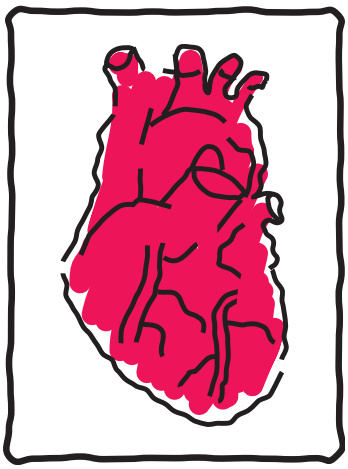

Prevention of cardiovascular disease: an evidence-based clinical aid 2004

The Practical Implementation Taskforce for the Prevention of Cardiovascular Disease

Contents

Recommendations for all patients F4
Recommendations for patients with established vascular disease F5
Recommendations for patients with diabetes without known cardiovascular disease F6
Recommendations for patients with non-diabetic renal disease F6
The approach for other high-risk patients F7
The approach for patients at low risk of a cardiovascular event F7
The approach for patients with macro- or microalbuminuria associated with diabetes or hypertension F8
Other interventions F8
Conclusion F8
Desktop reference F12

The Practical Implementation Taskforce for the Prevention of Cardiovascular Disease

A multidisciplinary group of specialists was assembled by communications agency Burson Marstellar with an unrestricted educational grant from Aventis Pharma. The taskforce members included:

Chairman:

Dr Greg R Fulcher, MD, FRACP, Endocrinologist, Royal North Shore Hospital, Sydney, NSW

Steering committee:

Dr John V Amerena, MB BS, FRACP, Cardiologist, Department of Clinical and Biomedical Sciences, University of Melbourne, Melbourne, VIC

Dr Greg W Conner, MB BS, FRACP, Cardiologist, Cardiovascular Diagnostic Services, Sydney, NSW

Other members:

Dr John F Beltrame, BSc, BMBS, FRACP, PhD, FESC, FACC, Senior Lecturer in Medicine, University of Adelaide, and Cardiologist, Queen Elizabeth Hospital, Adelaide, SA

Professor Stephen Colagiuri, MB BS, FRACP, Endocrinologist and Director of Diabetes Services, Prince of Wales Hospital, Sydney, NSW

Professor Richard E Gilbert, MD, PhD, Endocrinologist and Professor of Medicine, University of Melbourne Department of Medicine, St Vincent's Hospital, Melbourne, VIC

Professor Graeme J Hankey, MD, FRCP, FRACP, Neurologist, Royal Perth Hospital, Perth, WA

Associate Professor Anthony C Keech, MSc(Epidemiol), FRACP, Cardiologist and Deputy Director, NHMRC Clinical Trials Centre, Sydney, NSW

Professor Brian R McAvoy, MD, FRACGP, General Practitioner and Deputy Director, National Cancer Control Initiative, Melbourne, VIC

Professor Carol A Pollock, PhD, FRACP, Renal Physician and Professor of Medicine, University of Sydney, Royal North Shore Hospital, Sydney, NSW

Professor Malcolm J West, MB BS, FRACP, Cardiologist and Professor of Medicine, University of Queensland, Prince Charles Hospital, Brisbane, QLD

Supported by an unconditional educational grant by Aventis Pharma.
The views expressed in this MJA Focus are those of the authors.
Aventis Pharma had no input into the contents.

Prevention of cardiovascular disease: an evidence-based clinical aid 2004

Practical Implementation Taskforce for the Prevention of Cardiovascular Disease

Cardiovascular disease is the leading cause of morbidity and mortality in Australia. It is therefore important that all medical practitioners are familiar with the well documented risk factors for cardiovascular disease, as well as the outcome benefits of pharmacological and other interventions.

The large and ever-increasing body of clinical evidence, the range of patient groups at risk and the plethora of recommended interventions all make it increasingly difficult for busy doctors to adopt an integrated approach to prevention of vascular events. While absolute risk calculators, such as the Framingham Heart Study Prediction Score Sheets (www.nhlbi.nih.gov/about/framingham/riskabs.htm) or the New Zealand Cardiovascular Risk Factor Calculator (www.racp.edu.au/bp/resources/EBM_cardio.pdf), enable doctors to assign overall risk, guidelines for management are usually focused on single interventions. Moreover, the continual emergence of new data on vascular risk management redefines risk categories and approaches to risk management.

Prevention of cardiovascular disease: an evidence-based clinical aid was developed by a multidisciplinary group of physicians to address this issue and was first published by the *MJA* in July 2003. We have revised and updated our evaluation of current best practice based on a rigorous analysis of available published evidence to March 2004, and formulated a concise and up-to-date guide for the prevention of cardiovascular disease. This consensus of opinions is summarised in this document (see *Clinical aid, page F12*) and provided as a single-page chart for use in clinical practice as a desktop reference.

Patients were classified as being either at high or low risk of cardiovascular events (Box 1). It is widely considered that high-risk patients are those with clinically evident vascular disease, renal disease, diabetes or other risk factors conferring an annual risk of a future event of 2%–3% or greater. Risk can be calculated using an absolute risk-factor calculator (see above).

The major interventions considered were:

- lifestyle changes;
- cessation of smoking; and
- treatment of hypertension and dyslipidaemia.

Where new indications for treatment have been demonstrated in particular circumstances for a single product, this product is shown; otherwise, the class of agents is presented. We considered the results of recent trials that will potentially have a major impact on the management of high-risk patients. Such trials include the HOPE study,[1] the PROGRESS study[2] and the Heart Protection Study.[3] Furthermore, the recognition that proteinuria imparts substantial risk warranted the inclusion of specific advice for the population with this risk factor. Although the importance of homocysteine, Lp(a) and fibrinogen as cardiovascular risk factors was recognised, the infrequent measurement of these parameters in usual practice, together with the lack of proven interventions, justifies their omission from this review.

We anticipate further updates and revisions to the aid to maintain its currency in the context of a rapidly expanding cardiovascular evidence base. The management recommendations of this "living" document will continually evolve as new evidence is published.

1 Categories of patients based on future risk of a cardiovascular event

High-risk patients are those with:

- Clinically evident coronary heart disease (prior acute myocardial infarction, angina, or history of a revascularisation procedure)
- Clinically evident vascular disease (cerebrovascular or peripheral vascular disease)
- Diabetes
- Renal disease
- A risk of a future vascular event ⩾ 2%–3% per year, based on an aggregate of unfavourable risk characteristics*

Low-risk patients are those with:

- A risk of a future vascular event < 2%–3% per year*

* Determined using a calculation of the 5-year risk of any cardiovascular event and death, from a validated absolute-risk calculator such as the Framingham Heart Study Prediction Score Sheets or, in the case of type 2 diabetes, the UK Prospective Diabetes Study risk calculator (www.dtu.ox.ac.uk/index.html?maindoc=/riskengine/).

It should be noted that this clinical aid applies to the long-term management of cardiovascular risk in general practice or community-based physicians' practice. It does not cover the medical management of acute coronary syndromes or heart failure.

Recommendations for all patients

Healthy lifestyle

Advice concerning the benefits of smoking cessation, physical activity and healthy dietary choices should be given at a population and individual level. These measures are considered as first-line in any management decisions.

a) Cessation of smoking

There is extensive evidence that smoking is strongly related to mortality, largely because of an increased risk of CHD and stroke.[4] Furthermore, smoking cessation has been shown to decrease this risk in patients with and without established CHD.[5] In patients with peripheral vascular disease or stroke, smoking cessation is associated with improved exercise tolerance and survival, and decreased rates of limb amputation and recurrent stroke.[5]

b) Exercise

While there is limited evidence from RCTs of the value of exercise in primary prevention of cardiovascular disease, there is strong observational evidence that moderate, regular physical activity reduces the risk of both CHD[6] and stroke,[7] and that the risk is increased in people with a sedentary lifestyle.[8] For secondary prevention after AMI, two meta-analyses of exercise-based rehabilitation in up to 14 RCTs have shown reductions in mortality of between 20% and 25% (absolute risk reduction [ARR], 3.1%) at 3-year follow-up, although many of the trials allowed other risk-factor intervention as well.[9,10] While these data must be interpreted with

Glossary of abbreviations

ACE inhibitor – angiotensin-converting enzyme inhibitor
AIIRA – angiotensin II receptor antagonist
AMI – acute myocardial infarction
CCF – congestive cardiac failure
CHD – coronary heart disease
HDL cholesterol – high-density lipoprotein cholesterol
LDL cholesterol – low-density lipoprotein cholesterol
RCT – randomised controlled trial
TIA – transient ischaemic attack

caution, prescribing a moderate degree of regular physical exercise is consistent with published evidence.

c) Diet

Cohort studies have shown that eating fruit and vegetables reduces the risk of heart attack and stroke.[11] One RCT showed that a Mediterranean diet decreased mortality by 30% at 27 months after AMI (ARR, 4.0%).[12] In addition, a modest intake of fish (as little as 35 g daily) appears to decrease the relative risk of AMI.[13] Following general advice to decrease the intake of saturated fats and cholesterol and increase the intake of polyunsaturated fats favourably affects serum lipid levels and decreases the likelihood of CHD.[14] Finally, weight maintenance education should be part of routine advice for the general population, but is particularly important in patients at increased risk of cardiovascular events.

d) Stress

Recently, an Expert Working Group of the National Heart Foundation of Australia undertook a review of the evidence relating to major psychosocial risk factors to assess whether these influenced the development of CHD and acute coronary events.[15] They concluded that there was "no strong or consistent evidence for a causal association between chronic life events, work-related stressors (job control, demands and strain), type A behaviour patterns, hostility, anxiety disorders or panic attacks and CHD".[15] However, there was strong and consistent evidence of an independent and causal association between depression, social isolation and the prognosis of CHD and, importantly, the impact of these was of a similar order to conventional risk factors such as smoking.[15] It is therefore crucial that these psychosocial factors are considered during individual CHD risk assessments.

Recommendations for patients with established vascular disease

1. Normotensive patients with a history of cardiovascular disease

The HOPE,[1] PROGRESS[2] and, more recently, EUROPA studies[16] have examined the effects of preventive treatment with ACE inhibitors in normotensive high-risk patients. In the HOPE study, patients with CHD, peripheral vascular disease, stroke, or diabetes (types 1 or 2) and an additional risk factor were randomly allocated to receive ramipril 10 mg daily or placebo. Patients were included irrespective of a history of hypertension, but those with blood pressure greater than 140/90 mmHg or with a specific indication for treatment with an ACE inhibitor (eg, CCF) were excluded. The 3/1 mmHg lower blood pressure in the ramipril group at the end of the study was unlikely to explain the highly significant 22% reduction in the combined endpoint of cardiovascular death, stroke or heart attack (cardiovascular death [26% reduction; ARR, 2.0%], stroke [32% reduction; ARR, 1.5%], heart attack [20% reduction; ARR, 2.2%]; $P < 0.05$) or the 17% decrease in total mortality ($P < 0.05$).[1]

In the PROGRESS study,[2] patients with a previous history of stroke or TIA were randomly allocated to perindopril 4 mg ± indapamide 2.5 mg versus placebo, whether there was a history of hypertension or not. When given together this combination reduced the risk of recurrent stroke (fatal or non-fatal) and major vascular events in both normotensive and hypertensive patients with this background.[2] There was also a significant reduction in major coronary events (26%) and the development of heart failure (26%) in these patients with underlying cerebrovascular disease.[17] The magnitude of blood pressure reduction in the active treatment group was greater in the PROGRESS study (9/4 mmHg) than in the HOPE study (3/1 mmHg), making it less clear as to how much of the benefit seen in the PROGRESS study was independent of blood pressure reduction alone.

The recently published EUROPA study[16] looked at patients with known ischaemic heart disease, and participants were randomly allocated to receive perindopril 8 mg or placebo, independent of whether or not they had a history of hypertension. At 5 years, there was a significant 20% reduction in cardiovascular mortality, infarction and cardiac arrest in patients who received perindopril, with a blood pressure difference of 5/2 mmHg between the groups.

It appears that, in patients with a history of CHD or cerebrovascular disease, treatment with a high dose ramipril- or perindopril-based regimen will improve outcomes whether or not there is a history of hypertension, and that at least some of these benefits are independent of blood pressure reduction alone.

In the immediate post-infarct management of normotensive patients, a mortality benefit in the short term has also been demonstrated with β-blockers[18] and ACE inhibitors (particularly in patients with associated heart failure),[19] with less robust evidence for calcium channel blockers, verapamil and diltiazem.[20-22]

2. Patients with elevated blood pressure and a history of cardiovascular disease

While epidemiological studies have established that raised blood pressure is a major risk factor for cardiovascular events in patients with a history of AMI,[23] until recently there has been no systematic review or RCT that specifically examines blood pressure reduction in patients with established CHD, nor in those with peripheral vascular disease; however, the results of the HOPE, PROGRESS and EUROPA studies are applicable to patients with hypertension. In our recommendations, and those of both the JNC-7 Report[24] and the National Heart Foundation,[25] the benefits of blood pressure lowering in patients with CHD have been extrapolated mostly from primary prevention trials and from studies of patients after AMI.[1,18-22] Evidence of event reduction exists for patients taking calcium channel blockers,[20-22,26-29] diuretics and β-blockers,[29-35] and ACE inhibitors.[1,28,35] In patients with elevated blood pressure and a history of stroke or TIA, the evidence is strongest for the use of ACE inhibitors (ramipril 10 mg; and perindopril 4 mg when given with indapamide 2.5 mg),[1,2] diuretics and β-blockers.[34-38]

More recently, the INVEST study[39] examined patients with hypertension and known ischaemic heart disease. This study found that event rates were similar in both subjects taking a verapamil-based regimen and in those receiving atenolol-based therapy.

However, to achieve target blood pressures, most patients in both study groups were taking combination therapy that also included an ACE inhibitor and thiazide diuretic.

As over 50% of patients in the ALLHAT study[38] had a history of atherosclerotic cardiovascular disease, the result of this study should be considered when blood pressure lowering is contemplated for such patients.[38] Specifically, the results of treatment with ACE inhibitors, diuretics or calcium channel blockers were comparable. It should be noted, however, that there was an increased rate of development of diabetes mellitus in the thiazide diuretic treatment arm. In view of the impact of diabetes on cardiovascular event rates, this finding may have implications for cardiovascular disease beyond the 5-year treatment period covered by the trial.

3. Patients with dyslipidaemia and a history of cardiovascular disease

There is strong RCT evidence that lowering cholesterol levels decreases cardiovascular mortality and morbidity in patients who have been diagnosed with an acute coronary syndrome or myocardial infarction,[40] even if cholesterol levels are normal.[3,41,42] The most substantial data are from studies of simvastatin and pravastatin,[3,40-42] but, recently, results of the PROVE-IT study[43] suggest that intensive lipid lowering with atorvastatin 80 mg improves outcomes more than moderate lipid lowering in patients with acute coronary syndromes and cholesterol levels less than 6.2 mmol/L.[43] The Heart Protection Study[3] provides the most complete information of the benefits of lowering cholesterol level in a wide range of circumstances. Both men and women with total cholesterol levels greater than 3.5 mmol/L and with a history of cardiovascular disease (including those with a history of coronary disease, cerebrovascular disease, or peripheral vascular disease) achieved a significant reduction in major vascular events ($P < 0.001$) irrespective of the starting cholesterol level.

In men with low levels of HDL cholesterol and a history of CHD, gemfibrozil significantly reduced the risk of major cardiovascular events, in the absence of an effect on LDL cholesterol level.[44]

In patients with diabetes and CHD, the data are strongest for the use of statins,[3,40-42] but, again, in patients with low levels of HDL cholesterol gemfibrozil is efficacious.[44] To date, this evidence has been derived from subgroup analyses. In RCTs, it has been shown that both pravastatin and simvastatin reduce the incidence of stroke in patients with CHD,[3,41,42,45] but in those without CHD the evidence is strongest for simvastatin.[3] There are no "head-to-head" outcome studies of statins versus fibrates.

Recommendations for patients with diabetes without known cardiovascular disease

1. Patients with diabetes and "normal" blood pressure

In patients with diabetes, "normal" blood pressure is arbitrarily defined as being less than 130/85 mmHg and "ideal" blood pressure as less than 120/80 mmHg.[25] As the HOPE study[1] only included patients with diabetes if they had at least one cardiovascular risk factor, treatment of low-risk patients with diabetes (ie, those who have no additional cardiovascular risk factors) with an ACE inhibitor to prevent future CHD events is not supported by current data. Observation with repeated measurement of blood pressure at least annually is recommended.[25,46]

2. Patients with diabetes and elevated blood pressure

A systematic review of RCTs has shown that ACE inhibitors, diuretics, calcium channel blockers and β-blockers are all effective in primary prevention of cardiovascular events in patients with diabetes and hypertension.[47] There is no clear evidence that any of these classes is more effective than another in event reduction,[26,28] and currently drugs of all of these classes are recommended to treat blood pressure in patients with diabetes.[25] Despite this, an apparent greater reduction in major cardiovascular events (including heart failure) occurring with ACE inhibitors, compared with some calcium channel blockers,[48-50] has led us to list calcium channel blockers as second-line therapy. In addition to reducing cardiovascular events, ACE inhibitors have a major role in renal protection in patients with type 1 diabetes and hypertension.[51] Similar protection has recently been shown with the AIIRAs irbesartan[52,53] and losartan,[54] including patients with type 2 diabetes and left ventricular hypertrophy.[55]

3. Lowering cholesterol level in patients with diabetes

In the Heart Protection Study,[3,56] patients with diabetes with a total cholesterol level greater than 3.5 mmol/L had significantly fewer major vascular events ($P < 0.0001$) when taking simvastatin 40 mg, whether or not they had a prior history of CHD. To date, this is the largest intervention trial of statin therapy in patients with diabetes and thus should be considered the definitive trial. These data support the use of a statin for both primary and secondary prevention of major vascular events in patients with diabetes. Furthermore, three large primary prevention RCTs using lovastatin,[57] gemfibrozil[58] and bezafibrate[59] have each shown a benefit in preventing cardiovascular events. Thus, a predominant elevation of total or LDL cholesterol levels indicates a statin is appropriate initial therapy, whereas a fibrate could be an appropriate choice in patients with low levels of HDL cholesterol and raised triglyceride levels. When treating combined hyperlipidaemia, both classes of drug may be required, but there are no outcome data from using this approach and practitioners should exercise caution in prescribing this combination. Definitive trials on lipid management in patients with diabetes (eg, the FIELD study[60]) are still to be published.

4. Cardiovascular prevention with other therapies

As the HOPE study included patients with diabetes and dyslipidaemia (total cholesterol level > 5.2 mmol/L and HDL cholesterol level 0.9 mmol/L),[61] the use of ramipril in addition to other therapies should be advocated in diabetic patients with dyslipidaemia or other cardiovascular risk factors.

Recommendations for patients with non-diabetic renal disease

1. Patients with non-diabetic renal disease and "normal" blood pressure

Renal insufficiency is a well described predictor of cardiovascular outcomes.[62] Hypertension in patients with renal disease is defined as blood pressure greater than 130/85 mmHg,[25] although observational studies suggest that even a lower blood pressure confers an increased risk. Despite this, there is no RCT of antihypertensive therapy showing treatment benefit if blood pressure is below this threshold. Ongoing observation with repeated measurement of

blood pressure every 6 months is currently recommended for normotensive patients with non-diabetic renal disease.[24,25,46]

2. Patients with non-diabetic renal disease and hypertension

The benefits of treating hypertension in patients with established renal disease have largely been studied with surrogate endpoints, and the effects of lowering blood pressure on cardiovascular outcomes have not been specifically assessed. Nevertheless, patients with renal dysfunction are at high risk of CHD and it is reasonable to extrapolate from this that aggressive blood pressure lowering will confer a substantial benefit.[25]

Published data support the use of ACE inhibitors as first-line treatment for hypertension, with greater demonstrated efficacy in reducing proteinuria than calcium channel blockers.[51] Further, in a meta-analysis of a number of clinical trials, ACE inhibitors were more effective than other agents in delaying the development of end-stage renal disease; however, it could not be determined whether this was due to the lower blood pressure achieved with ACE inhibitors or to effects independent of blood pressure.[63] β-Blockers and diuretics are also recommended.[24,25] If calcium channel blockers are used they should be considered as second-line therapy after ACE inhibitors.[51]

More recent information in this patient group has been derived from the CATS[64] and COOPERATE[65] studies. The CATS study showed that, although renal function deteriorated markedly after a first AMI, it was significantly preserved by taking the ACE inhibitor captopril. Patients after a first anterior-wall AMI were allocated at random to receive captopril (up to 75 mg daily) or placebo, after completion of a streptokinase infusion. Renal function determined by calculating glomerular filtration rate was found to decline by 5.5 mL/min within 1 year versus only 0.5 mL/min in the captopril group ($P < 0.05$). The beneficial effects of captopril were most pronounced in patients with the most compromised renal function at baseline.

The COOPERATE study[65] aimed to assess the effects of ACE inhibitor and AIIRA therapy, both in combination as well as monotherapy at maximal dose. Participants were randomly assigned to receive losartan 100 mg daily or trandolapril 3 mg daily, or a combination of both drugs at equivalent doses. Survival analyses were done to compare the effects of each regimen on the primary combined endpoint of time to doubling of serum creatinine concentration or end-stage renal disease on an intention-to-treat basis. Eleven per cent of patients taking the combination treatment reached the combined primary endpoint, compared with 23% of patients taking trandolapril alone (hazard ratio, 0.38; 95% CI, 0.18–0.63; $P = 0.018$) and 23% of patients taking losartan alone (hazard ratio, 0.40; 95% CI, 0.17–0.69; $P = 0.016$). Combination treatment was found to safely retard the progression of non-diabetic renal disease compared with monotherapy; however, as some patients taking combined therapy reached the combined endpoint, further research on strategies for complete management of progressive non-diabetic renal disease is needed.

3. Lowering cholesterol level in patients with non-diabetic renal disease

Specific trials of lipid-lowering therapy have not been conducted in patients with non-diabetic renal disease. Thresholds for intervention have been derived by consensus and recommendations for the choice of agents have been based on the lipid-lowering characteristics of specific therapies.

The approach for other high-risk patients

Over the past decade, it has been recommended that the intensity of risk-factor management be governed by a patient's absolute risk of a CHD event. However, patients with mild levels of multiple risk factors may be at high risk because of the exponential additive contribution of each risk factor,[66] whereas other patients may have an overall low risk even if they have one markedly abnormal risk factor (Box 1).

1. High-risk patients with raised blood pressure

A number of systematic reviews have shown a reduction in total mortality, cardiovascular death, stroke, major coronary events and CCF in patients taking β-blockers, diuretics, ACE inhibitors or calcium channel blockers.[25,62,67] One unblinded RCT in 6600 people aged 70–84 years, comparing diuretics and/or β-blockers versus calcium channel blockers versus ACE inhibitors, showed no significant difference in blood pressure control or cardiovascular morbidity and mortality.[68] The ALLHAT study, involving hypertensive patients with at least one other CHD risk factor, supports these findings.[38,69] When the primary outcome was considered (fatal CHD or non-fatal AMI), diuretic-based therapy (chlorthalidone) was of similar efficacy to either therapy with a calcium channel blocker (amlodipine) or an ACE inhibitor (lisinopril). In fact, patients taking amlodipine had an increased risk of CCF (relative risk, 1.38; 95% CI, 1.25–1.52) and patients taking lisinopril had a higher risk of combined cardiovascular disease, stroke and CCF.[38] As amlodipine is a dihydropyridine calcium channel blocker, it may not be possible to extrapolate these results to the non-dihydropyridine calcium channel blockers.[69]

2. Lowering cholesterol level in patients at high risk of a cardiovascular event

Until recently, there was no evidence that lowering cholesterol level reduces total mortality in non-diabetic patients without cardiovascular disease, although systematic reviews and RCTs had shown that cholesterol reduction improves cardiovascular outcomes in high-risk populations.[3,57,70-72] The benefit is related to baseline risk and extent of cholesterol reduction rather than initial cholesterol level (within the range studied).

The lipid-lowering arm of the ASCOT study[73] demonstrated the benefits of lipid reduction for hypertensive patients with multiple cardiovascular risk factors. ASCOT examined 10 305 patients with hypertension and at least three other cardiovascular risk factors (excluding previous AMI or current angina) who had non-fasting cholesterol levels less than 6.5 mmol/L. Treatment with atorvastatin 10 mg conferred a 36% reduction in fatal CHD and non-fatal AMI compared with placebo ($P = 0.0005$). The benefits of lipid reduction were also evident among non-diabetic patients.

A total cholesterol level greater than 5 mmol/L is the current recommended threshold for treatment in patients with associated risk factors or vascular disease.[74]

The approach for patients at low risk of a cardiovascular event

Patients who are not in any of the above categories are at low risk of a cardiovascular event. There is a more liberal threshold for

intervention in this group in the knowledge that the treatment benefits will be smaller, but the recommendations for choice of therapy to lower blood pressure and lipid levels are identical to those in higher-risk patients.

1. Blood pressure management

We routinely adopt a more proactive approach for monitoring blood pressure than the current guidelines, which advocate that low-risk patients whose blood pressure is considered normal by current criteria should have blood pressure measurements either every 5 years (age < 60 years) or every 1–2 years (age > 60 years).[25,67] Current clinical practice would also be at variance with the guideline recommendations that drug therapy and lifestyle modification for hypertension should only be introduced in patients under 60 years if their systolic blood pressure is greater than 180 mmHg or diastolic blood pressure greater than 100 mmHg,[25,67] or in those over 60 years whose systolic blood pressure is greater than 160 mmHg.[27,29] Despite our personal views, we have included the current published recommendations.[25] In the ANBP-2 Study,[75] 6083 elderly subjects aged 65–84 years with hypertension were treated with either ACE inhibitors or diuretics and compared. Although a similar number of strokes occurred in each group, ACE inhibitor therapy was associated with better cardiovascular outcomes, particularly in men.[75]

2. Lipid management

Patients with normal lipid levels should be assessed every 5 years until middle age and then every 1–2 years. In the absence of other risk factors triggering a lower threshold for treatment, lipid-lowering therapy with a statin should be commenced for patients with predominant hypercholesterolaemia (total cholesterol > 8.0 mmol/L or total cholesterol : HDL cholesterol ratio > 8.0),[76] or with a fibrate for patients with low HDL cholesterol and high triglyceride levels.[74] (At present, the reimbursement criteria of the Pharmaceutical Benefits Schedule are at variance with National Heart Foundation guidelines).

The approach for patients with macro- or microalbuminuria associated with diabetes or hypertension

The finding of microalbuminuria (urinary albumin excretion 20–200 μg/min) or macroalbuminuria (urinary albumin excretion > 200 μg/min) should prompt a search for the presence of diabetes, hypertension or renal disease. If diabetes is present, the use of ramipril is appropriate for cardiovascular risk reduction.[1,61] Furthermore, there is good evidence to support the use of ACE inhibitors for renal risk reduction in normotensive patients with diabetes (type 1 or type 2) and microalbuminuria[1,77] and hypertensive patients with type 2 diabetes,[51] and the use of AIIRAs (irbesartan and losartan) in patients with type 2 diabetes.[52-54]

Other interventions

1. Antiplatelet therapies (aspirin, dipyridamole or clopidogrel)

Aspirin (75–150 mg/day) has been shown to have significant benefit for patients at high risk of cardiovascular disease, particularly in secondary prevention,[78,79] although blood pressure should be tightly controlled to minimise the risk of haemorrhagic stroke.[80-82]

It must be recognised, however, that the benefits of aspirin are not clear in older patients (> 70 years) with no previous cardiovascular events who, primarily due to age, remain at high risk of cardiovascular disease. This is highlighted by the recent FDA decision not to list primary prevention of cerebrovascular disease as an indication for aspirin in the elderly and to strongly support proposals for the conduct of such trials. The risks associated with gastrointestinal and cerebral bleeding in older patients may offset any cardiovascular protection benefits. The American Diabetes Association recommends the use of aspirin for patients with diabetes over the age of 30 years,[83] but there is no evidence of benefit in primary prevention in low-risk subjects.[80]

Alternative or additional antithrombotic therapies such as clopidogrel or dipyridamole (stroke or TIA only) may be required if aspirin is not tolerated or the patient experiences recurrent cardiovascular events while taking aspirin.[84-87]

It is beyond the scope of this review of cardiovascular prevention measures to focus on the management of acute coronary syndromes. However, it is important to highlight the results of a recent trial using combination antiplatelet therapy in patients with acute coronary syndromes: initiating therapy during the acute management phase in hospital was shown to have benefits up to 1 year after the initial presentation. The CURE study[88] showed that patients with acute coronary syndromes who were given a loading dose of 300 mg of clopidogrel followed by ongoing treatment with 75 mg daily for 9 months, in addition to their usual therapy (including aspirin), had a 20% reduction in the combined endpoint of cardiovascular death, AMI, and stroke (ARR, 2.1%).[89] Thus, many patients who leave hospital after an admission with unstable angina or non-ST elevation myocardial infarction will be receiving clopidogrel in addition to aspirin as combined antiplatelet therapy for atherothrombosis, which should be continued as long-term therapy.

The CREDO study showed a 27% relative risk reduction (ARR, 3.0%) in the combined endpoint of death, AMI and stroke at 1 year with the use of clopidogrel added to conventional therapy (including aspirin) after placement of a coronary stent.[89] Once again, early treatment translates into long-term preventive therapy, and thus a case can be made for the use of combination antiplatelet therapy (aspirin and clopidogrel) for preventing ischaemic events in appropriate patients. Definitive long-term trials of this combination to prevent events in patients with cardiovascular disease (but who have not presented with an acute coronary syndrome), or to avoid the need for coronary artery stenting, are currently under way.

2. Anticoagulation

Long-term anticoagulation to reduce thromboembolism may be required for patients with paroxysmal or chronic atrial fibrillation, proteinuria greater than 3 g/day, and those with a history of extensive anterior infarction or severe CCF.[90,91]

Conclusion

Prevention of cardiovascular disease: an evidence-based clinical aid 2004 is based on a review of current evidence and practice, incorporating data from RCTs, as well as recommendations from local and international guidelines. This clinical aid consolidates current evidence and recommendations into a single source and provides a reference tool for the optimal treatment of "at-risk" patients to prevent vascular events and improve clinical outcomes.

2 Competing interests

Name	Consultant fees	Honoraria/fees for service	Advisory/Steering Committee fees	Investigator-initiated research grants	Travel assistance
Dr John V Amarena	BMS, Boehringer Ingelheim, Novartis, Sanofi	Abbott, Aventis, BMS, MSD, Servier, Solvay	Aventis, BMS, Sanofi		Boehringer Ingelheim, Pfizer, Sanofi
Dr John F Beltame		Alphapharm, Aventis, Bayer, BMS, MSD, Pfizer, Roche, Sanofi, Servier	Aventis, BMS, Pfizer, Solvay		
Prof Stephen Colagiuri		MSD, Novo Nordisk, Roche, Servier	Member of MSD steering committee — unpaid		
Dr Greg W Conner	Abbott, AZ, Aventis, Bayer, Boehringer Ingelheim, BMS, GSK, MSD, Novartis, Pfizer, Roche, Sanofi, Schering-Plough, Servier	Abbott, AZ, Aventis, Bayer, Boehringer Ingelheim, BMS, GSK, MSD, Novartis, Pfizer, Roche, Sanofi, Schering-Plough, Servier	Abbott, AZ, Aventis, Bayer, Boehringer Ingelheim, BMS, GSK, MSD, Novartis, Pfizer, Roche, Sanofi, Schering-Plough, Servier		
Dr Greg R Fulcher		Aventis, BMS, MSD, Novo Nordisk, Sanofi, Eli Lilly	Aventis, GSK, MSD, Novo Nordisk, Sanofi,		Aventis, MSD
Prof Richard E Gilbert			Aventis, AZ, BMS, MSD	BMS	AZ, Servier
Prof Graeme Hankey	BMS, Sanofi	Aventis, BMS, MSD, Pfizer, Sanofi	BMS, Pfizer, Sanofi		
Assoc Prof Anthony C Keech		Laboratoires Fournier, MSD (contribution to department)		BMS, Laboratoires Fournier, MSD	Invited lectures only
Prof Brian R McAvoy		Aventis			
Prof Carol A Pollock		Aventis, Sanofi, Servier	BMS		
Prof Malcolm J West	Aventis, BMS, MSD	Aventis, BMS, MSD	BMS, MSD	BMS	Aventis, BMS, MSD

Abbott = Abbott Australasia; Aventis = Aventis Pharma; AZ = AstraZeneca; BMS = Bristol-Myers Squibb; GSK = GlaxoSmithKline; MSD = Merck Sharpe & Dohme/Amrad; Sanofi = Sanofi-Synthelabo

Acknowledgements

The taskforce steering committee would like to acknowledge the contributions of the writing committee: Dr Greg R Fulcher, Dr John V Amarena, Dr Greg W Conner, Professor Richard E Gilbert and Professor Graeme J Hankey.

Competing interests

A summary of the competing interests of the members of the Practical Implementation Task Force is given in Box 2.

References

1 The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; 342: 145-153.
2 PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; 358: 1033-1041.
3 Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; 360: 7-22.
4 Royal College of Physicians. Smoking and health now. London: Pitman Medical and Scientific, 1971.
5 US Department of Health and Human Services. The health benefits of smoking cessation: a report of the Surgeon General. DHHS Publication (CDC) 90-8416. Rockville, Md: US Department of Health and Human Services, Public Health Service, Centers for Disease Control, 1990.
6 Eaton C. Relation of physical activity and cardiovascular fitness to coronary heart disease. Part II: cardiovascular fitness and the safety and efficacy of physical activity prescription. *J Am Board Fam Pract* 1992; 5: 157-165.
7 Sacco R, Gan R, Boden-Albala B. Leisure-time physical activity and ischaemic stroke risk: the Northern Manhattan stroke study. *Stroke* 1998; 29: 380-387.
8 Berlin J, Colditz G. A meta-analysis of physical activity in the prevention of coronary heart disease. *Am J Epidemiol* 1990; 132: 612-628.
9 Oldridge N, Guyatt G, Fischer M, Rimm A. Cardiac rehabilitation after myocardial infarction. Combined experience of randomized clinical trials. *JAMA* 1988; 260: 945-950.

10 O'Connor G, Buring J, Yusuf S, et al. An overview of randomised trials of rehabilitation with exercise after myocardial infarction. *Circulation* 1989; 80: 234-244.
11 Joshipura K, Manson J, Stampfer M, et al. The effect of fruit and vegetable intake on risk for coronary heart disease. *Ann Intern Med* 2001; 134: 1106-1114.
12 De Lorgeril M, Salen P, Martin J, et al. Mediterranean diet, traditional risk factors and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* 1999; 99: 779-785.
13 Daviglus M, Stamler J, Orencia A, et al. Fish consumption and the 30-year risk of fatal myocardial infarction. *N Engl J Med* 1997; 36: 1046-1053.
14 Leren P. The Oslo diet-heart study — 11 year report. *Circulation* 1970; 42: 935-942.
15 Bunker S, Colquhoun D, Esler M, et al. "Stress" and coronary heart disease: psychosocial risk factors. National Heart Foundation of Australia position statement update. *Med J Aust* 2003; 178: 272-276.
16 The EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003; 362: 782-788.
17 PROGRESS Collaborative Group. Effects of a perindopril-based blood pressure lowering regimen on cardiac outcomes among patients with cerebrovascular disease. *Eur Heart J* 2003; 24: 475-484.
18 Yusuf S, Peto R, Lewis J, et al. Beta-blockade during and after myocardial infarction: an overview of the randomised trials. *Prog Cardiovasc Dis* 1985; 27: 335-371.
19 Acute Infarction Ramipril Efficacy (AIRE) Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993; 342: 821-828.
20 Opie L, Yusuf S, Kubler W. Current status of safety and efficacy of calcium channel blockers in cardiovascular diseases: a critical analysis based on 100 studies. *Prog Cardiovasc Dis* 2000; 43: 171-196.
21 Danish Study Group on verapamil in myocardial infarction. Effect of verapamil on mortality and major events after acute myocardial infarction (the Danish Verapamil Infarction Trial II – DAVIT II). *Am J Cardiol* 1990; 66: 779-785.
22 Multicentre Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988; 319: 385-392.
23 Flack J, Neaton J, Grimm R Jr, et al. Blood pressure and mortality among men with prior myocardial infarction. Multiple Risk Factor Intervention Trial Research Group. *Circulation* 1995; 92: 2437-2445.
24 Lenfant C, Chobanian A, Jones D, et al. Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7): resetting the hypertension sails. *Hypertension* 2003; 41: 1178-1179.
25 National Heart Foundation. Hypertension management guide for doctors 2004. Canberra: NHF, 2003. Available at: www.heartfoundation.com.au/index.cfm?page=36 (accessed May 2004).
26 Hansson L, Hedner T, Lund-Johansen P, et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular mortality in hypertension: the Nordic diltiazem (NORDIL) study. *Lancet* 2000; 356: 359-365.
27 Staessen J, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* 1997; 350: 757-764.
28 HANE Trial Research Group. Randomised, double-blind, multicentre comparison of hydrochlorothiazide, atenolol, nitrendipine, and enalapril in antihypertensive treatment: results of the HANE study. *BMJ* 1997; 315: 154-159.
29 Staessen J, Gasowski J, Wang J, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet* 2000; 355: 865-872.
30 Psaty B, Smith N, Siscovick D, et al. Health outcomes associated with antihypertensive therapies used as first line agents: a systematic review and meta-analysis. *JAMA* 1997; 277: 739-745.
31 Messerli F, Grossman E, Goldbourt U. Are beta-blockers efficacious as first line therapy for hypertension in the elderly? A systematic review. *JAMA* 1998; 279: 1903-1907.
32 Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *BMJ* 1985; 291: 97-104.
33 Dahlof B, Lindholm L, Hansson L, et al. Morbidity and mortality in the Swedish trial in old patients with hypertension (STOP-hypertension). *Lancet* 1991; 338: 1281-1285.
34 SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991; 265: 3255-3264.
35 Hansson L, Lindholm L, Niskanen L, et al. Effect of angiotensin-converting enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPP) randomised trial. *Lancet* 1999; 353: 611-616.
36 The INDANA (INdividual Data ANalysis of Antihypertensive intervention trials) Project Collaborators. Effect of antihypertensive treatment in patients having already suffered from stroke: gathering the evidence. *Stroke* 1997; 28: 2557-2562.
37 Rodgers A, Neal B, McMahon S. The effects of blood pressure lowering in cerebrovascular disease. *Neurol Rev Int* 1997; 2: 12-15.
38 The ALLHAT officers and coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288: 2981-2997.
39 Pepine C, Handberg E, Cooper-DeHoff R, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil–Trandolapril Study (INVEST): a randomised controlled trial. *JAMA* 2003; 290: 2805-2816.
40 Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344: 1383-1389.
41 The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998; 339: 1349-1357.
42 Sacks F, Pfeffer M, Moye L, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial Investigators. *N Engl J Med* 1996; 335: 1001-1009.
43 Cannon C, Brauwald E, McCabe C, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; 350: 1495-1504.
44 Rubins H, Robins S, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Intervention Trial Study Group. *N Engl J Med* 1999; 341: 410-418.
45 Pedersen T, Berg K, Cook T, et al. Safety and tolerability of cholesterol lowering with simvastatin during five years in the Scandinavian Simvastatin Survival Study (4S). *Arch Intern Med* 1996; 156: 2085-2092.
46 Wood D, de Backer G, Faergeman O, et al. Clinicians' manual on total risk management. In: Davenport L, ed. A guide to prevention of coronary heart disease. London: Science Press, 2000.
47 Fuller J, Stevens L, Chaturvedi N, Holloway J. Antihypertensive therapy for preventing cardiovascular complications in people with diabetes. *Cochrane Database Syst Rev* 2003; (1): CD002188.
48 Estacio R, Jeffers B, Hiatt W, et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 1998; 338: 645-652.
49 Tatti P, Pahor M, Byington R, et al. Outcome results of the Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 1998; 21: 597-603.
50 Agodoa L, Appel L, Bakris G, et al. African American study of kidney disease and hypertension (AASK) study group. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomised controlled trial. *JAMA* 2001; 285: 2719-2728.
51 Bakris G, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis* 2000; 36: 646-661.
52 Lewis E, Hunsicker L, Clarke W, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; 345: 851-860.

53 Parving H, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001; 345: 870-878.

54 Brenner B, Cooper M, de Zeeuw D, et al. Effect of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; 345: 861-869.

55 Lindholm L, Ibsen H, Dahlof B, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; 359: 1004-1010.

56 Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; 361: 2005-2016.

57 Downs J, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of the AFCAPS/TexCAPS Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998; 279: 1615-1622.

58 Koskinen P, Manttari M, Manninen V, et al. Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. *Diabetes Care* 1992; 15: 820-825.

59 Elkeles R, Diamond J, Poulter C, et al. Cardiovascular outcomes in type 2 diabetes. A double-blind placebo-controlled study of bezafibrate: the St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) Study. *Diabetes Care* 1998; 21: 641-648.

60 Keirnan E, Keech A. FIELD. Sydney: National Health and Medical Research Council Clinical Trials Centre, September 2003. Information available at: www.ctc.usyd.edu.au/trials/cardiovascular/field.htm (accessed May 2004).

61 Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000; 355: 253-259.

62 Mann J, Gerstein H, Pogue J, et al. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Ann Intern Med* 2001; 134: 629-636.

63 Giatras I, Lau J, Levey A. Effect of angiotensin-converting enzyme inhibitors on the progression of non-diabetic renal disease: a meta-analysis of randomized trials. Angiotensin-Converting-Enzyme Inhibition and Progressive Renal Disease Study Group. *Ann Intern Med* 1997; 127: 337-345.

64 Hillege H, van Gilst W, van Velduisen D, et al. Accelerated decline and prognostic impact of renal function after myocardial infarction and the benefits of ACE inhibition: the CATS randomised trial. *Eur Heart J* 2003; 24: 412-420.

65 Nakao N, Yoshimura A, Morita J, et al. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. *Lancet* 2003; 361: 117-124.

66 Smith S Jr, Greenland P, Grundy S. Beyond secondary prevention: identifying the high-risk patient for primary prevention: executive summary. AHA Conference Proceedings. Prevention conference V. American Heart Association; *Circulation* 2000; 101: 111-116.

67 Gueyffier F, Froment A, Gouton M. New meta-analysis of treatment trials of hypertension: improving the estimate of therapeutic benefit. *J Hum Hypertens* 1996; 10: 1-8.

68 Hansson L, Lindholm L, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999; 354: 1751-1756.

69 Appel L. The verdict from ALLHAT – thiazide diuretics are the preferred initial therapy for hypertension. *JAMA* 2002; 288: 3039-3042.

70 Katerndahl D, Lawler W. Variability in meta-analytic results concerning the value of cholesterol reduction in coronary heart disease: a meta-meta-analysis. *Am J Epidemiol* 1999; 149: 429-441.

71 Shepherd J, Cobbe S, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolaemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995; 333: 1301-1307.

72 LaRosa J, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999; 282: 2340-2346.

73 Sever P, Dahlöf B, Poulter N, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; 361: 1149-1158.

74 National Heart Foundation of Australia and The Cardiac Society of Australia and New Zealand. Lipid management guidelines – 2001. *Med J Aust* 2001; 175 (9 Suppl): S57-S88.

75 Wing L, Reid C, Ryan P, et al. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 2003; 348: 583-592.

76 New Zealand Guidelines Group. The assessment and management of cardiovascular risk. Wellington: New Zealand Guidelines Group, December 2003. Available at: www.nzgg.org.nz/guidelines/0035/CVD_Risk_Full.pdf (accessed Jun 2004).

77 Lovell H. Angiotensin converting enzyme inhibitors in normotensive diabetic patients with microlbuminuria. *Cochrane Database Syst Rev* 2000; (2): CD002183.

78 Hung J, Medical Issues Committee of the National Heart Foundation of Australia. Aspirin for cardiovascular disease prevention. *Med J Aust* 2003; 179: 147-152.

79 American Diabetes Association. Aspirin therapy in diabetes. *Diabetes Care* 2004; 27 (Suppl 1): S72-S73.

80 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy – 1: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; 308: 81-106.

81 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction and stroke in high risk patients. *BMJ* 2002; 324: 71-86.

82 Hansson L, Zanchetti A, Carruthers S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998; 351: 1755-1762.

83 American Diabetes Association. Aspirin therapy in diabetes. *Diabetes Care* 2000; 23 (Suppl 1): S61-S62.

84 Diener H, Cunha L, Forbes C, et al. European stroke prevention study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996; 143: 1-13.

85 CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; 348: 1329-1339.

86 Wilterdink J, Easton J. Dipyridamole plus aspirin in cerebrovascular disease. *Arch Neurol* 1999; 56: 1087-1092.

87 De Shryver E, ESPRIT Study Group. Dipyridamole in stroke prevention: effect of dipyridamole on blood pressure. *Stroke* 2003; 34: 2339-2342.

88 Yusuf S, Zhao F, Mehta S, et al. Clopidogrel in unstable angina to prevent recurrent events trial investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; 345: 494-502.

89 Steinhubl S, Berger P, Mann J 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002; 288: 2411-2420.

90 The European Atrial Fibrillation Trial Study Group. Optimal oral anticoagulant therapy in patients with non-rheumatic atrial fibrillation and recent cerebral ischemia. *N Engl J Med* 1995; 333: 5-10.

91 Llach F. Hypercoagulability, renal vein thrombosis and other thrombotic complications of the nephrotic syndrome. *Kidney Int* 1985; 28: 429-439.

(Received 21 May 2004, accepted 3 Aug 2004) ❑

Prevention of cardiovascular disease: an evidence-based clinical aid 2004*

	PATIENT RISK CATEGORY					
	Clinical manifestations of high risk					Calculated CVD risk§ < 10%–15% over 5 years (Note: individuals with extreme elevations in isolated risk factors may be independently at high risk)
TREATABLE RISK FACTORS	Clinically evident coronary heart disease ■ Previous AMI† ■ Chronic stable angina	Clinically evident cerebrovascular disease	Diabetes‡ [1]	Renal disease (Proteinuria or GFR < 80 mL/min)	Calculated CVD risk§ ⩾10%–15% over 5 years or high risk states ■ Familial dyslipidaemia ■ BP > 170/100 ■ Peripheral vascular disease	
Smoking	All smokers should be provided with an active cessation program + medication assistance, if appropriate.					
Physical inactivity Obesity	Diet low in saturated fat; increased physical activity (3 x 10 minutes daily); limit excessive alcohol consumption. Target body mass index (BMI) < 25 kg/m^2; waist < 80 cm for women and < 94 cm for men; waist : hip ratio < 1. [2,3]					
Normal BP (<140/90 mmHg) [3]	ACE inhibitor (ramipril 10 mg;¶ perindopril 8 mg) [4,5]	ACE inhibitor (ramipril 10 mg)¶ [4,6] Perindopril 4 mg + indapamide 2.5 mg [6,7]	BP < 130/85 [3] Observation, with repeated measurements annually [2,3] Consider treatment if other risk factors (eg, smoking) are present	BP < 130/85 [3] (BP < 125/75, if > 1 g proteinuria per day) [3] Observation, with repeated measurements 6 monthly [2,3,8]	Observation, with repeated measurements annually [2,3,8]	Observation, with repeated measurements every 5 years if < 60 years, every 2 years if > 60 years [2,3]
High BP (⩾140/90 mmHg) [3]	BP > 130/85 [3] ACE inhibitor (ramipril 10 mg;¶ perindopril 8 mg) [4,5] ACE inhibitor¶ [4,9-14] Non-ISA β-blocker† [3,15-18] Calcium channel blocker [3,14,18-20] Diuretic (thiazide) [3,14]	ACE inhibitor (ramipril 10 mg) ¶ [4,6] Diuretic (indapamide or thiazide) [6] Perindopril 4 mg + indapamide 2.5 mg [6,7]	BP > 130/85 [3] ACE inhibitor ¶ [3,4,14,21] β-Blocker** [3,21] Calcium channel blocker (2nd-line therapy to ACE inhibitor) [3,14,19,20,22] If LVF present, consider losartan [23] Diuretic (thiazide or chlorthalidone)** [3,14]	BP > 130/85 [3] ACE inhibitor¶ [4,24-27] β-Blocker [3,8] Calcium channel blocker (used with an ACE inhibitor) [22] Diuretic (thiazide) [3,8]	ACE inhibitor [3,8,14] β-Blocker [3,8] Calcium channel blocker (2nd-line therapy) [3,8,14,19,20] Diuretic (thiazide) [3,8,14]	Consider drug therapy if systolic BP > 150 or diastolic BP > 95 [3]
Dyslipidaemia	TC > 3.5 mmol/L Simvastatin 40 mg [28] TC > 4.0 mmol/L Pravastatin 40 mg [29,30] TC < 6.5 mmol/L Atorvastatin 80 mg [31] or Low HDL-C or high TG Fibrate (gemfibrozil) [32]	TC > 3.5 mmol/L Simvastatin 40 mg [28,33] TC > 4.0 mmol/L Pravastatin 40 mg [29,30]	TC > 3.5 mmol/L Simvastatin 40 mg [34] ACE inhibitor (ramipril 10 mg)¶ [4]	TC > 5.0 mmol/L Statin [35] Low HDL-C or high TG Fibrate (gemfibrozil) [35]	TC > 5.0 mmol/L Statin [35] TC < 6.5 mmol/L Atorvastatin 10 mg [36] Low HDL-C or high TG Fibrate (gemfibrozil) [35]	Consider drug therapy if TC > 8.0 mmol/L or TC : HDL-C ratio > 8.0 [37] Diagnosis of familial hypercholesterolaemia should be considered

Proteinuria/ microalbuminuria or GFR <80 mL/min	*ACE inhibitor (cardiovascular and renal risk reduction) (ramipril 10 mg)¶* [4] *ACE inhibitor (renal risk reduction) captopril* [24,27,38] *Statin (pravachol or simvastatin)* [29,30,34]	*ACE inhibitor (cardiovascular and renal risk reduction) (ramipril 10 mg)¶* [4] *ACE inhibitor (renal risk reduction)* [24,38]	*ACE inhibitor (cardiovascular and renal risk reduction) (ramipril 10 mg)¶* [4] *ACE inhibitor or irbesartan 300 mg (renal risk reduction)* [22,39-41]	*If > 1 g proteinuria:* *ACE inhibitor* [24-26,42] *Combination therapy trandolapril + losartan* [42]	*Check for diabetes or other causes* *If non-diabetic proteinuric nephropathy present:* *ACE inhibitor* [24] *Observation, with repeated measurements annually, if positive*	*Treat as per renal disease*
OTHER INTERVENTIONS						
Antiplatelet therapies	*Aspirin 75–150 mg for all patients at high risk of CVD.* [43,44] *Ensure that blood pressure is controlled to minimise risk of haemorrhagic stroke.* [45-47] *Alternative or additional antiplatelet therapy if aspirin not tolerated, or recurrent coronary heart disease/cerebrovascular disease events occur (dipyridamole, aspirin/dipyridamole, clopidogrel).* [48,49]					
Anticoagulation	*Paroxysmal atrial fibrillation; prior thromboembolic event; proteinuria > 3 g/day;* [50] *large anterior myocardial infarction; left ventricular aneurysm; intracardiac thrombus; or severe congestive cardiac failure.*					

AMI = acute myocardial infarction
ACE inhibitor = angiotensin-converting enzyme inhibitor
BP = blood pressure
CVD = cardiovascular disease
GFR = glomerular filtration rate
HDL-C = high-density lipoprotein cholesterol
LVF = left ventricular failure
non-ISA = non-intrinsic sympathomimetic activity
TC = total cholesterol
TG = triglycerides

* *Prevention of cardiovascular disease: an evidence-based clinical aid 2004* is intended as a guide for the management of vascular disease, integrating current local and international guidelines and clinical trial data. It should only be used in conjunction with the most recent published guidelines. Therapeutic choices are listed in alphabetical order and not by treatment priority, as this may differ for individual patients. Thresholds are referenced to current guidelines and indicate the level for commencement of therapy. Targets that should be aimed for by applying the recommended intervention are not given.

† Hypertensive and normotensive patients after AMI should receive non-ISA β-blockers.[15-17] There is evidence that, for patients who cannot take β-blockers, non-dihydropyridine calcium channel blockers may be beneficial.[51-53]

‡ Fasting blood sugar (≥ 8 h after consumption of food) ≥ 7.0 mm/L or non-fasting, ≥ 11.1 mmol/L.[1] These blood sugar levels suggest the possibility of diabetes; however, in the absence of symptoms, blood sugar levels should be confirmed on another occasion. Non-diagnostic estimations between 5.5 mmol/L and 7.0 mmol/L (fasting) and 5.5 mmol/L and 11.1 mmol/L (non-fasting) require a glucose tolerance test to confirm the diagnosis of diabetes. Routine management of diabetes will include attention to diet ± oral hypoglycaemic agents or insulin. Evidence that intensive glycaemic control will reduce macrovascular events is limited.

§ A patient's risk level is assessed using tools such as the Framingham calculator <www.nhlbi.nih.gov/about/framingham/riskabs.htm>. Family history may also modify assessment of a patient's risk. In addition, there is strong evidence of an independent and causal association between depression, social isolation and the prognosis of coronary heart disease, with the impact of these psychosocial factors being of a similar order to conventional risk factors such as smoking. It is therefore crucial that these factors are considered during individual coronary heart disease risk assessment. In circumstances in which a patient is in more than one risk category, a hierarchical approach (left to right) should be adopted.

¶ See titration schedule in the HOPE study.

** May interfere with diabetic control.

References for chart

1 Alberti K, Zimmet P. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabet Med* 1998; 15: 539-553.
2 Wood D, de Backer G, Faergeman O, et al. Clinicians' manual on total risk management. In: Davenport L, ed. A guide to prevention of coronary heart disease. London: Science Press, 2000.
3 National Heart Foundation. Hypertension management guide for doctors 2004. Canberra: NHF, 2003. Available at: www.heartfoundation.com.au/index.cfm?page=36 (accessed May 2004).
4 The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; 342: 145-153.
5 The EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003; 362: 782-788.
6 Rashid P, Leonardi-Bee J, Bath P. Blood pressure reduction and secondary prevention of stroke and other vascular events: a systematic review. *Stroke* 2003; 34: 2741-2748.
7 PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; 358: 1033-1041.
8 Lenfant C, Chobanian A, Jones D, et al. Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7): resetting the hypertension sails. *Hypertension* 2003; 41: 1178-1179.
9 Swedberg K, Held P, Kjekshus J, et al. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *N Engl J Med* 1992; 327: 678-684.
10 Kober L, Torp-Pedersen G, Carlsen J, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study. *N Engl J Med* 1995; 333: 1670-1676.
11 Acute Infarction Ramipril Efficacy (AIRE) Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993; 342: 821-828.
12 Pfeffer M, Brauwald E, Moye L, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and left ventricular enlargement trial. The SAVE Invesitgators. *N Engl J Med* 1992; 327: 669-677.
13 Swedberg K, Sharpe N. The value of angiotensin converting enzyme inhibitors for the treatment of patients with left ventricular dysfunction, heart failure or after acute myocardial infarction. *Eur Heart J* 1996; 17: 1306-1311.
14 The ALLHAT officers and coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288: 2981-2997.
15 Hennekens C, Albert C, Godfried S, et al. Adjunctive drug therapy of acute myocardial infarction — evidence from clinical trials. *N Engl J Med* 1996; 335: 1660-1667.
16 Yusuf S, Peto R, Lewis J, et al. Beta-blockade during and after myocardial infarction: an overview of the randomised trials. *Prog Cardiovasc Dis* 1985; 27: 335-371.
17 Gottleib S, McCarter R, Vogel R. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med* 1998; 339: 489-497.
18 Pepine C, Handberg E, Cooper-DeHoff R, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil–Trandolapril Study (INVEST): a randomised controlled trial. *JAMA* 2003; 290: 2805-2816.
19 Pahor M, Psaty B, Alderman M, et al. Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomised controlled trials. *Lancet* 2000; 356: 1949-1945.
20 Blood Pressure Lowering Treatment Triallists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet* 2000; 355: 1955-1964.
21 UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ* 1998; 317: 713-720.
22 Bakris G, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis* 2000; 36: 646-661.
23 Lindholm L, Ibsen H, Dahlof B, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; 359: 1004-1010.
24 The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric non-diabetic nephropathy. *Lancet* 1997; 349: 1857-1863.
25 Maschio G, Alberti D, Janin G, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency (AIPRI) Study Group. *N Engl J Med* 1996; 334: 939-945.
26 Giatras I, Lau J, Levey A. Effect of angiotensin-converting enzyme inhibitors on the progression of non-diabetic renal disease: a meta-analysis of randomized trials. Angiotensin-Converting-Enzyme Inhibition and Progressive Renal Disease Study Group. *Ann Intern Med* 1997; 127: 337-345.
27 Hillege H, van Gilst W, van Velduisen D, et al. Accelerated decline and prognostic impact of renal function after myocardial infarction and the benefits of ACE inhibition: the CATS randomised trial. *Eur Heart J* 2003; 24: 412-420.
28 Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 high risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; 360: 7-22.
29 The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998; 339: 1349-1357.
30 Sacks F, Pfeffer M, Moye L, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial Investigators. *N Engl J Med* 1996; 335: 1001-1009.
31 Cannon C, Brauwald E, McCabe C, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; 350: 1495-1504.
32 Rubins H, Robins S, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Intervention Trial Study Group. *N Engl J Med* 1999; 341: 410-418.
33 Collins D, Armitage J, Parish S, et al. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20,536 people with cerebrovascular disease or other high-risk conditions. *Lancet* 2004; 363: 757-767.
34 Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; 361: 2005-2016.
35 National Heart Foundation of Australia. Lipid management guidelines – 2001. *Med J Aust* 2001; 175 (9 Suppl): S57-S88.
36 Sever P, Dahlöf B, Poulter N, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; 361: 1149-1158.
37 New Zealand Guidelines Group. The assessment and management of cardiovascular risk. Wellington: New Zealand Guidelines Group, Dec 2003. Available at: www.nzgg.org.nz/guidelines/0035/CVD_Risk_Full.pdf (accessed Jun 2004).
38 Marcantoni C, Jafar T, Oldrizzi L, et al. The role of systemic hypertension in the progression of nondiabetic renal disease. *Kidney Int Suppl* 2000; 75: S44-48.
39 Lovell H. Angiotensin converting enzyme inhibitors in normotensive diabetic patients with microalbuminuria. *Cochrane Database Syst Rev* 2000; (2): CD002183.
40 Lewis E, Hunsicker L, Clarke W, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; 345: 851-859.
41 Morgensen C, Cooper M. Diabetic renal disease: from recent studies to improved clinical practice. *Diabet Med* 2004; 21: 4-17.
42 Nakao N, Yoshimura A, Morita J, et al. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. *Lancet* 2003; 361: 117-124.
43 Hung J, Medical Issues Committee of the National Heart Foundation of Australia. Aspirin for cardiovascular disease prevention. *Med J Aust* 2003; 179: 147-152.
44 American Diabetes Association. Aspirin therapy in diabetes. *Diabetes Care* 2004; 27 (Suppl 1): S72-S73.
45 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy – 1: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; 308: 81-106.
46 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction and stroke in high risk patients. *BMJ* 2002; 324: 71-86.
47 Hansson L, Zanchetti A, Carruthers S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998; 351: 1755-1762.
48 CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; 348: 1329-1339.
49 De Shryver E, ESPRIT Study Group. Dipyridamole in stroke prevention: effect of dipyridamole on blood pressure. *Stroke* 2003; 34: 2339-2342.
50 Llach F. Hypercoagulability, renal vein thrombosis and other thrombotic complications of the nephrotic syndrome. *Kidney Int* 1985; 28: 429-439.
51 Multicentre Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988; 319: 385-392.
52 Danish Study Group on verapamil in myocardial infarction. Effect of verapamil on mortality and major events after acute myocardial infarction (the Danish Verapamil Infarction Trial II – DAVIT II). *Am J Cardiol* 1990; 66: 779-785.
53 Opie L, Yusuf S, Kubler W. Current status of safety and efficacy of calcium channel blockers in cardiovascular diseases: a critical analysis based on 100 studies. *Prog Cardiovasc Dis* 2000; 43: 171-196. ❑

NOTES

NOTES