CLINICAL REVIEW
THE PREVENTION AND EARLY DETECTION OF THE VASCULAR COMPLICATIONS OF DIABETES

Long (web) version

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Short running title: Complications of diabetes
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SMM acts as guarantor. Both authors contributed equally to the preparation and writing of this review.

Abstract
Diabetes is a common cause of reduced life expectancy and premature morbidity, primarily from vascular causes. It is also the commonest cause of blindness in the working age groups, renal failure and non-traumatic lower limb amputation. The risk of these complications can be reduced by good glucose and blood pressure control, prescription of statins and aspirin and lifestyle changes aimed at reducing cardiovascular risk. If complications do develop, they must be diagnosed early: prompt intervention may prevent, delay or minimize the impact of end-stage disease. Every individual with diabetes should be included in an annual screening programme designed to detect complications early and to assess cardiovascular risk factors. Intervention can be tightened to slow progression of complications and specific protective measures begun, such as prescription of inhibitors of the renin-angiotensin system in nephropathy and provision of special footwear in peripheral neuropathy. More aggressive management significantly reduces the impact of both cardiovascular and specific complications of diabetes.
INTRODUCTION
The life expectancy of an individual with diabetes is reduced by 5 - 10 years. Premature cardiovascular disease (CVD) is the commonest cause of morbidity and mortality but the microvascular complications specific to diabetes (Table 1) also contribute. Diabetes is the commonest reason for requiring renal replacement therapy (RRT) worldwide, the commonest cause of blindness in the working age groups and the commonest cause of non-traumatic amputation. Yet the vast majority of these devastating events could be prevented, delayed or their impact minimized. This would require translation of our current knowledge about the effectiveness of structured diabetes care and the aggressive management of risk factors into good clinical care world-wide.

The main focus of this review will be on the prevention, early detection and initial management of the vascular complications of diabetes in adults.

SOURCES AND SELECTION CRITERIA
The following sources of information were used to compile this review:

• PubMed search using diabetic complications, retinopathy, diabetic nephropathy, microalbuminuria, diabetic foot, peripheral neuropathy, cardiovascular disease, ischaemic heart disease, peripheral arterial disease, cerebrovascular disease. Preference was given to original articles published within the last 3 years and to review articles in high-impact journals
• Search of the Cochrane Database of Systematic Reviews; Database of Abstracts and Reviews of Effectiveness, Cochrane Central Registry of Controlled Trials.
• Personal archives of references

WHY ARE THE COMPLICATIONS OF DIABETES IMPORTANT?
Complications are common and the cost to the individual and society is enormous. The onset of complications reduces quality of life, particularly if both microvascular and macrovascular disease is present (1). The CODE-2 study gathered data from 7000 individuals with Type 2 diabetes from 8 European studies (2). 72 % had at least one complication and 24 % had both microvascular and macrovascular complications. In one 6 month period, 13 % were admitted to hospital, with a mean length of stay of 23 days. The estimated average yearly cost per patient was Euro 2834. 55 % of this sum was attributed to costs of hospitalization, with only 7 % attributable to costs of insulin and oral glucose-lowering agents (3).

WHO DEVELOPS COMPLICATIONS?
The risk of developing complications is not uniform for everyone with diabetes. For the microvascular complications, nephropathy in particular, there is a strong genetic influence. Although a number of candidate genes have a small influence, no major gene effect has yet been identified. Duration of diabetes, glycaemic control and hypertension are the strongest risk factors for microvascular disease, and smoking, blood pressure, lipids and albuminuria for macrovascular disease (Table 2).
PATHOPHYSIOLOGY
Both the metabolic and haemodynamic abnormalities of diabetes contribute to the development of complications. Hyperglycaemia is a key feature for microvascular disease. Capillary endothelial cells, mesangial cells in the kidney, and neurons and Schwann cells in peripheral nerves cannot down-regulate their uptake of glucose in diabetes. Thus intracellular hyperglycaemia stimulates biochemical and haemodynamic pathways, illustrated in Figure 1. Signalling molecules and growth factors are activated, with consequent tissue damage (4). Genetic factors may influence any of these pathways. External “accelerators” such as hypertension, smoking and dyslipidaemia, also contribute. In macrovascular disease, genetic and accelerator factors, plus abnormalities in coagulation, all contribute.

Recently, a unifying mechanism linking the activation of these biochemical pathways to one abnormality has been suggested: hyperglycaemia-induced overproduction of superoxide by the mitochondrial electron transport chain (5). The proposed mechanism is shown in Figure 2.

EPIDEMIOLOGY

Macrovascular Disease
The main cause of death in both type 1 and type 2 diabetes is cardiovascular disease. The excess mortality is seen in all age groups, is most pronounced in young people with type 1 diabetes and is exacerbated by material deprivation (6). Pre-menopausal women loose their protection, mortality rates from ischaemic heart disease being similar in men and women with diabetes under 40 years of age (7,8; Figure 3). The risk of stroke is also increased 3-4 times that of the non-diabetic person (9). In type 2 diabetes, the risk of myocardial infarction and stroke are increased 2-5 times.

In diabetes, macrovascular disease tends to be diffuse, more distal and to be multivessel (Table 3). After an acute myocardial infarction, complications, especially heart failure, are common, and in-hospital and 6 month mortality are double that of the non-diabetic person. Although initial reperfusion results after thrombolysis are similar to those of non-diabetic individuals, reocclusion and reinfarction rates are higher. Restenosis rates after angioplasty are also higher, but the use of drug-eluting stents may reduce restenosis rates. Five year survival rates after coronary artery bypass graft or angioplasty are lower than for non-diabetic individuals.

Retinopathy
The World Health Organisation (WHO) estimates that diabetic retinopathy is the cause of blindness in approximately 5% of blind individuals globally (10). In several countries, the proportion of individuals registered blind or partially sighted due to diabetes has risen significantly between 1990’s and 2000, particularly in those aged >65 years (11,12). In the UK, the percentage has almost doubled. Older data suggests that almost all individuals develop some retinopathy after long duration diabetes, with perhaps 40-50% developing sight-threatening changes. However, in some centres the cumulative incidence of sight-threatening retinopathy is falling in both Type 1 (13,14) and Type 2 diabetes (15). Retinopathy is commoner in Blacks and Hispanics compared to Whites (16,17). In Type 2 diabetes, retinopathy is present in about one third of individuals at diagnosis, a reflection of the delay between onset of diabetes and diagnosis (18). The classification of retinopathy is shown in Table 4.
Nephropathy
Diabetic nephropathy is characterized by gradually increasing amounts of albumin in the urine, from normal albumin excretion to microalbuminuria, proteinuria and then declining renal function. About 50% of individuals with diabetes develop microalbuminuria at some point. Approximately one third of these will progress to proteinuria, one third will remain microalbuminuric and one third revert to normal albumin excretion (19; Figure 4). Microalbuminuria and proteinuria are commoner in the ethnic minorities (16,20). Once proteinuria is present, progression to end stage renal disease (ESRD) is inevitable. There is some evidence from select centres that the incidence of proteinuria in Type 1 diabetes has declined recently (13). In the UK, approximately 20% of individuals commencing RRT have diabetes (21). In the US, the figure has steadily increased over the last 15 years and now has plateaued at around 45%, a figure only surpassed by Malaysia at 53% (22). The numbers of patients with Type 1 diabetes beginning RRT have remained relatively constant, the increase primarily occurring in those with Type 2 diabetes (22). Data from the European Renal Association-European Dialysis and Transplant Association Registry suggests an 11.9% annual increase in patients with Type 2 diabetes beginning RRT, with the numbers of patients with Type 1 diabetes remaining relatively constant (23; Figure 5).

Neuropathy
The different forms of neuropathy are shown in Table 5. The life-time risk of any chronic peripheral neuropathy is 30-50% (24), with 10-20% developing severe symptoms (25,26). Neuropathy is present in ~10% of Type 2 diabetic patients at diagnosis. Peripheral neuropathy contributes to foot ulceration, which occurs in 2% of the diabetic population per annum, and lower limb amputation, occurring in 0.5% per annum (27). Erectile dysfunction occurs in up to 50% of men aged >50 years, compared to 15-20% of men without diabetes. The underlying pathogenesis is multifactorial, with neuropathy, vascular disease and psychological problems all contributing. The other neuropathies are rare but have a major impact on the individual’s quality of life and life-expectancy.

ASSOCIATION OF MICROVASCULAR COMPLICATIONS WITH MACROVASCULAR DISEASE
There is a very strong association of microvascular complications with CVD. The presence of any of the microvascular complications increases the likelihood of premature death from CVD (28-32). Some of this association is explained by shared classical and novel risk factors of CVD, such as C-reactive protein (CRP) and other markers of inflammation and endothelial or microvascular dysfunction (33-38; Figure 6). Many of these factors also cluster in non-diabetic, first degree family relatives of diabetic individuals with microalbuminuria or proteinuria. CVD risk is also higher in these family members, suggesting a familial or genetic process governing the development of both the CVD and microvascular pathology (39-41).

PREVENTION OF COMPLICATIONS (Table 6)
Glucose Control
The Diabetes Control and Complications Trial (DCCT) in Type 1 diabetes (42) and the UK Prospective Diabetes Study (UKPDS) in Type 2 diabetes (43) both
demonstrated that the better the glycaemic control, the lower the risk of microvascular complications. There is no threshold of HbA1c below which benefit is not gained (44,45). Provided the same level of HbA1c is achieved, the benefits are similar regardless of mode of treatment – insulin injections or continuous subcutaneous insulin infusion in Type 1 and metformin, sulphonylurea or insulin in Type 2 diabetes. In the randomized DCCT, there was a separation of almost 2 % in HbA1c in favour of the intensively managed group during the study. After 1 year of open follow-up, HbA1c was similar in those previously randomized to conventional and intensive management and levels remained similar for a further 7 years. However, after 4-8 years of open follow-up, the prevalence of microalbuminuria, proteinuria, retinopathy and neuropathy remained significantly lower in the group previously allocated to intensive therapy (46-48; Fig 7). Thus a period of good glycaemic control appears to reduce the risk of complications for much longer than the actual duration of the tight control, so-called “metabolic memory”.

The relationship of glucose control to the development of CVD is less strong: there was no significant reduction in macrovascular events in the intention to treat analysis of the UKPDS (43). However, in the epidemiological analysis, there was a 14 % reduction in the risk of myocardial infarction per 1 % reduction in HbA1c, compared with 37 % reduction for any microvascular event (45). The long-term follow-up of the DCCT has also demonstrated long-term benefits on the risk of cardiovascular disease, the risk of a CVD event being reduced by 42 % in the intensively managed group (49; Figure 8).

Blood Pressure

Almost all of the work on blood pressure and primary prevention of complications relates to Type 2 diabetes. In the UKPDS blood pressure arm, tight blood pressure control (144/82 vs 154/87 mmHg) reduced the incidence of any microvascular event by 37 % (50). A reduction in systolic BP of 10 mmHg was associated with a 13 % reduction in risk of any microvascular event and of 11 % for myocardial infarction (51). Several large, randomised controlled trials have demonstrated significant reductions in cardiovascular events with tight blood pressure control (52,53). The relative risk reduction is at least as great in the diabetic as in the non-diabetic population. Since the absolute risk of vascular disease is greater in diabetes, the absolute benefits of blood pressure reduction are greater.

The choice of initial antihypertensive agent is less important than actually reducing blood pressure. There is no blood pressure level below which benefit is not gained (51), the most important message being “the lower the better”. New guidelines now recommend targets of 130/80 mmHg (54), although in most trials, the mean achieved BP has been around 140/75 mmHg. Such levels are extremely difficult to reach in many individuals, requiring 3 or more antihypertensive agents in addition to life-style change. It is important to use once daily agents with good 24 h cover, and to consider combination tablets to aid compliance.

An exception to the above may be in preventing nephropathy. A Cochrane review suggests that angiotensin converting enzyme inhibitors (ACEI) are of greater benefit than other classes of agents in preventing microalbuminuria (55). A recent meta-analysis which did not support this conclusion has been heavily criticized on many counts (56). In the large, randomized, controlled BENEDICT study of normoalbuminuric, hypertensive type 2 diabetic patients, those randomized to receive an ACEI alone or with a calcium channel blocker (CCB) were almost half as likely to
develop microalbuminuria as those receiving a CCB agent alone or placebo (57). A similar trial using an angiotensin receptor blocker (ARB) is in progress (58) and a trial looking at the primary and secondary prevention effects of ARB-administration on retinopathy in Type 1 diabetes has also started (59).

**Lipids**

The characteristic lipid abnormalities in Type 2 diabetes are small, dense, highly atherogenic LDL-cholesterol particles, low HDL-cholesterol and high triglycerides. In the Heart Protection Study (HPS; 60) and Collaborative Atorvastatin Diabetes Study (CARDS; 61), the risk of a major CVD event was reduced by 37% individuals with Type 2 diabetes without clinically apparent CVD. The relative risk reduction is as great in the diabetic as the non-diabetic population, so that the absolute benefit is greater (62). Thus all individuals with diabetes aged >40 years should be prescribed statin therapy, even if they do not have overt CVD (54). Target levels of total cholesterol <4.5 and LDL-cholesterol <2.5 mmol/l have been suggested. Younger individuals have a very high life-time risk of CVD, even though their 10-year risk is relatively low, but there is no trial evidence. One approach is to offer statin therapy to those at particularly high risk (Table 6). Statins should be avoided in women from pre-conception to the end of breast feeding.

The place of fibrates is unclear. In the recent large, randomized controlled FIELD trial of fenofibrate in Type 2 diabetes, the risk of primary outcome coronary events was not reduced (63). However, despite the lack of robust evidence, addition of a fibrate to statin therapy should be considered if triglycerides remain >2.3 mmol/l, once LDL-cholesterol and blood glucose control are optimal (54).

None of the statin trials have explored benefits on prevention of microvascular complications. However, the DIAS (64) and FIELD studies (63) have demonstrated a significant reduction in the risk of progression from normal albumin excretion to microalbuminuria in type 2 diabetes with fenofibrate. The FIELD study also demonstrated a significant reduction in the need for laser treatment for retinopathy (63).

**Smoking**

In view of the high CVD risk of people with diabetes, stopping smoking is essential. Although the links of smoking to microvascular complications are weaker, stopping smoking is also likely to be of benefit.

**Aspirin**

Although there are no studies of primary prevention of CVD in diabetes, low-dose aspirin therapy is usually recommended, even in the absence of overt CVD.

**EARLY DETECTION AND SCREENING FOR COMPLICATIONS**

If despite intensive risk factor management from diagnosis, complications do develop, then they must be diagnosed early – prompt intervention may prevent or delay the emergence of end-stage disease such as blindness or the need for RRT or amputation. A systematic, structured screening programme, run annually is most cost-effective when done as a “one stop” package.

**Macrovascular Disease**
Screening for macrovascular disease rests primarily on symptoms of angina or claudication, with a low threshold for investigation. Although silent myocardial ischaemia is commoner in individuals with diabetes, routine exercise tolerance test or stress echocardiography are not yet recommended. A 12-lead resting electrocardiogram (ECG) has low sensitivity and specificity, although provides a useful baseline.

**Retinopathy**
Screening for retinopathy should include measurement of corrected visual acuity and assessment for retinopathy. Retinal photography, usually through dilated pupils and performed and interpreted by appropriately trained health care professionals, is the preferred method. Examination by an ophthalmic specialist is an acceptable alternative. Direct ophthalmoscopy through dilated pupils, performed by a trained individual, has low sensitivity and specificity and should only be used if no other option is available. Whatever method is chosen, it must have acceptable sensitivity and specificity, there must be an on-going quality assurance programme in place and if based on photography, the number of ungradeable images must be low (65).

Screening of individuals can easily be performed in the community using static or “mobile” cameras. The retinal images are read on site or by graders at a distant centre, using telemedicine and web-based technology (66,67). Population-based screening programmes do reduce the incidence of blindness due to diabetes (68) and also the proportion of patients referred to ophthalmology (69).

**Nephropathy**
Screening for nephropathy includes annual measurement of urine albumin and serum creatinine (Figure 9). The day-to-day variability in albumin excretion is around 40%. Thus multiple measures are needed if the initial screening test is positive. It is more important to look for trends in albumin excretion than to place weight on one particular value. An increasing albumin:creatinine ratio identifies individuals at very high risk of developing proteinuria, as well as CVD risk. Serum creatinine is a poor reflection of glomerular filtration. An estimated glomerular filtration rate (eGFR) should be calculated using the 4-variable equation derived from the Modification of Diet in Renal Disease study (70,71). Laboratories in the UK will now do this automatically and web-based calculators are readily available. The agreed classification of renal disease based on this eGFR is given in Table 7.

**Neuropathy and Peripheral Arterial Disease**
The aim is to identify individuals whose feet which are at high risk of ulceration or of gangrene. The four classical risk factors for the development of diabetic foot problems are deformity, neuropathy, ischaemia and infection. The tasks to be done are illustrated in Table 8 (www.NICE.org.uk/CG010NICEguideline). Additional tests of temperature and reflexes can be incorporated if wished and used to calculate the Neuropathy Disability Score (72). Enquiry should be made about erectile function. Tests of autonomic function are generally not performed routinely.

**MANAGING EARLY COMPLICATIONS**
**General**
Tightened glucose (42, 43) and blood pressure control (50) reduce the risk of progression of background diabetic retinopathy to sight-threatening disease and the
progression of neuropathy. The effect of glucose control on progression of nephropathy is less certain, but blood pressure control is extremely important.

**Cardiovascular Disease**
The most important factor is to have a low referral rate for investigation of symptoms which might reflect vascular disease, particularly ischaemic heart disease. The absolute benefits from statin therapy in secondary prevention of vascular disease are greater in the diabetic person (62).

**Retinopathy**
The FIELD study suggests that fenofibrate reduces the risk of progression (63), although fibrates are not recommended routinely yet. More frequent retinal examination may be required, with referral to Ophthalmology when sight-threatening disease is apparent (Table 10).

**Nephropathy**
Control of intra-renal and systemic blood pressure are of prime importance once there is microalbuminuria, proteinuria or reduced eGFR. All patients should be prescribed a long-acting, once daily ACEI or ARB, titrated up to the maximum recommended or tolerated dose to reduce intraglomerular pressure (73-76). Thereafter, tight control of systemic blood pressure should be achieved, using additional antihypertensive agents as required. Guidelines recommend a lower target of 125/75 mmHg for proteinuric patients or patients with eGFR <60 ml/min/1.73 m², although this is not evidence-based. Tight blood pressure control should slow the rate of decline of eGFR from 10-12 ml/min/year untreated to <5 ml/min/year. Antihypertensive therapy should also be intensified to prevent further increases in urine albumin excretion and if possible to reduce the levels.

The renin-angiotensin system is not completely blocked by ACEI, and individuals who “escape” may be at higher risk of progression. Several studies have examined the effects of combining ACEI therapy with an ARB (77, 78), or of the addition of an aldosterone antagonist (79). Although additional benefits on urine albumin excretion and blood pressure were demonstrated, the studies have all been fairly short term and relatively small.

Indications for referral to nephrology are given in Table 10

**Neuropathy and Peripheral Arterial Disease**
For individuals with foot disease, the most important aspects are support and education in good foot care, prophylactic foot care and provision of special footwear. Such an approach can reduce amputation rates by 30-50 % (80, 81). Early referral of those with ulcers or who have had ulcers previously to a specialist multidisciplinary team is essential ([www.NICE.org.uk/CGO10NICEguideline](http://www.NICE.org.uk/CGO10NICEguideline)).

Appropriate support and counseling should be available for men with erectile dysfunction. Investigations to exclude another cause (prolactin, FSH/LH, testosterone and SHGB) may be necessary. If treatment is requested, the oral phosphodiesterase type 5 inhibitors are less effective (approximately 60 %) in diabetic men. Alternatives include sublingual apomorphine, intra-utheral or intra-cavernosal drugs, vacuum devices or penile prostheses.
The Importance of Multifactorial Care
The Steno 2 study was a small randomised controlled trial of individuals with type 2 diabetes, microalbuminuria and hypertension (82). It demonstrated the importance of a structured, protocol-driven, multifactorial approach to managing the microvascular and macrovascular complications of diabetes (Steno 2). The intensively managed group received life-style advice, aspirin and ACEI therapy, with tighter targets for glucose, blood pressure and lipids in a specialist setting. The conventionally managed group received usual structured care in a primary care setting. Over an 8 year period, the risks of progression of microvascular and macrovascular disease were reduced by 40-60 % (Table 11).

COST-EFFECTIVENESS
Several analyses, based on different health care systems and different populations, all suggest that improving glycaemic control is cost-effective (83-85). One estimate suggests a saving of 35 billion (direct costs only) or 50 billion (including indirect costs) US dollars over 10 years, 4 % of the total annual US health care costs (83). The use of an ACEI or ARB in diabetes generally (86) and specifically in diabetic nephropathy (87, 88) is also cost-effective. Systematic eye screening for sight threatening retinopathy is also cost-effective (89).

HOW WELL ARE WE DOING?
Audits of intermediary outcomes such as HbA1c, blood pressure and blood lipid levels invariably demonstrate that targets are not being reached in the majority of individuals with diabetes, in all parts of the world (90, 91). Many patients are not prescribed aspirin, statins or ACE inhibitors when they are clearly indicated (91). Screening programmes for retinopathy and nephropathy are patchy, even in developed countries (92, 93), and non-existent in poorer countries. In the UK, the uptake for retinal screening was 57.3 % in 2005 (www.yhpho.uk). Patients find it difficult to comply with life-style advice, attendance for screening and with medication (94, 95). There is evidence that those who have most difficulty complying have poorer outcomes (96, 97).

HOW CAN WE IMPROVE?
Prevention of the complications of diabetes and/or minimization of their impact requires change across many fronts. Under the auspices of the Austrian Presidency, the European Union has developed a plan of the actions needed to be taken at a National level to develop diabetes care (www.diabetesconference.at/documents). The Finnish experience of doing so is described at www.diabetes.fi/english/programme.

The most successful interventions include many components of care contained within the Chronic Care Model (98, 99), as described recently for foot care (100):

- **Organisation of care**
  Recognition at national and political level that this is a priority; setting defined targets; evidence-based policies; incentives to deliver.

- **Clinical information systems**
  Registers of patients, stratified into risk categories; performance feedback for health care professionals and people with diabetes for quality assurance and development; prompts and reminders for patient and professionals

- **Clinical decision support**
  Evidence-based guidelines; referral pathways; training; electronic support if possible
• **Care delivery**  
Planned visits for screening and management; protocol-driven care; multidisciplinary team, including “expert patients”; urgent and emergency access pathways

• **Self-management support**  
Collaborative relationship, centered on patient’s priorities; involve patient in decision-making and target-setting

There are already many individual examples of novel ways of improving outcomes, such as nurse (101) or pharmacist led clinics (102), disease management programmes (103, 104), motivating and informing patients (105). In UK, the primary care Quality Outcomes Framework “payment by results” scheme has resulted in a large number of practices reaching the specified targets (www.icservices.nhs.uk). Overall, practices attained 93.2 % of the total available points for diabetes, a reflection of high level of process recording. As the quality targets for HbA1cs, lipids and blood pressure are tightened, it is likely that significant benefit will accrue.

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**OTHER SOURCES OF INFORMATION**

Diabetes UK  [www.diabetes.org.uk](http://www.diabetes.org.uk)

American Diabetes Association  [www.diabetes.org](http://www.diabetes.org)

International Diabetes Federation  [www.idf.org](http://www.idf.org)

EU-Austrian Conference on Prevention of Type 2 diabetes  [www.diabetesconference.at/documents](http://www.diabetesconference.at/documents)


Table 1
The long-term vascular complications of diabetes

<table>
<thead>
<tr>
<th>Microvascular</th>
<th>Macrovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Peripheral arterial disease</td>
</tr>
<tr>
<td>Risk Factors and Markers for the Development of Complications of Diabetes</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Non-modifiable</strong></td>
<td>Microvascular</td>
</tr>
<tr>
<td>• Genetic – susceptible or protective</td>
<td>++</td>
</tr>
<tr>
<td>• Ethnicity</td>
<td>+</td>
</tr>
<tr>
<td>• Duration of diabetes</td>
<td>++</td>
</tr>
</tbody>
</table>

| **Modifiable/Potentially Modifiable** |
|--------------------------------------|-------------------|-------------------|
| • Glycaemic control                  | ++                | +                  |
| • Blood pressure                     | ++                | ++                |
| • Blood lipids                       | +                 | ++                |
| • Smoking                            | +                 | ++                |
| • BMI or waist:hip ratio             | +                 | +                  |
| • Other microvascular complications  | +                 | +                  |
| • Cardiovascular complications       | +                 | +                  |
| • Social deprivation                | +                 | +                  |

<table>
<thead>
<tr>
<th><strong>Novel Risk Markers</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Markers of inflammation (eg C-reactive protein (CRP))</td>
</tr>
<tr>
<td>• Markers of endothelial dysfunction (eg von Willebrand factor)</td>
</tr>
</tbody>
</table>
Table 3

**Macrovascular Disease in Diabetes**

Main cause of death in both Type 1 and Type 2 diabetes
Excess mortality in all age groups, especially the young
Pre-menopausal women lose their protection
Diffuse, distal, multivessel disease
Re-occlusion/re-infarction rate higher after thrombolysis
Restenosis rates higher after angioplasty, although drug-eluting stenting may help
Five year survival after CABG lower than non-diabetic
## Table 4

**Grading of diabetic retinopathy**

<table>
<thead>
<tr>
<th>None</th>
<th>Normal retina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>Microaneurysms</td>
</tr>
<tr>
<td></td>
<td>Retinal haemorrhages</td>
</tr>
<tr>
<td></td>
<td>Any exudates</td>
</tr>
<tr>
<td>Preproliferative</td>
<td>Venous beading</td>
</tr>
<tr>
<td></td>
<td>Venous loop or reduplication</td>
</tr>
<tr>
<td></td>
<td>Intraretinal microvascular retinal abnormality (IRMA)</td>
</tr>
<tr>
<td></td>
<td>Multiple deep, round haemorrhages</td>
</tr>
<tr>
<td></td>
<td>Cotton wool spots</td>
</tr>
<tr>
<td>Proliferative</td>
<td>New vessels on the disc</td>
</tr>
<tr>
<td></td>
<td>New vessels elsewhere</td>
</tr>
<tr>
<td></td>
<td>Preretinal or vitreous haemorrhage</td>
</tr>
<tr>
<td></td>
<td>Preretinal fibrosis +/- fibrous retinal detachment</td>
</tr>
<tr>
<td>Maculopathy</td>
<td>Exudate within one disc diameter of the fovea</td>
</tr>
<tr>
<td></td>
<td>Circinate or group of exudates within macula</td>
</tr>
<tr>
<td></td>
<td>Retinal thickening within one disc diameter of the fovea</td>
</tr>
<tr>
<td></td>
<td>Any microaneurysm or haemorrhage within one disc diameter of fovea</td>
</tr>
</tbody>
</table>
Table 5

Neuropathies in Diabetes

Peripheral neuropathies
- Distal symmetric sensori-motor
- Femoral neuropathy (amyotrophy)
- Mononeuropathies – ocular, truncal
- Pressure palsies – median, ulnar, lateral popliteal

Autonomic neuropathy
- Postural hypotension
- Bladder dysfunction
- Gastric paresis
- Constipation/diarrhea
- Gustatory sweating
- Erectile dysfunction
<table>
<thead>
<tr>
<th>Prevention of Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose control</td>
</tr>
<tr>
<td>the lower the HbA1c the better (avoiding undue hypoglycaemia)</td>
</tr>
<tr>
<td>HbA1c &lt;7.0 % if on insulin; &lt;6.5 % if not on insulin</td>
</tr>
<tr>
<td>Blood pressure</td>
</tr>
<tr>
<td>the lower the blood pressure the better (avoiding symptomatic hypotension)</td>
</tr>
<tr>
<td>&lt;130/80 mmHg</td>
</tr>
<tr>
<td>(&lt;125/75 mmHg if proteinuria)</td>
</tr>
<tr>
<td>eGFR &lt;60 ml/min/1.73 m² or CVD</td>
</tr>
<tr>
<td>Lipids</td>
</tr>
<tr>
<td>Statin if aged &gt;40 years</td>
</tr>
<tr>
<td>Statin if aged &lt;40 years and microvascular complications, hypertension, metabolic syndrome or strong family history of CVD</td>
</tr>
<tr>
<td>Total cholesterol &lt;4.5 mmol/l</td>
</tr>
<tr>
<td>LDL-cholesterol &lt;2.5 mmol/l</td>
</tr>
<tr>
<td>Fibrate if triglycerides &gt;2.3 mmol/l with good LDL-cholesterol</td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>If aged &gt;40 years</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Stop</td>
</tr>
<tr>
<td>Lifestyle</td>
</tr>
<tr>
<td>Weight loss, exercise, healthy eating</td>
</tr>
</tbody>
</table>
Table 7

**Classification of Chronic Kidney Disease**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>normal GFR; GFR &gt;90 ml/min/1.73 m² with other evidence of kidney disease*</td>
</tr>
<tr>
<td>2</td>
<td>mild impairment; GFR 60-90 ml/min/1.73 m² with other evidence of kidney disease*</td>
</tr>
<tr>
<td>3</td>
<td>moderate impairment; GFR 30-59 ml/min/1.73 m²</td>
</tr>
<tr>
<td>4</td>
<td>severe impairment; GFR 15-29 ml/min/1.73 m²</td>
</tr>
<tr>
<td>5</td>
<td>established renal failure; GFR &lt;15 ml/min/1.73 m² or on dialysis</td>
</tr>
</tbody>
</table>

* other evidence of kidney disease may be: microalbuminuria, persistent proteinuria, persistent haematuria after exclusion of all other causes, structural abnormalities of the kidney demonstrated on ultrasound, or biopsy-proven glomerular nephritis
Table 8
Screening for Peripheral Neuropathy and Peripheral Arterial Disease

- Enquire about symptoms of peripheral neuropathy and peripheral vascular disease
- Ask about previous foot ulceration or amputation
- Ask about physical or visual difficulty in self-management of foot care
- Inspect feet for evidence of deformity, neuropathy, ischaemia, infection
- Detect neuropathy by 10-g monofilament or 128-Hz tuning fork or biothesiometer. Non-traumatic pin-prick
- Assess arterial circulation- dorsalis pedis and posterior tibial foot pulses; Doppler ankle: brachial pressure ratio if available
<table>
<thead>
<tr>
<th>Problem</th>
<th>Seen by Ophthalmologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden loss of vision</td>
<td>same day</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>same day</td>
</tr>
<tr>
<td>New vessel formation</td>
<td>within two weeks</td>
</tr>
<tr>
<td>Vitreous or preretinal haemorrhage</td>
<td>within two weeks</td>
</tr>
<tr>
<td>Rubeosis iridis</td>
<td>within two weeks</td>
</tr>
<tr>
<td>Hard exudates within 1 disc diameter of fovea</td>
<td>within 12 weeks</td>
</tr>
<tr>
<td>Clinically significant macular oedema</td>
<td>within 12 weeks</td>
</tr>
<tr>
<td>Unexplained retinal findings</td>
<td>within 12 weeks</td>
</tr>
<tr>
<td>Severe non-proliferative disease</td>
<td>within 12 weeks</td>
</tr>
</tbody>
</table>

Adapted from The National Screening Programme for Diabetic Retinopathy Workbook, version 3. [www.nscretinopathy.org.uk](http://www.nscretinopathy.org.uk)
Table 10

Diabetic Nephropathy: When to Referral to Nephrology

- eGFR <45 ml/min/1.73 m² (earlier if possible) or serum creatinine >150 µmol/l
- fall in eGFR >20 % per year
- nephrotic syndrome
- doubt about the diagnosis
- uncontrolled blood pressure
- Hb <10 g/dl after exclusion of other causes
- Abnormalities in bone chemistry
Table 11

The benefits of multifactorial intervention: the Steno-2 Study

<table>
<thead>
<tr>
<th>Complication</th>
<th>Hazard Ratio (95 % Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>0.47 (0.24-0.73)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>0.39 (0.17-0.87)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>0.42 (0.21-0.86)</td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
<td>0.37 (0.18-0.79)</td>
</tr>
</tbody>
</table>
FIGURE LEGENDS
(Note: The figures are in the accompanying Microsoft Power Point module)

Figure 1
Schematic illustration of the metabolic pathways in the development of vascular complications of diabetes
TGF-β: transforming growth factor β; CTGF: connective tissue growth factor; GH: growth hormone; VEGF: vascular endothelial growth factor; DAG-PKC: diacylglycerol (DAG)-protein kinase C (PKC); MAPK: mitogen activated protein kinase (MAPK); NFκB: nuclear factor kappa B. Adapted from reference 4.

Figure 2
The unifying hypothesis for the development of microvascular complications.
ROS: reactive oxygen species; PARP: poly (ADP-ribose) polymerase; GAPDH glyceraldehydes 3-phosphate dehydrogenase; DAG-PKC: diacylglycerol (DAG)-protein kinase C (PKC).

Figure 3
Cardiovascular disease (CVD) morbidity rates in 23,000 individuals with diabetes diagnosed aged <30 years and in the general population, by attained age and gender, 1972-1999.

Reprinted from reference 7 with permission

Figure 4
Development of nephropathy
Increasing urine albumin excretion, from normal to microalbuminuria to proteinuria, is accompanied by rising blood pressure and cardiovascular risk. The life-time risk of microalbuminuria is around 50%. One third of these patients will progress to proteinuria and eventually end-stage renal disease (ESRD).

Figure 5
Trends in incidence of renal replacement therapy (RRT) in the management of Type 1 (A) and Type 2 (B) diabetes in 10 European Renal registries, by gender and age. The numbers on the right hand side indicate the incidence per million age and gender.
related population for each group for the year 2000. Reproduced from reference 23 with permission.

**Figure 6**  
Risk factors which might contribute to the close association of microvascular and macrovascular disease in diabetes  
TG: triglycerides  
HDL: HDL-cholesterol

**Figure 7**  
The prevalence of microalbuminuria, proteinuria, high serum creatinine, hypertension and neuropathy after 8 years of open follow-up of patients who completed the Diabetes Control and Complications Trial (DCCT). The prevalence of progression of retinopathy, proliferative retinopathy and laser treatment are at 4 years.  
Open bars: patients previously randomized to intensive therapy during the DCCT.  
Closed bars: patients previously randomized to conventional therapy during the DCCT.  
Data derived from references 46-48.

**Figure 8**  
Cumulative incidence of the first of any of the predefined cardiovascular disease outcomes (Panel A). As compared with conventional treatment, intensive treatment reduced the risk of any predefined cardiovascular disease outcome by 42 percent (95 percent confidence interval, 9 to 63 percent; P=0.02) (Panel A). Reproduced from reference 9 with permission.

**Figure 9**  
Screening for diabetic nephropathy
REFERENCES


65. National Screening Committee. Diabetic Retinopathy Screening Workbook: guidance on setting up a systematic programme. www.nscretinopathy.org.uk


