



Prevention of cardiovascular disease: an evidence-based clinical aid

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for the Practical Implementation Taskforce for the Prevention of Cardiovascular Disease



Contents

Recommendations for all patients	5
Recommendations for patients with established vascular disease	6
Recommendations for patients with diabetes without known cardiovascular disease	7
Recommendations for patients with non-diabetic renal disease	7
The approach for other high-risk patients	8
The approach for patients at low risk of a cardiovascular event	8
The approach for patients with macro- or microalbuminuria associated with diabetes or hypertension	9
Other interventions	9
Conclusion	9
Desktop reference	12

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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 have an integrated approach to prevention of vascular events. While absolute risk calculators such as the Framingham Heart Study Prediction Score Sheets (<http://www.nhlbi.nih.gov/about/framingham/riskabs.htm>) or the New Zealand Cardiovascular Risk Factor Calculator (<http://nps.org.au/Docs/pdfs/Cardiovascularrisk.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.

Because of this, a multidisciplinary group of physicians evaluated current best practice, based on a rigorous analysis of available published evidence to April 2003, and formulated a concise and up-to-date guide for the prevention of cardiovascular disease. This consensus of opinions has been summarised in this document (see *page 12*) and is 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). 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 >3%. 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 study² 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

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, history of a revascularisation procedure)
- Clinically evident vascular disease (cerebrovascular or peripheral vascular disease)
- Diabetes
- Renal disease
- A risk of a future vascular event > 3% per year, based on an aggregate of unfavourable risk characteristics*

Low-risk patients are those with:

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.

Finally, we expect that this will be a “living” document and that management recommendations will continually evolve as new evidence is published.

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 CHD⁶ and stroke,⁷ and that the risk is increased in people with a sedentary

Glossary of abbreviations

ACE inhibitor – angiotensin-converting enzyme inhibitor
AMI – acute myocardial infarction
CCF – congestive cardiac failure
CHD – coronary heart disease
HOPE study – Heart Outcomes Prevention Evaluation study
HDL cholesterol – high-density lipoprotein cholesterol
LDL cholesterol – low-density lipoprotein cholesterol

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, 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 caution, the prescription of 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 (absolute risk reduction, 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 were related to 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 Further, 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. 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

Both the HOPE study¹ and the PROGRESS study² have examined the effects of preventive treatment with an ACE inhibitor in normotensive high-risk patients. In the HOPE study, 9297 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; absolute risk-reduction, 2.0%], stroke [32% reduction; absolute risk-reduction, 1.5%], heart attack [20% reduction; absolute risk reduction, 2.2%]; $P < 0.05$) or the 17% decrease in total mortality ($P < 0.05$).¹ Based on these data, normotensive patients with a history of cardiovascular disease, or with diabetes and one additional risk factor, should be considered for treatment with ramipril 10 mg for prevention of cardiovascular events, unless the practitioner considers that ACE inhibitors are contraindicated. In the PROGRESS study, perindopril 4 mg and indapamide 2.5 mg, when given together, reduced the risk of recurrent stroke (fatal or non-fatal) and major vascular events in both normotensive and hypertensive patients with previous stroke or TIA.²

In the immediate post-infarct management of the normotensive patient, a mortality benefit in the short term has also been demonstrated with β -blockers¹⁶ and ACE inhibitors (particularly in patients with associated heart failure),¹⁷ with less robust evidence for calcium channel blockers, verapamil and diltiazem.¹⁸⁻²⁰

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

While epidemiological studies have established that blood pressure is a major risk factor for cardiovascular events in patients with a history of AMI,²¹ there is no systematic review or RCT that specifically examines blood pressure reduction in patients with established CHD, nor in those with peripheral vascular disease. In our recommendations, and those of both the Sixth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure²² and the National Heart Foundation,²³ the benefits of blood pressure lowering in patients with CHD have been extrapolated from primary prevention trials and from studies of patients after AMI.^{2,16-20} Evidence of event reduction exists for patients taking calcium channel blockers,^{18-20,24-27} diuretics and β -blockers,²⁷⁻³³ and ACE inhibitors.^{1,26,33} 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.³²⁻³⁶ As over 50% of patients in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) had a history of atherosclerotic cardiovascular disease, the result of this study should be considered when blood pressure lowering is contemplated for such patients.³⁶ Specifically, the results of treatment with either ACE inhibitors, diuretics or calcium channel blockers were comparable.

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,³⁷ even if cholesterol levels are normal.^{3,38,39} The most substantial data are from studies of simvastatin and pravastatin.^{3,37-39} Of these studies, the Heart Protection Study³ has provided 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.⁴⁰

In patients with diabetes and CHD, the data are strongest for the use of statins,^{3,37-39} but again in patients with low levels of HDL cholesterol, gemfibrozil is efficacious.⁴⁰ 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,^{3,38,39,41} 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.²² As the HOPE study¹ 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.

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.⁴² There is no clear evidence that any of these classes is more effective than another in event reduction,^{26,24} and, currently, drugs of all of these classes are recommended to treat blood pressure in patients with diabetes.^{22,23} Despite this, an apparent greater reduction in major cardiovascular events occurring with ACE inhibitors, compared with some calcium channel blockers,⁴³⁻⁴⁵ 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.⁴⁶ Similar protection has recently been shown with the angiotensin II receptor antagonists irbesartan^{47,48} and losartan⁴⁹ in patients with type 2 diabetes.

3. Lowering cholesterol level in patients with diabetes

In the Heart Protection Study,³ 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,⁵⁰ gemfibrozil⁵¹ and bezafibrate⁵² 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 a 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) 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),⁵³ 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.⁵⁴ Hypertension in patients with renal disease is defined as blood pressure greater than 130/85 mmHg,²² 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.^{22,55}

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.²³

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.⁴⁶ Furthermore, 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.⁵⁶ β -Blockers and diuretics are also recommended.^{22,23} If calcium channel blockers are used they should be considered second-line therapy after ACE inhibitors.⁴⁶

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,⁵⁷ whereas other patients may have an overall low risk even if they have one markedly abnormal risk factor (Box).

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.^{22,23,54,58} 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.⁵⁹ The ALLHAT study, involving hypertensive patients with at least one other CHD risk factor, supports these findings.^{36,60} When the primary outcome was considered (fatal CHD or non-fatal AMI), diuretic-based therapy (chlor-thalidone) 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.³⁶ As amlodipine is a dihydropyridine calcium channel blocker, it may not be possible to extrapolate these results to the non-dihydropyridine calcium channel blockers.⁶⁰

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

We found no evidence that lowering cholesterol level reduces total mortality in non-diabetic patients without cardiovascular disease, although systematic reviews and RCTs have shown that cholesterol reduction improves cardiovascular outcomes in high-risk populations.^{3,50,61–63} The benefit is related to baseline risk and extent of cholesterol reduction rather than initial cholesterol level (within the range studied). 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.⁶⁴

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 (> 60 years).^{23,58} Current clinical practice would also be at variance with the guideline recommenda-

tions that drug therapy and lifestyle modification for hypertension should only be introduced in patients under 60 years if their systolic blood pressure is > 180 mmHg or diastolic > 100 mmHg,^{23,58} or in those over 60 years whose systolic blood pressure is > 160 mmHg.^{25,27} Despite our personal views we have included the current published recommendations in the desktop reference.²³ In the second Australian National Blood Pressure Study (ANBP2), 6083 elderly subjects (aged 65–84 years) with hypertension, treated with either ACE inhibitors or diuretics, were compared. Although a similar number of strokes occurred in each group, taking ACE inhibitors was associated with better cardiovascular outcomes, particularly in men.⁶⁵

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 (> 6.5 mmol/L), or with a fibrate for patients with low HDL cholesterol and high triglyceride levels.⁶⁴ (At present, the reimbursement criteria of the Pharmaceutical Benefits Schedule are at variance with current 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.^{1,53} 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^{1,66} and hypertensive patients with type 2 diabetes,⁴⁶ and the use of angiotensin II receptor antagonists (irbesartan and losartan) in patients with type 2 diabetes.^{47–49}

Other interventions

1. Antiplatelet therapies (aspirin, dipyridamole or clopidogrel)

Aspirin (75–325 mg/day) has been shown to have significant benefit in patients with acute coronary syndromes, stroke/TIA, stable angina, peripheral vascular disease, and in those with hypertension,^{67,68} although blood pressure should be tightly controlled to minimise the risk of haemorrhagic stroke.⁶⁹ The American Diabetes Association recommends the use of aspirin for patients with diabetes over the age of 30 years,⁶⁸ but there is no evidence of benefit in primary prevention in low-risk subjects.⁶⁷

Alternative or additional antithrombotic therapies such as clopidogrel or dipyridamole (stroke/TIA only) may be

required if aspirin is not tolerated or the patient experiences recurrent cardiovascular events while taking aspirin.^{70–72}

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 (Clopidogrel in Unstable angina to prevent Recurrent Events)⁷³ 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/day 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 (absolute risk reduction, 2.1%).⁷⁴ 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, and this should be continued as long-term therapy.

The CREDO study (Clopidogrel for the Reduction of Events During Observation) showed a 27% relative risk reduction (absolute risk reduction, 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.⁷⁴ 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 > 3 g/day, and those with a history of extensive anterior infarction or severe CCF.^{75,76}

Conclusion

Prevention of cardiovascular disease: an evidence-based clinical aid is based on a review of current evidence and practice and incorporates data from local and international guidelines, as well as RCTs. It is designed to consolidate and update current evidence and recommendations into a single source. It provides a reference tool for the optimal treatment of an “at-risk” patient to prevent first and future vascular events and improve outcomes.

Competing interests

A summary of the competing interests of the members of the Practical Implementation Taskforce is given in Box (see page 10).

Competing interests

Name	Consultant fees	Honoraria/fees for service	Advisory/Steering Committee fees	Investigator-initiated research grants	Other (eg, travel assistance)
Dr John V Amerena	BMS	Aventis, Servier, MSD, BMS	Aventis, BMS		
Dr John F Beltrame		Aventis, BMS, MSD	Aventis, BMS		
Dr Greg W Conner	MSD, Servier, BMS, Sanofi, Aventis	MSD, Servier, BMS, Sanofi, Aventis	MSD, Servier, BMS, Sanofi, Aventis		
Dr Greg R Fulcher	MSD	MSD, BMS, Sanofi, Aventis	MSD, BMS, Aventis, Sanofi		
Prof Graeme J Hankey	BMS, Sanofi	Aventis, BMS, Sanofi	BMS, Sanofi		
Assoc Prof Anthony C Keech		MSD (contribution to department)		MSD, BMS	
Prof Brian L Lloyd	BMS, MSD, Aventis	BMS, MSD, Aventis	BMS		Travel to meetings — MSD, Aventis, BMS
Prof Brian R McAvoy		Aventis			
Dr Michael L Neale		Sanofi	Aventis		
Prof Carol A Pollock		Sanofi, Servier, Aventis	BMS		
Assoc Prof Krishna Sudhir		BMS, Sanofi, Aventis		BMS	
Dr Robert D Waltham		MSD, BMS, Aventis, Servier			
Prof Malcolm J West	Aventis, BMS, MSD	Aventis, BMS, MSD	BMS, MSD	BMS	Travel — Aventis, BMS, MSD

Aventis = Aventis Pharma; BMS = Bristol-Myers Squibb; MSD = Merck Sharpe & Dohme/Amrad; Sanofi = Sanofi-Synthelabo.

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

PATIENT RISK CATEGORY						
High risk						Low risk [§]
TREATABLE RISK FACTORS	Clinically evident coronary heart disease ■ Previous AMI [†] ■ Chronic stable angina	Clinically evident cerebrovascular disease Peripheral vascular disease	Diabetes [‡] ¹	Renal disease	Other risks [§] including ■ Familial hypercholesterolaemia ■ Low levels of HDL cholesterol	
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, titrate to 10 mg) [¶] ⁴	ACE inhibitor (ramipril, titrate to 10 mg) [¶] ⁴ Perindopril 4 mg + indapamide 2.5 mg (cerebrovascular disease) ²⁵	BP < 130/85 ⁵ Observation, with repeated measurements annually ^{2,3,5}	BP < 130/85 ⁵ Observation, with repeated measurements 6 monthly ^{2,3,5}	Observation, with repeated measurements annually ^{2,3,5}	Observation, with repeated measurements every 5 years if < 60 years, every 2 years if > 60 years ^{2,3,5}
High BP (≥140/90 mmHg) ³	BP > 130/85 ⁵ ACE inhibitor (ramipril, titrate to 10 mg) [¶] ⁴ ACE inhibitor [¶] ^{4,6,7,8,9,10,11} Non-ISA b-blocker [†] ^{5,12,13,14,15} Calcium channel blocker ^{5,11,12,16,17} Diuretic (thiazide) ^{5,11,12}	ACE inhibitor (ramipril, titrate to 10 mg) [¶] ⁴ b-Blocker ^{5,12,26,27} Diuretic (thiazide) ^{5,12,26,27} Perindopril 4 mg + indapamide 2.5 mg (cerebrovascular disease) ²⁵	BP > 130/85 ⁵ ACE inhibitor [§] ^{28,29} (ramipril, titrate to 10 mg) [¶] ⁴ b-Blocker** ^{5,12} Calcium channel blocker (2nd-line therapy to ACE inhibitor) ^{5,12,16,17,30,31} Diuretic (thiazide)** ^{5,12}	BP > 130/85 ⁵ ACE inhibitor [¶] ^{4,23,34,35} b-Blocker ^{5,12} Calcium channel blocker (used with an ACE inhibitor) ³⁰ Diuretic (thiazide) ^{5,12}	ACE inhibitor ^{3,5,11,12} b-Blocker ^{3,5,12} Calcium channel blocker (2nd-line therapy) ^{5,11,12,16,17} Diuretic (thiazide) ^{5,11,12}	Drug therapy if: ■ Systolic BP > 180 or diastolic BP > 100 ² ■ Systolic BP > 160 and age > 60 years ³⁶ ■ BP > 140/90 with end-organ damage and/or subclinical disease (microalbuminuria, ST/T wave changes on ECG, left ventricular hypertrophy, retinopathy) ^{2,5,12}
Dyslipidaemia	TC > 3.5 mmol/L Simvastatin 40 mg ²¹ TC > 4.0 mmol/L Pravastatin 40 mg ^{3,18,19} or Low HDL-C/high TG Fibrate (gemfibrozil) ²²	TC > 3.5 mmol/L Simvastatin 40 mg ²¹ TC > 4.0 mmol/L Pravastatin 40 mg ^{3,18,19} or Low HDL-C/high TG Fibrate (gemfibrozil) ²²	TC > 3.5 mmol/L Simvastatin 40 mg ²¹ TC > 5.0 mmol/L Statin ^{3,18,19} Low HDL-C/high TG Fibrate (gemfibrozil) ²² ACE inhibitor (ramipril, titrate to 10 mg) [¶] ⁴	TC > 5.0 mmol/L Statin ³ Low HDL-C/high TG Fibrate (gemfibrozil) ³	TC > 5.0 mmol/L Statin ³ Low HDL-C/high TG Fibrate (gemfibrozil) ³	TC > 6.5 mmol/L Statin, if lifestyle changes ineffective ³ TC > 7.5 mmol/L Consider diagnosis of familial hypercholesterolaemia; also secondary causes, other risk factors, and low HDL-C/high TG levels

Proteinuria/ microalbuminuria	<p>Check for diabetes or other causes</p> <p>If evident:</p> <p>ACE inhibitor (cardiovascular and renal risk reduction) (ramipril, titrate to 10 mg)^{¶ 4}</p> <p>ACE inhibitor (renal risk reduction)^{23,24}</p>	<p>Check for diabetes or other causes</p> <p>If evident:</p> <p>ACE inhibitor (cardiovascular and renal risk reduction) (ramipril, titrate to 10 mg)^{¶ 4}</p> <p>ACE inhibitor (renal risk reduction)^{23,24}</p>	<p>ACE inhibitor (cardiovascular and renal risk reduction) (ramipril, titrate to 10 mg)^{¶ 4}</p> <p>ACE inhibitor or irbesartan 300 mg (renal risk reduction)^{30,32,33}</p>	<p>Check for diabetes or other causes</p> <p>If > 1 g proteinuria:</p> <p>ACE inhibitor^{4,23,34,35}</p> <p>Observation, with repeated measurements 6 monthly, if positive</p>	<p>Check for diabetes or other causes</p> <p>If evident:</p> <p>ACE inhibitor^{23,32}</p> <p>Observation, with repeated measurements annually, if positive</p>	<p>Check for diabetes or other causes, as may represent a high-risk group</p> <p>Observation, with repeated measurements annually, if positive</p>
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OTHER INTERVENTIONS	
Antiplatelet therapies	<p>Aspirin 75 mg for all patients at high risk of cardiovascular disease.^{37,38} Ensure that blood pressure is controlled to minimise risk of haemorrhagic stroke.^{39,40}</p> <p>Alternative or additional antiplatelet therapy if aspirin not tolerated, or recurrent coronary heart disease/cerebrovascular disease events occur (dipyridamole, aspirin/dipyridamole, clopidogrel)^{20,41,42}</p>
Anticoagulation	<p>Consider in patients with paroxysmal atrial fibrillation; chronic atrial fibrillation; prior thromboembolic event; proteinuria > 3 g/day;⁴³ large anterior myocardial infarction; left ventricular aneurysm; intracardiac thrombus; or severe congestive cardiac failure</p>

<p>Reference key</p> <p>■ Evidence from meta-analyses or Cochrane Collaboration reviews.</p> <p>■ Evidence from meta-analyses or Cochrane Collaboration reviews extrapolated to the subgroup.</p> <p>■ Supported by Australian or international guidelines or peer published opinion.</p> <p>Specific references are given when there is evidence from meta-analyses or Cochrane Collaboration reviews relating to that particular patient subgroup. When evidence relating to a specific subgroup is not available, general evidence is extrapolated to the subgroup, or references to guidelines or supporting documentation are given.</p>	<p>AMI = acute myocardial infarction</p> <p>ACE inhibitor = angiotensin-converting enzyme inhibitor</p> <p>BP = blood pressure</p> <p>ECG = electrocardiogram</p> <p>non-ISA = non-intrinsic sympathomimetic activity</p> <p>TC = total cholesterol</p> <p>HDL-C = high-density lipoprotein cholesterol</p> <p>TG = triglycerides</p>
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* *Prevention of cardiovascular disease: an evidence-based clinical aid* 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.^{13,14,15} There is evidence that, for patients who cannot take β-blockers, non-dihydropyridine calcium channel blockers may be beneficial.^{44,45,46}

‡ 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, single estimations between 5.5 mmol/L and 11.1 mmol/L require confirmation and/or 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 <<http://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.

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