

# Global Guideline for Type 2 Diabetes

## Chapter 12: Cardiovascular risk protection

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# Cardiovascular risk protection

Cardiovascular risk protection through blood glucose control, blood pressure control, and lifestyle interventions is dealt with elsewhere in this guideline (see *Glucose control*, *Blood pressure control*, *Lifestyle management*). This section deals with cardiovascular risk assessment, lipid modifying therapy, and anti-platelet therapy.

## Recommendations

### ■ Standard care

CV1 Assess cardiovascular risk at diagnosis and at least annually thereafter:

- current or previous cardiovascular disease (CVD)
- age and BMI (abdominal adiposity)
- conventional cardiovascular (CV) risk factors including smoking and serum lipids, and family history of premature CVD
- other features of the metabolic syndrome and renal damage (including low HDL cholesterol, high triglycerides, raised albumin excretion rate)
- atrial fibrillation (for stroke).

Do not use risk equations developed for non-diabetic populations. The UKPDS risk engine may be used for assessment and communication of risk.

CV2 Ensure optimal management through lifestyle measures (see *Lifestyle management*), and measures directed at good blood glucose and blood pressure control (see *Glucose control*, *Blood pressure control*).

CV3 Arrange smoking cessation advice in smokers contemplative of reducing or stopping tobacco consumption.

CV4 Provide aspirin 75-100 mg daily (unless aspirin intolerant or blood pressure uncontrolled) in people with evidence of CVD or at high risk.

CV5 Provide active management of the blood lipid profile:

- a statin at standard dose for all >40 yr old (or all with declared CVD)
- a statin at standard dose for all >20 yr old with microalbuminuria or assessed as being at particularly high risk
- in addition to statin, fenofibrate where serum triglycerides are >2.3 mmol/l (>200 mg/dl), once LDL cholesterol is as optimally controlled as possible
- consideration of other lipid-lowering drugs (ezetimibe, sustained release nicotinic acid, concentrated omega 3 fatty acids) in those failing to reach lipid-lowering targets or intolerant of conventional drugs.

Reassess at all routine clinical contacts to review achievement of lipid targets: LDL cholesterol <2.5 mmol/l (<95 mg/dl), triglyceride <2.3 mmol/l (<200 mg/dl), and HDL cholesterol >1.0 mmol/l (>39 mg/dl).

CV6 Refer early for further investigation and consideration of revascularization those with problematic or symptomatic peripheral arterial disease, those with problems from coronary artery disease, and those with evidence of carotid disease.

### ■ Comprehensive care

CV<sub>c</sub>1 Assessment will be as for *Standard care*, but with more aggressive investigation of asymptomatic peripheral arterial disease, coronary artery disease, and carotid disease. Lipid profiles may be investigated more extensively to give better direct assessments of LDL cholesterol and apolipoproteins. A specialist lipidologist may be consulted.

CV<sub>c</sub>2 Interventions will be as for *Standard care* but with aggressive lipid lowering for all, using multiple therapies and more expensive/efficacious statins except where LDL cholesterol, triglycerides and HDL cholesterol are all within target ranges.

CV<sub>c</sub>3 Antiplatelet agents to consider might include clopidogrel substituted for aspirin, in particular for those with multiple CVD events/problems, peripheral arterial disease, or previous coronary bypass grafting.

CV<sub>c</sub>4 Renin-angiotensin system blockers are an option for added CV risk protection.

### ■ Minimal care

CV<sub>m</sub>1 Assessment will be as for *Standard care*, with lipid profile measures if available.

CV<sub>m</sub>2 Management will be as for *Standard care*, but using statins or fibrates only where these are available at reasonable cost from generics' manufacturers, and in particular for those with known CVD. Statins may be used even if the serum lipid profile cannot be measured.

CV<sub>m</sub>3 Revascularization procedures will generally not be available, but where possible those limited by symptoms should be so referred.

## Rationale

Cardiovascular disease is the major cause of mortality and morbidity in people with Type 2 diabetes. Indeed some studies have suggested a risk similar to that of people without diabetes but with declared CVD. While others 'merely' show markedly increased risk, some cohorts with particular risk factors have shown extreme risk. Assessment,

but more particularly aggressive management, of CV risk factors in Type 2 diabetes is then seen as a core part of care. Some of the risk relates to blood pressure control and blood glucose control and is addressed elsewhere in this guideline, as are the lifestyle interventions which generally benefit the whole spectrum of CV risk factors.

## Evidence-base

The epidemiological evidence that cardiovascular disease is the major cause of mortality in people with Type 2 diabetes is extensive, as is the evidence that the risk is considerably elevated above that of the background population, even where that population is itself prone to high levels of vascular disease. More controversy surrounds the extent of the increased risk. A much quoted paper by Haffner et al. [1] suggested that people with Type 2 diabetes have a CV risk equivalent to non-diabetic people with previous CVD, but this has not in general been supported by other data [2]. The evidence that people with Type 2 diabetes have an abnormal, atherogenic, lipid profile (high triglycerides, low HDL cholesterol, small dense LDL) is generally accepted, and leads all the major guidelines which have addressed the area to recommend assessment of a full serum lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol (derived), triglycerides) as a guide to therapy [3-7].

Since people with Type 2 diabetes may or may not have a high LDL cholesterol (as in the general population), and may have triglyceride/HDL levels anywhere from normal to highly abnormal, decision paths to therapy are uncertain and do vary between evidence-based recommendations. A further problem is assessment of risk. The HPS study (of simvastatin) recruited people with diabetes even if they had no history of cardiovascular risk, and the results showed strong benefit [8]. CARDS similarly studied people with diabetes who had no overt evidence of CVD, and showed marked benefit with atorvastatin [9]. These studies suggest statin treatment for all people with Type 2 diabetes without assessment of risk, if over 40 yr of age. This view is not universally accepted.

The situation is complicated by the difficulty of assessing CV risk in people with diabetes, due to a two-to-three-fold underestimation of risk from tables, charts and engines derived from the Framingham study. This led the NICE group to suggest risk estimation based on a lower threshold than used generally in the UK at that time [6], but the advent of the validated risk engine based on the UKPDS study does now allow CV risk to be appropriately calculated [10]. Nevertheless, since the calculation almost inevitably suggests high risk in people with other risk factors, the universal application of statins in the middle-aged and older groups may be justified. The Canadian guideline states that there is a strong evidence-base for considering nearly everyone with Type 2 diabetes as high risk [5]. However, little evidence is available on people with younger-onset Type 2 diabetes, or their CV risk, although this would seem likely to be high relative to their peers.

Cost-effectiveness of statins is not generally addressed by the evidence-based guidelines, but rather is assumed. Lately simvastatin prices have collapsed in many parts of the world with expiry of patents. This is likely to make them cost-effective in most parts of the world.

The guidelines also address the issue of management of serum triglyceride and HDL cholesterol levels, an area where the evidence-base is softer, but all conclude that management with fibrates is indicated if serum triglyceride levels are raised (triglycerides and HDL cholesterol being inversely correlated). However, there is no easy consensus on the levels at which fibrates should be introduced, or on how they should be introduced in combination with statins. The results of the FIELD trial may help to resolve this in late 2005.

While there are safety concerns with lipid-lowering drugs, and notably even rare life-threatening problems related to muscle necrosis, the drugs are life-saving to a degree many times exceeding the safety risk (with appropriate therapeutic cautions), even when fibrates (except gemfibrozil) are used in combination with statins in people with higher risk.

The evidence-base for other lipid-lowering drugs (extended-acting nicotinic acid, concentrated omega 3 fatty acids, ezetimibe) is weaker – indeed these are barely addressed by published evidence-based guidelines, except the Australian lipid control document [4]. These drugs are also expensive for the degree of lipid-lowering gained and, as noted in the Australian guideline, some may lead to minor deterioration of blood glucose control. It would seem, therefore, that their use should be reserved for uncontrolled hyperlipidaemia on the first-line agents, or intolerance of these.

The use of anti-platelet agents is also addressed by some of the major guidelines (most extensively by the Australian macrovascular prevention guideline and the NICE lipid-lowering guideline [3,6]), with a general recommendation of endorsement for the widespread use of low-dose aspirin, the most specific evidence coming from within the ETDRS and HOT studies [11,12], and the most complete review that of Eccles and colleagues [13]. The Canadian guideline [5] notes a more recent meta-analysis of anti-platelet therapy showing a significant  $22 \pm 2\%$  ( $\pm$ SE) reduction in vascular events among all high-risk patients in 195 trials but only a non-significant  $7 \pm 8\%$  reduction in people with diabetes (9 trials) [14]. Nevertheless, efficacy is accepted, although the risk of bleeding results in advice in the NICE [6] and SIGN guidelines [7] restricting use to people at calculated risk (which would, however, be most people with

Type 2 diabetes) and with some caution over uncontrolled hypertension. The use of clopidogrel (at least as effective but much more expensive), where considered, is only recommended for people with aspirin intolerance.

Most other aspects of CV risk protection, notably blood glucose and blood pressure control, physical activity, and body weight control, are addressed elsewhere in this and other guidelines. However, there is also an evidence-base for integrated multiple risk factor intervention in particularly high-risk people (with microalbuminuria), showing very powerful absolute and relative risk reductions [15]. Evidence on smoking and CVD is not generally addressed, the advice given simply being in line with general medical practice, based on consideration of evidence for the general population.

## Consideration

Cardiovascular risk protection for people with Type 2 diabetes is an area which is found to be of high need, but with good and often strong evidence of ability to meet that need. One obvious problem is the need to extrapolate evidence in some areas from groups of people who do not have diabetes, for example as regards aspirin therapy. However, because event rates are much higher in people with diabetes (particularly with regard to 'primary' prevention) the gains and cost-effectiveness are also potentially much better, so that the risks of extrapolation of evidence are relatively low. This is especially true because the processes of arterial damage in people with Type 2 diabetes are similar pathologically to those occurring in the general population, though usually present (as in the case of platelet abnormalities) to a more abnormal degree.

Accordingly, the recommendations are for very active management. Statins and aspirin use are given prominence, as best founded in evidence, but the associations of hypertriglyceridaemia and low HDL cholesterol with poor outcomes, together with the limited trial evidence, lead also to strong recommendations over use of fibrates. In these circumstances assessment of risk has a relatively minor role, but is found useful educationally, and clearly can only be done formally using a risk engine properly validated for cohorts of people with diabetes in continuing care.

## Implementation

The recommendations require access to measurement of a full lipid profile and supporting biochemistry, and to aspirin and statins and fibrate drugs as a minimum. Structured annual assessment and record-keeping should be instituted.

## Evaluation

Evaluation is by achieved lipid levels, especially LDL cholesterol and triglycerides, and numbers of people treated (and in particular with elevated levels or existing cardiovascular disease) with statins, fibrates, and aspirin. In general, cardiovascular outcome rates are difficult to assess except in very large populations.

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