Cardiovascular Risk Factors

Hypertension

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

Dyslipidemia: Diabetes Lipid Therapies

Adie Viljoen1 & Anthony S. Wierzbicki2
1Department of Chemical Pathology, Lister Hospital, Stevenage, UK
2Guy’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 (bendrofluzide); 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.
**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>
<thead>
<tr>
<th>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].</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category</strong></td>
</tr>
<tr>
<td>WHO criteria for the general population*</td>
</tr>
<tr>
<td>Optimal</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>High normal</td>
</tr>
<tr>
<td>Grade 1 hypertension (mild)</td>
</tr>
<tr>
<td>Subgroup: borderline</td>
</tr>
<tr>
<td>Grade 2 hypertension (moderate)</td>
</tr>
<tr>
<td>Grade 3 hypertension (severe)</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
</tr>
<tr>
<td>Subgroup: borderline</td>
</tr>
<tr>
<td>Hypertension-related tissue damage (WHO criteria)</td>
</tr>
<tr>
<td>Grade I: none</td>
</tr>
<tr>
<td>Grade II: subclinical damage (e.g. retinopathy, proteinuria)</td>
</tr>
<tr>
<td>Grade III: clinical damage (e.g. heart failure, ischemia)</td>
</tr>
<tr>
<td>Degree of proteinuria</td>
</tr>
<tr>
<td>Microalbuminuria: 30–300 mg/24 hours (20–200 mg/min)</td>
</tr>
<tr>
<td>Macroalbuminuria: &gt;300 mg/24 hours (&gt;300 mg/min)</td>
</tr>
<tr>
<td>* Desirable blood pressure limits in the diabetic population are suggested in Figure 40.6.</td>
</tr>
</tbody>
</table>

**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,
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

---

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 40.1  The metabolic syndrome. HDL, high density lipoprotein.

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.

Figure 40.3  Various mechanisms have been proposed to explain how insulin or the hyperinsulinaemia that accompanies it could increase BP.
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).

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.
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.

- **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
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:HDLE 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 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 chlorothalidone (chlorothalidone), 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 β1- and β2-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-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-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 hyperglycaemia 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 β1-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].
**Part 8** Macrovascular Complications in Diabetes

![Image of a graph showing the progression of diabetic nephropathy with and without antihypertensive treatment.](image)

**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.

### 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, β₁-selective blockers and CCAs are equally valid alternatives with regard to BP reduction.

### α₁-Adrenoceptor antagonists

α₁-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].
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].

α1-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 β1-blocker plus CCA; or β1-blocker plus α1-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 nonsignificant 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 T2DM.

---

**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].**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Relative risk with tight control (mean, 95% confidence intervals)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes-related deaths</td>
<td>0.76 (0.62–0.92)</td>
<td>0.19</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.82 (0.63–1.08)</td>
<td>0.17</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.79 (0.59–1.07)</td>
<td>0.13</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.56 (0.35–0.89)</td>
<td>0.013</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>0.51 (0.19–1.37)</td>
<td>0.17</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>0.63 (0.44–0.89)</td>
<td>0.009</td>
</tr>
</tbody>
</table>
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].
Reproduced from UKPDS [4,91], with permission.

References

Part 8 Macrovascular Complications in Diabetes


Dyslipidemia: Diabetes Lipid Therapies

Adie Viljoen1 and Anthony S. Wierzbicki2

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 (CHD) risk equivalent [3–5]. This concept is based originally on a Finnish cohort [6], which showed comparable risk of CHD between subjects with type 2 diabetes detected by screening. Int J Obes Relat Metab Disord 2000; 24(Suppl 3):S6–11.


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 three-fold increase in risk of developing CHD and stroke in later life. This risk is notably increased in those developing diabetic neph-
Cardiovascular Risk Factors

Chapter 40

673

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 10000 participants, could not show a significant beneficial effect on CVD outcome when targeting near-normal glucose levels in T2DM as determined by a HbA₁c <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 (HbA1c <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 18686 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
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 glycerated. 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 (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 heterogeneous 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,
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 glycemic control. This effect is related to the dose of nicotinic acid. The study of the effect of extended release niacin on glycemic control. This effect is related to the dose of nicotinic acid. The study of the effect of extended release niacin on glycemic control. This effect is related to the dose of nicotinic acid. The study of the effect of extended release niacin on glycemic control. This effect is related to the dose of nicotinic acid.

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 than 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, hypertriglycerideremia 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 PROspектив 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
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-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.


**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.

<table>
<thead>
<tr>
<th>Drug/treatment group</th>
<th>Component of the cardiometabolic syndrome Change (%)</th>
<th>DM risk reduction (%)</th>
<th>CVD risk reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDL decrease</td>
<td>HDL increase</td>
<td>TG decrease</td>
</tr>
<tr>
<td>Metformin</td>
<td>0–10</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>SU</td>
<td>0–5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TZD</td>
<td>−5 to 10</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Statin</td>
<td>20–55</td>
<td>0–15</td>
<td>15–25</td>
</tr>
<tr>
<td>Fibrate</td>
<td>0–10</td>
<td>2–16</td>
<td>15–24</td>
</tr>
<tr>
<td>Orlistat</td>
<td>0–5</td>
<td>+3</td>
<td>1</td>
</tr>
<tr>
<td>Sibutramine</td>
<td>0–5</td>
<td>+9</td>
<td>25</td>
</tr>
</tbody>
</table>

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


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


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.


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.


