40 Cardiovascular Risk Factors

Hypertension

Peter M. Nilsson
Department of Clinical Sciences, Lund University, University Hospital, Malmö, Sweden

Dyslipidemia: Diabetes Lipid Therapies

Adie Viljoen[1] & Anthony S. Wierzbicki[2]
[1] Department of Chemical Pathology, Lister Hospital, Stevenage, UK
[2] Guy's & St Thomas' Hospitals, London, UK

Hypertension

Peter M. Nilsson

Keypoints

- Hypertension is up to twice as common in people with diabetes as in the general population, affecting 10–30% of people with type 1 diabetes mellitus (T1DM) and 60–80% of those with type 2 diabetes (T2DM).
- Hypertension is associated with insulin resistance and other features of the metabolic syndrome. Insulin resistance could raise blood pressure (BP) by loss of insulin's normal vasodilator activity or through effects of the accompanying hyperinsulinemia.
- BP rises during the early microalbuminuric phase of diabetic nephropathy, especially in young patients with T1DM.
- Hypertension worsens both macrovascular and microvascular complications in diabetes. The effects of BP on the risk of fatal coronary heart disease are 2–5 times greater than in people without diabetes. The risks of nephropathy and end-stage renal failure are also increased 2–3 times by hypertension.
- All people with diabetes should be carefully screened for hypertension and evidence of hypertensive tissue damage at diagnosis and at least annually thereafter. Treatment is required for values that consistently exceed 130–140/80–85 mmHg – lower than the World Health Organization/International Society of Hypertension thresholds defined for hypertension in the general population. The blood lipid profile should also be checked.
- The treatment of hypertension begins with lifestyle management, including reduced dietary fat and salt intakes, weight loss for obese patients, smoking cessation and increased regular physical activity. These measures can lower BP by up to 11/8 mmHg.
- First-line antihypertensive drugs suitable for use in patients with diabetes are diuretics, such as low dose bendroflumethiazide (bendrofluazide); or cardioselective beta-blockers, calcium-channel antagonists (CCAs), angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type 1 (AT1) receptor blockers (ARBs). Subjects of African decent tend to have low renin hypertension, and may not respond to beta-blockers or ACE inhibitors. Drugs can be selected for their beneficial effects on coexistent problems, e.g. angina or arrhythmia (beta-blockers, CCAs), heart failure (ACE inhibitors, certain beta-blockers), previous myocardial infarction (ACE inhibitors, beta-blockers) or nephropathy (ACE inhibitors, ARBs).
- Over two-thirds of people with diabetes need combinations of two or more antihypertensive drugs to control hypertension. Effective combinations include beta-blocker plus CCAs; ACE inhibitor/ARB plus diuretic (non-potassium-sparing); and CCA plus ACE inhibitor/ARB.

Textbook of Diabetes, 4th edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Introduction

Hypertension often accompanies diabetes mellitus, both type 1 (T1DM) and type 2 (T2DM). The association between the two conditions has long been recognized. In 1923, the Swedish physician Eskil Kylin described a syndrome of diabetes, hypertension and hyperuricemia [1], which are now regarded as aspects of the broader "metabolic syndrome" that has been linked to insulin resistance (IR) [2,3]. The relationship between diabetes and hypertension is complex. Both are common and so are likely to be associated by chance, but in some instances, they may have a common cause; moreover, hypertension can develop as a consequence of diabetic nephropathy, while some drugs used to treat hypertension can induce diabetes in susceptible subjects.

Hypertension is important because, like diabetes, it is a major cardiovascular risk factor and one that synergizes with the deleterious effects of diabetes. It is also a risk factor for microvascular complications: nephropathy and retinopathy. The management of hypertension in diabetes has been widely debated, and there is still a need to agree on treatment targets and strategies. During the last decade, several well-constructed trials have added considerably to the evidence base [4–8], demonstrating convincingly the benefits of lowering blood pressure (BP), but also highlighting how difficult this can be to achieve in practice.

Size of the problem

Hypertension is widely defined according to the World Health Organization/International Society of Hypertension (WHO/ISH) criteria (Table 40.1). People with diabetes are still at risk of macrovascular and microvascular complications at BP levels below these thresholds, and the treatment target range is therefore lower (130–140/80–85 mmHg).

Overall, hypertension (according to the WHO criteria) is up to twice as common in people with diabetes as in the general population [9]. In white Europeans, 10–30% of subjects with T1DM and 60–80% of those with newly diagnosed T2DM are hypertensive [10]. There are racial and ethnic differences in the prevalence of hypertension, which presumably are at least partly genetically determined: for example, hypertension (and macrovascular disease) is less frequent among the Pima Indians and Mexican-Americans [11]. Impaired glucose tolerance (IGT) is also associated with hypertension (20–40% of cases), perhaps reflecting the common origins of these aspects of the metabolic syndrome [12].

There is evidence that the true prevalence of hypertension is increasing in the diabetic population (especially T2DM) after allowing for the greater number of cases identified through improved screening and the lowering of thresholds for treatment of BP [13]. The causes probably include the rising prevalence of obesity and longer survival of older people with diabetes.

Table 40.1 Criteria for hypertension and related tissue damage, defined by the World Health Organization (WHO) and the International Society for Hypertension, 1999 [33].

Category	Systolic (mmHg)	Diastolic (mmHg)
WHO criteria for the general population*		
Optimal	<120	<80
Normal	<130	<85
High normal	130–139	85–89
Grade 1 hypertension (mild)	140–159	90–99
Subgroup: borderline	140–149	90–94
Grade 2 hypertension (moderate)	160–179	100–109
Grade 3 hypertension (severe)	≥180	≥110
Isolated systolic hypertension	≥140	<90
Subgroup: borderline	140–149	<90
Hypertension-related tissue damage (WHO criteria)		
Grade I: none		
Grade II: subclinical damage (e.g. retinopathy, proteinuria)		
Grade III: clinical damage (e.g. heart failure, ischemia)		
Degree of proteinuria		
Microalbuminuria: 30–300 mg/24 hours (20–200 mg/min)		
Macroalbuminuria: >300 mg/24 hours (>300 mg/min)		

* Desirable blood pressure limits in the diabetic population are suggested in Figure 40.6.

Causes of hypertension in diabetes

Associations between hypertension and diabetes are listed in Table 40.2. Essential hypertension and isolated systolic hypertension are both common in the non-diabetic population (especially in the elderly). It is estimated that essential hypertension accounts for about 10% of cases in people with diabetes. Other important causes are the hypertension that coexists with IR, obesity and IGT in the metabolic syndrome, and hypertension secondary to diabetic nephropathy, as discussed in detail below.

Hypertension in the metabolic syndrome

This syndrome consists of IR, IGT (including T2DM), a characteristic dyslipidemia – hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, and raised low density lipoprotein (LDL), with an excess of small dense LDL particles – truncal obesity, procoagulant changes (raised plasminogen activator inhibitor 1 and fibrinogen levels) and hyperuricemia [2,14,15]. As these abnormalities are all risk factors for atherogenesis, the syndrome is completed by a marked tendency to vascular aging leading to macrovascular disease, especially coronary heart disease (CHD) and stroke (Figure 40.1). As discussed in Chapter 11, IR has been proposed by Reaven [2], DeFronzo and Ferrannini [14] and others [15] to be a fundamental cause of hypertension and cardiovascular disease (CVD) as well as T2DM. IR is partly genetically determined, and acquired factors such as obesity,

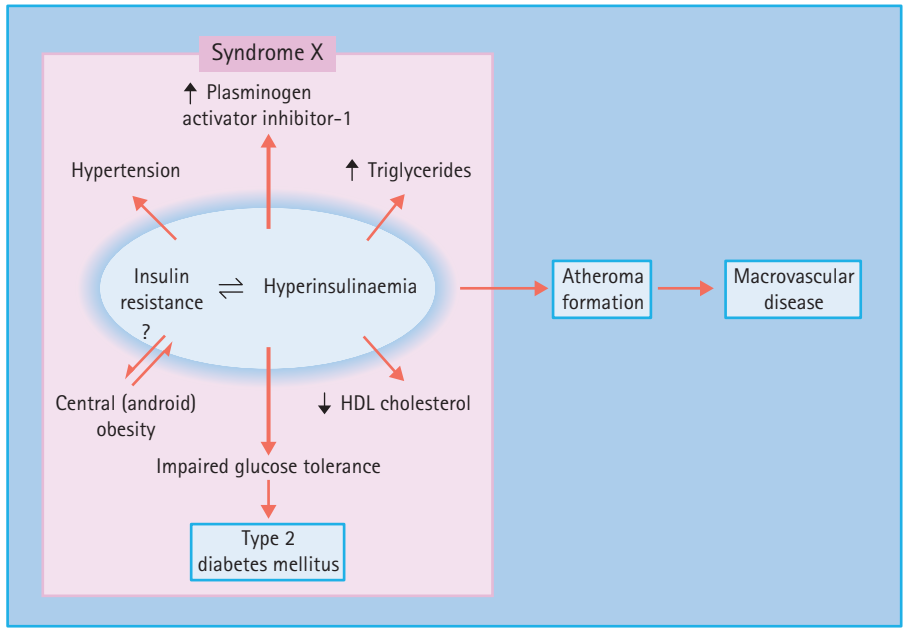

Figure 40.1 The metabolic syndrome. HDL, high density lipoprotein.

Table 40.2 Associations between hypertension and diabetes.

Hypertension associated with T2DM (insulin resistance syndrome X, metabolic syndrome)
Hypertension associated with nephropathy in T1DM
Coincidental hypertension in patients with diabetes
Essential hypertension
Isolated systolic hypertension
Renal scarring (e.g. from recurrent pyelonephritis)
Diabetogenic antihypertensive drugs
Potassium-losing diuretics (chlorthalidone, high-dose thiazides)
Beta-blockers (high dose)
Combined diuretics and beta-blockers
Drugs causing obesity, hypertension and glucose intolerance
Glucocorticoids
Combined oral contraceptive pills
Antipsychotics
Endocrine disorders causing hypertension and glucose intolerance
Acromegaly
Cushing syndrome
Conn syndrome
Pheochromocytoma

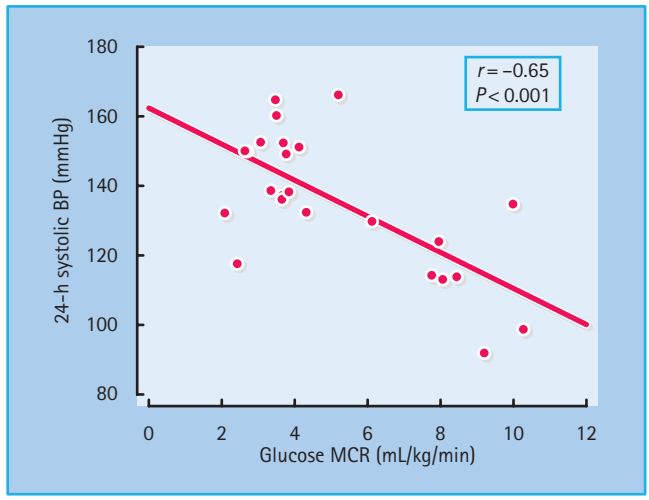

Figure 40.2 Hypertension is associated with insulin resistance. Insulin sensitivity, measured as the metabolic clearance rate (MCR) of glucose during an insulin clamp study, is inversely related to the mean 24-hour systolic and ambulatory blood pressure. Reproduced from Pinkney *et al.* [17], with permission from the Editor.

physical inactivity and perhaps malnutrition *in utero* and during early infancy may also contribute [16]. In support of the latter, family studies have revealed a correlation between the BP of the mother and her offspring that appears to be non-hereditary in origin; early growth retardation is suggested to program abnormal development of the vasculature as well as the tissues that regulate glucose homeostasis.

IR is closely associated with high BP in both humans and animals. Experimental induction of IR (e.g. feeding rats with fructose) is accompanied by a rise in BP. More persuasively, an inverse relationship has been demonstrated in humans between BP and insulin sensitivity [17] (Figure 40.2). Various mechanisms have been proposed to explain how IR and/or the hyperinsulinemia that accompanies it could increase BP (Figure 40.3). First, there is some evidence that insulin is an endothelium-dependent vasodilator, releasing nitric oxide (NO) from the endothelium, which relaxes vascular smooth muscle [18,19]; blunting of this

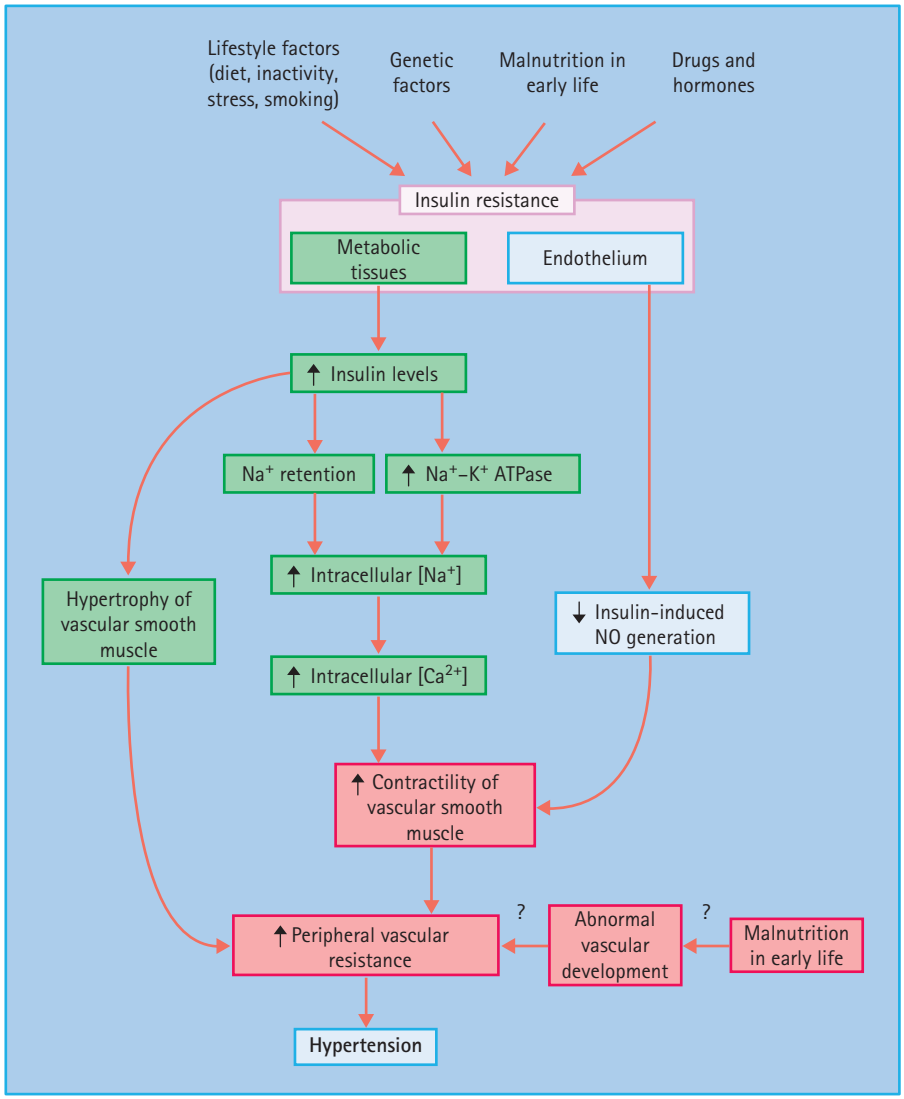

Figure 40.3 Possible mechanisms of hypertension in conditions of insulin resistance. NO, nitric oxide.

effect, caused by insensitivity to the action of insulin on the endothelium as well as on metabolically important tissues, could contribute to the increased peripheral resistance that is the hallmark of hypertension in obesity and T2DM. Impaired endothelium-mediated vasodilatation is associated with IR states and may have a key role in the initiation and progression of atherosclerosis [20].

By contrast, insulin also has several actions that tend to raise BP, and there is some evidence that these are accentuated in IR states, presumably because sensitivity is preserved to the effects of the raised insulin levels. Insulin acts on the distal renal tubule to retain Na^+ ions and water [20,21], an effect that still operates in IR subjects [22], and so could contribute to the rise in total body Na^+ content that occurs in obesity and T2DM [23]. Insulin also stimulates the cell membrane Na^+–K^+ ATPase, which would raise intracellular Na^+ concentrations in vascular smooth muscle and, by increasing systolic Ca^{2+} levels, would enhance contractility and increase peripheral resistance [22,23]. Through its effects on the CNS, insulin may stimulate the sympathetic outflow. Theoretically, this could also increase BP, although direct evidence in humans is lacking [22,24]. Finally, insulin may stimulate the proliferation of vascular smooth muscle cells, which could lead to medial hypertrophy and increased peripheral resistance [22,25].

Hypertension and diabetic nephropathy

This association is most obvious in young patients with T1DM, in whom the presence of hypertension is strikingly related to renal damage and even minor degrees of proteinuria. BP begins to rise when the urinary albumin excretion (UAE) enters the microalbuminuric range (>30 mg/24 hours) and is usually over the WHO threshold when UAE reaches the macroalbuminuric stage (>300 mg/24 hours) [26]. The association may be partly genetically determined: subjects with diabetes and microalbuminuria commonly have parents with hypertension and may also inherit overactivity of the cell-membrane Na^+–H^+ pump (indicated by increased Na^+–Li^+ counter-transport in red blood cells),

which would tend to raise intracellular Na^+ concentrations and thus increase vascular smooth muscle tone [27].

The basic mechanisms of hypertension include decreased Na^+ excretion with Na^+ and water retention. Peripheral resistance is increased, to which raised intracellular Na^+ will contribute. The role of the renin angiotensin aldosterone system (RAS) is uncertain, as both increased and decreased activity has been reported [28,29]. These discrepancies may be explained by differences in diet, treatment, metabolic control and the type and duration of diabetes. Na^+ retention and hypertension would be predicted to suppress the RAS, while renin levels may be influenced by other complications of diabetes: renal tubular acidosis type 4 causes hyporeninemic hypoaldosteronism and neuropathy can also lower plasma renin, while renin may be raised in retinopathy and advanced nephropathy. Patients with microalbuminuria who are insulin-resistant appear to be particularly susceptible to hypertension [30].

Impact of hypertension in diabetes

A large proportion of hypertensive people with diabetes show signs of cardiovascular aging and target-organ damage [10]. Hypertension, as an independent risk factor for atherogenesis, synergizes with the effects of diabetes and significantly increases the development and progression of CHD, cerebrovascular and peripheral vascular disease. Overall, the effects of hypertension on deaths from CHD are increased by 2–5 times in people with diabetes, with the greatest increase occurring at the lowest BP levels (Figure 40.4).

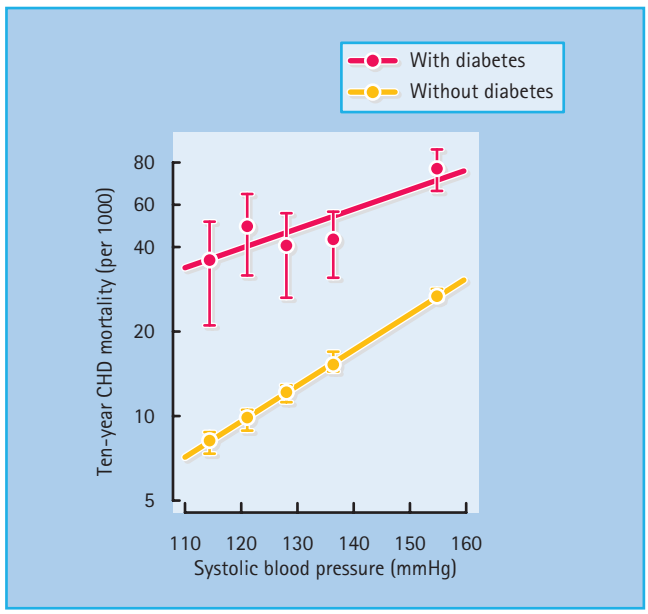

Figure 40.4 Synergistic effects of diabetes and hypertension on deaths from coronary heart disease (CHD). Data from 342 815 people without diabetes and 5163 people with diabetes aged 35–57 years, free from myocardial infarction at entry. Reproduced with permission from O. Vaccaro, paper presented at the 26th Annual Meeting of the European Diabetes Epidemiology Group, Lund, 1991.

The deleterious effects of hypertension on left ventricular function are also accentuated by the presence of diabetes. These include impaired left ventricular relaxation [31] and increased left ventricular mass [32], the latter being an independent predictor of premature death from CHD.

Hypertension also predisposes to the development of certain microvascular complications, particularly nephropathy and end-stage renal failure (ESRF), for which the risk is increased by 2–3 times (see Chapter 37). Hypertension is also a risk factor for retinopathy, as has been confirmed by the beneficial effects of improved BP control in patients with T2DM, reported by the UK Prospective Diabetes Study (UKPDS) [4].

Screening for hypertension in diabetes

As the two conditions are so commonly associated, people with diabetes must be regularly screened for hypertension and vice versa. Hypertensive patients, especially if obese or receiving treatment with potentially diabetogenic drugs, should be screened for diabetes at diagnosis and during follow-up. Should hyperglycemia be detected, potentially diabetogenic antihypertensive drugs should be reduced or changed to others or used in combinations that do not impair glucose tolerance, and normoglycemia can then often be restored.

All people with diabetes should have their BP checked at diagnosis and at least annually thereafter. This is especially important in those with other cardiovascular risk factors, such as nephropathy (which is associated with a substantial increase in the cardiovascular mortality rate), obesity, dyslipidemia, smoking or poor glycemic control.

Measurement of blood pressure

BP should be measured with the patient in the supine or sitting position, with an accurate sphygmomanometer and a cuff of appropriate size (i.e. wider for obese subjects with an arm circumference of >32 cm). Systolic and diastolic BP should be recorded, to the nearest 2 mmHg if using a manual sphygmomanometer, from phases I and V (i.e. appearance and final disappearance of the sounds of Korotkoff). Usual precautions should be taken to ensure reliability and avoid "white coat" stress effects which can acutely raise BP. Conditions should be quiet and relaxed, and at least two readings should be taken initially and then repeated at intervals over weeks or months to determine the subject's typical values and any trend to change. Office BP could be complemented by repeated home BP recordings.

BP should also be checked with the patient in the upright position (1 minute after standing), because there may be a significant postural fall (>20 mmHg systolic) in patients with diabetic autonomic neuropathy, the elderly or those treated with vasodilators or diuretics. Marked postural hypotension, which can coexist with supine hypertension, may indicate the need to change or reduce antihypertensive medication, especially if symptoms are provoked.

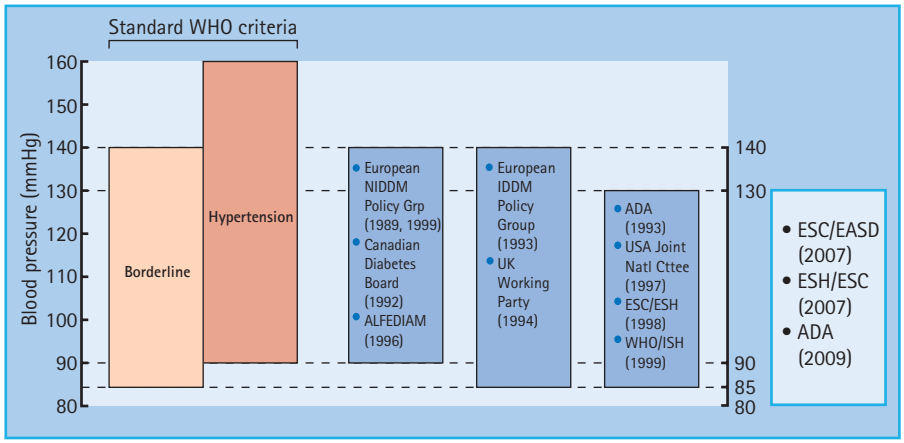

Figure 40.5 Blood pressure treatment targets suggested for subjects with diabetes, compared with the World Health Organization/International Society of Hypertension definition of hypertension and borderline hypertension [34]. ALFEDIAM, Association de langue française pour l'étude du diabète et des maladies métaboliques; ADA, American Diabetes Association; ESC, European Society of Cardiology; EASD, European Association for the Study of Diabetes; ESH, Europe Society of Hypertension.

Ambulatory BP monitoring over 24 hours may be useful in some cases to exclude "white coat" effects, and in patients with early nephropathy who have nearly normal BP during the day, but who may be at risk of hypertensive tissue damage because they fail to show the physiologic BP dip during sleep [33].

Diagnosis of hypertension in diabetes

The criteria issued in 1999 by WHO and ISH [34] define hypertension as an office BP exceeding 140/90 mmHg (Korotkoff I–V), and borderline hypertension as being below these limits but above 130 mmHg systolic and/or 85 mmHg diastolic (Figure 40.5) [34]. Established hypertension is diagnosed when readings consistently exceed 140/90 mmHg over several weeks, or when the BP is very high (diastolic BP >110 mmHg), or when there are clinical signs of tissue organ damage from long-standing hypertension.

It is clear from numerous epidemiologic studies that the WHO/ISH threshold is too high in people with diabetes because of their additional risk of both macrovascular and microvascular disease, and that there are definite benefits from treating microalbuminuric subjects whose diastolic BP is <90 mmHg [35]. Various other expert bodies have suggested alternative, generally lower target levels (Figure 40.5). A consensus would be to aim for a BP of less than 130–140 mmHg systolic and below 80–85 mmHg diastolic, and to treat any subject whose BP is consistently above one or both of these thresholds.

Investigation of hypertension in diabetes

Initial investigation of the hypertensive patient with diabetes aims to exclude rare causes of secondary hypertension (Table 40.2), to assess the extent of tissue organ damage caused by hypertension and diabetes (Table 40.1) and to identify other potentially treatable risk factors for vascular disease. The major points in the medical history and examination are shown in Table 40.3.

• *Cardiac function.* A standard 12-lead electrocardiogram may show obvious ischemia, arrhythmia or left ventricular hypertrophy; the latter is more accurately demonstrated by echocardiography, which will also reveal left ventricular dysfunction and decreased ejection fraction. Exercise testing (or stress-echo) testing and 24-hour Holter monitoring may also be appropriate.

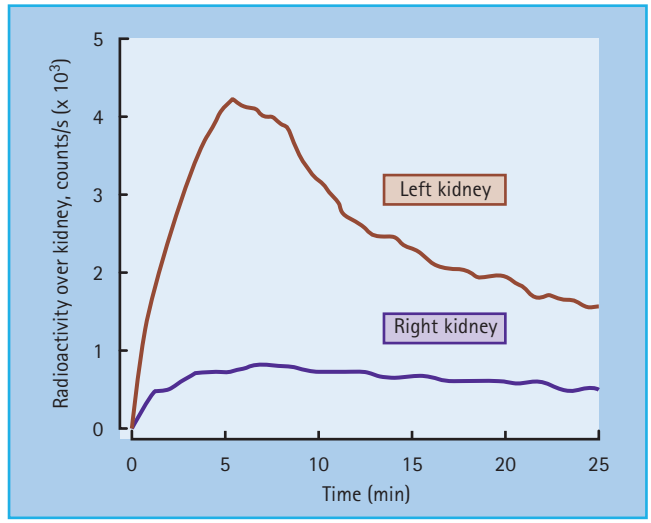

Figure 40.6 Renal artery stenosis affecting the right kidney, in a patient with diabetes and hypertension. Uptake of the isotope on this side is markedly reduced and delayed.

• *Renal function.* A fresh urine sample should be tested for microalbuminuria (see Chapter 37) and another examined microscopically for red and white blood cells, casts, and other signs of renal disease. Microscopic hematuria can occasionally occur in patients with T1DM (particularly children) in the apparent absence of significant renal dysfunction, but coexistent renal disease must always be excluded. Serum urea, creatinine and electrolytes should be checked. If the serum creatinine concentration is raised, measurement of the glomerular filtration rate (GFR) should be considered, ideally using a specific clearance method such as chromium ethylenediamine tetra-acetic acid (Cr-EDTA), iohexol or cystatin C. Further specialist investigations that may be needed include an isotope renogram and other tests for renal artery stenosis (Figure 40.6). This complication of renal

Table 40.3 Investigation of the patient with diabetes and hypertension.

Investigations	Questions to be answered
History	Is hypertension significant?
Cardiovascular symptoms	Does hypertension have an underlying cause?
Previous urinary disease	• Renal
Smoking and alcohol use	• Endocrine
Medication	• Drug-induced
Family history of hypertension or cardiovascular disease	Has hypertension caused tissue damage?
Examination	• Left ventricular hypertrophy
Blood pressure erect and supine	• Ischemic heart disease
Left ventricular hypertrophy	• Cardiac failure
Cardiac failure	• Peripheral vascular disease
Peripheral pulses (including renal bruits and radiofemoral delay)	• Renal impairment
	• Fundal changes
Ankle–brachial index	
Fundal changes of hypertension	Are other cardiovascular risk factors present?
Evidence of underlying endocrine or renal disease	• Smoking
Electrocardiography	• Hyperlipidemia
Left ventricular hypertrophy	• Poor glycemic control
Ischemic changes	• Positive family history of cardiovascular disease
Rhythm	
Chest radiography	
Cardiac shadow size	
Left ventricular failure	
Echocardiography	
Left ventricular hypertrophy	
Dyskinesia related to ischemia	
Blood tests	
Urea, creatinine, electrolytes	
Fasting lipids	
Urinary tests	
(Micro-)albuminuria	

arterial atherosclerosis may affect up to 20% of older patients with T2DM and, if bilateral, can lead to severe and sometimes permanent renal impairment if angiotensin-converting enzyme (ACE) inhibitors are given.

• *Lipid profile.* Fasting serum lipid concentrations should be checked. If total cholesterol or triglyceride levels are found to be elevated after repeated measurements, further investigation of lipoprotein subclasses – very low density lipoprotein (VLDL), LDL, HDL, as well as the apo-B:apo-A1 lipoprotein ratio – is recommended. Treatment for hyperlipidemia should be considered if the total cholesterol is >4.5 mmol/L, the LDL cholesterol level is >2.5 mmol/L or the LDL:HDL cholesterol ratio is >4 [36]. This is discussed in more detail in the second half of this chapter.

Other forms of secondary hypertension may be indicated by clinical findings of endocrine or renal disease, significant hypokalemia (plasma potassium <3.5 mmol/L without previous diuretic treatment), failure of hypertension to respond to standard treatment or a sudden decline in GFR after starting treatment with ACE inhibitors (suggestive of renal artery stenosis).

Management of hypertension in diabetes

Strict BP control is the primary goal of treatment. In recent years, target treatment levels have declined progressively to the current recommendation of a mean office BP less than 130–140/80–85 mmHg, for all patients who can tolerate this without side effects such as orthostatic reactions or compromising arterial circulation in critical vascular beds. Recent observations indicate that subgroups of susceptible patients might exist who will not tolerate a dramatic BP reduction below 130 mmHg systolic BP and so caution should be exercised.

Management begins with lifestyle modification, but few patients respond to this alone, and most will require more than one antihypertensive drug to control BP adequately [4,5].

Non-pharmacologic treatment

The treatment of hypertension in patients with diabetes must be based on structured lifestyle intervention. This means weight reduction or weight stabilization in the obese, sodium restriction, diet modification and regular physical exercise (moderate intensity, 40–60 minutes, 2–3 times weekly). Dietary intake of saturated fat has been associated with impaired in insulin sensitivity and should therefore be reduced [37]. Alcohol should be restricted to 2–3 units/day in men and 2 units/day in women, but omitted altogether if hypertension proves difficult to control.

Smoking causes an acute increase in blood pressure and greater variability overall [38]. Smoking cessation is especially important, as smoking not only accelerates the progression of atherosclerosis and vascular aging, but also impairs insulin sensitivity [39] and worsens albuminuria [40]. Treatment with nicotine supplementation for 4–6 weeks (chewing gum or patches), bupropion or varenicline may be useful.

When adopted in full by the patient, lifestyle modification can be extremely effective. The above measures can lower systolic and diastolic BP by 11 and 8 mmHg, respectively [41] – as much as many antihypertensive drugs – and sometimes enough to obviate the need for drug therapy. Weight reduction in obese patients can similarly reduce BP.

Antihypertensive drug therapy

Numerous drugs are available to lower BP, but some are better suited than others to the particular needs of subjects with diabetes because of their favorable or neutral effects on glucose metabolism and other factors. Most patients (at least two-thirds) will require combinations of antihypertensive drugs to control BP – an average of around three different drugs in two large studies [4,5]. Accordingly, the clinician must be able to use a wide variety

of antihypertensive drugs and to choose combinations that exploit pharmacologic synergy. Combination therapy usually means that lower dosages of individual drugs can often be used, thus reducing the risk of their adverse effects.

Diuretics

Diuretics are often effective antihypertensive agents for people with diabetes, in whom the total body sodium load is increased and the extracellular fluid volume expanded [42]; however, diuretics that increase urinary potassium and magnesium losses can worsen hyperglycemia, as insulin secretion is impaired by potassium depletion, and insulin sensitivity in peripheral tissues may also be decreased [43]. The use of high-dose thiazide diuretics – equivalent to ≥5 mg/day bendroflumethiazide (bendrofluazide) – is reported to increase the risk of hypertensive patients developing diabetes by up to threefold; this does not seem to occur with low dosages (up to 2.5 mg/day bendroflumethiazide) [44]. Potassium depletion is particularly severe with high-dose chlortalidone (chlorthalidone), less with furosemide (frusemide) and bendroflumethiazide and apparently negligible with indapamide. This mechanism is irrelevant to C-peptide-negative subjects with T1DM who are totally dependent on exogenous insulin. Thiazides may also aggravate dyslipidemia [45], although low dosages probably carry a small risk. Thiazides have also been associated with gout and impotence and are generally avoided in middle-aged men with diabetes and hyperuricemia or erectile dysfunction; nevertheless some evidence suggests that the risk of erectile failure may have been overstated. Diuretics may precipitate hyperosmolar hyperglycemia syndrome and should be avoided or used at the lowest effective dose in patients with a history of this complication.

Diuretics have been shown to prevent CVD successfully in elderly subjects with T2DM and systolic hypertension [46], but one observational study suggested that the use of diuretics increased cardiovascular mortality in hypertensive patients with T2DM who were still hyperglycemic in spite of treatment [47]. Overall, these drugs are effective and safe when used appropriately in patients with diabetes.

Diuretics suitable for use in diabetic hypertension include furosemide, bendroflumethiazide (≤2.5 mg/day), hydrochlorothiazide, spironolactone and indapamide. Low dosages should be used, sometimes in combination with potassium supplements or potassium-sparing drugs, such as amiloride. If ineffective, diuretics should be combined with another first-line drug (e.g. an ACE inhibitor or an angiotensin II-receptor antagonist [ARB]), rather than given at increased dosage. Spironolactone is best not combined with an ACE inhibitor, as this increases the risk of hyperkalemia. Furosemide is useful in patients with renal impairment (serum creatinine >150 μmol/L) or edema.

Serum urea, creatinine and potassium should be checked when starting diuretic therapy and every 6–12 months thereafter, as dangerous disturbances in plasma potassium levels can develop, especially in patients with diabetes and renal impairment.

β-Adrenergic blocking agents

Beta-blockers may significantly lower BP levels in patients with diabetes and hypertension, even though renin release (a major target for these drugs) is commonly reduced in diabetes because of Na^+ and fluid retention. These drugs are often ineffective in Afro-Caribbean patients, who commonly have low renin hypertension. Other mechanisms of action that reduce BP include reductions in heart rate and cardiac output via interaction with β_1- and β_2-receptors in the myocardium and in the vessel wall.

Like diuretics, beta-receptor blockers may aggravate both hyperglycemia and dyslipidemia [48]. These effects depend on both the dosage and the degree of selectivity of the individual drug. The hyperglycemic effect is attributed to inhibition of β_2-adrenergic-mediated insulin release and decreased insulin action in peripheral tissues; the long-term risks of a person without diabetes developing the disease may be increased by sixfold [49] and even more if given together with thiazides. Some studies suggest that the hazards of both hyperglycemia and hyperlipidemia have been exaggerated and may be both dose-dependent and secondary to weight gain [50]. The metabolic side effects of beta-blockers can be reduced by using low dosages combined with other agents, particularly dihydropyridine calcium channel antagonists (CCAs), or by intensifying non-pharmacologic efforts to decrease weight and improve physical activity.

Beta-blockers have other side effects relevant to diabetes. They may interfere with the counter-regulatory effects of catecholamines released during hypoglycemia, thereby blunting manifestations such as tachycardia and tremor and delaying recovery from hypoglycemia [51]. In clinical practice, however, this rarely presents a serious problem, especially when cardioselective β_1-blockers are used. Beta-blockers may also aggravate impotence, and are generally contraindicated in second- or third-degree atrioventricular (AV) heart block, severe peripheral vascular disease, asthma and chronic airway obstruction. Recent studies have shown that certain beta-blockers such as metoprolol and carvedilol [52,53] can be used favorably in cardiac failure in patients with diabetes, as shown in the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF) study, in which 25% of the patients had diabetes [52].

Atenolol is a commonly used drug, as it is cardioselective and water soluble, which reduces CNS side effects and renders its metabolism and dosage more predictable. It is mostly effective as a single daily dose, which probably encourages compliance. In the UKPDS, its effect was comparable to that of the ACE inhibitor, captopril [54]; however, it should be kept in mind that the stroke preventive effect of atenolol is 16% less than other antihypertensive drugs, based on data from meta-analyses. Metoprolol is an alternative, in moderate dosages. Both non-selective and selective beta-blockers are effective in the secondary prevention of myocardial infarction (MI) after an initial event in patients with diabetes [55]. Metoprolol or carvedilol may be indicated in patients who also have heart failure [52,53], and beta-blockers

in general are useful in patients who also have angina or tachyarrhythmias.

Calcium-channel antagonists

These useful vasodilator agents do not generally worsen metabolic control when used at conventional dosages, although sporadic cases of hyperglycemia have been reported after starting a calcium-channel antagonist (CCA) of the dihydropyridine class [56]. This may be caused by inhibition of insulin secretion (a calcium-dependent process) in susceptible patients, or a compensatory sympathetic nervous activation, which antagonizes both insulin secretion and action, following vasodilatation.

CCAs have a slight negative inotropic effect and are contraindicated in significant cardiac failure; they often cause mild ankle edema, but this is caused by relaxation of the peripheral precapillary sphincters and raised capillary pressure rather than to right ventricular failure. Because of their potent vasodilator properties, these drugs can cause postural hypotension and can aggravate that brought about by autonomic neuropathy. Non-dihydropyridine CCAs (e.g. verapamil) reduce proteinuria in diabetic nephropathy, but this effect is not seen with dihydropyridine derivatives such as nifedipine, amlodipine, felodipine and isradipine [57].

Because of their other cardiac actions, these drugs are particularly indicated in hypertensive patients who also have angina (e.g. sustained-release nifedipine and diltiazem) or supraventricular tachycardia (e.g. verapamil). Their vasodilator properties may also be beneficial in peripheral vascular disease. CCAs are ideally combined with selective β_1-blockers, but the specific combination of verapamil and beta-blockers (especially together with digoxin) must be avoided because of the risk of conduction block and asystole. Overall, CCAs appear less or similarly cardioprotective but better at preventing stroke than either beta-blockers or thiazide diuretics [58,59].

Amlodipine given once daily is an evidence-based and convenient preparation for general use, and felodipine, isradipine and sustained-release nifedipine are suitable alternatives.

Angiotensin-converting enzyme inhibitors

ACE inhibitors may be used in diabetic hypertension, even in cases where the general RAS is not activated as the drugs may interfere with local angiotensin action in specific target tissues. When used alone, however, these agents have a limited hypotensive action in many black patients, who tend to have suppressed RAS activity.

ACE inhibitors have no adverse metabolic effects and may even improve insulin sensitivity [60]; hypoglycemia has rarely been reported [61]. These drugs are particularly beneficial in diabetic nephropathy by reducing albuminuria and possibly delaying progression of renal damage [62]. Their antiproteinuric effect may be caused specifically by relaxation of the efferent arterioles in the glomerulus, which are highly sensitive to vasoconstriction by angiotensin II, thus reducing the intraglomerular hypertension that is postulated to favor albumin filtration; however, the importance of this mechanism remains controversial [63]. ACE inhibitors are also indicated in cardiac failure, in combination with relatively low dosages of diuretics.

A dry cough is reported by 10–15% of patients treated with ACE inhibitors, because these drugs also interfere with the breakdown of kinins in the bronchial epithelium. Changing to another ACE inhibitor or an ARB may avoid this problem. ACE inhibitors occasionally precipitate acute renal failure, particularly in the elderly and in subjects taking non-steroidal anti-inflammatory drugs (NSAIDs), or who have bilateral renal artery stenosis. Other side effects (rashes, neutropenia, taste disturbance) are unusual with the low dosages currently recommended, but become more prominent in renal failure. Because ACE inhibitors cause potassium retention, they should not generally be taken concurrently with potassium-sparing diuretics (spironolactone and amiloride) or potassium supplements. Serum creatinine and potassium levels should be monitored regularly, especially in patients with renal failure or type 4 renal tubular acidosis, in whom hyperkalemia can rapidly reach dangerous levels.

Ramipril, enalapril, captopril, lisinopril and perindopril are all established ACE inhibitors that are suitable for use in people with diabetes; enalapril, lisinopril, perindopril and ramipril are given once daily for hypertension. The first dose of an ACE inhibitor should be small and taken just before bedtime to minimize postural hypotension, which may be marked in subjects receiving diuretics or on a strict sodium-restricted diet. The same problem may arise in patients with autonomic neuropathy. ACE inhibitors are now recommended in patients with left ventricular dysfunction following MI (see Chapter 41). Ramipril has been shown to prevent cardiovascular morbidity and mortality in high-risk patients with diabetes, with or without pre-existing ischemic heart disease [64].

Angiotensin II type 1 receptor blockers

This promising new class includes losartan, irbesartan, valsartan, candesartan and telmisartan, which act on the AT1 receptor to decrease BP. They are metabolically neutral [65] and, unlike the ACE inhibitors, do not cause cough. They are effective antihypertensive drugs in people with diabetes [66] and have been shown to slow the progression of nephropathy in patients with diabetes and varying degrees of albuminuria (in the RENAAL, IDNT and PRIME-2 studies) [67–69]. Losartan has also been shown (in a subgroup of the LIFE study) to be better than atenolol in reducing both cardiovascular endpoints (by 25%) and total mortality (by 40%) in high-risk patients with T2DM with hypertension and left ventricular hypertrophy [70]. Interestingly, the combination of an ACE inhibitor (lisinopril) with an AT1-antagonist (candesartan) was more effective than either agent alone in lowering BP and UAE in patients with T2DM [71]; however, in the recent ONTARGET study, no extra benefits were recorded for the combination of telmisartan and ramipril on cardiovascular endpoints compared to monotherapy [72].

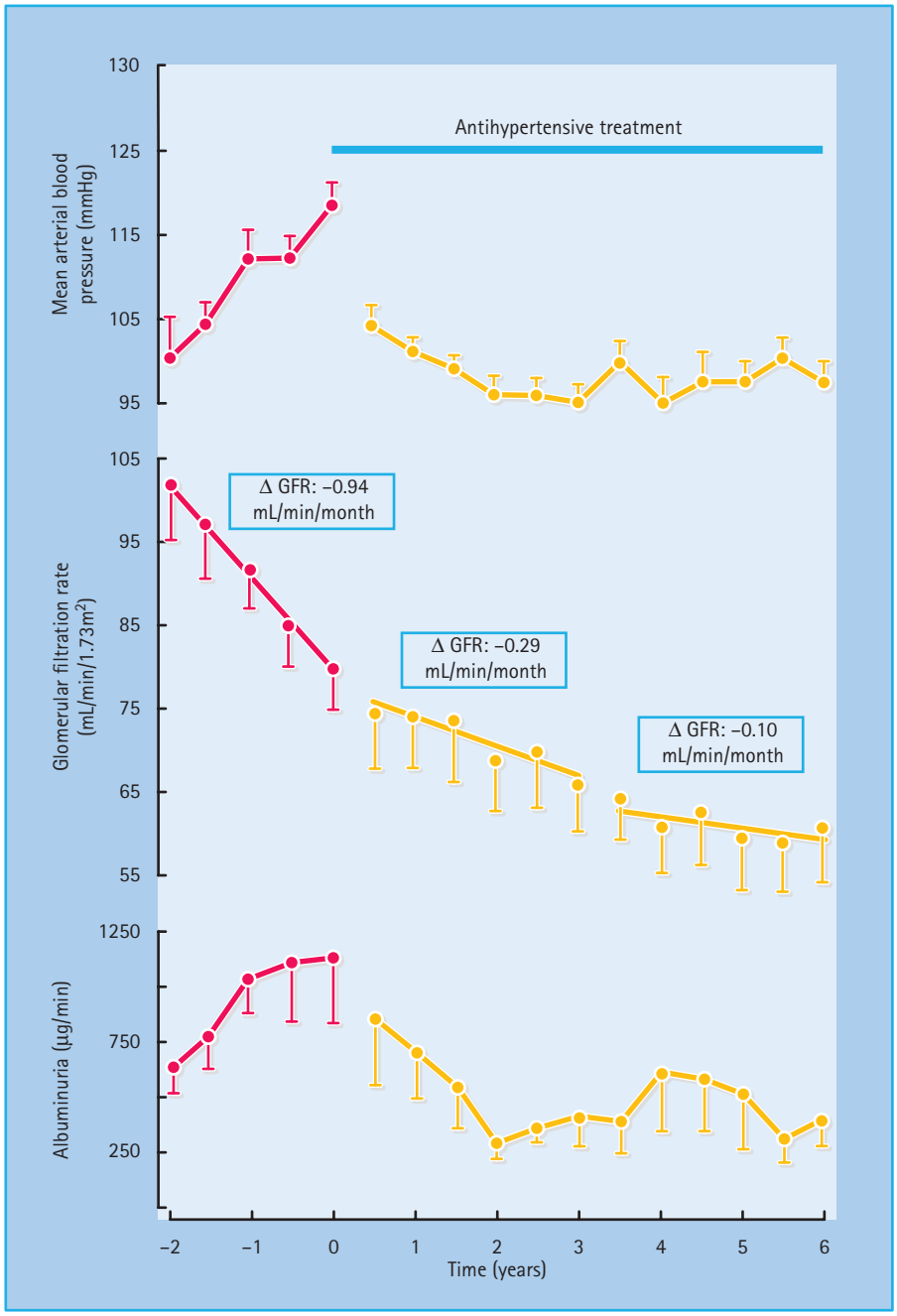

Figure 40.7 Treating hypertension slows the progression of diabetic nephropathy. Lowering blood pressure significantly decreased the rate of decline in the glomerular filtration rate (GFR) and urinary albumin excretion. Reproduced from Parving *et al.* [79], with permission.

α_1-Adrenoceptor antagonists

α_1-Blockers can lower BP effectively and also improve dyslipidemia and insulin sensitivity. Doxazosin is normally well tolerated, especially in combination therapy; side effects include nasal congestion and postural hypotension. Doxazosin has been reported to be inferior to the diuretic chlortalidone in the prevention of stroke and heart failure [73].

Treatment strategies

In general, lifestyle modification should be tried initially for 3 months or so. If moderate hypertension (diastolic BP >100 mmHg, or systolic BP >160 mmHg) or signs of hypertensive tissue damage are present, then drug therapy should be started at the outset. Initially, monotherapy with one of the first-line drugs suggested above should be used, the choice being influenced by other factors such as coexistence of angina, heart failure or nephropathy. All drug treatment should aim for being evidence-based and cost-effective in the individual patient.

Hypertension in T1DM

ACE inhibitors are especially suitable if the patient has albuminuria or more advanced stages of diabetic nephropathy. Diuretics, β_1-selective blockers and CCAs are equally valid alternatives with regard to BP reduction.

If renal function is moderately impaired (serum creatinine values >150 μmol/L), thiazide diuretics become less effective, and furosemide or other loop diuretics should be used instead; however, in established ESRF (serum creatinine >500 μmol/L) furosemide may be toxic, and dialysis must be started. In some patients, hypoglycemia attacks may be masked by use of beta-blockers.

Hypertension in T2DM

BP control is generally more important than the choice of individual drugs. First-line agents, according to evidence from clinical studies, are ACE inhibitors, ARBs, beta-blockers, low-dose thiazide diuretics (in the elderly), furosemide and CCAs [4–8].

Ramipril has evidence-based support for its use in patients with T2DM because of their high cardiovascular risk [64]. Beta-blockers (in combination with low-dose aspirin) are indicated as secondary prevention for patients who have had a MI, as long as no serious contraindications are present. Low doses of thiazide diuretics are useful in elderly patients with diabetes, as this class of drugs has proven efficacy in preventing stroke and all-cause mortality in elderly hypertensive patients [8].

α_1-Blockers may be used as part of combination therapy, especially in patients with dyslipidemia (high triglycerides and low HDL cholesterol levels) and prostatic hyperplasia. Indapamide is well tolerated and has no metabolic side effects. Spironolactone may also be of value [74], especially for elderly obese female patients with hypertension and hypervolemia with a low renin profile.

Combination therapy

Combination therapy is needed in most people with diabetes (especially those with T2DM) to achieve satisfactory BP control [4,5]. It is often better to use low dose combinations than to increase dosages of single agents, as side effects are commonly dose-dependent. As already mentioned, potassium-sparing agents (spironolactone and amiloride) should not be combined with an ACE inhibitor, because of the increased risk for hyperkalemia.

Certain combinations of antihypertensive drugs have proved very safe and effective in low to moderate doses, e.g. ACE inhibitor plus diuretic, for example in the ADVANCE study [75]; CCA plus ACE inhibitor, for example in the ACCOMPLISH study [76]; selective β_1-blocker plus CCA; or β_1-blocker plus α_1-blocker. In some high risk patients a combination treatment could also be considered as initial therapy.

Special considerations in ethnic groups

Hypertension in diabetes represents a serious medical problem in many ethnic groups, such as African-Americans [77]. In non-white European patients, beta-blockers and ACE inhibitors are often less effective at lowering BP because the RAS is already underactive. Diuretics and CCAs are often drugs to be preferred, particularly in African-Americans [78].

Outcome of treating hypertension in diabetes

It has long been recognized that effective treatment of hypertension can slow the progression of diabetic nephropathy, lowering UAE and decreasing the rate of fall of the GFR [79] (Figure 40.7).

The assumptions that improved BP control would improve cardiovascular and other prognoses in T2DM have been confirmed by the UKPDS [4]. In this study, tighter BP control (averaging 144/82 mmHg) for over 8 years led to significant improvements in several outcomes, compared with less strict control that averaged 154/87 mmHg (Table 40.4). Interestingly, the most powerful effects were related to microvascular complications (retinopathy and nephropathy), although significant reductions were seen in the risk of stroke (44%) and heart failure (56%). MI and peripheral vascular disease showed non-significant reductions (Table 40.4; Figures 40.8 and 40.9).

Overall, therefore, tight BP control has been proven to provide substantial benefits for hypertensive patients with diabetes. Moreover, this treatment strategy seems to be cost-effective, at least according to the health economics analyses in the UKPDS [80]; however, it must be kept in mind that these benefits will not last if a continuous BP reduction cannot be achieved long-term, as shown by the 10-year follow-up of the UKPDS [81].

Conclusions

The diagnosis and treatment of hypertension is of great importance for the person with diabetes [34,36,82–84]. The treatment targets are demanding and require considerable effort from both patient and physicians, but the benefits are now undisputed.

New antihypertensive drugs are constantly being introduced but have to prove themselves for both efficacy and tolerability. Even some antidiabetic drugs appear to lower BP as well as blood glucose [85], but safety concerns are important (see Chapter 29).

In the future, the application of cardiovascular genomics may substantially change the approach to treating hypertension in

Table 40.4 Impact of stricter control of hypertension on diabetic complications, macrovascular disease and diabetes-related deaths in T2DM. Data from the UKPDS [4].

Measure	Relative risk with tight control (mean, 95% confidence intervals)	*P* value
Diabetes-related deaths	0.76 (0.62–0.92)	0.19
All-cause mortality	0.82 (0.63–1.08)	0.17
Myocardial infarction	0.79 (0.59–1.07)	0.13
Stroke	0.56 (0.35–0.89)	0.013
Peripheral vascular disease	0.51 (0.19–1.37)	0.17
Microvascular disease	0.63 (0.44–0.89)	0.009

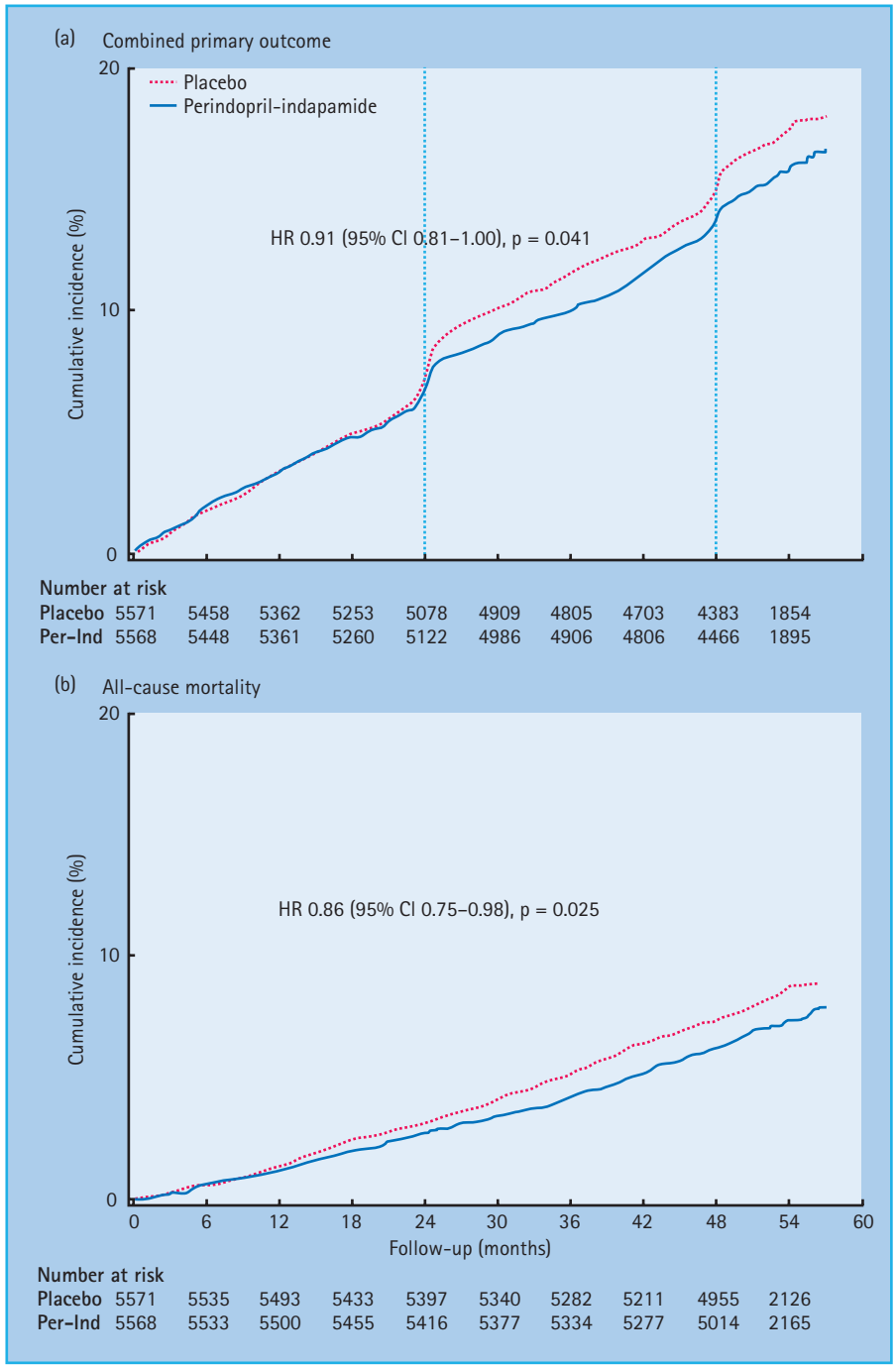

Figure 40.8 Kaplan–Meier curves for the primary outcome and all-cause mortality in the two study groups in the ADVANCE Trial [74]. The combined primary outcome were composites of major macrovascular and microvascular events. Major macrovascular events were cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Major microvascular events were new or worsening nephropathy or retinopathy.

diabetes [86], aiming at tailoring treatment according to the genotype of the individual patient.

In addition, further large-scale studies with large numbers of hypertensive patients with T2DM are awaited [87]. In the recent ACCORD-Blood pressure study [88] there was no significant difference in the primary composite outcome of cardiovascular events between patients randomized to achieve a systolic blood pressure goal below 120 mmHg versus below 140 mmHg, even if a reduction in stroke was noticed (secondary end-point) in the intensive arm. This means that the optimal blood pressure goal for patients with hypertension and T2DM is still not established [89].

Finally, it takes a multifactorial approach to address and to treat all major cardiovascular risk factors, not only BP, to achieve lasting cardiovascular protection, as evidenced by the Steno-2 trial [90].

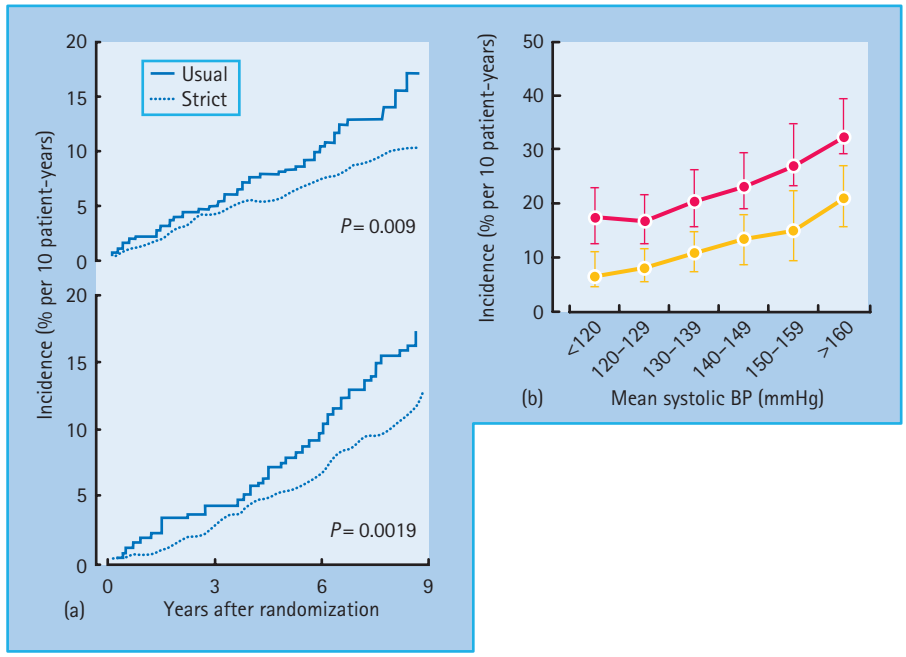

Figure 40.9 Treating hypertension improves the prognosis in T2DM. (a) Stricter BP control (mean pressure 144/82 mmHg) significantly reduced the risks of both microvascular complications (*top*) and diabetes-related death (*bottom*), compared with less strict control (mean 154/82 mmHg). (b) The relationship between BP and rates of microvascular disease and MI. Lowering the BP progressively reduced the risk of microvascular complications, but there was no significant effect on MI. The red line represents MI and the yellow line represents microvascular complications. Reproduced from UKPDS [4,91], with permission.

References

1 Kylin E. Studien über das Hypertone-Hyperglykämie-Hyperurikämisyndrom. *Zeitschrift Inn Med* 1923; **7**:105–112.

2 Reaven GM. Role of insulin resistance in human disease. *Diabetes* 1988; **37**:1595–1607.

3 Meigs JB, D'Agostino RB Sr, Wilson P, Cupples LA, Nathan DM, Singer DE. Risk variable clustering in the insulin resistance syndrome: the Framingham Offspring Study. *Diabetes* 1997; **46**:1594–1600.

4 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *Br Med J* 1998; **317**:703–713.

5 Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius 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.

6 Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. 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.

7 Tuomilehto J, Rastenyte D, Birkenhäger WH, Thijs L, Antikainen R, Bulpitt CJ, *et al.* Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. *N Engl J Med* 1999; **340**:677–684.

8 Lindholm LH, Hansson L, Ekbom T, Dahlöf B, Lanke J, Linjer E, *et al.* Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2 Study Group. *J Hypertens* 2000; **18**:1671–1675.

9 Wiseman MJ, Viberti GC, Mackintosh D, Jarrett RJ, Keen H. Glycaemia, arterial pressure and microalbuminuria in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1984; **26**:401–405.

10 Hypertension in Diabetes Study Group. Hypertension in Diabetes Study (HDS). II. Increased risk of cardiovascular complications in hypertensive type 2 diabetic patients. *J Hypertens* 1993; **11**:319–325.

11 Haffner S, Mitchell B, Stern M, Hazuda HP, Patterson JK. Decreased prevalence of hypertension in Mexican-Americans. *Hypertension* 1990; **16**:225–232.

12 Salomaa VV, Strandberg TE, Vanhanen H, Naukkarinen V, Sarna S, Miettinen TA. Glucose tolerance and blood pressure: long-term follow up in middle aged men. *Br Med J* 1991; **302**:493–496.

13 Cooper R, Cutler J, Desvigne-Nickens P, Fortmann SP, Friedman L, Havlik R, *et al.* Trends and disparities in coronary heart disease, stroke, and other cardiovascular diseases in the United States: findings of the national conference on cardiovascular disease prevention. *Circulation* 2000; **102**:3137–3147.

14 DeFronzo R, Ferrannini E. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic disease. *Diabetes Care* 1991; **14**:173–194.

15 Pyörälä M, Miettinen H, Halonen P, Laakso M, Pyörälä K. Insulin resistance syndrome predicts the risk of coronary heart disease and stroke in healthy middle-aged men: the 22-year follow-up results of the Helsinki Policemen Study. *Arterioscler Thromb Vasc Biol* 2000; **20**:538–544.

16 Barker DJP, ed. *Fetal and Infant Origins of Adult Disease*. London: British Medical Journal, 1992.

17 Pinkney JH, Mohamed-Ali V, Denver AE, Foster C, Sampson MJ, Yudkin JS. Insulin resistance, insulin, proinsulin, and ambulatory blood pressure in type II diabetes. *Hypertension* 1994; **24**:362–367.

18 Scherrer U, Randin D, Vollenweider P, Vollenweider L, Nicod P. Nitric oxide release accounts for insulin's vascular effects in humans. *J Clin Invest* 1994; **94**:2511–2515.

19 Rongen GA, Tack CJ. Triglycerides and endothelial function in type 2 diabetes. *Eur J Clin Invest* 2001; **31**:560–562.

20 DeFronzo RA, Goldberg M, Agus ZS. The effects of glucose and insulin on renal electrolyte transport. *J Clin Invest* 1976; **58**:83–90.

21 Natali A, Quiñones Galvan A, Santora D, Pecori N, Taddei S, Salvetti A, *et al.* Relationship between insulin release, antinatriuresis and hypokalaemia after glucose ingestion in normal and hypertensive man. *Clin Sci* 1993; **85**:327–335.

22 Hall JE, Summers RL, Brands MW, Keen H, Alonso-Galicia M. Resistance to metabolic actions of insulin and its role in hypertension. *Am J Hypertens* 1994; **7**:772–788.

23 Morris AD, Petrie JR, Connell JMC. Insulin and hypertension. *J Hypertens* 1994; **12**:633–642.

24 Anderson EA, Balon TW, Hoffman RP, Sinkey CA, Mark AL. Insulin increases sympathetic activity but not blood pressure in borderline hypertensive humans. *Hypertension* 1992; **19**:621–627.

25 Capron L, Jarnet J, Kazandjian S, Housset E. Growth-promoting effects of diabetes and insulin on arteries: an *in vivo* study of rat aorta. *Diabetes* 1986; **35**:973–978.

26 Mathiesen ER, Rønn B, Jensen T, Storm B, Deckert T. Relationship between blood pressure and urinary albumin excretion in development of microalbuminuria. *Diabetes* 1990; **39**:245–249.

27 Walker JD, Tariq T, Viberti GC. Sodium–lithium countertransport activity in red cells of patients with insulin-dependent diabetes and nephropathy and their parents. *Br Med J* 1990; **301**: 635–638.

28 Drury PL, Bodansky HJ, Oddie CJ, Edwards CRW. Factors in the control of plasma renin activity and concentration in type 1 diabetics. *Clin Endocrinol* 1984; **20**:607–618.

29 Zatz R, Brenner BM. Pathogenesis of diabetic microangiopathy: the hemodynamic view. *Am J Med* 1986; **80**:443–453.

30 Groop L, Ekstrand A, Forsblom C, Widen E, Groop PH. Insulin resistance, hypertension and microalbuminuria in patients with type II (non-insulin-dependent) diabetes mellitus. *Diabetologia* 1993; **36**: 642–647.

31 Liu JE, Palmieri V, Roman NJ, Bella JN, Fabsitz R, Hoard BV, *et al.* The impact of diabetes in left ventricular filling pattern in normotensive and hypertensive adults: the strong heart study. *J Am Coll Cardiol* 2001; **37**:1943–1949.

32 Kuperstein R, Hanly P, Niroamand M, Fasson Z. The importance of age and obesity on the relation between diabetes and left ventricular mass. *J Am Coll Cardiol* 2001; **37**:1957–1962.

33 Schernthaner G, Ritz E, Phillipp T, Bretzel R. The significance of 24-hour blood pressure monitoring in patients with diabetes mellitus. *Dtsch Med Wochenschrift* 1999; **124**:393–395.

34 World Health Organization–International Society of Hypertension Guidelines for the Management of Hypertension, 1999. Guidelines Subcommittee. *J Hypertens* 1999; **17**:151–183.

35 Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993; **16**:434–444.

36 Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and other Societies on coronary prevention. Summary of recommendations. *Eur Heart J* 1998; **19**:1434–1503.

37 Vessby B, Tengblad S, Lithell H. Insulin sensitivity is related to the fatty acid composition of serum lipids and skeletal muscle phospholipids in 70-year old men. *Diabetologia* 1994; **37**: 1044–1050.

38 Stewart MJ, Jyothinagaram S, McGinley IM, Padfield PL. Cardiovascular effects of cigarette smoking: ambulatory blood pressure and BP variability. *J Hum Hypertens* 1994; **8**:19–22.

39 Facchini F, Hollenbeck C, Jeppesen J, Chen YD, Reaven GM. Insulin resistance and cigarette smoking. *Lancet* 1992; **339**:1128–1130.

40 Chase PH, Garg SK, Marshall G, Berg CL, Harris S, Jackson WE, *et al.* Cigarette smoking increases the risk of albuminuria among subjects with type 1 diabetes. *JAMA* 1991; **265**:614–617.

41 Treatment of Mild Hypertension Research Group. The Treatment of Mild Hypertension Study: a randomized, placebo-controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. *Arch Intern Med* 1991; **151**:1413–1423.

42 Weidman P, Beretta-Piccoli C, Keusch G, Glück Z, Mujagic M, Grimm M, *et al.* Sodium-volume factor, cardiovascular reactivity and hypotensive mechanism of diuretic therapy in mild hypertension associated with diabetes mellitus. *Am J Med* 1979; **67**:779–784.

43 Pollare T, Lithell H, Berne C. A comparison of the effects of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. *N Engl J Med* 1989; **321**:868–873.

44 Berglund G, Andersson O, Widgren B. Low-dose antihypertensive treatment with a thiazide diuretic is not diabetogenic: a 10-year controlled trial with bendroflumethiazide. *Acta Med Scand* 1986; **220**:419–424.

45 MacMahon SW, Macdonald GJ. Antihypertensive treatment and plasma lipoprotein levels: the associations in data from a population study. *Am J Med* 1987; **80**(Suppl. 2A):40–47.

46 Curb JD, Pressel SL, Cutler JA, Savage PJ, Applegate WB, Black H, *et al.*; Systolic Hypertension in the Elderly Program Cooperative Research Group. Effect of diuretic-based anti-hypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. *JAMA* 1996; **276**:1886–1892.

47 Alderman MH, Cohen H, Madhavan S. Diabetes and cardiovascular events in diabetes patients. *Hypertension* 1999; **33**:1130–1134.

48 Pollare T, Lithell H, Selinus I, Berne C. Sensitivity to insulin during treatment with atenolol and metoprolol: a randomized, double blind study of effects on carbohydrate and lipoprotein metabolism in hypertensive patients. *Br Med J* 1989; **198**:1152–1157.

49 Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in the Community Study. *N Engl J Med* 2000; **342**:905–912.

50 Sawicki PT, Siebenhofer A. Beta-blocker treatment in diabetes mellitus. *J Intern Med* 2001; **250**:11–17.

51 Lager I, Blohme G, Smith U. Effect of cardioselective and non selective beta-blockade on the hypoglycemic response in insulin-dependent diabetics. *Lancet* 1979; **i**:458–462.

52 Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, *et al.*; MERIT-HF Study Group. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). *JAMA* 2000; **283**:1295–1302.

53 Krum H, Ninio D, MacDonald P. Baseline predictors of tolerability to carvedilol in patients with chronic heart failure. *Heart* 2000; **84**:615–619.

54 UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *Br Med J* 1998; **317**: 713–720.

55 Kjekshus J, Gilpin E, Cali G, Blackey AR, Henning H, Ross J Jr. Diabetic patients and beta-blockers after acute myocardial infarction. *Eur Heart J* 1990; **11**:43–50.

56 Chellingsworth MC, Kendall MJ, Wright AD, Singh BM, Pasi J. The effects of verapamil, diltiazem, nifedipine and propranolol on metabolic control in hypertensives with non-insulin-dependent diabetes mellitus. *J Hum Hypertens* 1989; **3**:35–39.

57 Bakris GL, Weir MR, DeQuattro V, McMahon FG. Effects of an ACE inhibitor/calcium antagonist combination on proteinuria in diabetic nephropathy. *Kidney Int* 1998; **54**:1283–1289.

58 Pahor M, Psaty BM, Alderman MH, Applegate WB, Williamson JD, Cavazzini C, *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**:1949–1954.

59 Neal B, MacMahon S, Chapman N; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet* 2000; **356**:1955–1964.

60 Lithell HO. Effects of antihypertensive drugs on insulin, glucose and lipid metabolism. *Diabetes Care* 1991; **14**:203–209.

61 Herings RM, de Boer A, Stricker BH, Leufkens HG, Porsius A. Hypoglycaemia associated with use of inhibitor of angiotensin converting enzyme. *Lancet* 1995; **345**:1195–1198.

62 Lewis EJ, Hunsickler LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993; **329**:1456–1462.

63 Bank N, Klose R, Aynedjan HS, Nguyen D, Sablay LB. Evidence against increased glomerular pressure initiating diabetic nephropathy. *Kidney Int* 1987; **31**:898–905.

64 Heart Outcomes Prevention Evaluation 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.

65 Goodfriend TL, Elliott ME, Catt KJ. Angiotensin receptors and their antagonists. *N Engl J Med* 1996; **334**:1649–1654.

66 Ruilope L. RAS blockade: new possibilities in the treatment of complications of diabetes. *Heart* 2000; **84**:32–34.

67 Brenner B, Cooper ME, de Zeeuw D, de Zeeuw D, Keane WF, Mitch WE, *et al.* Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; **345**:861–869.

68 Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, *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.

69 Parving HH, Lehnert H, Bröckner-Mortensen J, Gomis R, Andersen S, Arner P; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001; **345**:870–878.

70 Lindholm LH, Ibsen H, Dahlöf B, Devereux RB, Beevers G, de Faire U, *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**:1004–1008.

71 Mogensen CE, Neldam S, Tikkanen I, Oren S, Viskoper R, Watts RW, *et al.* Randomized controlled trial of dual blockage of renin-angiotensin and non-insulin dependent diabetes: the Candesartan and Lisinopril Microalbuminuria (CALM) Study. *Br Med J* 2000; **321**:1440–1444.

72 ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; **358**:1547–1559.

73 ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA* 2000; **283**:1967–1975.

74 Ramsay LE, Yeo WW, Jackson PR. Diabetes, impaired glucose tolerance and insulin resistance with diuretics. *Eur Heart J* 1992; **13**(Suppl. G):68–71.

75 Patel A; ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007; **370**:829–840.

76 Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V, *et al.*; ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008; **359**:2417–2428.

77 Jamerson K, de Quattro V. The impact of ethnicity on response to antihypertensive therapy. *Am J Med* 1996; **101**:22S–32S.

78 Flack JM, Hamaty M. Difficult-to-treat hypertensive populations: focus on African-Americans and people with type 2 diabetes. *J Hypertens* 1999; **17**(Suppl.):S19–S24.

79 Parving HH, Andersen AR, Smidt UM, Hommel E, Mathiesen ER, Svendsen PA. Effect of antihypertensive treatment on kidney function in diabetic nephropathy. *Br Med J (Clin Res Ed)* 1987; **294**:1443–1447.

80 UK Prospective Diabetes Study Group. Cost effectiveness analysis of improved blood pressure control in hypertensive patients with type 2 diabetes: UKPDS 40. *Br Med J* 1998; **317**:720–726.

81 Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N Engl J Med* 2008; **359**:1565–1576.

82 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, *et al.*; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**:2560–2572.

83 Rydén L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ, *et al.*; Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC); European Association for the Study of Diabetes (EASD). Guidelines on diabetes, prediabetes, and cardiovascular diseases: executive summary. *Eur Heart J* 2007; **28**:88–136.

84 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, *et al.*; The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Management of arterial hypertension of the European Society of Hypertension; European Society of Cardiology: 2007 guidelines for the management of arterial hypertension: *J Hypertens* 2007; **25**:1105–1187.

85 Sarafidis P, Nilsson PM. The effects of thiazolidinedione compounds on blood pressure levels: a systematic review. *Blood Pressure* 2006; **15**:135–150.

86 Pratt RE, Dzau VJ. Genomics and hypertension: concepts, potentials, and opportunities. *Hypertension* 1999; **33**:238–247.

87 Lauritzen T, Griffin S, Borch-Johnsen K, Wareham NJ, Wolffenbuttel BH, Rutten G; Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care. The ADDITION study: proposed trial of the cost-effectiveness of an intensive multifactorial intervention on morbidity and mortality among people with type 2 diabetes detected by screening. *Int J Obes Relat Metab Disord* 2000; **24**(Suppl 3):S6–11.
88 The ACCORD Study Group. Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. *N Engl J Med* 2010; Mar 14. [Epub ahead of print].
89 Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, *et al.*; Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens* 2009, Oct 15. [Epub ahead of print].
90 Gaede P, Lund-Andersen H, Parving H-H, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008; **358**:580–591.
91 Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, *et al.* Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ* 2000; **321**(7258):412–419.

Dyslipidemia: Diabetes Lipid Therapies

Adie Viljoen[1] *and Anthony S. Wierzbicki*[2]

Keypoints

- The greatest long-term risk in diabetes is cardiovascular disease (CVD), with macrovascular disease being the cause of 80% of mortality in people with diabetes.
- Epidemiologic studies have established that glycemic control, nephropathy and lipids are risk factors for CVD in type 1 diabetes.
- Low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, smoking and hypertension are the principal risk factors in type 2 diabetes mellitus (T2DM).
- In T2DM, optimized glycemic control has modest effects in reducing CVD endpoints.
- Reduction of LDL cholesterol with statins has consistently shown cardiovascular event reductions >30%.
- The dyslipidemia of T2DM is associated with elevated triglycerides, reduced HDL cholesterol and small dense particles.
- Fibrates, when used as monotherapy, have shown a modest reduction in events in T2DM in the FIELD study.
- Post hoc analysis of the Coronary Drug Project with niacin suggests possible benefits on cardiovascular endpoints.
- Trials now underway will allow the efficacy of combination lipid-lowering therapies in diabetes to be determined.
- Optimal control of all risk factors can reduce cardiovascular events and mortality in diabetes by 50%.

Introduction

An association between diabetes and heart disease was described more than a century ago. Two decades later, in 1906, it was hypothesized that this association was caused by atherosclerosis. The importance of diabetes as a cardiovascular disease (CVD) risk factor became established following the Framingham Study and this was subsequently confirmed by other landmark studies [1,2]. The magnitude of diabetes as a CVD risk factor is substantial, with the increase in cardiovascular risk being two- to fourfold. Many guidelines regard diabetes as a coronary heart disease (CHD) risk equivalent [3–5]. This concept is based originally on a Finnish cohort [6], which showed comparable risk of CHD outcomes such as myocardial infarction (MI) and CHD death between subjects with type 2 diabetes mellitus (T2DM) for >10 years and subjects with established CHD (Figure 40.10). This was still apparent after adjusting for known risk factors such as age, sex, hypertension, total cholesterol and smoking. The Organization to Assess Strategies for Ischemic Syndromes (OASIS) study showed that patients with diabetes and no previous CVD have the same long-term morbidity and mortality as patients with established CVD but no diabetes after hospitalization for unstable coronary artery disease (CAD) [7]; however, there is a wide variation in the rate of CHD in diabetes which depends on the population studied, duration of diabetes, as well as existing risk factors [8,9]. This equivalence has not been confirmed by a subsequent study and it also seems less valid in older subjects where those with existing CHD have a greater risk than non-CHD patients with diabetes [9,10]. Most of the literature that reports on CVD risk and diabetes only considers T2DM. Even though people with type 1 diabetes mellitus (T1DM) are clearly at increased risk for CVD [11,12], no study has specifically examined whether subjects with T1DM have a CVD risk that is comparable or higher than those with T2DM. In T1DM there may even be a higher risk of premature CVD. In a cohort of 292 patients with T1DM followed for 20–40 years, the cumulative mortality rate from CAD was 35% by age 55 [11]. As T1DM mostly presents at an earlier age, it remains more difficult to assess and compare this but rates of CVD are increased at all ages [13].

Concomitant CVD risk factors also differ according to the type of diabetes. For example, those with T1DM have a two- to threefold increase in risk of developing CHD and stroke in later life. This risk is notably increased in those developing diabetic neph-

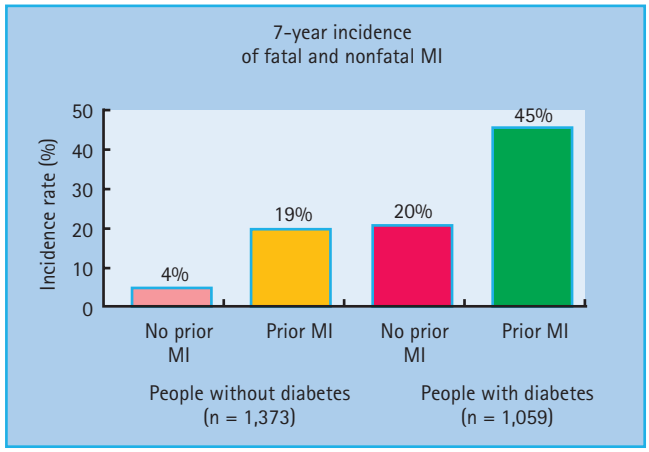

Figure 40.10 Equivalence of cardiovascular risk in patients with previous coronary heart disease (CHD) and those with diabetes. MI, myocardial infarction. Reproduced from Haffner *et al.* [6], with permission from Massachusetts Medical Society.

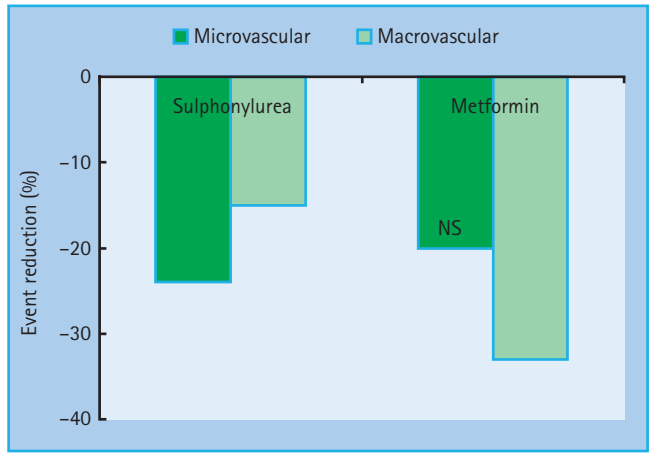

Figure 40.11 Results of the UK Prospective Diabetes Study (UKPDS) at 10 years follow-up. Reproduced from Holman *et al.* [24], with permission from Massachusetts Medical Society.

ropathy. Other markers of CVD risk in people with diabetes include diabetic retinopathy, autonomic neuropathy, erectile dysfunction, microalbuminuria and proteinuria [14].

In general, people with diabetes have a two- to fourfold CVD risk compared with the non-diabetic population [15]. Even though guidelines do not recommend formal CVD risk estimation in those with diabetes because of the significant risk these patients already have and the tendency of the Framingham algorithm to underestimate risk in this group, clinicians may still opt to estimate the risk by employing various risk calculators of which the UK Prospective Diabetes Study (UKPDS) is the most used [16]. It should be noted however, that these risk calculators predict risk with variable accuracy [17]. As all methods of CVD risk estimation suffer from distinct limitations, clinical judgment remains necessary to assess risk accurately and select and titrate appropriate treatment [18,19].

Cardiovascular disease risk factors in diabetes

Glucose

A risk continuum exists across a broad glucose concentration range which incorporates individuals without diabetes, with the risk of CVD being the lowest when the fasting blood glucose is 4–4.9 mmol/L [20–22]. Despite the well-established association between blood glucose and atherosclerosis, surprisingly few studies have been able to show an improvement in cardiovascular outcome by reduction in blood glucose. In T1DM, the Epidemiology of Diabetes Interventions and Complications (EDIC) study [23] which followed subjects after the completion the Diabetes Control and Complications Trial found that glucose lowering was associated with a long-term benefit with regard to cardiovascular complications that became apparent only years after recruitment. In T2DM, 10-year follow-up data from the UKPDS intensive glucose therapy showed long-term beneficial

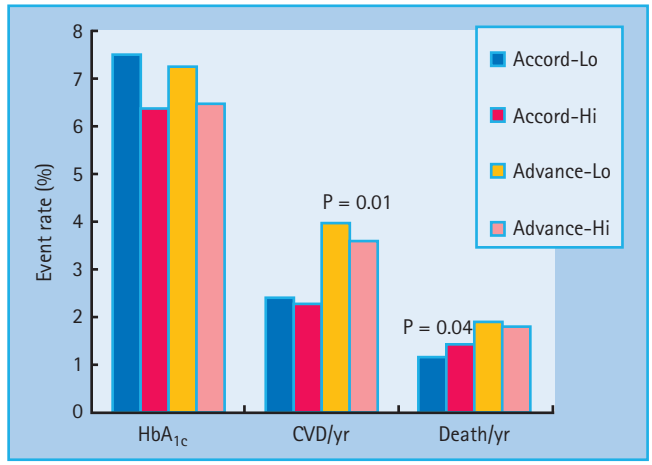

Figure 40.12 Effects of improved diabetes control to an HbA_{1c} <6.5% (48 mmol/mol) in the ACCORD and ADVANCE studies. CVD, cardiovascular disease; Lo, intensive glycemic control; Hi, conventional glycemic control. Data from ACCORD group *N Engl J Med* 2008; **358**:2545 and ADVANCE group *N Engl J Med* 2008; **358**:2560.

effects on macrovascular outcomes [24]; however, unlike the microvascular benefits, risk reductions for MI and death from any cause were observed only with extended post-trial follow-up (Figure 40.11). These results suggested that improved glucose control may result in a larger cardiovascular risk reduction in patients with T1DM than among those with T2DM, which is consistent with the results of one meta-analysis. Furthermore, neither the recent Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) [25] nor the Action to Control Cardiovascular Risk in Diabetes (ACCORD) [26] trials, each including in excess of 10 000 participants, could not show a significant beneficial effect on CVD outcome when targeting near-normal glucose levels in T2DM as determined by a HbA_{1c} <6.5% (48 mmol/mol) (Figure 40.12). More worrying was the finding in the ACCORD trial that

near-normal glucose control was actually associated with a significantly increased risk of death from any cause and death from cardiovascular causes, the very outcomes the trial was designed to prevent [27]. Several other outcomes trials are underway, which should improve our understanding of the problem of glycemic control and CVD [28].

Dyslipidemia

Compared with hyperglycemia, targeting dyslipidemia has proven much more effective in preventing the macrovascular complications of diabetes; however, for many years the benefits of intervention on lipoproteins as cardiovascular risk factors in diabetes were uncertain. The principal reason was that people with diabetes were excluded from trials of lipid-lowering therapies. Thus, virtually no data exist from early studies with bile acid sequestrants, fibrates or nicotinic acid.

The reasons for the excess CVD risk in diabetes are numerous and varied and in part relate to the lipid abnormalities seen in diabetes. Enhanced glycation of lipoproteins has direct effects on lipoprotein metabolism as glycated lipoproteins are handled differently by lipoprotein receptors, particularly of the scavenger group, thus promoting atherogenesis [29]. Enhanced glycation also amplifies the effects of oxidative stress on lipoproteins and therefore affects both T1DM and T2DM [30]. The term diabetic dyslipidemia refers to the lipid abnormalities typically seen in persons with T2DM and is synonymous with atherogenic dyslipidemia [31,32]. It is characterized by elevated triglyceride-rich remnant lipoproteins (routinely measured as hypertriglyceridemia), small dense LDL particles and low HDL cholesterol concentrations. Several factors are likely to be responsible for diabetic dyslipidemia: insulin effects on liver apolipoprotein production, downregulation of lipoprotein lipase (LPL) as opposed to hepatic lipase, increased cholesteryl ester transfer protein (CETP) activity, and peripheral actions of insulin on adipose and muscle.

Low density lipoprotein cholesterol

LDL cholesterol is identified as the primary target of lipid-lowering therapy. Analysis of the UKPDS showed that LDL cholesterol was the strongest risk factor for CHD in this population and HDL cholesterol was the second strongest [33]. Even relatively modern studies discouraged recruitment or restricted entry to patients with hypercholesterolemia and reasonable glycemic control (HbA_{1c} <8% [64 mmol/mol]) as in the Scandinavian Simvastatin Survival Study (4S) [34]. Only recently have studies been performed recruiting large groups of people with T2DM. The 4S trial included only 202 people with diabetes out of 4444 participants. In this small group of subjects, simvastatin therapy was associated with a 55% reduction in major CHD (fatal and non-fatal CHD) ($P = 0.002$) compared with a 32% reduction in major CHD in subjects without diabetes [35]. It was concluded that the absolute benefit of cholesterol lowering in patients with diabetes may be greater than that in patients without diabetes because the patients with diabetes have a higher absolute risk of atherosclerotic events and CHD. This notion was later confirmed in several other studies that also recruited people with diabetes as a subgroup [36].

A number of studies have been specifically performed with statins in diabetes. Most notable of these were the Collaborative Atorvastatin Diabetes Study (CARDS) [37] and the Heart Protection Study (HPS) [38] where subjects were randomized in a double-blind placebo-controlled fashion to 10 mg/day atorvastatin in CARDS and to 40 mg/day simvastatin in the HPS. This produced, respectively, a 40% and 33% reduction in LDL cholesterol associated with a 37% and 31% reduction in combined cardiovascular endpoints. The HPS is the largest statin study to date and included a subgroup of 5963 patients with diabetes (29% of the total study group) [39]. The CARDS trial only included people with diabetes and more than one additional risk factor (e.g. uncontrolled hypertension and/or microalbuminuria) but without prior overt CVD. The study was terminated 2 years prematurely having shown unexpected early benefit. By contrast, the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) study of similar design to CARDS and also using atorvastatin showed a non-significant 15% reduction in events [40]. In end-stage diabetes with renal failure, aggressive LDL cholesterol reduction reduced events by a non-significant 8% despite a 41% reduction in LDL cholesterol [41]. Thus, the benefits of statin therapy seem to occur early in disease in diabetes.

Overall, the accumulated evidence therefore supports the efficacy of statin therapy in reducing cardiovascular risk in patients with diabetes. A meta-analysis, which evaluated the efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomized trials of statins, reported a 9% proportional reduction in all-cause mortality and a 21% proportional reduction in major vascular events per 1 mmol/L reduction in LDL cholesterol (Figure 40.13) [42].

There are few data on diabetes and other drugs that reduce LDL cholesterol as people with diabetes were excluded from trials of bile acid sequestrants. The cholesterol absorption inhibitor, ezetimibe, works by reducing the upper intestinal cholesterol

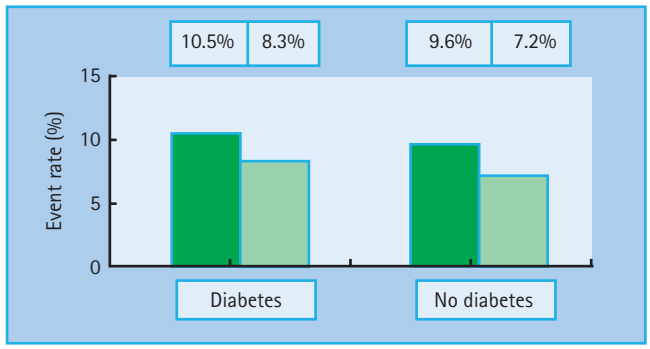

Figure 40.13 Comparison of the effects of reducing low density lipoprotein (LDL) cholesterol on cardiovascular events in patients with and without diabetes. Reproduced from Cholesterol Treatment Triallists Collaborators. *Lancet* 2005; **366**:1267–1278, with permission from Elsevier.

absorption to produce in monotherapy a 20–25% reduction in LDL cholesterol and, in contrast to bile acid sequestrants, it has remarkably little effect on other lipid fractions. People with diabetes were excluded from the Simvasatatin Ezetimibe Aortic Stenosis study [43]. More recently, it has received several potential setbacks with respect to surrogate marker measurements as well as pointers of potential detrimental effects [44]. Two ongoing trials, the Improved Reduction of Outcomes: Vytorian Efficacy International Trial (IMPROVE-IT), in which simvastatin plus ezetimibe is compared with simvastatin plus placebo, and the Study of Heart and Renal Protection (SHARP) trial, in which simvastatin plus ezetimibe is compared with placebo, will hopefully provide answers to these questions.

Low density lipoprotein subfractions

The LDL class comprises a heterogeneous population of particles [45]. LDL is heterogeneous with respect to lipid composition, charge, density, and particle size and shape. The sizes of LDL particles fall between the large triglyceride-enriched very low density lipoprotein (VLDL) particles and the dense and small protein-rich HDL. In addition, these small dense LDL particles may be more atherogenic than would be suspected by their concentration alone, because *in vitro* and cell culture studies suggest they may be more readily oxidized and glycated. Oxidized LDL delivers cholesterol to the atherosclerotic plaque in an unregulated way through uptake by the macrophage and is increased in diabetes [46].

Another aspect is the fatty acid composition of the LDL particle. Linoleic acid is the main polyunsaturated fatty acid in the LDL particle, and this is increased in diabetes. The reason for this may be because of the decreased activity of the insulin sensitive enzyme, 5α-desaturase. There is a strong correlation between linoleic acid in the LDL particle and propensity of the LDL particle to be oxidized. Uncontrolled diabetes results in increased free radical formation which leads to increased oxidation. The fact that the LDL particles are smaller and denser means that they carry relatively less cholesterol per particle. Estimation of the LDL cholesterol may therefore be misleading as there will be more LDL particles for any cholesterol concentration.

Large numbers of studies, including the Quebec Cardiovascular study [47], have confirmed the association of small dense LDL with CVD which reported that men with small dense LDL particles had an increased risk of CAD compared with men with normal-sized LDL particles, independent of LDL cholesterol, triglyceride and the total cholesterol:HDL cholesterol ratio; however, no prospective studies have specifically examined whether altering particle size profiles results in benefits on cardiovascular events although analysis of the Veterans Affairs High Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) study does suggest some role for this mechanism [48].

Even with effective LDL cholesterol treatment, the residual risk of further cardiovascular events remains high, emphasizing the importance of improving other abnormalities and other CVD risk factors commonly observed in these patients.

Triglycerides

The reason for the elevated triglycerides in diabetes is complex, however, because of this derangement, it has been suggested that diabetes should not be called mellitus but rather lipidus [49]. Defects in insulin action and hyperglycemia can lead to changes in plasma lipoproteins in patients with diabetes. Alternatively, especially in the case of T2DM, the obesity and insulin-resistant metabolic disarray that are at the root of this form of diabetes could, themselves, lead to lipid abnormalities exclusive of hyperglycemia [32]. This molecular interplay between lipid and carbohydrate metabolism has led to what might be termed a "lipocentric" view of the pathogenesis of insulin resistance and T2DM [50]. As fatty acids have such a central role in insulin sensitivity, obesity and T2DM, it follows that the major disturbance in lipoprotein metabolism in diabetes is found in the triglyceride-rich lipoproteins, stemming from abnormalities in chylomicron synthesis and clearance [51].

Triglycerides (also referred to as triacylglycerol) are formed from a single molecule of glycerol combines with three fatty acids and represent a heterogeneous group of molecules which most frequently are measured collectively, as a "family" of analytes [52]. Elevated serum triglyceride levels are associated with increased risk for atherosclerotic events [53,54]. As high serum triglyceride levels are associated with abnormal lipoprotein metabolism, as well as with other cardiovascular risk factors including obesity, insulin resistance, diabetes and low levels of HDL cholesterol, it becomes more difficult to distinguish between cause and effect and to establish hypertriglyceridemia as an independent cardiovascular risk factor. Some causes of hypertriglyceridemia have no apparent effect on atherosclerotic vascular disease, making it difficult to prove that elevated triglycerides are a risk factor [55]. Nevertheless, several meta-analyses have found that triglycerides are an independent risk factor for CHD [54,56,57].

The two main sources of plasma triglycerides are exogenous (i.e. from dietary fat) carried in chylomicrons and endogenous (from the liver) and carried in VLDL particles. In capillaries within fat and muscle tissue, these lipoproteins and chylomicrons are hydrolyzed by LPL into free fatty acids. LPL is activated by apolipoprotein C-II, cleaving the triglyceride core and releasing free fatty acids, which can be oxidized by muscle for energy or kept in adipose tissue for future use, and inhibited by the action of apolipoprotein C-III [58]. In routine clinical practice, hypertriglyceridemia is the most frequent lipoprotein abnormality found in uncontrolled diabetes. The mechanisms for these include increased production or absorption, or reduced catabolism (mainly because of decreased activity of LPL). Liver apolipoprotein B production (the major protein component of VLDL and LDL) is increased in T2DM. This is indirectly brought about by increased lipolysis which occurs in adipose tissue, a consequence of insulin resistance and/or insulin deficiency. The increased lipolysis results in increased fatty acid release from fat cells with increase in fatty acid transport to the liver. Studies in tissue cultures, animal experiments [59] and humans [60] suggest that fatty acids modulate liver apolipoprotein B secretion.

Microsomal triglyceride transfer protein (MTP) assembles the chylomicron in the intestine and the VLDL particle in the liver. MTP has been shown to be increased in the intestine of subjects with diabetes [61]. Cholesterol absorption also seems to be adversely influenced in subjects with diabetes. The Niemann–Pick C1-like 1 protein, which has a critical role in the absorption of cholesterol, is increased in people with diabetes. The ATP-binding cassette transporters ABC-G5 and ABC-G8 dimerize to form a functional complex necessary for efflux of dietary cholesterol and non-cholesterol sterols from the intestine and liver. These proteins have been shown to be reduced in diabetes in both liver and intestine. LPL is an insulin-dependent enzyme being responsible for the conversion of lipoprotein triglyceride into free fatty acids. It has several other activities relating to lipid and carbohydrate metabolism [62]. Both patients with T1DM and T2DM have reduced LPL activity which is further suppressed by adipose-derived cytokines such as tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) [32].

Statins form the mainstay of lipid management based on their efficacy in lowering LDL cholesterol, but their effects on components of the atherogenic dyslipidemia associated with T2DM are more modest, reducing triglycerides at most by 15–30% and raising HDL cholesterol typically by less than 10%. There is no clear consensus on the benefits of directly targeting hypertriglyceridemia [63]. As the interventions usually affect both triglycerides and HDL cholesterol, it also becomes more difficult to distinguish between the individual benefits.

Fibrates

The "fibrate" class of lipid-lowering drugs is useful for lowering elevated triglyceride or non-HDL cholesterol levels as these agents, which act on peroxisomal proliferator-activated receptor α (PPARα), increase lipoprotein lipase activity, reduce apolipoprotein C-III and may increase HDL cholesterol or decrease fibrinogen [64]. Despite this, clinical trials of these drugs have reported mixed results in general, and most early trials recruited only a few patients with diabetes [65,66].

The VA-HIT study evaluated the potential benefits of gemfibrozil in 2531 men with an acute MI. Patients with relatively low LDL cholesterol (<3.6 mmol/L) and low HDL cholesterol (<1.0 mmol/L) were recruited. A significant reduction in the primary endpoint (fatal and non-fatal MI) of 22% was achieved [67]. One-third of participants had T2DM. These outcomes were achieved despite relatively small changes in HDL cholesterol (8%) and no change in LDL cholesterol (0%). An exploration of the effect of gemfibrozil showed that the principal effect of the fibrate treatment was a 31% reduction in triglycerides which reflects changes in particle sizes, but was not related to event reduction [68]. A subgroup analysis of the subjects with diabetes showed a relative risk reduction of 32% compared to 18% in the non-diabetic group [69], however, the enthusiasm for fibrate use has been considerably dampened by results of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study [70]. This trial randomized 9795 subjects with T2DM to fenofibrate

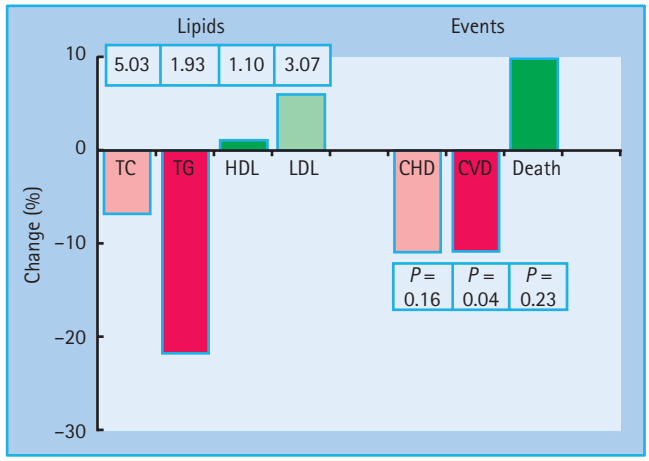

Figure 40.14 Reductions in mortality, coronary heart disease (CHD) and cardiovascular events with fenofibrate therapy in the FIELD study. HDL, high density lipoprotein; LDL, low density lipoprotein; TC, total cholesterol; TG, triglycerides. Reproduced from Keech *et al.* [70], with permission from Elsevier.

(200 mg/day) or placebo who were not on statin treatment at the beginning of the study, and participants in the trial were treated for 5 years. The study reported a non-significant 11% reduction in the primary endpoint of CHD although a significant reduction in total cardiovascular events was achieved with fenofibrate therapy ($P = 0.035$) (Figure 40.14). The study was confounded by asymmetrical statin drop-in with many more patients on placebo arm being initiated on statin therapy during the trial (17%) than those on the fenofibrate arm (8%) [65]. It is therefore difficult to compare fibrate trials as they seem to give heterogenous results depending on the compound used, and no fibrate trials have shown to reduce all cause mortality. Nevertheless, meta-analyses suggest they may reduce non-fatal MI [71]. It is hoped that the ACCORD trial, which randomized fenofibrate in addition to baseline 20–40 mg simvastatin, can provide more definitive answers.

Niacin

Nicotinic acid (niacin) is another potential drug to address the combination of hypertriglyceridemia and low HDL cholesterol. Because of its favorable effects on LDL cholesterol, it has been referred to as the "broad-spectrum" lipid drug [72]. Nicotinic acid was the first lipid-lowering agent to show a significant reduction in cardiovascular events, but not in mortality. The Coronary Drug Project randomized 3908 men with previous MI to either nicotinic acid or placebo [73]. Major CHD events, non-fatal MI and cerebrovascular events were reduced, but there was no effect on mortality; however, in the 15-year post-trial follow-up, nearly 9 years after termination of the trial, mortality from all causes was 11% lower in the nicotinic acid group [74]. Several long-term clinical studies with niacin have since demonstrated a reduction in CHD events and mortality when used in combination with other lipid-modifying drugs which include: colestipol (a bile acid sequestrant) [75], fibrate [76] and statins [77]. Unfortunately,

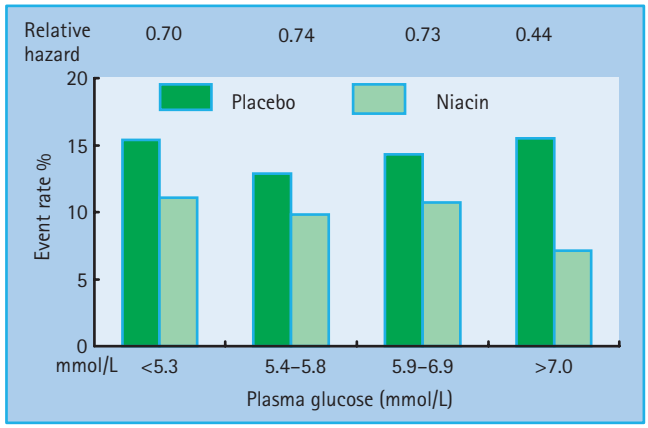

Figure 40.15 Reduction in coronary heart disease in patients with a fasting plasma glucose >7 mmol/L from a post hoc analysis of the Coronary Drug Project. Reproduced from Canner *et al.* [81], with permission from Excerpta Medica.

niacin has been hampered by its side effects, particularly flushing, although strategies exist to reduce this [78], and by hyperglycemia [79]. No long-term outcome trials with niacin in people with diabetes have been conducted. Furthermore, niacin adversely affects glycemic control. This effect is related to the dose of nicotinic acid. The study of the effect of extended release niacin on diabetic dyslipidemia found that, at week 16, whereas the HbA_{1c} did not change significantly in the 1 g group, in the 1.5 g group there was an increase from 7.2% (55 mmol/mol) to 7.5% (58 mmol/mol) [80]. Wider variations are seen in clinical practice [79]. Analysis of data from the Coronary Drug Project showed that regardless of how patients were grouped, niacin appeared as effective in lowering cardiovascular outcomes in patients with hyperglycemia as patients with normoglycemia (Figure 40.15) [81].

Guidelines are conflicting on the use of niacin in diabetes. The current position statement from the American Diabetes Association (ADA) suggests the use of nicotinic acid as an option in treating lipoprotein fractions other then LDL cholesterol [82]. It reports that only modest changes in glucose occur and that these are generally amenable to adjustment of diabetes therapy. A previous statement discouraged its routine use as do the recent National Institute for Health and Clinical Excellence (NICE) guidelines for management of diabetes in England and Wales [83]. Large outcome studies are currently underway. The Atherothrombosis Intervention in Metabolic syndrome with low HDL cholesterol/high triglyceride and Impact on Global Health outcomes (AIM-HIGH) hopes to report in 2011 [84]. The large Oxford-based outcome trial with extended release niacin/laropiprant (an inhibitor of prostaglandin receptor D1 which reduces the flushing), the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) [85], includes 28 000 patients with cardiovascular disease or at high risk of developing it, including a pre-specified subgroup of 6000 with diabetes, and is scheduled to report in 2013.

Other triglyceride-reducing agents

Hypoglycemic agents may also have an effect on triglyceride concentrations because of the peripheral actions of insulin on adipose and muscle or via their action on LPL. In poorly controlled T1DM and even ketoacidosis, hypertriglyceridemia and reduced HDL cholesterol is seen to occur, and this is most often corrected with insulin therapy. In T2DM, metformin [86], sulfonylureas [87] and acarbose [88] all show modest reductions in triglycerides which correlate with glycemic control [89,90]. In general, thiazolidinediones have better overall effects on lipids than sulfonylureas or insulin [91], but pioglitazone and rosiglitazone have distinctly different effects on the lipid profile [64,92]. Pioglitazone is associated with a reduction in triglycerides whereas rosiglitazone is associated with increased concentrations. Both medications raised LDL cholesterol, but the increase was significantly greater with rosiglitazone than pioglitazone. Pioglitazone did not significantly change apolipoprotein B levels but did reduce LDL particle concentration. Conversely, rosiglitazone increased both apolipoprotein B and LDL particle concentrations. Both medications increased HDL cholesterol, with pioglitazone having no effect on serum apolipoprotein AI levels while rosiglitazone was associated with a decrease in apolipoprotein AI levels. Differential effects on CVD outcomes in recent meta-analyses have recently been reported. Outcome data for rosiglitazone are awaited. In the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial, a prospective trial in patients with T2DM, no evidence for an increased cardiovascular event rate was found [93]. An outcome trial for pioglitazone, the PRO spective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE) study, which added pioglitazone to the current treatment in patients with T2DM, showed that treatment with pioglitazone was associated with reductions in major atherosclerotic events as defined in the main secondary endpoint [94]. The differential effects on lipid profiles may in part explain the differences these two drugs have on CVD outcomes as reported by recent meta-analyses (Figure 40.16) [95,96].

A number of other existing interventions reduce triglycerides secondary to their action in reducing weight [97]. Orlistat has been shown to prevent progression to diabetes in the XENical in the prevention of diabetes in obese subjects (XENDOS) study [98], and both sibutramine [99] and rimonabant [100,101] (prior to their suspension) showed benefits on lipids in patients with the metabolic syndrome and diabetes. Rimonabant had a non-significant benefit on coronary atherosclerosis as assessed by intravascular ultrasound in line with its lipid effects [102,103].

High density lipoprotein cholesterol

Analogous to LDL, the HDL class also comprises a heterogeneous population of particles. The inverse relationship between HDL cholesterol levels and atherosclerotic CVD provides the epidemiologic basis for the widely accepted hypothesis that HDL is atheroprotective [104,105]. Experimental studies, which include limited work on humans, have shown that HDL has several

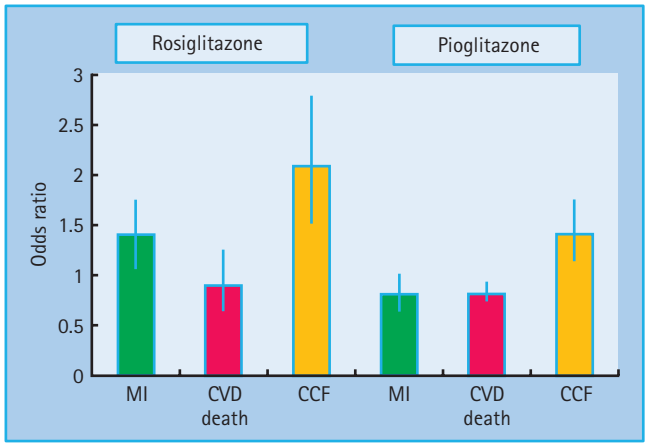

Figure 40.16 Effects of thiazolidinedione drugs on coronary heart disease (CHD) in trials using rosiglitazone and pioglitazone. CCF, congestive cardiac failure; CVD, cardiovascular disease; MI, myocardial infarction. Reproduced from Singh *et al. JAMA* 2007; **298**:1189, with permission from the American Medical Association.

distinct but potentially overlapping atheroprotective functions. These include the well-known reverse cholesterol transport [106] as well as reductions in oxidative stress and innate immune inflammation [107]. More HDL-associated proteins are involved in immune/inflammatory functions than in lipid transport and metabolism, suggesting the fundamental role for HDL in innate immunity [108]. There are several reasons that could account for the decrease in HDL cholesterol in diabetes [32]. CETP-mediated exchange of VLDL triglyceride for HDL cholesteryl esters is accelerated in the presence of hypertriglyceridemia [45]. The clinical laboratory measures the cholesterol component of HDL; substitution of triglyceride for cholesteryl ester in the core of the HDL particle therefore leads to a decrease in this measurement of HDL cholesterol. The triglyceride, but not cholesteryl ester, in HDL is a substrate for plasma lipases, especially hepatic lipase which converts HDL to a smaller particle being more rapidly cleared from the plasma. Precursors of advanced glycation end-products (AGEs) can also impair reverse cholesterol transport by HDL.

As opposed to LDL cholesterol lowering, therapies to intervene in order to raise HDL cholesterol have proven to be "not that simple." Some HDL therapies may reduce CVD without actually changing HDL cholesterol concentrations [109]. The Intravascular Ultrasound Study (IVUS) of the effects of 5 weekly infusions of a hyperfunctional apolipoprotein A-1 $(apoA\text{-}1)_{Milano}$ produced significant regression of coronary atherosclerosis after 3 months. In contrast, in the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) trial, which investigated the CETP inhibitor, torcetrapib, in 15 000 patients, HDL cholesterol increased by 72% and LDL cholesterol decreased by 25%, although this trial was terminated early as the treatment arm had an increase of major cardiovascular events by 25% and death from cardiovascular causes by 40%, possibly related to the hypertensive properties of this particular molecule [110].

Guidelines vary when it comes to treatment targets for HDL cholesterol, mostly because there is no evidence base for intervention at the moment [111]. The Joint British Societies Guidelines and NICE argue that there is no treatment target for HDL cholesterol as it is only modestly altered, and not independently of changes in other lipid variables in the clinical trials [5,83,112]. Furthermore, there are no drugs available yet that independently alter HDL cholesterol. The American Heart Association and the ADA suggest lowering triglycerides to below 1.7 mmol/L (150 mg/dL) and raising HDL to more than 1.15 mmol/L (40 mg/dL) [3,82,113]. In women, an HDL cholesterol goal of 0.3 mmol/L (10 mg/dL) higher than this should be considered.

Future drug developments and drug targets

Drugs that target the exogenous and or the endogenous pathways of cholesterol metabolism may prove to be useful in the future [114,115]. These include Niemann–Pick C1-like 1 protein inhibitors, new PPAR agents and MTP inhibitors. Interventions that regulate fatty acid synthesis may also prove to be beneficial. Stearoyl-coenzyme A desaturase 1 catalyzes the synthesis of monounsaturated fatty acids and has emerged as a key regulator of metabolism [116]. Recent studies in human and animal models have highlighted that modulation of stearoyl-coenzyme A desaturase 1 activity by dietary intervention or genetic manipulation strongly influences several facets of energy metabolism to affect susceptibility to obesity, insulin resistance, diabetes and hyperlipidemia. HDL mimetic therapies may also prove to be beneficial. Other CETP inhibitors are also still under investigation [117]. Although numerous drug classes have been devised, many, such as torcetrapib, have recently failed in late phase III trials even after showing good initial results on lipids in human and in animal models. Other drugs, such as rimonabant, have shown unfavorable side effect profiles which led to the suspension of marketing in the European Union. Given the importance of atherosclerosis as a cause of morbidity and mortality in diabetes, numerous therapeutic approaches are in development, and all will require systematic evaluation through endpoint clinical trials to validate their effects in animal models or on surrogate markers [103].

Conclusions

CVD is a very common complication of diabetes. Up to 80% of all people with diabetes will die from macrovascular complications. Lifestyle intervention is both effective and paramount to prevent and treat diabetes and its dyslipidemia. Statins have revolutionized preventive cardiovascular medicine and this has formed the foundation of therapeutic lipid intervention (Figure 40.17). The abnormalities in lipids and lipoproteins represent only one factor among several that are responsible for the increased risk in persons with diabetes (Table 40.5) and therefore multifactorial intervention is required, and this reduces events and mortality by 50% (Figure 40.18) [118,119].

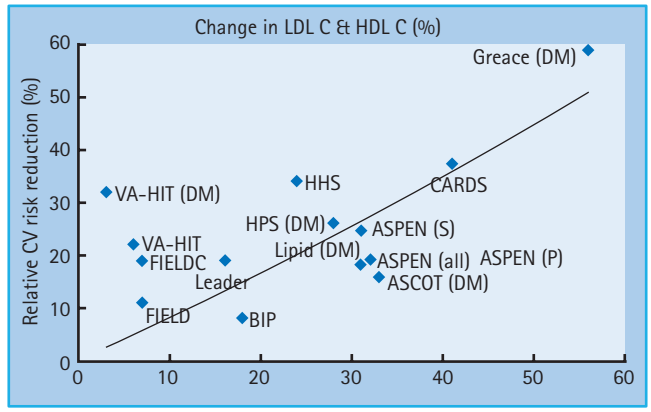

Figure 40.17 Comparative effects of different lipid lowering drugs on cardiovascular disease (CVD) in patients with diabetes. ASPEN, Atorvastatin Study for the Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; BIP, Bezafibrate Infarct Prevention; CARDS, Collaborative Atorvastatin Diabetes Study; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; FIELDc, FIELD study (corrected data); GREACE; Greek Evaluation of Atorvastatin in Coronary Events; HHS, Helsinki Heart Study; HPS, Heart Protection Study; LEADER, Lower Extremity Arterial Disease Event Reduction; LIPID, Lipid Intervention with Pravastatin in Ischaemic Disease; VA-HIT, Veterans Affairs High Density Lipoprotein Cholesterol Intervention Trial; DM, diabetes sub-group; P, primary prevention subgroup; S, secondary prevention subgroup; HDL C, high density lipoprotein cholesterol; LDL C, low density lipoprotein cholesterol. Reproduced from Wierzbicki AS. *Diab Vasc Dis Res* 2006; **3**:166–171, with permission from Medinews.

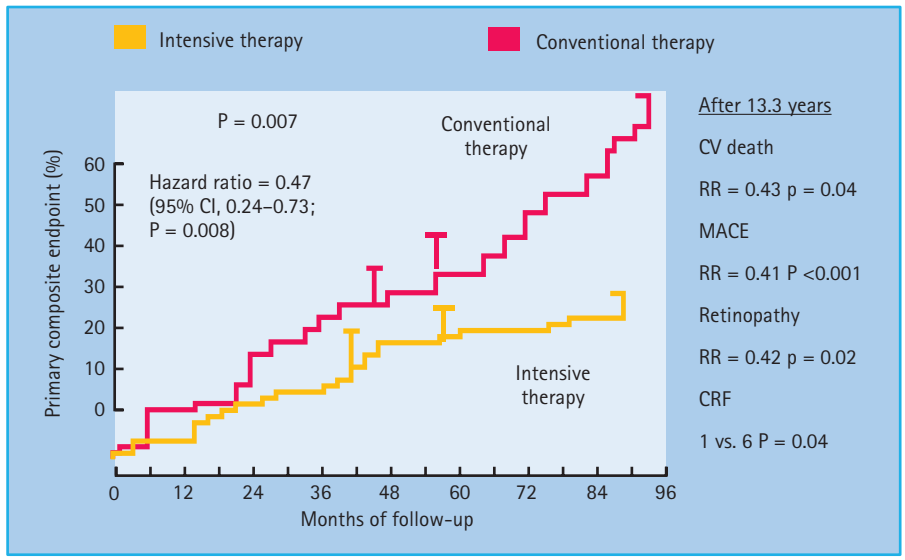

Figure 40.18 Effects of improved multiple risk factor intervention on mortality and cardiovascular events in diabetes. CABG, coronary artery bypass graft; CV, cardiovascular; MI, myocardial infarction; PAD, peripheral arterial disease; PC, percutaneous coronary intervention. Data from Gaede *et al. N Engl J Med* 2003; **348**:383–393 and Gaede *et al. N Engl J Med* 2008; **358**:580–591.

Table 40.5 Effects of different cardiovascular therapies on lipids and other cardiovascular risk factors and endpoint trial evidence of effects in prevention of diabetes and cardiovascular disease.

Drug/treatment group	Component of the cardiometabolic syndrome Change (%)					DM risk reduction (%)	CVD risk reduction (%)
	LDL decrease	HDL increase	TG decrease	SBP decrease	Glucose decrease		
Metformin	0–10	15	15	0–5	10	45–48	35
SU	0–5	0	0	3	0	?	20
TZD	–5 to 10	9	12	5	8	51–58	–10 to +43
Statin	20–55	0–15	15–25	0	0	0–14	20–55
Fibrate	0–10	2–16	15–24	0–8	0–6	0–23	10–34
Niacin	10–20	10–25	15–35	0	(+5)	?	22–31
Orlistat	0–5	+3	1	1	4	43	?
Sibutramine	0–5	+9	25	+4	4	?	?

CVD, cardiovascular disease; DM, diabetes mellitus; HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure; SU, sulfonylurea; TG, triglycerides; TZD, thiazolidinedione.

References

1 Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. *JAMA* 1979; **241**:2035–2038.

2 Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. *Diabetes Care* 1979; **2**:120–126.

3 Expert Panel on Detection EAToHBCIAATPI. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP). *JAMA* 2001; **285**:2486–2497.

4 Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, *et al.* Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Eur J Cardiovasc Prev Rehabil* 2007; **14**(Suppl 2):S1–113.

5 British Cardiac Society, British Hypertension Society, Diabetes UK, *et al.* JBS 2: the Joint British Societies' guidelines for prevention of cardiovascular disease in clinical practice. *Heart* 2005; **91**(Suppl 5):1–52.

6 Haffner SM, Lehto S, Ronnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998; **339**:229–234.

7 Malmberg K, Yusuf S, Gerstein HC, Brown J, Zhao F, Hunt D, *et al.* Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. *Circulation* 2000; **102**:1014–1019.

8 Howard BV, Best LG, Galloway JM, Howard WJ, Jones K, Lee ET, *et al.* Coronary heart disease risk equivalence in diabetes depends on concomitant risk factors. *Diabetes Care* 2006; **29**:391–397.

9 Evans JM, Wang J, Morris AD. Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction: cross sectional and cohort studies. *Br Med J* 2002; **324**:939–942.

10 Simons LA, Simons J. Diabetes and coronary heart disease. *N Engl J Med* 1998; **339**:1714–1715.

11 Krolewski AS, Kosinski EJ, Warram JH, Leland OS, Busick EJ, Asmal AC, *et al.* Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. *Am J Cardiol* 1987; **59**:750–755.

12 Jensen T, Borch-Johnsen K, Kofoed-Enevoldsen A, Deckert T. Coronary heart disease in young type 1 (insulin-dependent) diabetic patients with and without diabetic nephropathy: incidence and risk factors. *Diabetologia* 1987; **30**:144–148.

13 Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. All-cause mortality rates in patients with type 1 diabetes mellitus compared with a non-diabetic population from the UK general practice research database, 1992–1999. *Diabetologia* 2006; **49**:660–606.

14 Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med* 1984; **310**:356–360.

15 Kannel WB. Lipids, diabetes, and coronary heart disease: insights from the Framingham Study. *Am Heart J* 1985; **110**:1100–1107.

16 Stevens RJ, Kothari V, Adler AI, Stratton IM. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). *Clin Sci (Lond)* 2001; **101**:671–679.

17 Coleman RL, Stevens RJ, Retnakaran R, Holman RR. Framingham, SCORE, and DECODE risk equations do not provide reliable cardiovascular risk estimates in type 2 diabetes. *Diabetes Care* 2007; **30**:1292–1293.

18 Viljoen A. Cardiovascular risk estimation: making sense of the numbers. *Int J Clin Pract* 2008; **62**:1300–1303.

19 Reynolds TM, Twomey PJ, Wierzbicki AS. Concordance evaluation of coronary risk scores: implications for cardiovascular risk screening. *Curr Med Res Opin* 2004; **20**:811–818.

20 DECODE Study Group. Is fasting glucose sufficient to define diabetes? Epidemiological data from 20 European studies. European Diabetes Epidemiology Group. Diabetes epidemiology: collaborative analysis of diagnostic criteria in Europe. *Diabetologia* 1999; **42**:647–654.

21 Meigs JB, Nathan DM, Wilson PW, Cupples LA, Singer DE. Metabolic risk factors worsen continuously across the spectrum of nondiabetic glucose tolerance. The Framingham Offspring Study. *Ann Intern Med* 1998; **128**:524–533.

22 Levitan EB, Song Y, Ford ES, Liu S. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. *Arch Intern Med* 2004; **164**:2147–2155.

23 Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, *et al.* Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005; **353**:2643–2653.

24 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359**:1577–1589.

25 Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, *et al.* Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358**:2560–2572.

26 Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, *et al.* Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**:2545–2559.

27 Dluhy RG, McMahon GT. Intensive glycemic control in the ACCORD and ADVANCE trials. *N Engl J Med* 2008; **358**:2630–2633.

28 Cefalu WT. Glycemic targets and cardiovascular disease. *N Engl J Med* 2008; **358**:2633–2635.

29 Beauchamp MC, Michaud SE, Li L, Sartippour MR, Renier G. Advanced glycation end products potentiate the stimulatory effect of glucose on macrophage lipoprotein lipase expression. *J Lipid Res* 2004; **45**:1749–1757.

30 Lyons TJ, Jenkins AJ. Lipoprotein glycation and its metabolic consequences. *Curr Opin Lipidol* 1997; **8**:174–180.

31 Durrington PN. Diabetic dyslipidaemia. *Baillieres Best Pract Res Clin Endocrinol Metab* 1999; **13**:265–278.

32 Goldberg IJ. Diabetic dyslipidemia: causes and consequences. Clinical review 124. *J Clin Endocrinol Metab* 2001; **86**:965–971.

33 Turner RC, Millns H, Neil HA, *et al.* Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *Br Med J* 1998; **316**:823–828.

34 Scandinavian Simvastatin Survival Study (4S) Investigators. Randomised trial of cholesterol lowering in 4444 patients with coro-

nary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344**:1383–1389.
35 Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease: a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 1997; **20**:614–620.
36 Sacks FM, Tonkin AM, Shepherd J, Braunwald E, Cobbe S, Hawkins CM, *et al.* Effect of pravastatin on coronary disease events in subgroups defined by coronary risk factors: the Prospective Pravastatin Pooling Project. *Circulation* 2000; **102**:1893–1900.
37 Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, *et al.* Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; **364**:685–696.
38 MRC/BHF Heart Protection Study Investigators. 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.
39 Collins R, Armitage J, Parish S, Sleigh P, Peto R; 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.
40 Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN). *Diabetes Care* 2006; **29**:1478–1485.
41 Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, *et al.* Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005; **353**:238–248.
42 Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, *et al.* Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 2008; **371**:117–125.
43 Rossebo AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, *et al.* Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008; **359**:1343–1356.
44 Wierzbicki AS. Muddy waters: more stormy SEAS for ezetimibe. *Int J Clin Pract* 2008; **62**:1470–1473.
45 Austin MA. Triglyceride, small, dense low-density lipoprotein, and the atherogenic lipoprotein phenotype. *Curr Atheroscler Rep* 2000; **2**:200–207.
46 Scheffer PG, Teerlink T, Heine RJ. Clinical significance of the physicochemical properties of LDL in type 2 diabetes. *Diabetologia* 2005; **48**:808–816.
47 St-Pierre AC, Cantin B, Dagenais GR, St-Pierre AC, Cantin B, Dagenais GR, *et al.* Low-density lipoprotein subfractions and the long-term risk of ischemic heart disease in men: 13-year follow-up data from the Quebec Cardiovascular Study. *Arterioscler Thromb Vasc Biol* 2005; **25**:553–559.
48 Otvos JD, Collins D, Freedman DS, Shalauvova I, Schaefer EJ, McNamara JR, *et al.* Low-density lipoprotein and high-density lipoprotein particle subclasses predict coronary events and are favorably changed by gemfibrozil therapy in the Veterans Affairs High-Density Lipoprotein Intervention Trial. *Circulation* 2006; **113**:1556–1563.
49 Shafrir E, Raz I. Diabetes: mellitus or lipidus? *Diabetologia* 2003; **46**:433–440.
50 Savage DB, Petersen KF, Shulman GI. Disordered lipid metabolism and the pathogenesis of insulin resistance. *Physiol Rev* 2007; **87**:507–520.
51 Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 2006; **444**:840–846.
52 Thienpont LM, Van UK, De Leenheer AP. Reference measurement systems in clinical chemistry. *Clin Chim Acta* 2002; **323**:73–87.
53 McBride P. Triglycerides and risk for coronary artery disease. *Curr Atheroscler Rep* 2008; **10**:386–390.
54 Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, *et al.* Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation* 2007; **115**:450–458.
55 Austin MA, McKnight B, Edwards KL, Bradley CM, McNeely MJ, Psaty BM, *et al.* Cardiovascular disease mortality in familial forms of hypertriglyceridemia: a 20-year prospective study. *Circulation* 2000; **101**:2777–2782.
56 Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. *Am J Cardiol* 1998; **81**:7B–12B.
57 Assmann G, Schulte H, von EA. Hypertriglyceridemia and elevated lipoprotein(a) are risk factors for major coronary events in middle-aged men. *Am J Cardiol* 1996; **77**:1179–1184.
58 Grundy SM. Hypertriglyceridemia, atherogenic dyslipidemia, and the metabolic syndrome. *Am J Cardiol* 1998; **81**:18B–25B.
59 Taghibiglou C, Carpentier A, Van Iderstine SC, Chen B, Rudy D, Aiton A, *et al.* Mechanisms of hepatic very low density lipoprotein overproduction in insulin resistance: evidence for enhanced lipoprotein assembly, reduced intracellular ApoB degradation, and increased microsomal triglyceride transfer protein in a fructose-fed hamster model. *J Biol Chem* 2000; **275**:8416–8425.
60 Lewis GF, Uffelman KD, Szeto LW, Weller B, Steiner G. Interaction between free fatty acids and insulin in the acute control of very low density lipoprotein production in humans. *J Clin Invest* 1995; **95**:158–166.
61 Lally S, Tan CY, Owens D, Tomkin GH. Messenger RNA levels of genes involved in dysregulation of postprandial lipoproteins in type 2 diabetes: the role of Niemann–Pick C1-like 1, ATP-binding cassette, transporters G5 and G8, and of microsomal triglyceride transfer protein. *Diabetologia* 2006; **49**:1008–1016.
62 Mead JR, Irvine SA, Ramji DP. Lipoprotein lipase: structure, function, regulation, and role in disease. *J Mol Med* 2002; **80**:753–769.
63 Garg A, Simha V. Update on dyslipidemia. *J Clin Endocrinol Metab* 2007; **92**:1581–1589.
64 Rubenstrunk A, Hanf R, Hum DW, Fruchart JC, Staels B. Safety issues and prospects for future generations of PPAR modulators. *Biochim Biophys Acta* 2007; **1771**:1065–1081.
65 Wierzbicki AS. FIELDS of dreams, fields of tears: a perspective on the fibrate trials. *Int J Clin Pract* 2006; **60**:442–429.
66 Wierzbicki AS. Interpreting clinical trials of diabetic dyslipidaemia: new insights. *Diabetes Obes Metab* 2007; **11**:261–270.
67 Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, *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 Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999; **341**:410–418.

68 Robins SJ, Collins D, Wittes JT, Papademetriou V, Deedwania PC, Schaefer EJ, *et al.* Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. *JAMA* 2001; **285**:1585–1591.

69 Robins SJ, Rubins HB, Faas FH, Schaefer EJ, Elam MB, Anderson JW, *et al.* Insulin resistance and cardiovascular events with low HDL cholesterol: the Veterans Affairs HDL Intervention Trial (VA-HIT). *Diabetes Care* 2003; **26**:1513–1517.

70 Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, *et al.* Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005; **366**:1849–1861.

71 Saha SA, Kizhakepunnur LG, Bahekar A, Arora RR. The role of fibrates in the prevention of cardiovascular disease: a pooled meta-analysis of long-term randomized placebo-controlled clinical trials. *Am Heart J* 2007; **154**:943–953.

72 Carlson LA. Nicotinic acid: the broad-spectrum lipid drug – a 50th anniversary review. *J Intern Med* 2005; **258**:94–114.

73 Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA* 1975; **231**:360–381.

74 Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, *et al.* Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol* 1986; **8**:1245–1255.

75 Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L. Beneficial effects of combined colestipol–niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* 1987; **257**:3233–3240.

76 Carlson LA, Rosenhamer G. Reduction of mortality in the Stockholm Ischaemic Heart Disease Secondary Prevention Study by combined treatment with clofibrate and nicotinic acid. *Acta Med Scand* 1988; **223**:405–418.

77 Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, *et al.* Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001; **345**:1583–1592.

78 Oberwittler H, Baccara-Dinet M. Clinical evidence for use of acetyl salicylic acid in control of flushing related to nicotinic acid treatment. *Int J Clin Pract* 2006; **60**:707–715.

79 Vogt A, Kassner U, Hostalek U, Steinhagen-Thiessen E. Evaluation of the safety and tolerability of prolonged-release nicotinic acid in a usual care setting: the NAUTILUS study. *Curr Med Res Opin* 2006; **22**:417–425.

80 Grundy SM, Vega GL, McGovern ME, Tulloch BR, Kendall DM, Fitz-Patrick D, *et al.* Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. *Arch Intern Med* 2002; **162**: 1568–1576.

81 Canner PL, Furberg CD, Terrin ML, McGovern ME. Benefits of niacin by glycemic status in patients with healed myocardial infarction (from the Coronary Drug Project). *Am J Cardiol* 2005; **95**:254–257.

82 Standards of medical care in diabetes, 2008. *Diabetes Care* 2008; **31**(Suppl 1):S12–S54.

83 National Institute for Health and Clinical Excellence (NICE). *Type 2 Diabetes: The Management of Type 2 Diabetes (update)*. London: National Institute for Health and Clinical Excellence; 2008 Dec 5. Report No.: CG66.

84 National Heart LaBIN. Niacin plus statin to prevent vascular events: AIM-HIGH. ClinicalTrials gov, 2006. Available at: http://www.clinicaltrials.gov/ct/show/NCT00120289. Accessed July 18, 2006.

85 A randomized trial of the long-term clinical effects of raising HDL cholesterol with extended release niacin/laropiprant. Clinical Trials Gov, 2007. Available at: http://clinicaltrials.gov/ct2/show/NCT00461630. Accessed January 26, 2009.

86 Saenz A, Fernandez-Esteban I, Mataix A, Ausejo Segura M, Roqué i Figuls M, Moher D. Metformin monotherapy for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2005; **3**:CD002966.

87 Howard BV, Xiaoren P, Harper I, Foley JE, Cheung MC, Taskinen MR. Effect of sulfonylurea therapy on plasma lipids and high-density lipoprotein composition in non-insulin-dependent diabetes mellitus. *Am J Med* 1985; **79**:78–85.

88 Van de Laar FA, Lucassen PL, Akkermans RP, van de Lisdonk EH, Rutten GE, van Weel C. Alpha-glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis. *Diabetes Care* 2005; **28**:154–163.

89 Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, *et al.* Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med* 2007; **147**:386–399.

90 Huupponen RK, Viikari JS, Saarimaa H. Correlation of serum lipids with diabetes control in sulfonylurea-treated diabetic patients. *Diabetes Care* 1984; **7**:575–578.

91 Yki-Jarvinen H. Thiazolidinediones. *N Engl J Med* 2004; **351**: 1106–1118.

92 Deeg MA, Tan MH. Pioglitazone versus rosiglitazone: effects on lipids, lipoproteins, and apolipoproteins in head-to-head randomized clinical studies. *PPAR Res* 2008; **2008**:520465.

93 Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ; RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 2009; **373**:2125–2135.

94 Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, *et al.* Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005; **366**:1279–1289.

95 Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; **356**:2457–2471.

96 Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 2007; **298**:1180–1188.

97 Wierzbicki AS. Low HDL-cholesterol: common and under-treated, but which drug to use? *Int J Clin Pract* 2006; **60**:1149–1153.

98 Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004; **27**:155–161.

99 Fujioka K, Seaton TB, Rowe E, Jelinek CA, Raskin P, Lebovitz HE, *et al.* Weight loss with sibutramine improves glycaemic control and other metabolic parameters in obese patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2000; **2**:175–187.

100 Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF, RIO-Diabetes Study Group. Efficacy and tolerability of rimonabant in

overweight or obese patients with type 2 diabetes: a randomised controlled study. *Lancet* 2006; **368**:1660–1672.

101 Rosenstock J, Hollander P, Chevalier S, Iranmanesh A. SERENADE: the Study Evaluating Rimonabant Efficacy in Drug-naive Diabetic Patients: effects of monotherapy with rimonabant, the first selective CB1 receptor antagonist, on glycemic control, body weight, and lipid profile in drug-naive type 2 diabetes. *Diabetes Care* 2008; **31**:2169–2176.

102 Nissen SE, Nicholls SJ, Wolski K, Rodés-Cabau J, Cannon CP, Deanfield JE, *et al.* Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: the STRADIVARIUS randomized controlled trial. *JAMA* 2008; **299**:1547–1560.

103 Wierzbicki AS. Surrogate markers, atherosclerosis and cardiovascular disease prevention. *Int J Clin Pract* 2008; **62**:981–987.

104 Abbott RD, Wilson PW, Kannel WB, Castelli WP. High density lipoprotein cholesterol, total cholesterol screening, and myocardial infarction: the Framingham Study. *Arteriosclerosis* 1988; **8**: 207–211.

105 Boden WE. High-density lipoprotein cholesterol as an independent risk factor in cardiovascular disease: assessing the data from Framingham to the Veterans Affairs High-Density Lipoprotein Intervention Trial. *Am J Cardiol* 2000; **86**:19L–22L.

106 Cuchel M, Rader DJ. Macrophage reverse cholesterol transport: key to the regression of atherosclerosis? *Circulation* 2006; **113**:2548–2555.

107 Barter P. Effects of inflammation on high-density lipoproteins. *Arterioscler Thromb Vasc Biol* 2002; **22**:1062–1063.

108 Vaisar T, Pennathur S, Green PS, Gharib SA, Hoofnagle AN, Cheung MC, *et al.* Shotgun proteomics implicates protease inhibition and complement activation in the antiinflammatory properties of HDL. *J Clin Invest* 2007; **117**:746–756.

109 Nissen SE, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, Yasin M, *et al.* Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA* 2003; **290**:2292–2300.

110 Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, *et al.* Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007; **357**:2109–2122.

111 Sacks FM. The role of high-density lipoprotein (HDL) cholesterol in the prevention and treatment of coronary heart disease: expert group recommendations. *Am J Cardiol* 2002; **90**:139–143.

112 National Institute for Health and Clinical Excellence (NICE). *Lipid Modification*. London, UK: NICE, June 17, 2008. Report no. CG67.

113 Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, *et al.* Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; **110**:227–239.

114 Wierzbicki AS. Lipid-altering agents: the future. *Int J Clin Pract* 2004; **58**:1063–1072.

115 Viljoen A. New approaches in the diagnosis of atherosclerosis and treatment of cardiovascular disease. *Recent Pat Cardiovasc Drug Discov* 2008; **3**:84–91.

116 Flowers MT, Ntambi JM. Role of stearoyl-coenzyme A desaturase in regulating lipid metabolism. *Curr Opin Lipidol* 2008; **19**:248–256.

117 Krishna R, Anderson MS, Bergman AJ, Jin B, Fallon M, Cote J, *et al.* Effect of the cholesteryl ester transfer protein inhibitor, anacetrapib, on lipoproteins in patients with dyslipidaemia and on 24-h ambulatory blood pressure in healthy individuals: two double-blind, randomised placebo-controlled phase I studies. *Lancet* 2007; **370**:1907–1914.

118 Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; **348**:383–393.

119 Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008; **358**:580–591.