eye (which would require referral to an ophthalmologist).**

Screening intervals

New Zealand guidelines recommend that retinal screening is carried out every two years for a person with diabetes who does not have retinopathy (Table 1).[3]

A referral for screening should be made at the time of a confirmed diagnosis for people with type 2 diabetes because many people already have some degree of retinopathy at this stage. With type 1 diabetes, vision threatening retinopathy is very rare in the first five years after diagnosis or before puberty so screening may commence after this time.[3]

For people with diabetes who have early signs of retinopathy, screening should be more frequent. The frequency of screening is determined by the Guidelines and the clinician's opinion, taking into consideration factors such as the severity of the retinopathy, glycaemic control, blood pressure and the risk of progression (see sidebar).[3]

Diabetic retinopathy can progress rapidly during pregnancy. Women with diabetes who become pregnant should be

screened in the first trimester of their pregnancy. If no retinopathy is detected and the diabetes is well controlled the two-yearly screening schedule may be continued. If a minimal degree of retinopathy is detected or if the diabetes is not well controlled, three-monthly screening for the remainder of the pregnancy is recommended. Referral to an ophthalmologist is required if more than minimal retinopathy is detected.[3] N.B. Women who develop gestational diabetes during pregnancy are not generally at increased risk of retinopathy unless they have pre-existing disease.

Copies of the Ministry of Health retinopathy screening guidelines and a CD for training purposes can be obtained from:

www.moh.govt.nz/moh.nsf/indexmh/retinal-screening-grading-and-referral-guidelines-2006-resources-2008

Retinal screening methods

The current "gold standard" method for screening for diabetic retinopathy in New Zealand is digital photography of the retina while the pupil is dilated. Non-mydriatic photography is however widely used and, although not suitable for every patient, does avoid the inconvenience of pupil dilation. If retinal photography is unavailable the fundus (interior surface of the eye) can be examined through a dilated pupil using slit-lamp biomicroscopy. An assessment of visual acuity should also be carried out.[3]

Conventional retinal examination involves using an ophthalmoscope to view the fundus through a dilated pupil, in a darkened room. However it is difficult for even the most experienced examiners to achieve high sensitivity of retinopathy detection with this method. Macular oedema is also not generally able to be detected with an ophthalmoscope.

After screening, the examiner grades the degree of retinopathy in each eye and applies an overall grading, depending on the worst affected eye. It is important that the examiner follows standardised New Zealand screening protocols for grading.[3] The grade of retinopathy determines what follow-up action is taken.

Fluorescein angiography can be used to detect macular oedema if this is suspected. This involves dye being injected into the arm and images taken as the dye progresses through the blood vessels in the retina.

Table 1: Summary of screening recommendations for diabetic retinopathy[3]

	First retinal screen	Screening interval: no retinopathy	Screening interval: retinopathy detected
Type 1 diabetes	Five years after diagnosis or after puberty	Two-yearly	More frequent than two-yearly, determined by severity, glycaemic control and other risk factors
Type 2 diabetes	Soon as possible after confirmed diagnosis	Two-yearly	
Pregnancy + diabetes	First trimester of pregnancy	Two-yearly	Frequent throughout pregnancy (also if poor glycaemic control, even if no retinopathy)

Management of risk factors for diabetic retinopathy

The duration of diabetes is the most significant risk factor for diabetic retinopathy.[3, 6, 9] Poor glycaemic control is also a major contributor to both the risk of development and progression of diabetic retinopathy.[3] Other modifiable risk factors include hypertension and nephropathy.[3] Elevated blood lipid levels have a weaker association with diabetic retinopathy but contribute to overall cardiovascular risk in a patient with diabetes.

If a person with diabetes is found to have signs of mild retinopathy, managing risk factors can help prevent more advanced changes from developing.

To reduce the risk of progression of diabetic retinopathy, focus on:

- Maintaining good glycaemic control – establish an individualised HbA_{1c} target (see Page 8)
- Managing hypertension – New Zealand cardiovascular guidelines recommend reducing blood pressure to < 130/80 mm Hg for people with diabetes,[10] however this level may not be achievable for some people. In the presence of microalbuminuria or renal disease more aggressive control may be required to reduce blood pressure to < 125/75 mm Hg.[10]
- Advising on management of lifestyle factors, especially smoking cessation and promoting exercise and a healthy diet
- Reducing blood lipid levels as part of overall cardiovascular health – aim for a reduction towards the target level of total cholesterol < 4.0 mmol/L,[10] although this level may not always be achievable (see Page 16)

Intensive glycaemic control

Factors that worsen the general prognosis for people with diabetes also worsen diabetic retinopathy. Intensive glycaemic control has been found to reduce the rate of

Clinical factors that may affect screening intervals

In some circumstances, risk factors may be present indicating that earlier re-screening or referral to an ophthalmologist should be considered.

These factors include:[3]

- Poor compliance – failure to attend appointments for screening on two or more occasions
- Poorly controlled diabetes – HbA_{1c} > 75 mmol/mol (> 9%)
- Duration of diabetes – including type 1 diabetes for greater than seven years
- Rate of progression of retinopathy
- Insulin treatment in people with type 2 diabetes
- Poorly controlled hypertension
- Renal failure
- Ethnicity – Māori, Pacific and Asian peoples are at a higher risk of complications of diabetes
- Asymmetrical disease – i.e. significant worsening in one eye

Pupil dilation

Retinal examination usually involves pupil dilation using tropicamide 1% eye drops. This is safe for most people with diabetes, including those being treated for chronic open angle glaucoma (but not closed angle glaucoma).

Patients should be warned that pupil dilatation may temporarily cause:[3]

- Distorted vision
- Disturbance of balance
- Lack of tolerance to bright light or sunlight – advise patients to take sunglasses with them to their clinic appointment
- Impairment in driving or using machinery – advise patients to arrange transport to and from their appointment and to **avoid driving** or using machinery for several hours afterwards (until vision returns to normal)

In extremely rare cases, dilation of the pupil can cause acute closed-angle glaucoma. This occurs because the iris is pushed into the angle (the junction of the iris and the cornea), blocking drainage and increasing intraocular pressure, which in turn can damage the optic nerve. Symptoms include pain, redness and decreased vision in the affected eye, coloured halos around lights, headache, nausea and vomiting. Acute closed-angle glaucoma is an emergency situation but is usually able to be treated using a regimen of ocular drugs and laser treatment.[8]

progression of diabetic retinopathy. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study placed people with type 2 diabetes on either intensive glycaemic control (target HbA_{1c} level of <6.0%) or standard treatment (target HbA_{1c} level of 7.0 – 7.9%). After four years, diabetic retinopathy had progressed in 7.3% of people on intensive glycaemic control compared with progression in 10.4% of people on standard therapy (P = 0.003).[12]

Intensive glycaemic control appears to reduce the risk of most complications of diabetes, including retinopathy but it has to be balanced against the increase in risks, such as severe hypoglycaemia, and some concerns about increased risk of mortality.

See article "HbA_{1c} targets in people with type 2 diabetes – do they matter" on Page 8 for more information about intensive glycaemic control, including discussion of risk factors and adverse effects.

Hypertension as an independent risk factor

Hypertension is an independent risk factor for visual degradation. Over time, hypertension directly damages the retina, choroid and optic nerve and can result in events such as retinal vein and artery occlusion, retinal emboli, ischaemic optic neuropathy, glaucoma and age related macular degeneration. People with diabetes and poor blood pressure control are at an increased risk of progression of diabetic retinopathy.[13]

Management of hypertension is essential for people with diabetes, however there is conflicting evidence as to whether intensive control is beneficial for reducing progression of diabetic retinopathy, and what blood pressure level is required. The UK Prospective Diabetes Study (UKPDS) found a 34% reduction in the risk of progression of retinopathy after nine years in patients with tight control of blood pressure (target < 150/85 mmHg, using captopril or atenolol).[14] However, the later ACCORD study found no significant benefit for diabetic retinopathy progression in those on intensive hypertensive control (< 120 mmHg, 10.4%) compared with standard treatment (<140 mmHg, 8.8%), nor a benefit in cardiovascular

outcomes.[12] The differing parameters for intensive blood pressure control and time frames of these studies may have contributed to the different conclusions.

Intensive lipid control

Optimal lipid levels are advised in people with diabetes for cardiovascular risk reduction, but the beneficial effect of intensive lipid control on diabetic retinopathy is less clear, and there is little or no evidence that statins have any benefit for retinopathy.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, which involved patients from New Zealand, Australia and Finland showed that there was a beneficial reduction in microvascular complications in people with type 2 diabetes taking fenofibrate for lipid control.[15] Researchers found that laser therapy for retinopathy was needed more frequently in people with poorer glycaemic control or blood pressure control, but plasma lipid concentrations were not associated with the need for laser treatment. Patients on fenofibrate therapy (3.1%) had a reduced need for laser treatment for retinopathy compared to placebo (14.6%), but only if they had a degree of pre-existing retinopathy before lipid-lowering treatment commenced (P = 0.004). There was no significant difference in the need for laser treatment between people taking fenofibrate (9.6%) and placebo (12.3%) overall (P = 0.19) or in the subset of patients without pre-existing retinopathy (11.4% fenofibrate group vs. 11.7% placebo, P = 0.87). Researchers concluded that fenofibrate appears to reduce the need for laser treatment for diabetic retinopathy, but that this mechanism was not related to plasma concentrations of lipids.[15]

The recent ACCORD study found that diabetic retinopathy had progressed in 6.5% of people on intensive dyslipidaemia therapy (160 mg daily of fenofibrate plus simvastatin) compared with 10.2% on standard therapy (simvastatin plus placebo) (P = 0.006).[12]

Fenofibrate is not currently registered in New Zealand or funded on the pharmaceutical schedule. It is in the fibric acid derivative class of drugs which also includes

Aspirin and retinopathy

Many patients with diabetes and a high cardiovascular risk will be taking aspirin. If the patient also has retinopathy, should aspirin be continued?

The Early Treatment Diabetic Retinopathy Study found that 650 mg aspirin per day had no effect on the progression of retinopathy or the development and duration of vitreous haemorrhage. It was concluded that aspirin is not beneficial for the treatment of retinopathy, but there is normally no contraindication to its use in patients with retinopathy, when required for cardiovascular disease or other indications.[11]

bezafibrate (registered and funded) and gemfibrozil (registered). Statins remain the primary agent for lipid control in people with type 2 diabetes.

Other micro- and macrovascular complications

There is a strong association between diabetic retinopathy and other microvascular complications such as nephropathy and neuropathy, and all are associated with a higher cardiovascular risk. Managing risk factors for retinopathy will generally also decrease the risk of these other complications of diabetes.

A person with coexisting retinopathy, renal and foot disease is at a high cardiovascular risk as well as high risk for requiring amputation.

Diabetic "foot-eye" syndrome is a distinct set of symptoms that has been observed in people, usually with type 2 diabetes. It is characterised by:[16]

- A foot ulcer attributable to peripheral neuropathy
- Diabetic retinopathy
- Self neglect, indifference towards illness

Patients who present with "foot-eye" syndrome have a poor prognosis due to underlying severe cardiovascular disease.[16]

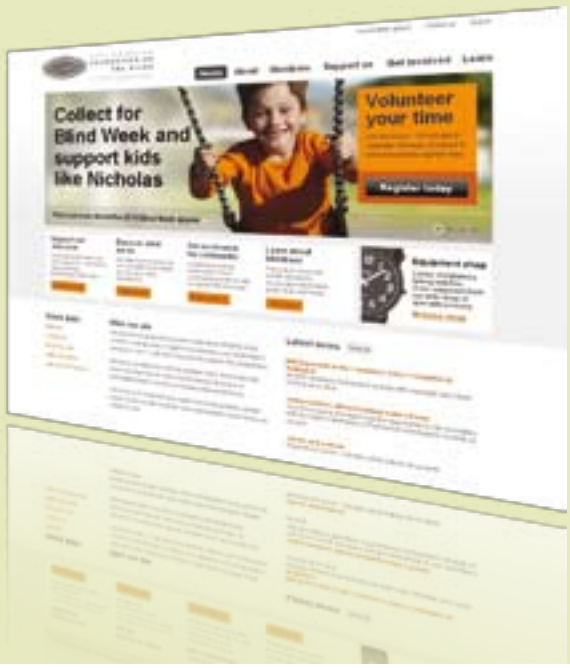
Genetic factors may also play a role

Despite good diabetic control and management of risk factors, diabetic retinopathy still progresses in some people. Conversely, some people with uncontrolled risk factors do not progress to diabetic retinopathy. Genetic factors are thought to play a role in the susceptibility to diabetic retinopathy.[17]

Getting help with reduced vision

Community organisations and agencies such as the Royal New Zealand Foundation of the Blind offer information about low vision counselling, training, and other special services for people with vision impairments.

For further information visit: **www.rnzfb.org.nz**

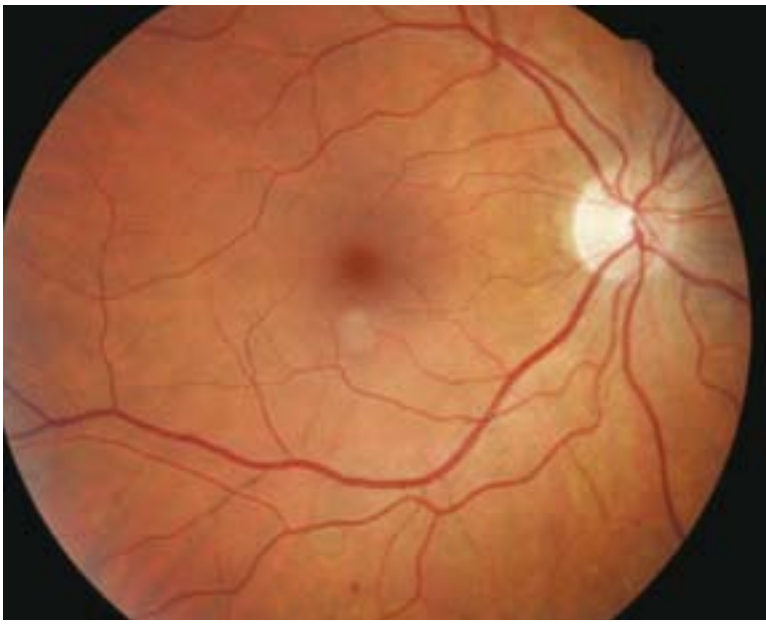


Characteristics of diabetic retinopathy

What causes diabetic retinopathy and how does it manifest?

The microvascular changes that occur throughout the body as a result of diabetes, also affect the eye. Microvascular changes within the retina are the most likely to adversely affect vision.

Diabetic retinopathy can be classified as non-proliferative (background) or proliferative. Visual loss and blindness occurs via two different mechanisms – macular oedema and proliferative retinopathy. Macular oedema can occur at any stage of diabetic retinopathy and is caused by blood vessel leakage and retinal thickening, due to breakdown of the blood-retinal barrier. It is the most frequent cause of vision loss in people with type 2 diabetes. Proliferative retinopathy occurs as a result of vascularisation induced by ischaemia, causing loss of vision due to haemorrhage or retinal detachment.[18]

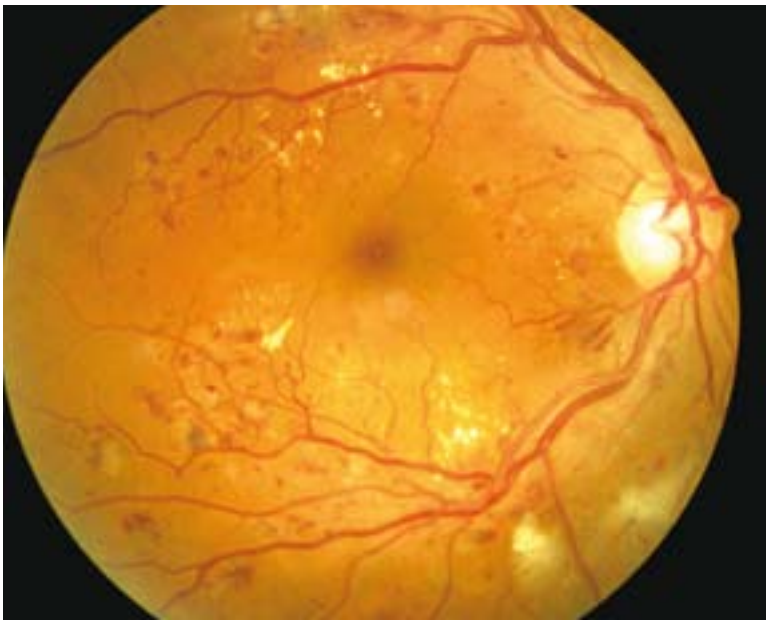


Above: A normal retina

Non-proliferative retinopathy

Lesions include:

- Microaneurysms – small swellings that form on small retinal blood vessels; if the swellings leak or burst, plasma or blood can leak into the adjacent tissue.
- Haemorrhages – leakage of blood from the small vessels into adjacent tissues; haemorrhages deeper in the retinal tissue (dot and blot) are more common in diabetes, superficial haemorrhages (flame) in the nerve fibre layer are more common with hypertension
- Hard exudates – leakage of serum proteins and lipids caused by breakdown of the blood-retina barrier; appearing as white or yellow crystalline deposits in the retina, sometimes forming a circular



Above: Retina showing signs of retinopathy including exudates and haemorrhages[3]

pattern around a leaking microaneurysm

- Cotton wool spots – formed from an accumulation of axoplasm due to occlusion of pre-capillary arterioles; appearing as soft, fluffy, white lesions, often at right angles to the direction of the nerve fibre layer
- Macular oedema – damage to the central vision caused by functional damage and necrosis of retinal capillaries; the leading cause of visual impairment in people with diabetes
- Venous loops and beading – damage to vessel walls resulting in formation of loops or beading (sausage shaping) of the blood vessels; often a sign that more severe proliferative retinopathy is developing

Proliferative retinopathy

- Restricted blood supply to the retina (retinal ischaemia) caused by diabetes, can lead to the release of Vascular Endothelial Growth Factor (VEGF) which initiates the formation of new blood vessels (neo-vascularisation)
- The new blood vessels break through and grow along the surface of the retina, the posterior hyaloid face (the wall between the retina and the vitreous cavity inside the eye) and in severe cases, the iris
- The new blood vessels are fragile and easily broken, leading to haemorrhage in the vitreous cavity or pre-retinal space, compromising vision almost immediately
- Over time, as the density of the newly formed blood vessels increases, fibrous tissue is formed which can adhere to the retina and posterior hyaloid face of the eye
- The traction between the vitreous and the fibrous tissue connections can cause retinal oedema, tears and detachments

Symptoms

Early to moderate stages of diabetic retinopathy are usually without any noticeable symptoms. Symptoms may be experienced in proliferative retinopathy, particularly with haemorrhage and retinal detachment.

Vitreous haemorrhage occurs suddenly but is not usually associated with any pain. The blood which enters the vitreous cavity occludes the vision and is seen as spots or areas of visual loss. If not treated, repeated haemorrhages result in progressive visual loss in most cases.[19]

Retinal detachment is described as flashing lights and floating spots in the peripheral vision or as a "curtain" progressing across the visual field.[20]

NB: Sudden onset of visual symptoms or deterioration requires referral for specialist assessment, rather than for routine screening for retinopathy.

How is diabetic retinopathy treated?

Laser photocoagulation is the primary treatment for sight-threatening diabetic retinopathy, however it is not always completely successful in restoring visual loss. Better results are achieved if treatment is carried out earlier in the disease process.[18] For the majority of cases the goal of treatment with laser photocoagulation is to reduce the rate of visual loss or to stabilise visual acuity.

During laser photocoagulation, a laser is applied to the retina, causing burns. Different methods of laser surgery (or combinations of methods) are carried out depending on the pathology being treated.

Surgery is usually completed in one session, but if both eyes require treatment, this normally occurs several weeks apart.

Adverse effects and complications of laser photocoagulation can include:

- Headache – usually relieved with rest and simple analgesia, but if severe or persistent, glaucoma must be ruled out
- Pain – anaesthetic drops are applied, but an uncomfortable stinging sensation can occur as time progresses
- Blurred vision (temporary)
- Visual field restriction
- Decreased contrast sensitivity
- Impaired night vision or colour vision

Vitreous surgery

Vitreous surgery may be required in patients with some types of retinal detachment, vitreous haemorrhages and severe proliferative retinopathy. Vitreous surgery has the potential for serious complications including significant visual loss and eye pain.

A vitrectomy is performed under local or general anaesthesia. A tiny incision is made in the eye and the vitreous gel clouded by blood is replaced by a saline solution. After the procedure the eye may be red and sensitive, an eye patch may be required for a few days or weeks to protect the vision, and antibiotic eye drops may be required to reduce the risk of infection.

Intravitreal corticosteroids

If laser photocoagulation has been unsuccessful, in some cases patients may be trialled on corticosteroids, injected into the vitreous of the eye. This method can be effective, but re-injections are usually needed and there is a potential for significant adverse effects such as infection, glaucoma and cataract formation.[18]

ACKNOWLEDGMENT Thank you to **Dr Paul Drury**, Clinical Director, Auckland Diabetes Centre and **Associate Professor Gordon Sanderson**, Ophthalmology, Dunedin School of Medicine, University of Otago for expert guidance in developing this article.

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Statins and memory loss

Dear bpac,

I have had two patients with memory issues report to me that other doctors have suggested they should consider stopping their simvastatin and see if this helps with their memory. What is the evidence for the effects of simvastatin on memory/cognitive function?

Dr Catherine Fisk, GP
Auckland

Memory loss is a rarely reported adverse effect of statins, without proven causality. Several cases of memory loss have been reported to various adverse drug reaction databases, some of which were confirmed by re-challenge with the statin.[1]

The proposed mechanism for memory loss relates to the essential role of cholesterol in myelin production. Statins, especially atorvastatin and simvastatin which are more lipophilic, may cross the blood-brain barrier and decrease the amount of central nervous system cholesterol necessary for the formation of myelin. Inadequate myelin production may result in demyelination of nerve fibres in the central nervous system and thus lead to memory loss.[2]

Memory impairment is common among people in the older age group and can be due to a variety of causes or conditions, often multifactorial. It may be difficult to precisely determine whether a statin is implicated in a case of memory loss.

If a patient experiences memory loss (or any other adverse effect) while taking a statin, the following approach could be considered:

- Stop the statin, observe whether symptoms improve, then re-challenge
- Lower the dose
- Switch to a different type of statin
- If symptoms persist, consider other lipid lowering treatments e.g. nicotinic acid or bezafibrate

There have also been rare reports of impairment of cognitive function with statins, however the evidence is conflicting and inconclusive. While some studies have observed a mild detrimental effect of statins on cognition, others have shown a beneficial effect. In a recent population-based study, there was no significant difference in cognitive performance between elderly participants treated with statins and those who were untreated (controls).[3] There are, however, isolated case reports that raise the possibility that statins, in rare cases, may be associated with cognitive impairment.[4]

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Tepid sponging no longer recommended in children with fever

Dear bpac

I was surprised to see in your article "Identifying the risk of serious illness in children with fever" (BPJ 29, July 2010) that tepid sponging to reduce a high temperature in a child is no longer recommended. What is the reason for this?

GP, Dunedin

International guidelines such as NICE (United Kingdom) recommend that "tepid sponging" (sponging with warm water) should not be used to reduce fever in children.[1] This may represent a change in practice for some clinicians, who have traditionally recommended this method to parents.

Tepid sponging is no longer in favour as there is evidence that it does not effectively reduce fever and can increase infant discomfort. A Cochrane review failed to find any conclusive evidence of benefit of tepid sponging. However, almost all children who underwent tepid sponging showed typical signs of discomfort and irritability including shivering, "goose bumps" and crying.[2]

Fever is a normal immunological response to infection. Although fever can be upsetting to parents and cause significant anxiety, intervention is only required if it is causing irritability and distress to the child. Paracetamol is the first-line treatment for fever in children.[1] Increased fluids should be encouraged and the child should be neither over-wrapped nor under-dressed.

See "Identifying the risk of serious illness in children with fever" (BPJ 29, July 2010) for further information about managing fever in children at home and warning signs that indicate further intervention is required.

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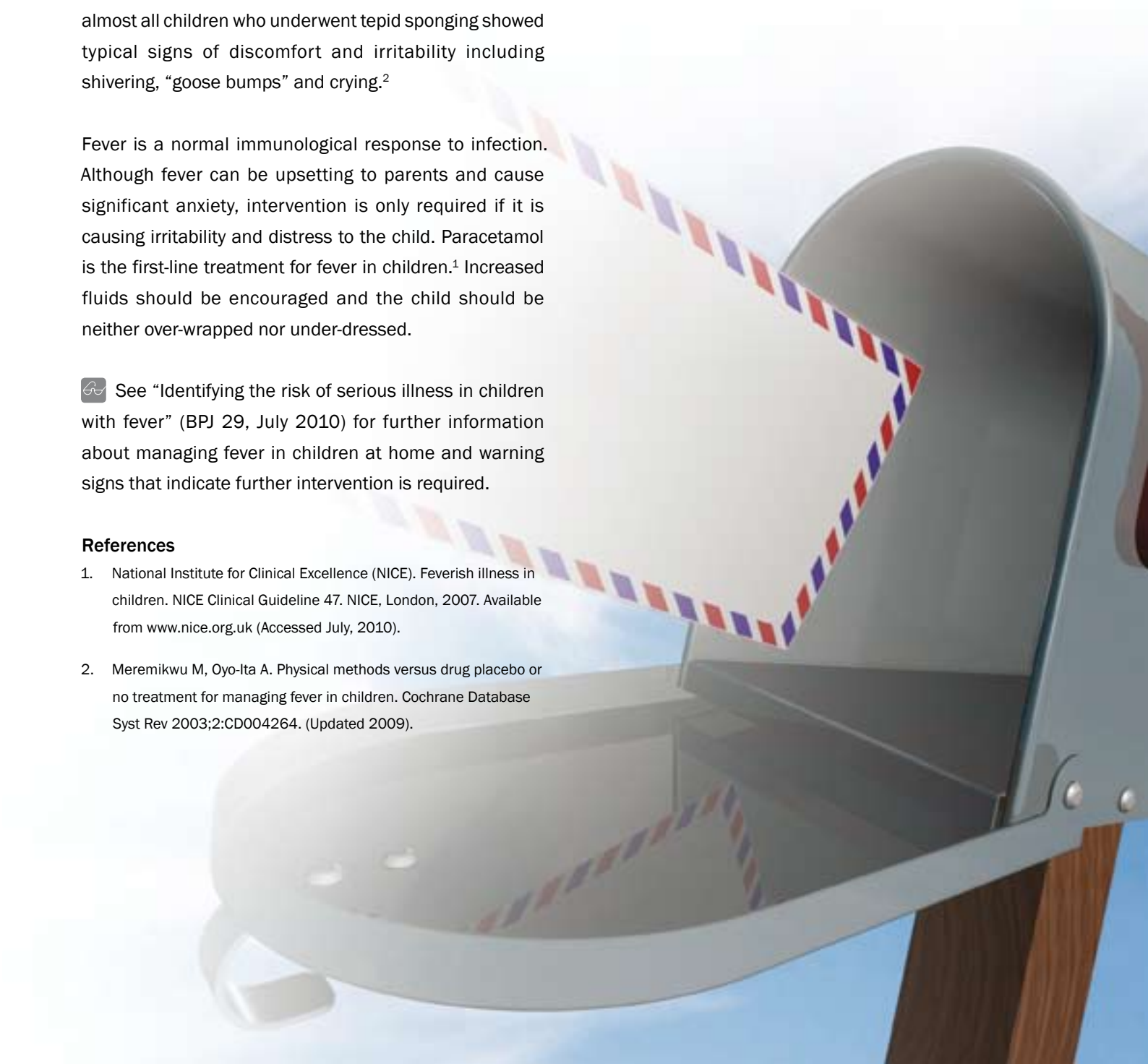

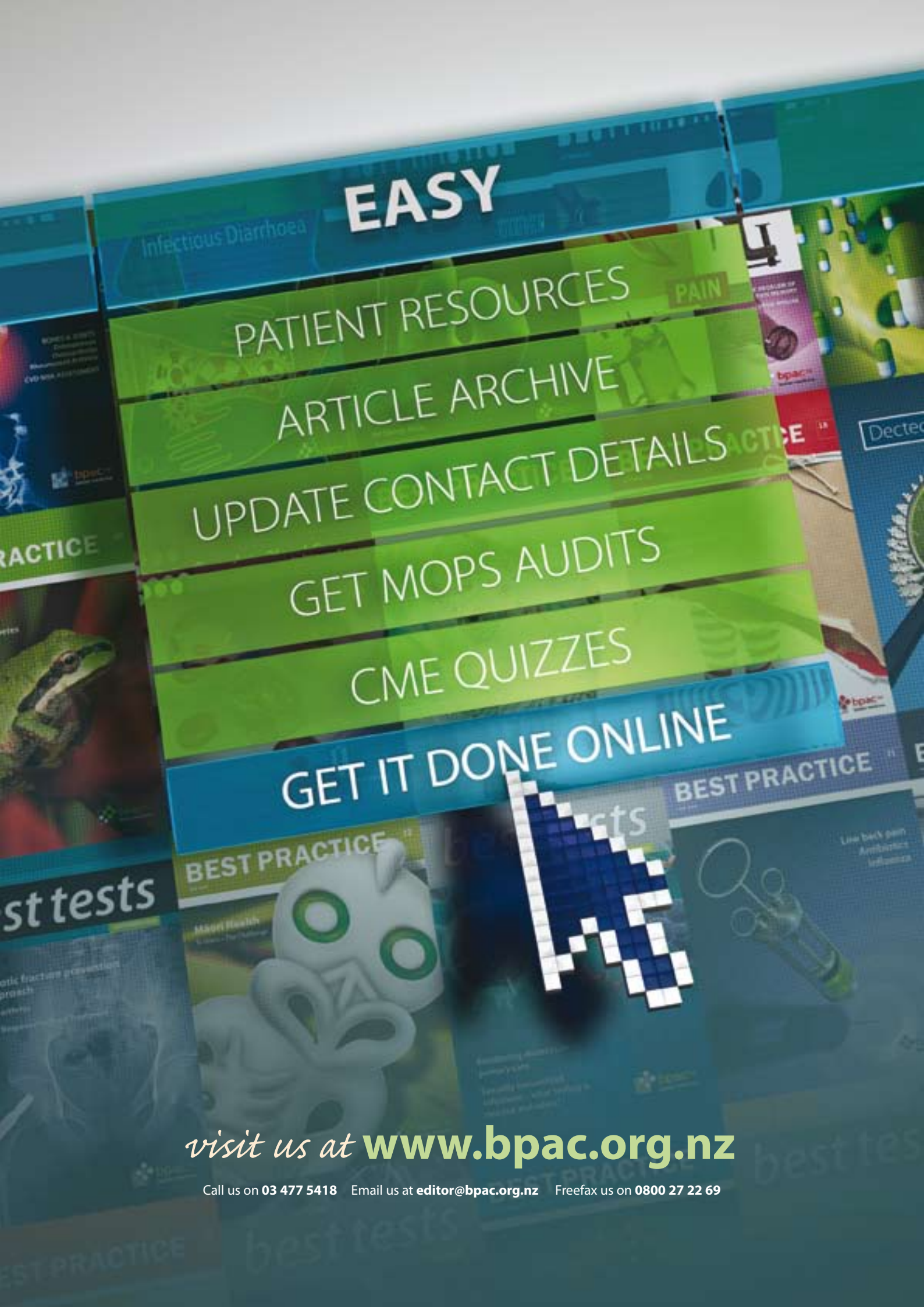
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