ABCD position statement on lipid modifying drug therapy in diabetes

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ABSTRACT

Cardiovascular disease (CVD) prevention in diabetes is a major therapeutic issue. There are currently several UK based published guidelines for the management of cardiovascular risk in diabetes. Treatment thresholds and targets for the use of lipid modifying drugs vary according to which guideline is consulted. In the light of the variations between guidelines, ABCD endorses an individual 'tailored' approach, underpinned by clinical and economic pragmatism. Assessment should include the presence of CVD and other risk factors as well as management of conditions which may alter the lipid profile.

Compelling reasons to use statins in adults with diabetes include: clinically manifest CVD; high or marked elevation of LDL (often from a defined genetic cause); treated hypertension, or those with persistent proteinuria (microalbuminuria or proteinuria) or reduced filtration function (eGFR <60 ml/min); and include the majority of diabetes patients above 50 years of age without additional CVD risk factors. Due to limited trial data assessing lipid lowering and clinical outcome in the 30–50 year age group, a 'tailored' approach to statin use rather than a 'statin for all' should be applied to those with type 1 diabetes. Statin therapy for younger type 2 diabetes (children and those aged up to 40) also needs further clarification and should currently be restricted to those at highest CVD risk.

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KEY WORDS

lipids; cardiovascular risk; statins; type 1 diabetes; type 2 diabetes

Background

Cardiovascular disease in diabetes is a major therapeutic issue. Elevations in total (and LDL) cholesterol and serum triglycerides, and reduced HDL cholesterol are established predictors of increased risk. Both the epidemiology and intervention trials assessing modification of these lipid parameters have been the basis of treatment guidelines, although the interpretation of the data appears to differ in the current UK based recommendations.

Potential competing treatment paradigms

Two separate treatment paradigms have emerged from the recent guidelines for the use of statin therapy in patients with diabetes: (i) a 'statin-for-all' paradigm which supports the role of statin therapy regardless of the lipid level (and perhaps regardless of cost), and (ii) a 'lipid target' paradigm which uses lipid (total or LDL cholesterol) concentrations, often incorporated into risk assessments to guide treatment and dose adjustments, in order to achieve lipid targets. Importantly, the different guidelines have included different treatment thresholds and targets.

Current guidelines

There are currently several UK based published guidelines for the management of cardiovascular risk in diabetes. Recommendations for the use of lipid modifying drugs with regard to treatment thresholds and targets vary according to which guideline is consulted.

- Current practice in primary care is based on the Quality and Outcomes Framework (QOF) targets which only consider level of total cholesterol (above 5mmol/L) for treatment and make no evaluation of cardiovascular disease (CVD) risk or other lipid parameters.
- National Institute for Health and Clinical Excellence (NICE) guidance on the management of type 2 diabetes[1] recommends CVD risk assessment using risk prediction charts and statin treatment thresholds of 5.0mmol/L for total cholesterol or 3.0mmol/L for LDL cholesterol. This has recently been reinforced in the Department of Health statement,[2] although this is at variance with the more recent NICE guidance on statins[3] where the 20% 10-year CVD risk treatment recommendation would identify patients with type 2 diabetes and cholesterol levels below 5.0mmol/L.
- By contrast, guidance from the Joint British Societies (JBS-2) recommends that CVD risk in all adult diabetes is high enough to justify universal use of statin therapy with a treatment target of total cholesterol 4.0mmol/L (and LDL of 2.0mmol/L). The diabetic groups included were those over 40 years of age with type 1 and 2 diabetes, and 18–39 year-olds with type 1 diabetes with severe retinopathy (not defined) or nephropathy (established proteinuria or microalbuminuria).[4] The International Diabetes Federation has extended this to 'standard dose statins for all with type 2 diabetes aged more than 20 with microalbuminuria or assessed at being at particularly high risk'.[5]

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Statin use in diabetes

In the light of the above variations between the guidelines, ABCD endorses an individual 'tailored' approach, underpinned by the evidence base as well as clinical and economic pragmatism.

Compelling reasons to use statins in adults with diabetes

- Clinically manifest cardiovascular disease (e.g. angina, myocardial infarction, revascularisation procedures, peripheral vascular disease, and cerebrovascular disease including transient cerebral ischaemia).
- High or marked elevation of LDL (e.g. >5.0mmol/L in defined genetic causes such as concomitant familial hypercholesterolaemia or familial combined hyperlipidaemia).
- Treated hypertension, or those with persistent proteinuria (microalbuminuria or proteinuria) or reduced filtration function (estimated glomerular filtration rate [eGFR] <60ml/min).
- The majority of diabetes patients above 50 years of age without additional CVD risk factors.

Clinical scenarios where consensus is lacking for statin use in diabetes

- Current smokers, regardless of age.
- Obesity (BMI >30).
- Metabolic syndrome (especially given varying classification).
- Any degree of diabetic retinopathy.
- Type 1 diabetes, aged less than 50 years without other CVD risk factors.

Whereas the definition of the metabolic syndrome is inconsistent, there is increasing evidence that central obesity and dyslipidaemia predict CVD independent of established risk factors, and that statin use in this group may achieve greater relative risk reduction.[6–8]

Reasons to withhold statin therapy in diabetes

- Females of childbearing age/pregnancy or breast feeding.
- New diagnosis of type 1 diabetes aged <40 years.
- Younger age (<40 years) in the absence of diabetes complications.
- Statin allergy.
- Confirmed statin-associated adverse reaction or co-administration of other therapies where there is potential for drug interaction.
- Co-existent diagnosed muscular disease with elevated serum muscle enzymes.

Factors to consider before statin initiation

Genetic factors

- Risk of CVD is partly attributable to the degree of LDL elevation which often has a distinct genetic basis. Common genetic conditions do not occur with any greater frequency in diabetes groups, but adults with co-existent polygenic (prevalence about 1:200) or familial monogenic hypercholesterolaemia (prevalence 1:500 in the heterozygous form) clearly do require statin therapy.
- A marked elevation in both cholesterol and triglyceride may be a feature of familial combined hyperlipidaemia (prevalence 1:250) where either a statin or fibrate would be drug of choice initially, although combination therapy is often indicated.
- Type 3 or remnant hyperlipidaemia (prevalence 1:10 000) is often manifest by diabetes or hypothyroidism and is best treated initially with fibrate therapy.

Metabolic/drug factors

- Secondary and modifiable causes of a raised cholesterol include thiazide diuretics at standard therapeutic dose and untreated hypothyroidism. Identification and correction could in some cases achieve desirable lipid targets.
- Beta-blockers are no longer recommended for initial antihypertensive drug choice,[4] but have a clear role in the treatment and secondary prevention of coronary heart disease (CHD). They should be avoided in cases of marked hypertriglyceridaemia with previous pancreatitis to reduce the enhanced risk of future episodes.[9]

Liver function tests

- The clinical scenario of non-alcoholic steato-hepatitis may be prevalent in over 10% of obese subjects with type 2 diabetes.[10] There is no current evidence base for the most appropriate hypolipidaemic drug selection in this area.
- Several drugs that modify lipid metabolism have licensing literature indicating avoidance when there is 'hepatic impairment' (glitazones), 'persistently abnormal liver function tests' (statins), or 'severe hepatic impairment' (fibrates). In particular, the licensing regulations state that statins should be discontinued if serum transaminases rise to and persist at three-times the upper limit of the reference range. The recent NICE guidance on secondary prevention of myocardial infarction recommended pre-statin measurement of liver function, but that statins should not routinely be excluded even if transaminases initially exceeded three-times the upper limit of the reference range.[11]
- A more detailed investigation of hepatic disease may involve liver ultrasound, plus liver biopsy in some cases. There would also be the need to assess for haemochromatosis and hepatitis C, both of which are associated with diabetes and hepatic dysfunction.
- In many cases with moderate disturbance of liver function, ABCD agrees broadly with the NICE secondary prevention guidance[11] that there may still be the need to utilise statins (and also fibrates and pioglitazone). In such situations monitoring of liver function is advised, with withdrawal of therapy if there is a greater than two-fold doubling from baseline levels of liver enzymes.
- There are now studies reporting that steatosis may respond beneficially to agents such as statins and glitazones in glucose intolerant subjects,[12] and thus improvements in liver enzyme activity may be more often noted than deterioration.

Dietary factors

- Diet 'responders' are occasionally seen, where total and LDL cholesterol levels may fall by more than 10%, and rarely may achieve lipid targets.
- Reducing saturated fat or trans fatty acid content of the diet may, in some cases, reduce plasma LDL by 5–20%. Trans fatty acids which are produced by catalytic hydrogenation of polyunsaturated fats result in solidification of fats, which is used by the food industry in the production of margarines, biscuits and peanut

butter. These fats have an LDL and triglyceride elevating effect as well as an effect in reducing HDL.
• The addition of monounsaturated (e.g. olive oil) and polyunsaturated fats (of the naturally occurring cis-configuration) modestly reduce total and LDL cholesterol levels.
• Weight loss often has a greater effect on triglyceride lowering than cholesterol lowering.
• Plant sterols (phytosterols) and stanols inhibit the absorption of cholesterol from the gut. The esterification of sterol and stanols permits incorporation into foods such as margarine spreads and yoghurts without altering taste or texture of the food substance. Sterol products may reduce LDL cholesterol by up to 10–15%. There is a small additive LDL lowering effect when used in combination with statin drugs.

Practical considerations in prescribing statins in diabetes

1. Dose of statin

The major statin-based outcome trials involving individuals with diabetes have used fixed doses of statins, e.g. simvastatin (20–80mg) and pravastatin (40mg), atorvastatin (10–80mg), rosuvastatin (10–40 mg) and fluvastatin (80mg). Each currently available statin has different LDL cholesterol lowering dose-efficacy, up to a maximum lowering of total cholesterol by up to 55%. All statins lower both small and large LDL particles as part of statin-induced LDL reduction.
• Statins at lower dose exert most of their LDL lowering and at this dose have a reduced side-effect potential. Many individuals will achieve target cholesterol levels at the lowest dose of statin used.
• A doubling of dose does not double the lipid response but has only a small (up to 5–6%) increment of benefit. If pre-treatment total- (or LDL-) cholesterol levels are high or if lipid lowering response is poor, up titration to maximum dose may be necessary to maximise lipid lowering.
• Triglyceride lowering (by up to 10–20%) is also observed with all statins in a dose dependent fashion, which appears to correlate with LDL lowering.
• A modest HDL cholesterol increase of 5–12% has been noted in general use which appears independent of statin dose used, although no alteration in HDL cholesterol levels were seen in studies of statins in diabetes.
• The majority of statin use in diabetes in the UK should utilise generic simvastatin 20–40mg/day, or pravastatin 20–40mg/day as an alternative. If there is poor total- (or LDL-) cholesterol lowering response, an alternative more effective statin should be considered before using a statin + non-statin drug (e.g. fenofibrate, niaspan or ezetimibe) combination.
• In practice, measurement of the impact of lipid lowering should be undertaken initially at three months then at six to 12 month intervals, not least to assess continuing efficacy through compliance.

2. Baseline lipid status in type 2 diabetes and CVD risk

The recent recommendation from the Department of Health,[2] which uses a total cholesterol of 5.0mmol/L for both statin initiation and treatment target, seems inappropriate for an individual with type 2 diabetes and co-existent hypertension – in this scenario the absolute CVD risk with lower cholesterol levels is above the NICE 20% 10-year threshold and would justify treatment. In the Collaborative Atorvastatin Diabetes Study (CARDS) over 30% of the cohort had cholesterol below 5.0mmol/L and the relative risk reduction with statin therapy was equivalent to the group with baseline cholesterol higher than 5.0mmol/L.[13]
• Additional risk factors such as hypertension would justify the use of statin therapy regardless of baseline serum cholesterol levels.

3. Timing of initiation of statin therapy with vascular disease

The majority of outcome trials introduced lipid lowering therapy one to three months following a clinical vascular event. A few trials reported earlier statin initiation (one to 14 days) with no additional benefit as on later clinical end-points.[14–16] However, in practice, ABCD supports the NICE secondary prevention guidance[11] recommending early initiation of statins after acute vascular events to ensure take up of treatment and possibly to enhance concordance with therapy.

4. Drug–drug interactions and statin adverse drug reactions

Drug-induced side-effects from statins in outcome trials were similar to those observed with placebo, and in routine clinical practice statins are very well tolerated. However, with increased statin dose escalation, there is an increased risk of defined side-effects. There is a case for using sub-maximal statin dosage, or for considering conversion to an alternative statin with different metabolic or lipophilic characteristics in order to reduce side-effect potential and/or to reach treatment targets.

Idiosyncratic and dose related adverse effects include abdominal pain, dyspepsia, myalgia (with/without creatine kinase rise), raised liver enzymes, erectile dysfunction and sleep disturbance. Rhabdomyolysis is extremely rare with statins (3.4/100 000 patient years), although there is a 10-fold greater incidence with co-administration of gemfibrozil.[17] Another rare scenario attributed to statins is symptomatic peripheral neuropathy,[11] and treatment should be discontinued in all these clinical scenarios, prior to clarifying statins as the causative agent.

Drug interactions may depend upon the cytochrome P450 enzyme system – a metabolic pathway for several statins. Only pravastatin is metabolised by sulphation, oxidation and glutathione conjugation. Potential adverse drug interactions due to the cytochrome P450 3A pathway, which is specific for simvastatin and atorvastatin, include a combination with erythromycin, warfarin, anticoagulants, azol antifungals (ketoconazole), some oral contraceptives, nicotinic acid, cyclosporin, grapefruit juice and protease inhibitors. The above observations have particular relevance to those who receive statins for a long period, e.g. younger groups.

Statin combinations with pioglitazone[18] or fenofibrate[19] in diabetes have been shown to have no clinical hazard in large randomised controlled trials. Statin combination

with sustained release fenofibrate (160mg or 267mg), bezafibrate (400mg), or with ezetimibe (10mg) and niaspan, has been found to be efficacious and safe in short-term clinical trials in type 1 and type 2 diabetes. Until positive outcome data are published with these add-on strategies, short-term efficacy data should be the basis for pragmatic application of combining the drug classes for dyslipidaemia. Monitoring of muscle, renal and hepatic function would be advisable where there is combination statin-fibrate therapy, especially in the context of diabetic nephropathy.

ABCD supports the NICE recommendation for use of fibrates alone in statin-intolerant patients with established CVD and diabetes,[11] and additionally those at equivalent CVD risk.

ABCD also supports the NICE recommendation to increase intake of omega-3 fatty acids after myocardial infarction in diabetes.[11]

5. Age factors

Elderly patients

Outcome studies have demonstrated benefit in patients aged up to 84 years, and in principle there should be no upper age cut-off for statin initiation. However, lipid lowering therapy should be used cautiously, if at all, in the frail elderly diabetes patient with limited life expectancy due to end-stage CVD or cancer. The incidence of adverse reactions may be increased with doubtful efficacy in this context.

Younger age

The higher incidence of CHD in type 1 diabetes compared to non-diabetic groups is established, although this reflects high relative risk compared to a younger population where the absolute CHD incidence is low. Importantly, the increased CVD risk in type 1 diabetes is modest in the absence of nephropathy.[20,21] Observational data from the UK General Practice Research Database have shown that a 10-year CVD risk >15% is only apparent after the age of 45. The observed rate of CVD in the 35–45 year-old age band was only 0.69% *per annum*.[22]

There is a view that the higher lifetime risk of CVD in type 1 diabetes accelerates the onset of CVD by at least 10 years, and therefore early statin initiation is appropriate, as in younger patients with familial hypercholesterolaemia.

However, ABCD currently takes the view that this approach would be best considered on an individual basis where type 1 diabetes alone was not the categorical basis for early statin initiation.

To date there is only one lipid lowering trial assessing clinical outcome in the 30–50 year age group, but there was no separate analysis of those 650 subjects with type 1 diabetes. In addition, it was unclear whether nephropathy was a common feature of the cohort.[23]

- There would be a strong case for considering statin selection where there are other cardiovascular risk factors including established nephropathy. ABCD supports the case for lipid lowering therapy in younger men and women aged 30–40 years with persistent microalbuminuria in association with other CVD risk factors (e.g. current smoking, treated hypertension or nephropathy, family history of premature CVD). Evidence confirming increased CVD incidence following poor glycaemic control (e.g. HbA_{1c} >9%) in type 1 diabetes over 20 years' duration[24] suggests those in this category would merit consideration of statin therapy.
- The risk during pregnancy, lactation and intercurrent illness where co-administration of antibiotics which potentially interact with statin metabolism, favours a 'tailored' approach to statin use rather than a 'statin for all' approach.
- Statin therapy for younger type 2 diabetes (children and those aged up to 40) also needs to be clarified and should currently be restricted to younger adults at highest CVD risk.

HDL in diabetes

The use of HDL cholesterol is an important measure in estimation of CVD risk in diabetes. Type 2 diabetes is often characterised by a low HDL as part of a diabetic dyslipidaemia, while type 1 diabetes often has a higher HDL cholesterol. A low HDL cholesterol level in type 1 diabetes is thus considered of adverse prognostic significance, and may be a feature of obesity/insulin resistance.

The majority of lipid lowering trials have shown an approximate 30% reduction in CHD events, indicating a residual CHD risk of 60–70%. In the Heart Protection Study[23] 20% of the simvastatin cohort still experienced CVD events. Further review of the trials has confirmed a gradient of risk:benefit in both the statin and placebo arms based on a low *versus* high HDL. Additionally, statin therapy has only minimal effects on raising HDL with the trials indicating that CHD risk of a low HDL is not altered by statin therapy.

These findings underscore the role of other modifiable risk factors other than the LDL concentration, e.g. HDL cholesterol, compositional (size) changes of LDL and raised serum triglycerides as well as non-lipid factors. Non-statin drugs (fibrates, niaspan, and pharmacological doses of fish oils) may have a role.

Multifactorial risk factor approach

The Steno 2 study assessed microalbuminuric type 2 diabetes and currently offers the best guide to the expected outcome from a multifactorial approach.[25]

The study was a nine-point intervention in a group considered to be at high CVD risk. Subjects were instructed to reduce the intake of total and saturated fat, moderate exercise was encouraged at least three times weekly, smokers were offered smoking cessation classes, ACE inhibitors or angiotensin receptor blockers were used in maximum dosage irrespective of blood pressure, and stepwise addition of hypotensive therapy was incorporated, with a target blood pressure of 130/80mmHg. All received vitamin supplements, aspirin 150mg/day, and had oral hypoglycaemic and titrated dosage of insulin as necessary to achieve a target HbA_{1c} of 6.5%. Finally, statin titration, with fibrates added if triglycerides were >4.0mmol/L, were also prescribed. In response to this strategy, there were important risk reductions in microvascular endpoints and in cardiovascular disease (hazard ratio 0.47).

ABCD position statement on lipid modifying drug therapy in diabetes

Key points

- Despite increased risk of cardiovascular disease (CVD) in both type 1 and type 2 diabetes, *not all* should receive statin therapy. Adopting a 'tailored to the individual approach', as part of a multifactorial CVD risk intervention, is advocated
- Treatment target of cholesterol 4.0mmol/L (or LDL 2.0mmol/L) is recommended. Statins should also be initiated where CVD risk is evident at lower baseline cholesterol
- Treatment should include assessments of lipid profile as well as thyroid, hepatic and muscle function to exclude secondary causes, and ensure safety
- Dyslipidaemia (low HDL and hypertriglyceridaemia) does enhance risk – consider other agents after statins, e.g. fibrate or niaspan. Fish oils should be used with marked hypertriglyceridaemia and considered after myocardial infarction
- *Type 2 diabetes.* The vast majority over 40 years of age should receive statin therapy as they have a >20% 10-year CVD risk (often due to other CVD risk factors, e.g. hypertension etc)
- *Type 1 diabetes.* Treat if age >50 years, >40 years with complications, and amongst 18–39 year-olds selective assessment based on other risk factors and complications, including poor glycaemic control and long duration of diabetes, or first degree relative with early onset CVD

Conflict of interest statement

MDF and PHW have received honoraria for lectures and advisory board membership from several pharmaceutical companies involved in the manufacture of lipid lowering therapy and treatments for diabetes.

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