Problem Solving in
Cardiology

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Contents

Abbreviations

4S	Scandinavian Simvastatin Survival Study
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	angiotensin-converting enzyme
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AF	atrial fibrillation
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ARBITER 6-HALTS	Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6: HDL and LDL Treatment Strategies in Atherosclerosis
ASCOT-LLA	Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm
ASD	atrial septal defect
ATHENA	A Placebo-Controlled, Double Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter
AV	atrioventricular
AVNRT	atrioventricular nodal re-entry tachycardia
AVR	aortic valve replacement
AVRT	atrioventricular re-entry tachycardia
A-VSaO$_2$	difference between arterial and mixed venous oxygen saturations
BD	twice daily
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass graft
CaCC	calcium-activated chloride channel
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CAST	Cardiac Arrhythmia Suppression Trial
CCS	Canadian Cardiovascular Society
CF	cystic fibrosis
CHADS	Congestive heart failure, Hypertension, Age over 75, Diabetes, Stroke/TIA
CK	creatine kinase
CO	cardiac output
COMMIT	Clopidogrel and Metoprolol in Myocardial Infarction Trial
COPE	Colchicine for Acute Pericarditis
CORE	Colchicine for Recurrent Pericarditis
COURAGE	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation
CT	computed tomography
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
CVD	cardiovascular disease
CVP	central venous pressure
DANAMI-2	Danish Trial in Acute Myocardial Infarction-2
DIGAMI	Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction
DINAMIT	Defibrillator in Acute Myocardial Infarction Trial
ECG	electrocardiogram
EF	ejection fraction
EGSYS	Evaluation of Guidelines in Syncope Study
ENaC	epithelial sodium channel
EPHESUS	Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study

ESD	end-systolic dimension	LVEDD	left ventricular end-diastolic diameter
EUROPA	EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease	LVEDP	left ventricular end-diastolic pressure
FINESSE	Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events	LVEF	left ventricular ejection fraction
		LVESD	left ventricular end-systolic diameter
FRISC	Fragmin during Instability in Coronary Artery Disease	LVH	left ventricular hypertension
		LVOT	left ventricular outflow tract
GISSI	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico	MADIT	Multicenter Automatic Defibrillator Implantation Trial
		MBL	mannose binding lectin
GRACE	Global Registry of Acute Coronary Events	MERLIN TIMI-36	Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes
GTN	glyceryl trinitrate		
HACEK	Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella	MI	myocardial infarction
		MIST	Migraine Intervention with STARFlex Technology
HCM	hypertrophic cardiomopathy	MR	mitral regurgitation
HDL	high-density lipoprotein	MRI	magnetic resonance imaging
HDU	high dependency unit	MRSA	methicillin-resistant *Staphylococcus aureus*
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A		
		NICE	National Institute for Clinical Excellence
HOPE	Heart Outcomes Prevention Evaluation	NO	nitric oxide
HR	hazard ratio	NSAID	non-steroidal anti-inflammatory drug
HYVET	Hypertension in the Very Elderly Trial	NSTEMI	non-ST elevation myocardial infarction
IABP	intra-aortic balloon pump		
ICD	implantable cardioverter defibrillator	NSVT	non-sustained ventricular tachycardia
Ig	immunoglobulin	NYHA	New York Heart Association
INSTEAD	INvestigation of STEnt Grafts in Patients with Type B Aortic Dissection	OD	once daily
		PACE	Promoting Healthy Ageing with Cognitive Exercise
IONA	Impact of Nicorandil in Angina	PCI	percutaneous coronary intervention
ISIS-2	Second International Study of Infarct Survival	PCO_2	partial pressure of carbon dioxide
ISSUE 2	International Study on Syncope of Uncertain Etiology 2	PCWP	pulmonary capillary wedge pressure
		PDA	patent ductus arteriosus
IVC	inferior vena cava	PEA	pulseless electrical activity
JBS	Joint British Societies	PEFR	peak expiratory flow rate
JUPITER	Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin	PFO	patent foramen ovale
		POISE	Perioperative Ischaemia Evaluation trial
LADIP	Loire-Ardèche-Drôme-Isère-Puy-de-Dôme	POST	Prevention of Syncope Trial
		PPCI	primary percutaneous coronary intervention
LBBB	left bundle branch block		
LDL	low-density lipoprotein	PTCA	percutaneous transluminal coronary angioplasty
LMW	low molecular weight		
LV	left ventricular	RA	right atrium

RALES	Randomized Aldosterone Evaluation Study	SVC	superior vena cava
RCRI	Revised Cardiac Risk Index	SVR	systemic vascular resistance
REACT	Rescue Angioplasty Versus Conservative Treatment or Repeat Thrombolysis	SYNPACE	SYNcope and PACing trial
		TC	total cholesterol
		TIMI	Thrombolysis in Myocardial Infarction
RV	right ventricular	t-PA	tissue plasminogen activator
RVEDP	right ventricular end-diastolic pressure	TRITON TIMI-38	TRial to assess Improvement in Therapeutic Outcomes by optimising platelet iNhibition with prasugrel – Thrombolysis In Myocardial Infarction 38
RVSP	right ventricular systolic pressure		
SAVE PACE	Search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction		
		UFH	unfractionated heparin
SAM	systolic anterior motion	UKPDS	United Kingdom Prospective Diabetes Study
SBP	systolic blood pressure		
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial	VPS	Vasovagal Pacemaker Study
		VSD	ventricular septal defect
SHOCK	Should we emergently revascularize Occuded Coronaries for shocK	VT	ventricular tachycardia
		WHO	World Health Organization
SR	slow release	WOSCOPS	West of Scotland Coronary Prevention Study
STEMI	ST elevation myocardial infarction		

Primary Prevention

PROBLEM

1   Risk stratification and guidelines

Case History

A 65-year-old man attended a routine clinic assessment following his recent retirement and was found to have a serum total cholesterol of 6.1 mmol/l. His fasting triglyceride was measured at 1.6 mmol/l, high-density lipoprotein cholesterol at 1.0 mmol/l (total : high-density lipoprotein cholesterol ratio >6) and fasting plasma glucose was normal. His blood pressure was measured at 150/84 mmHg in the clinic. He has a waist circumference of 94 cm. He has no past medical history and does not take any regular medications. He does not smoke cigarettes. He insisted that he adheres rigorously to a healthy diet with five portions of fruits and vegetables daily, and since his retirement, has also been cycling and playing golf at least three times per week.

What are the indications and targets for lipid-lowering therapy?

Does he need treatment for his blood pressure?

Background

This man does not have documented cardiovascular disease (CVD). Therefore, treatment will be aimed at primary prevention of cardiovascular events. Lipid-lowering therapy with statins (HMG-CoA reductase inhibitors) has been shown to reduce cardiovascular events in the setting of primary prevention in the WOSCOPS (West of Scotland Coronary Prevention Study) and ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm) studies. The latter randomized patients with hypertension without overt coronary heart disease and total cholesterol of <6.5 mmol/l to atorvastatin

10 mg or placebo, and was terminated early because of significant reductions in cardio-vascular events compared with placebo (Figure 1.1).

The recent Joint British Societies (JBS) guidelines recommend therapeutic intervention in the context of primary prevention in patients with:

- diabetes mellitus;
- blood pressure >160/100 mmHg or lesser degree of hypertension with evidence of target organ damage;
- total cholesterol : high-density lipoprotein cholesterol ratio >6;
- familial hypercholesterolaemia, or;
- an estimated CVD risk of >20% over 10 years.

Therefore, the measurement of lipid levels should be performed as part of an overall cardiovascular risk assessment. Monitoring of lipid levels remains relevant, as the benefit of statin therapy is proportional to the reduction in cholesterol, in particular low-density lipoprotein cholesterol. Total cholesterol of <4 mmol/l or low-density lipoprotein cholesterol of <2 mmol/l are the recommended targets. Fasting lipid measurements are generally not required for total cholesterol measurements, although serum triglycerides may be affected by dietary intake.

The second JBS guidelines now recommend a move towards the more global CVD risk, which includes the risk of stroke (fatal/non-fatal stroke, intracerebral haemorrhage and transient ischaemic attack) in addition to coronary events. The new CVD charts are based on the Framingham risk function and specify three levels of 10-year CVD risk: ≥30%, ≥20% and ≤10%, which are represented by three colour bands on the chart (Figure 1.2). Lipid-lowering therapy (statin) is recommended in this case, as his 10-year cardiovascular risk is >20% based on the charts.
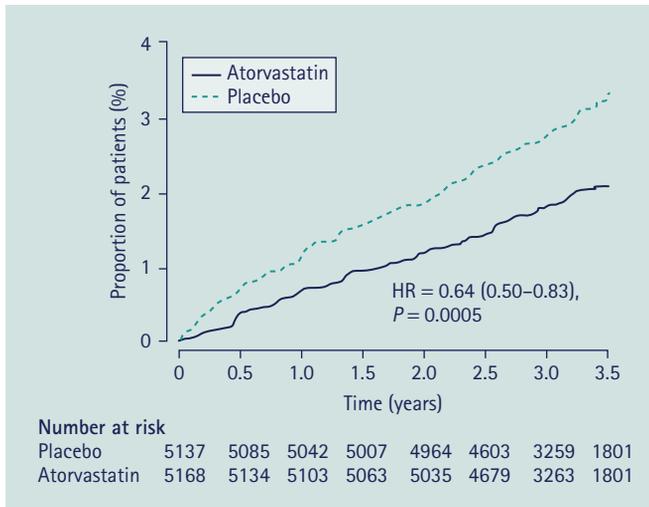
Figure 1.1 Cumulative incidence of fatal and non-fatal coronary events from the ASCOT-LLA study (Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm). HR, hazard ratio.

Does he need treatment for his blood pressure?

The need for antihypertensive treatment is similarly guided by more than just absolute blood pressure measurements. In this man's case, blood pressure should be rechecked to confirm persistently elevated blood pressure. In addition to the assessment of cardiovascular risk (as discussed previously), evidence of target organ damage (e.g. retinopathy, proteinuria, evidence of left ventricular hypertrophy) should also be sought. The presence of target organ damage implies an elevated cardiovascular risk and the need for intervention.

The targeting of antihypertensive treatment at absolute (CVD) risk is underpinned by evidence from meta-analyses of outcome trials. These studies show that the relative risk

A

NON–DIABETIC MEN

Age under 50 years

Non-smoker　　Smoker

Age 50–59 years

Age 60 years and over

CVD risk <10% over next 10 years
CVD risk <10–20% over next 10 years
CVD risk <20% over next 10 years

CVD risk over next 10 years 30%

10%　20%

SBP = systolic blood pressure mmHg
TC : HDL = serum total cholesterol to HDL cholesterol ratio
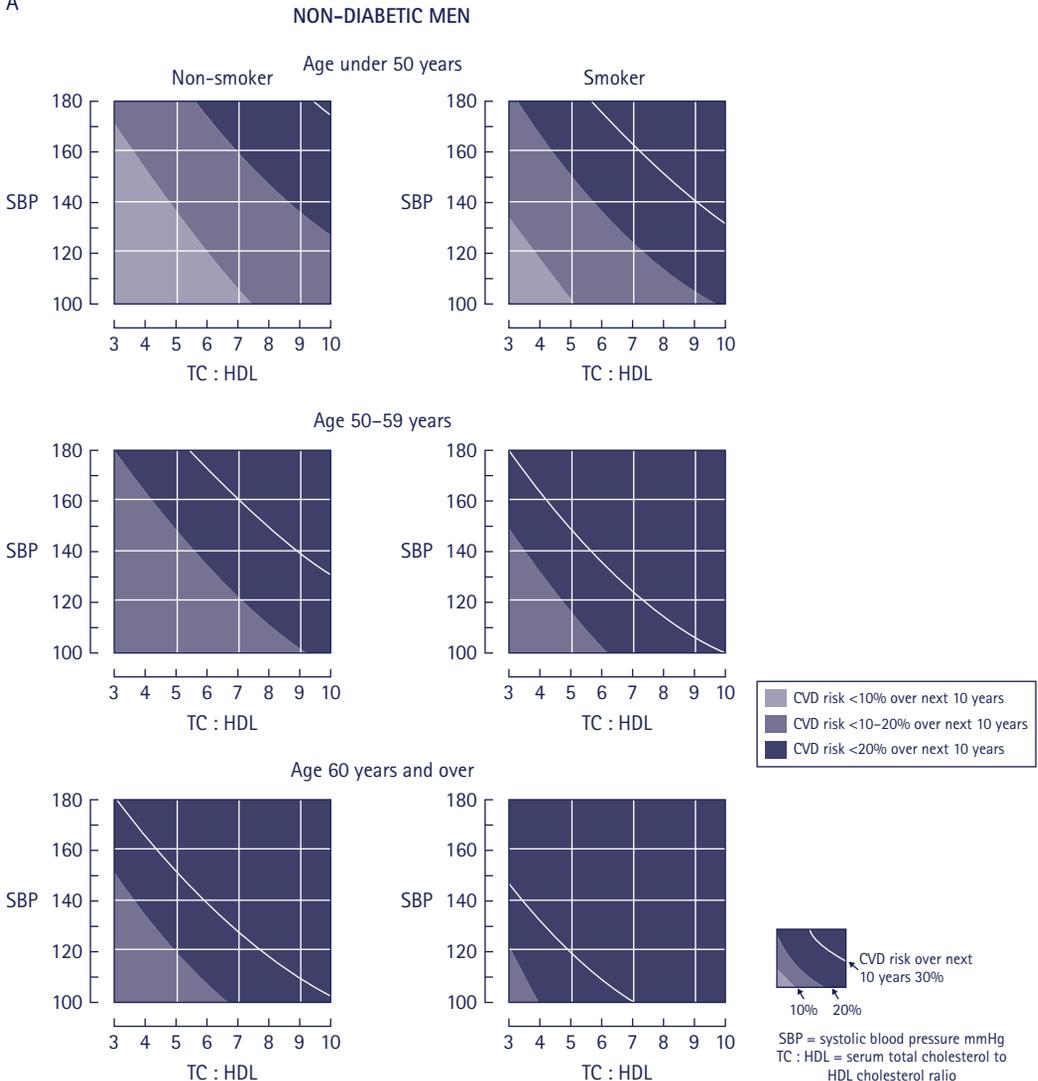
B   NON–DIABETIC WOMEN
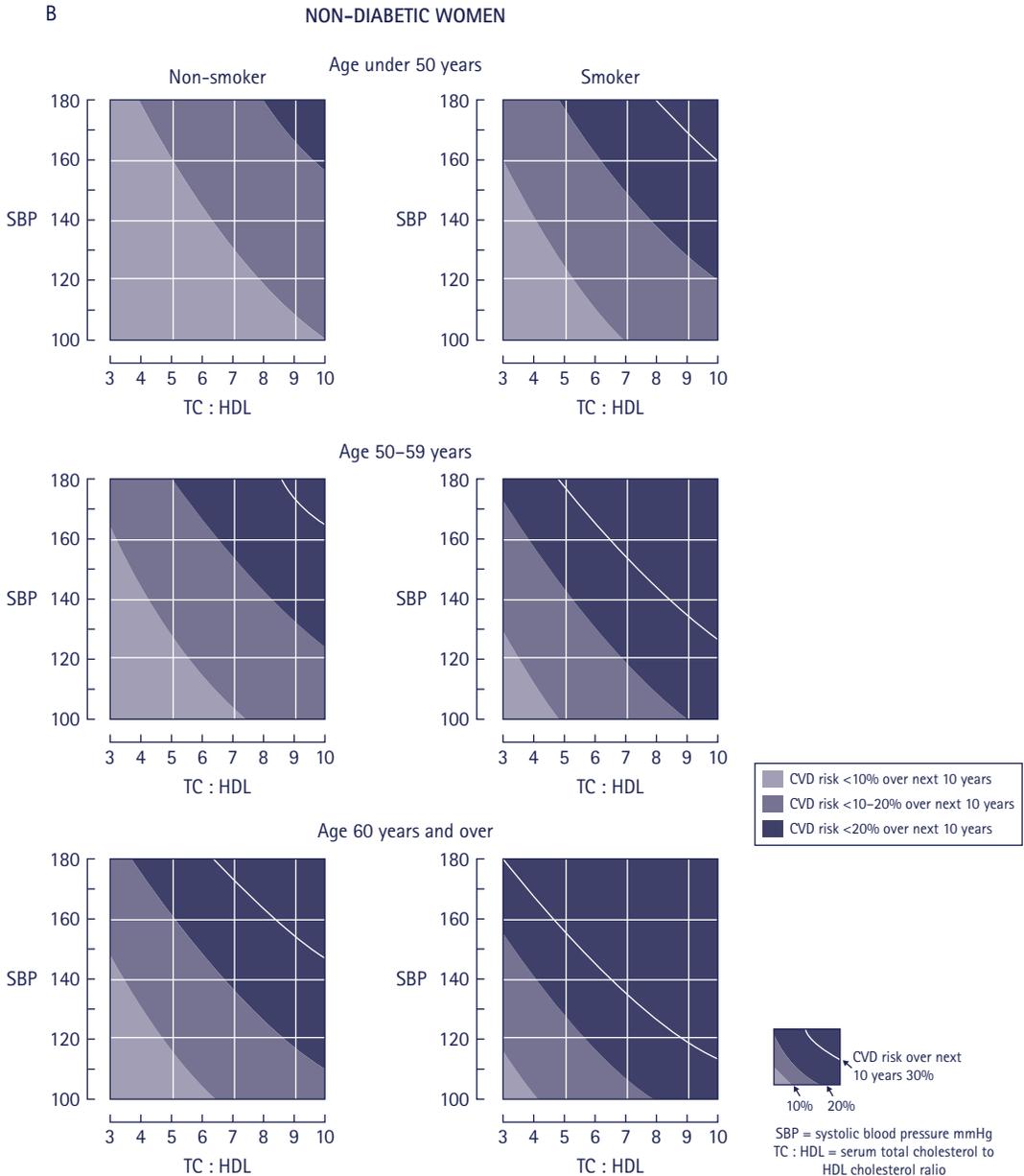
Figure 1.2 Smokers and non-smokers. (A) Non-diabetic men; (B) non-diabetic women. CVD, cardiovascular disease; HDL, high-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol.

reduction by antihypertensive treatment is approximately constant, with a 38% reduction in stroke and 16% reduction in coronary events. Even in patients with mild hypertension, treatment reduces cardiovascular complications by approximately 25%, but as the absolute risk is low, the absolute benefit will be low, which translates into a higher number needed to treat and greater costs to prevent one cardiovascular event. In

contrast, treatment of patients at a 10-year CVD risk of ≥20% results in greater absolute benefit, which corresponds to a lower number needed to treat for 5 years of 40 – this means treatment of 40 patients for 5 years to prevent one cardiovascular complication. Hence, decisions on treatment at lower levels of CVD risk will be influenced by the patient's attitude to treatment and the benefit anticipated from treatment.

Current practice guidelines recommend that all patients with average BP 140–159 or 90–99 mmHg should be offered antihypertensive drug treatment if (Figure 1.3):

● there is any complication of hypertension or target organ damage, or diabetes;
● the 10-year CVD risk is ≥20% despite advice on non-pharmacological measures.

Antihypertensive therapy is recommended if hypertension is confirmed by repeat blood pressure measurement.

Figure 1.3 Blood pressure (BP) threshold for intervention. *If initial BP >180/110, confirm over 1–2 weeks unless malignant phase hypertension (if initial BP 160–179/100–109, confirm over 3–4 weeks then treat; if initial BP 140–159/90–99, confirm over 12 weeks then treat).

Recent Developments

The assessment and treatment of cardiovascular risk has evolved from one targeting individual risk factors to a global multifactorial approach. This is clearly supported by the benefit of lipid-lowerin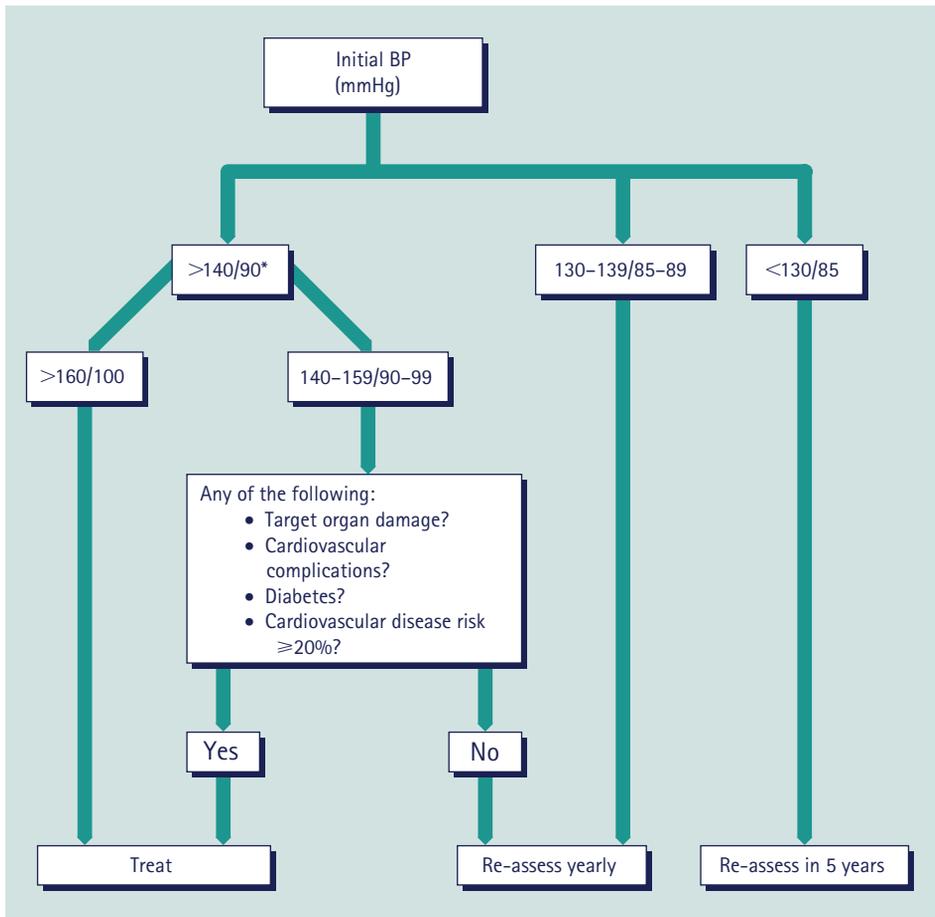g therapy in patients with hypertension (ASCOT-LLA) and diabetes mellitus (Collaborative Atorvastatin Diabetes Study). In contrast to glycaemic reduction in diabetes, which yielded only a modest reduction in cardiovascular events, a global multifactorial intervention strategy has been shown to significantly reduce cardiovascular morbidity and mortality.

Conclusion

Cardiovascular risk increases with increasing blood pressure level, and in association with other risk factors such as diabetes mellitus and hypercholesterolaemia. This is the basis for using a multiple risk factor approach to cardiovascular risk assessment (Figure 1.2). Indeed, the threshold for treatment of high blood pressure is based not on absolute blood pressure measurement alone, but in conjunction with other risk factors and cardiovascular risk (Figure 1.3).

Further Reading

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P R O B L E M

02   Antihypertensive therapy

Case History

A 76-year-old man has two blood pressure measurements taken 8 weeks apart, which confirm a persistently elevated blood pressure of 166/94 mmHg. He is aware of the need for blood pressure-lowering treatment in view of his hypertension and cardiovascular risk. He has impaired fasting glycaemia but no history of cardiovascular disease.

How is hypertension graded?

Which antihypertensive agent should he be treated with?

Background

How is hypertension graded?

The grading of hypertension has evolved over time as data on the association between blood pressure and cardiovascular events accumulated. The current grading of hypertension includes a category of 'high-normal' and is outlined in Table 2.1.

Which antihypertensive agent should he be treated with?

The choice of first-line antihypertensive therapy has been the subject of a number of clinical studies. The ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study of >40 000 patients is the largest study to date and compared a thiazide diuretic (chlorthalidone), a calcium channel blocker (amlodipine), an angiotensin-converting enzyme (ACE) inhibitor (lisinopril) and an α-blocker (doxazosin) as a first-line agent in the treatment of hypertension. The doxazosin arm was terminated earlier due to an excess of a combined endpoint of cardiovascular events

Table 2.1 **Blood pressure classification**		
Blood pressure category	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Normal	<120	<80
High–normal	135–139	85–89
Mild (grade 1)	140–159	90–99
Moderate (grade 2)	160–179	100–110
Severe (grade 3)	>180	>110

(particularly heart failure and stroke) compared with chlorthalidone, which was confirmed in a subsequent analysis. There was no difference in the primary outcome of fatal and non-fatal myocardial infarction and all-cause mortality in the lisinopril and amlodipine arms compared with chlorthalidone. Hence, thiazide diuretic, ACE inhibitor and calcium channel blockers are acceptable first-line antihypertensive agents. The choice of antihypertensive agent for individual patients should take into account the presence and absence of compelling indications and contraindications (Table 2.2).

In contrast, recent data have challenged the efficacy of the β-blocker atenolol compared with the other classes of antihypertensive therapy. The ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) study with 19 257 patients followed-up for a median of 5.5 years demonstrated significantly fewer cardiovascular events and lower all-cause mortality among patients randomized to the amlodipine–perindopril compared with the atenolol–bendroflumethiazide based treatment. These data led to a review by the Guideline Development Group at the National Institute of Clinical Excellence, which concluded that β-blockers should not be used as first-line treatment for hypertension in the absence of compelling indications (Figure 2.1).

However, β-blockers may still be considered in younger patients intolerant of ACE inhibitors or angiotensin II antagonists, of child-bearing potential (potentially teratogenic effects) and patients with high sympathetic drive. If β-blockers are used in these

Table 2.2 **Compelling indications and contraindications**		
Class of drugs	**Compelling indications**	**Contraindications**
α–blockers	Benign prostatic hyperplasia	Urinary incontinence
Angiotensin-converting enzyme inhibitors	Heart failure, left ventricular dysfunction or established coronary heart disease, type 1 diabetic nephropathy, secondary stroke prevention (with thiazide)	Pregnancy, renovascular disease
Angiotensin receptor blocker	Angiotensin-converting enzyme inhibitor intolerance (heart failure), type 2 diabetic nephropathy, hypertension with left ventricular hypertrophy	Pregnancy, renovascular disease
β–blockers	Myocardial infarction, angina, heart failure	Asthma or chronic obstructive pulmonary disease, heart block
Dihydropyridine calcium channel blockers	Elderly patients, isolated systolic hypertension	–
Rate-limiting (non-dihydropyridine) calcium channel blockers	Angina	Heart block, heart failure
Thiazide diuretics	Elderly patients, isolated systolic hypertension, heart failure, secondary stroke prevention	Gout

Angiotensin-converting enzyme inhibitors and angiotensin II antagonists should be used with caution in patients with renal impairment; angiotensin-converting enzyme inhibitors and angiotensin II antagonists may be preferred in patients at high risk of developing diabetes (e.g. glucose intolerance, metabolic syndrome and family history of diabetes).
The use of β-blockers in heart failure may lead to transient deterioration in symptoms.
Thiazides may precipitate gout and concomitant allopurinol should be considered.
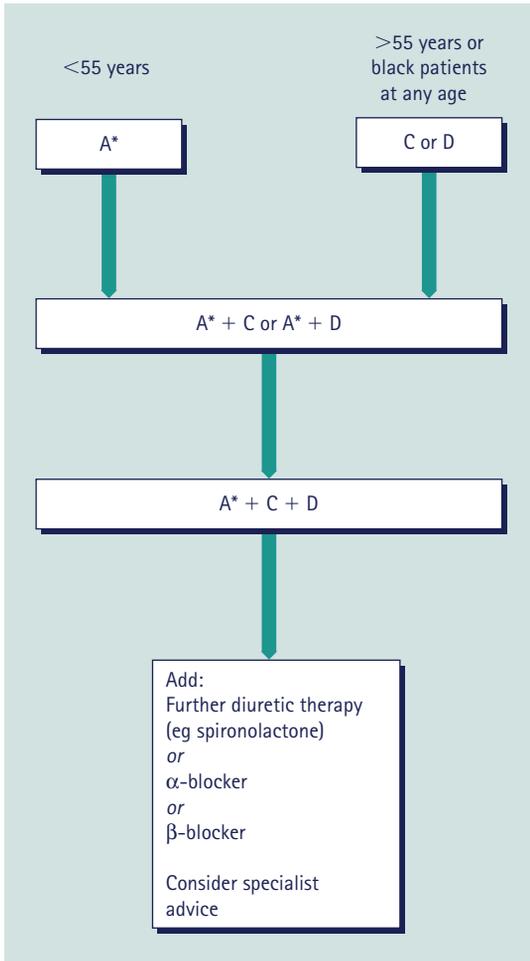
Figure 2.1 Algorithm for the treatment of hypertension (NICE update 2006). A, angiotensin-converting enzyme (ACE) inhibitors (*or angiotensin antagonist if ACE inhibitor intolerant); C, calcium channel blocker; D, thiazide diuretic. β-blockers are not preferred initial therapy for hypertension but are an alternative to A in patients <55 years in whom A is not tolerated or is contraindicated (includes women of child-bearing potential). Black patients are only those of African or Caribbean descent. In the absence of evidence, all other patients should be treated as non-black.

patients, a calcium channel blocker (not thiazide) should be added if additional antihypertensive treatment is needed to avoid the increased risk of diabetes with β-blocker–thiazide diuretic combination. The risk of diabetes may be particularly relevant in patients of South Asian origin and patients with impaired glucose tolerance or impaired fasting glycaemia, who are already at increased risk of developing diabetes.

In this case, a dihydropyridine calcium channel blocker, such as amlodipine, would be reasonable in view of his age, systolic hypertension and impaired fasting glycaemia. Blood pressure should be treated to a target of 140/85 mmHg. An ACE inhibitor or

angiotensin receptor blocker may be added for further blood pressure control if the target is not achieved.

The majority of patients with hypertension will require more than one antihypertensive agent. Some experts have recommended the use of combination therapy as first-line agents in patients with systolic blood pressure of over 160 mmHg since monotherapy, regardless of the agent used, is unlikely to reduce the systolic blood pressure to the treatment target. Indeed, combination tablets may improve compliance with treatment and should certainly be considered when patients are established on two or more antihypertensive agents. Currently available combination tablets include thiazide–ACE inhibitor combinations and calcium channel blocker–angiotensin receptor blocker combinations.

Importantly, antihypertensive therapy should not be withheld because of advanced age. Although there was initial concern with blood pressure lowering in the elderly, these concerns are largely dispelled by the recent HYVET (Hypertension in the Very Elderly Trial) study. The HYVET study included 3845 patients with hypertension over the age of 80 years and was terminated early due to significant reductions in strokes and all-cause mortality with blood pressure reduction (using a combination of indapamide and perindopril).

Recent Developments

Aliskiren, the first in the class of drugs dubbed direct renin inhibitors has recently been approved for the treatment of hypertension. The effect of this new antihypertensive agent on morbidity and mortality has yet to be tested in large randomized trials, but a number of clinical studies have confirmed the efficacy of aliskiren in reducing blood pressure and albuminuria. The blood pressure-lowering effects appear to be comparable with other antihypertensive agents (e.g. ACE inhibitors and calcium channel blockers) and may even be superior to thiazide diuretics. The blood pressure-lowering effects appear to be synergistic with calcium channel blockers and thiazide diuretics. Aliskiren also appears to be well tolerated with the rates of side effects comparable with placebo. Hence, aliskiren may be considered in patients with uncontrolled hypertension on conventional therapy.

The recent Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study compared fixed dose perindopril-indapamide versus placebo in patients with type-2 diabetes. The treatment arm achieved a systolic blood pressure of about 135 mmHg compared to 140 mmHg in the placebo group. Total mortality was lower in the perindopril-indapamide group compared to placebo (7.3% vs 8.5%) over 4.3 years, with fewer coronary events, reduced progression of nephropathy and microalbuminuria.

This was followed by the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial compared intensive blood pressure lowering to a target of less than 120 mmHg (systolic) versus conventional target of 140 mmHg in 4733 patients with type-2 diabetes. Although there was a small absolute reduction in stroke (0.32% vs 0.53%), there were significantly more adverse events related to intensive blood pressure reduction (3.3% vs 1.3%, $P < 0.001$). There was no difference in total mortality. These data suggest that there may be little benefit in lowering systolic blood pressure below 135 mmHg in patients with diabetes.

Conclusion

The pharmacological treatment of hypertension has evolved considerably over the years. Recent randomized trials have compared old drugs against the newer ones. The current treatment algorithm reflects the results of these studies. In uncomplicated hypertension, ACE inhibitors (or angiotensin receptor blockers), thiazide diuretics or calcium channel blockers are recommended first-line agents. Their use in combination offers further blood pressure reduction. The presence of compelling indications or contraindications should also be considered in selecting the appropriate antihypertensive treatment.

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PROBLEM

03 Dyslipidaemia

Case History

A 54-year-old South Asian man with hypertension and a 2-year history of type 2 diabetes mellitus attended a routine clinical assessment. He had a waist circumference of 90 cm. He did not have documented cardiovascular disease. His total cholesterol was 4.6 mmol/l, fasting triglyceride 4.8 mmol/l, high-density lipoprotein (HDL) cholesterol 0.8 mmol/l and HbA1c 7.9%. He is currently on simvastatin 40 mg daily in addition to his antihypertensive and oral hypoglycaemic agents.

Is this man's lipid profile satisfactory?

What are the current recommendations for the treatment of dyslipidaemia?

Background

This man has multiple cardiovascular risk factors and fulfils the International Diabetes Federation criteria for the metabolic syndrome (Table 3.1). This clinical syndrome describes the frequent coalition of multiple risk factors and identifies individuals at high risk of cardiovascular events. However, the definition of metabolic syndrome, particu-

Table 3.1 International Diabetes Federation definition of metabolic syndrome
Central obesity
Waist circumference – ethnicity specific
Plus any two of: • Raised triglycerides (>1.7 mmol/l)* • Reduced high-density lipoprotein cholesterol (<1.03 mmol/l for men, <1.3 mmol/l for women)* • Raised blood pressure (systolic ≥130 mmHg, diastolic ≥85 mmHg or diagnosed hypertension) • Raised fasting plasma glucose (≥5.6 mmol/l or diagnosed type 2 diabetes)
Ethnic group and waist circumference
Europids (men >94 cm; women >80 cm)
Chinese and South Asians (men >90 cm; women >80 cm)
Japanese (men >85 cm; women >90 cm)
Ethnic south and central Americans (use South Asian recommendations)
Sub-Saharan Africans (use European data)
Eastern Mediterranean and Middle-East population (use European data)

larly in different ethnic groups, the clinical value and incorporation of metabolic syndrome into clinical practice have been the subject of considerable debate. Current guidelines do not recommend the use of metabolic syndrome over conventional risk estimation (based on Framingham risk scoring) for the assessment of cardiovascular risk.

Based on conventional risk assessment, this man's estimated cardiovascular risk is well in excess of 20% over 10 years. Statin therapy has been shown to reduce the risk of major vascular events (fatal/non-fatal myocardial infarction and stroke) by 21%, which in this case, would leave significant residual cardiovascular risk. Treatment of his dyslipidaemia may reduce this risk further. Of note, epidemiological studies suggest that South Asians in the UK have about 40% excess risk of coronary disease, but the treatment targets have not been modified to take this into consideration. Hence, this man requires further treatment for his dyslipidaemia.

What are the current recommendations for the treatment of dyslipidaemia?

Lifestyle modification with dietary intervention, increasing physical activity and weight loss should be offered to all patients at high cardiovascular risk. However, lifestyle intervention should be complemented by pharmacological treatment in high-risk patients. Statin therapy, with the primary aim of lowering total and low-density lipoprotein (LDL) cholesterol is the first-line lipid-lowering treatment. Simvastatin 40 mg OD has been recommended as first-line treatment by recent National Institute for Clinical Excellence (NICE) guidance, but in the absence of diabetes or metabolic syndrome, no specific treatment targets were set for primary prevention of cardiovascular events. Indeed, further lipid testing was not routinely recommended by NICE guidance in these patients with uncomplicated hypercholesterolaemia in the setting of primary prevention. An alternative statin, such as pravastatin (less metabolism via the cytochrome P450 pathway) or lower dose statin, may be used if simvastatin 40 mg is not tolerated.

However, the need for more intensive lipid management has been recognized in patients with diabetes and metabolic syndrome. Although a statin remains the first-line treatment, unlike recommendations for people with 'uncomplicated' hyperlipidaemia (e.g. without vascular disease, diabetes, albuminuria or metabolic syndrome), the total and LDL cholesterol should be treated to a target of 4 mmol/l and 2 mmol/l respectively. The doses and associated reduction in LDL cholesterol are listed in Table 3.2. An increase in the dose of simvastatin to 80 mg OD, or an alternative statin of similar efficacy and cost

Table 3.2 Doses of commonly used statins and reduction in low–density lipoprotein (LDL) cholesterol		
Drug	**Dose (mg/day)**	**% LDL cholesterol reduction**
Atorvastatin	10	39
Pravastatin	40	34
Simvastatin	20–40	35–41
Fluvastatin	40–80	25–35
Rosuvastatin	5–10	39–45

may be considered if the targets are not achieved. Further LDL cholesterol reduction may also be achieved with the addition of ezetimibe, which inhibits the absorption of dietary and biliary cholesterol (Figure 3.1).

Unlike the effect on LDL cholesterol, the effect of statins on triglycerides and HDL cholesterol are less impressive. Current data suggest that triglycerides and HDL cholesterol may be considered targets for treatment following lowering of LDL cholesterol in high-risk patients. Treatment options include fibrates, nicotinic acid and fish oils. Aggressive glycaemic control may lower serum triglycerides and other causes of hyper-triglycidaemia should be excluded (e.g. renal impairment or liver, particularly alcohol-related disease).

A meta-analysis of 53 trials using fibrates and 30 trials using nicotinic acid reported a 25% and 27% reduction in major coronary events respectively. A fibrate (particularly fenofibrate) has been recommended as first-line treatment of hypertriglycidaemia
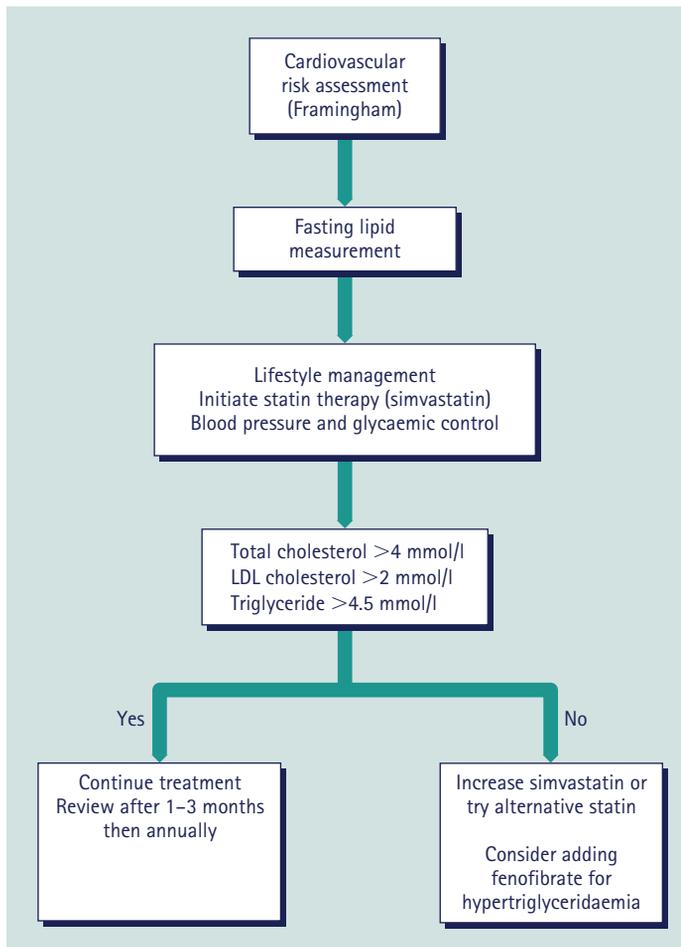

Figure 3.1 Treatment of dyslipidaemia. LDL, low–density lipoprotein.

(triglyceride >4.5 mmol/l) after treatment of other potential causes. In some cases of persistent dyslipidaemia despite intensification of statin therapy, combination treatment should be considered. Combining statins with fibrates or niacin offers significant reductions in triglycerides and increases in HDL cholesterol. The combined use of fibrates and statins has been limited by concerns over myositis and rhabdomyolysis. However, recent pharmacokinetic studies indicate that fenofibrate, unlike gemfibrozil, do not increase blood levels of statins and, therefore, may be safe to use in combination therapy.

The combination of niacin and statin probably does not increase the risk of myositis or rhabdomyolysis, but niacin does appear to worsen glycaemic control, albeit correctable with titration of antihyperglycaemic medications. Hence, treatment with niacin should generally be managed by lipid specialists. Combination therapy with statins and fish oils also offers additional triglyceride lowering compared with statin therapy alone, although increases in HDL cholesterol levels usually will not match those seen with fibrates or niacin. The indications and contraindications of different classes of lipid-lowering therapy are listed in Table 3.3.

Recent Developments

Rimonabant, a selective endocannabinoid receptor antagonist, generated considerable interest as multi-centre trials (the RIO studies) confirmed the efficacy of rimonabant in reducing body weight (sustained for up to 2 years) compared to placebo, which was associated with significant improvements in HDL cholesterol, triglycerides and glycaemic control (in patients with diabetes). Despite these promising results, the associated adverse psychiatric effects of anxiety and depression have led to its withdrawal.

Table 3.3 Indications and contraindications for different classes of lipid–lowering drugs

Drugs‡	Indications	Caution	Contraindications
HMG-CoA reductase inhibitor (statins)	Atherosclerotic vascular disease Raised cardiovascular risk Hypercholesterolaemia	Renal impairment Concurrent use of drugs metabolized via P450	Avoid with gemfibrozil Significant liver disease Previous myositis with statins
Fibrates	Type III hyperlipoproteinaemia Hypertriglyceridaemia	Renal failure Concurrent statin therapy†	Gemfibrozil with statin
Nicotinic acid	Hypertriglyceridaemia Mixed hyperlipidaemia (low high–density lipoprotein cholesterol)	Renal failure Liver disease Diabetes (worsen glycaemic control)	Diarrhoea or flushing (may worsen symtoms)
Fish oils (ω–3–acid ethyl esters)	Hypertriglyceridaemia Post-myocardial infarction	Haemorrhagic disorders Aspirin-sensitive asthma	None

†Some statins are metabolized via the P450 pathway (e.g. atorvastatin and simvastatin). Other drugs metabolized via this pathway may interact with these statins (e.g. ciclosporin, antifungals and amiodarone). Expert advice should be sought.
‡Fibrates, nicotinic acid and anion exchange resins (not listed) should not be used routinely in the setting of primary prevention.

The recent JUPITER trial has also challenged conventional cholesterol-based risk factor management. This large study included patients with satisfactory cholesterol levels but raised highly-sensitive C-reactive protein levels, and demonstrated significant reduction in cardiovascular events with rosuvastatin in these patients compared to placebo. The highly-sensitive CRP however, is not yet widely available. Nonetheless, this study has generated considerable debates with potential expansion of the indications for statin therapy in the prevention of cardiovascular events.

Modified-release niacin has also generated significant interests as an add-on to statin therapy. The ARBITER 6-HALTS trial compared niacin and ezetimibe in patients already on statins with carotid intima-media thickness (CIMT) as the surrogate endpoint. The addition of niacin resulted in regression of CIMT, but there were no significant changes with ezetimibe.

Conclusion

Treatment of total and LDL cholesterol is the primary aim of lipid treatment. This may be achieved in the majority of cases with the use of statins (simvastatin 40 mg OD is recommended for primary prevention of cardiovascular events by current NICE guidance). However, residual cardiovascular risk remains high even when LDL cholesterol is treated to target levels. The treatment of dyslipidaemia should therefore be considered. Combining statins with fenofibrate or niacin offers significant reductions in triglycerides and increases in HDL cholesterol. Referral to specialist lipid clinics should be considered.

Further Reading

Grundy SM, Cleeman JI, Merz CN, *et al;* Coordinating Committee of the National Cholesterol Education Program; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Arterioscler Thromb Vasc Biol* 2004; **24**: e149–61.

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Ridker PM, Danielson E, Fonseca FA, *et al.* Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008; **359**: 2195–207.

The right problem-solving strategies can make the difference between putting a challenge behind you and wallowing in an endemic issue. Branford and Stein presented the IDEAL problem-solving method in 1984. This easy-to-remember heuristic device represents the 5 steps of this evergreen problem-solving method. IDEAL problem-solvers I-dentify the source of the problem, D-efine its context, E-xplore solutions strategies, A-ct on the best solution, and L-ook back and evaluate the process: 1) IDEAL First Step: Identify. Problem solving consists of using generic or ad hoc methods in an orderly manner to find solutions to problems. Some of the problem-solving techniques developed and used in philosophy, artificial intelligence, computer science, engineering, mathematics, or medicine are related to mental problem-solving techniques studied in psychology. The term problem solving means slightly different things depending on the discipline. For instance, it is a mental process in psychology and a computerized process in