Statin therapy in people with diabetes

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Article points

1. Statins should be considered for most patients with diabetes.
2. The approved drugs in the class are well tolerated.
3. The effect of statins depends on the choice of drug and the prescribed dose.
4. The majority of the effect is seen with the first dose.
5. Effective strategies exist to deal with muscle symptoms.

Key words

- Cardiovascular disease
- Guidelines
- Safety
- Statins
- Tolerability

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Statins were discovered in the 1970s and entered clinical use in the 1980s. They are powerful agents that lower plasma low-density lipoprotein cholesterol and are well tolerated. This article explores the pharmacological differences between the statins, their efficacy and safety, and the potential barriers to use, with a focus on people with diabetes.

Statin therapy should be considered as an option for most people with diabetes. This is regardless of their age, whether or not they have cardiovascular disease (CVD), and whether they are male or female. There is good evidence that statin therapy reduces the risk of major vascular events, including heart attack and stroke, and coronary revascularisation procedures.

This was underscored by a meta-analysis that reviewed data on 18 686 people with diabetes in addition to 71 370 without diabetes extracted from a total of 14 randomised trials (Cholesterol Treatment Trialists' Collaborators et al, 2008). There was a statistically significant one-fifth proportional reduction in major vascular events per mmol/L reduction in low-density lipoprotein (LDL) cholesterol in those people with diabetes. A similar figure to that was seen in those without diabetes. The reduction in relative risk was similar irrespective of vascular disease history, age, sex and other baseline factors. The key message was that after 5 years of statin therapy, 42 people with diabetes per 1000 were saved from having a vascular event. The researchers concluded that most people with diabetes should now be considered for statin therapy except for where – as is usually the case in children – their risk is low, or where statin therapy has been shown to be unsuitable, such as in pregnancy.

Data from the UKPDS (UK Prospective Diabetes Study) confirmed that LDL cholesterol was the major coronary heart disease (CHD) risk factor (*Table 1*). In this study, LDL cholesterol concentration was the most effective predictor of the risk of myocardial infarction (MI), with a 1 mmol/L increase in LDL cholesterol being associated with a 57% increase in the risk of MI (Turner et al, 1998). Statins, however, were not used in the UKPDS.

History of statins

Statins were discovered in the 1970s and entered clinical use in the 1980s. They are powerful agents that lower plasma LDL cholesterol and are well tolerated.

Statins work by inhibiting the conversion of 3-hydroxy-3-methylglutaryl coenzyme A reductase to mevalonate. The liver is the major organ for cholesterol synthesis and LDL catabolism. LDL cholesterol and apolipoprotein B concentrations in the plasma are dependent on hepatic LDL activity. The reduction of cholesterol synthesis achieved with statins (approximately 40% *in vivo*) leads to an up-regulation of hepatic LDL receptors. It is these receptors that determine the levels of LDL cholesterol plasma concentrations by removing LDL from the plasma to the liver (Vega et al, 1988; Gaw et al, 1993; Brown and Goldstein, 1997; Betteridge, 2010).

Pharmacology of statins

Statins vary in their ability to be absorbed, in their bioavailability, in plasma protein binding

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1. Most statins are metabolised in the liver. Simvastatin, atorvastatin and lovastatin are metabolised through cytochrome P450 (CYP) 3A4, and fluvastatin through CYP 2C9. Rosuvastatin is mainly excreted unchanged in the faeces and has only limited metabolism through the CYP 2C9 and 2C19 pathways. Pravastatin is not metabolised through the CYP system, with 60% being excreted through the urine.

and in their method of excretion and solubility. Lovastatin and simvastatin are metabolised to their active form in the liver, whereas the other statins are administered in their active form. The degree of absorption varies from approximately 30–40% with atorvastatin, pravastatin and lovastatin, through approximately 50% with rosuvastatin, on to 80% with simvastatin and pitavastatin, and up to 98% with fluvastatin. All the statins are highly protein-bound except for pravastatin, and their half-lives are fairly short except in the case of atorvastatin and rosuvastatin. Pravastatin, fluvastatin and rosuvastatin are hydrophilic, whereas the others are lipophilic (Betteridge, 2010).

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Lipophilic statins cross the blood–brain barrier more readily, which may lead to central nervous system complaints such as insomnia, although this is rare. Hydrophilic statins exhibit greater hepatoselectivity and have less influence on smooth muscle proliferation (Chong et al, 2001; Schachter, 2005).

Drug–drug interactions are determined by the metabolism of the agent, which, as described above, is mainly through the CYP system (Betteridge and Khan, 2003; Gaw et al, 2003). If there is competition and the CYP enzymes are inhibited by other drugs, then increased statin plasma levels can occur (Betteridge, 2010).

Statins are very efficacious at lowering total and LDL cholesterol. Their effect depends on

References 1. National Institute for Health and Clinical Excellence. Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes. Technology Appraisal Guidance No. 248. London: NICE; 2012 (www.nice.org.uk). **2.** Buse JB, Nauck MA, Forst T et al. Efficacy and safety of exenatide once weekly versus liraglutide in subjects with type 2 diabetes (DURATION-6): a randomised, open-label study. *Diabetologia* 2011; 54(Suppl 1): S38 4. **3.** BYDUREON® (Summary of Product Characteristics).

the dose and is maximal for each dose after 3–4 weeks. The response is independent of baseline LDL cholesterol. The majority of the LDL cholesterol-lowering effect occurs with the first dose and each doubling results in further reduction of approximately 6% (Stein et al, 1998). Atorvastatin and rosuvastatin appear to be the most potent (Jones et al, 1998; Jones et al, 2003; *Figure 1*); atorvastatin comes off patent in May 2012. Research from Keele University indicates that the price of atorvastatin could fall by as much as 95% after it loses patent protection. The current annual cost of atorvastatin is £32 120 per 100 patients, and this could drop to £1606 per 100 patients if the atorvastatin cost drops as much as simvastatin's did, between July 2003 and November 2010, after that came off patent (Pulse, 2012).

Pleiotropic effects of statins include improvement of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant properties, inhibition of inflammatory responses, and stabilisation of atherosclerotic plaques. These and several other emergent properties could act in combination with the potent LDL cholesterol-lowering effects of statins to exert early as well as lasting cardiovascular protective effects (Davignon, 2004).

Relative lowering effects of statins

The effect of statins on plasma triglycerides vary depending on baseline levels. If baseline triglyceride levels are >2.8 mmol/L, similar percentage reductions are seen to those in LDL cholesterol. But when baseline levels of triglycerides are low, the effect is more modest (Stein et al, 1998). The effect on high-density lipoprotein (HDL) cholesterol is also modest, at approximately 5–10% (Betteridge, 2010).

Dyslipidaemia in diabetes

In people with type 2 diabetes, the dyslipidaemia that is seen is typically hypertriglyceridaemia, hypercholesterolaemia and decreased HDL cholesterol. The higher triglyceride levels are associated with an increase in very low-density lipoprotein, intermediate-density lipoprotein and small dense LDL, which is atherogenic. There is also increased activity of cholesteryl ester transfer protein (CETP) and an increase in plasma fibrinogen concentrations related to the increased concentration of triglycerides (Durrington, 2003).

The lipoprotein abnormalities are less common in type 1 diabetes, unless control is poor. However, in type 1 diabetes, the risk of CHD increases dramatically in the presence of proteinuria, which elevates the risk up to 40-fold (Borch-Johnsen and Kreiner, 1987).

When insulin resistance is present, and in those people who are able to secrete sufficient insulin to control the blood glucose, there is often hypertriglyceridaemia, a low HDL cholesterol level, hypercholesterolaemia and

Table 1. The "deadly quintet" for CHD in people with type 2 diabetes. These were analysed in a stepwise selection model of major risk factors for 280 coronary artery disease events at 10 years in 2693 UKPDS participants with complete data (Turner et al, 1998).*

Risk factor	Statistical significance
Raised LDL cholesterol	$P<0.0001$
Low HDL cholesterol	$P=0.0001$
Raised HbA_{1c}	$P=0.0022$
Raised systolic blood pressure	$P=0.0065$
Smoking	$P=0.056$

CHD=coronary heart disease; HDL=high-density lipoprotein; LDL=low-density lipoprotein; UKPDS=UK Prospective Diabetes Study.

*The risk factors were adjusted for age and sex. Triglyceride level remained a risk factor for CHD after adjusting for age and sex, but it did not prove to be an independent risk factor after taking into account the other model parameters.

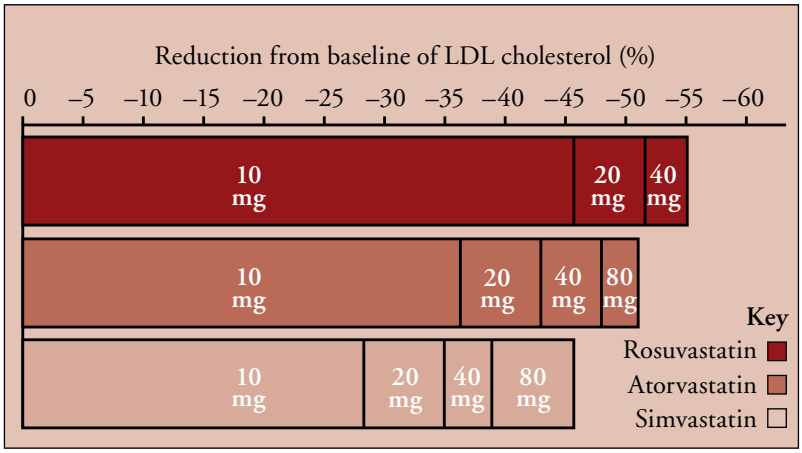

Figure 1. Comparison of the reduction from baseline of LDL cholesterol with three statins at various doses. Adapted from Jones et al (2003).

Page points

1. Large-scale clinical trials involving people with diabetes have shown that statins substantially reduce cardiovascular disease morbidity and mortality in both primary and secondary prevention.
2. Future therapies to raise high-density lipoprotein (HDL) cholesterol are under investigation. The inhibition of cholesteryl ester transfer protein is an effective way to increase HDL and ongoing trials of dalcetrapib and anacetrapib are currently in progress. No outcome data is available as yet.
3. Statin therapies offer clear benefits across broad populations, and as generic formulations become more available, efforts to expand access should become a priority.

hypertension (Wannamethee et al, 1998). This is known as the metabolic syndrome, which can ultimately lead to diabetes (Haffner et al, 1990).

In diabetes more LDL particles reside longer in the plasma and the smaller particle size facilitates penetration of LDL particles in the arterial sub-intimal space. These particles are more susceptible to oxidation and oxidised LDL leads to atherosclerosis. Of note, plasma triglycerides account for around 70% of the variance in small dense LDL particle numbers (Mazzone, 2008).

Efficacy

Statins are some of the most studied drugs for the prevention of CVD and dealing with single studies is thus beyond the scope of this article. Large-scale clinical trials involving people with diabetes have shown that statins substantially reduce CVD morbidity and mortality in both primary and secondary prevention (Brugts et al, 2009; Cholesterol Treatment Trialists' Collaboration et al, 2010).

The increased benefit associated with more intensive statin therapy (Cannon et al, 2006; Shepherd et al, 2006) supports the "lower is better" theory for very high-risk patients, consistent with the US National Cholesterol Education Program (NCEP) guidelines (Grundy et al, 2004).

Guidelines

NICE has published a guideline for type 2 diabetes (NICE, 2009), in which the treatment goals are a total cholesterol level of <4 mmol/L and an LDL cholesterol level of <2 mmol/L.

The US NCEP guidelines have gone one step further than NICE by recommending a target LDL cholesterol level of <1.8 mmol/L in people with diabetes and established CVD (Grundy et al, 2004).

The American approach to hypertriglyceridaemia (defined as a triglyceride level of >2.2 mmol/L), which affects many people with diabetes, is to target LDL cholesterol first, and then use non-HDL cholesterol as a secondary target for treatment with a goal of 0.8 mmol/L higher than the LDL goal (Brunzell et al, 2008).

Contrary to NICE (2009) guidance, which recommends a fibrate when triglycerides are raised, the authors' approach in this situation is to use a non-HDL goal (0.8 mmol/L above the LDL goal), intensify statin therapy and, if necessary, add ezetimibe. There is now outcome data for ezetimibe in combination with statin therapy from the SHARP (Study of Heart and Renal Protection) study confirming the benefit of lipid lowering in chronic renal disease (Baigent et al, 2011).

Additionally, the approach to very high triglycerides (>11 mmol/L fasting), should be a low total fat diet, plus a fibrate, plus omega-3 fish oils (Hartweg et al, 2007; McEwen et al, 2010).

The importance of HDL cholesterol

HDL concentrations were inversely related to CVD risk in the UKPDS, with an HDL increase of 0.1 mmol/L being associated with a 15% reduction in number of CVD events (Turner et al, 1998). HDL cholesterol is likely to be beneficial through its role in reverse cholesterol transport, taking cholesterol from the arterial wall and returning it to the liver. This particle also has anti-inflammatory, antioxidant and antithrombotic properties (Mazzone et al, 2008).

Future therapies to raise HDL cholesterol are under investigation. The inhibition of CETP is an effective way to increase HDL and ongoing trials of dalcetrapib and anacetrapib are currently in progress. No outcome data are available as yet.

Safety and tolerability

An analysis of 170 255 people from 76 randomised controlled trials confirmed that statin therapy significantly reduced all-cause mortality, CVD mortality, fatal and non-fatal MI, revascularisation, and a composite of fatal and non-fatal strokes (Mills et al, 2011). Adverse events were generally mild. The conclusions were that statin therapies offer clear benefits across broad populations, and as generic formulations become more available, efforts to expand access should become a priority (Mills et al, 2011).

In CARDS (the Collaborative Atorvastatin Diabetes Study), there was little difference in the rate of treatment-associated adverse events

(23% versus 25.4%), serious adverse events (1.1% versus 1.1%), and discontinuation due to adverse events (2.9% versus 3.4%) in those receiving atorvastatin compared with those receiving placebo. In this study, HbA_{1c} in the placebo group was 62 mmol/mol (7.8%) at baseline and 64 mmol/mol (8.0%) at the end of the trial, whereas in the atorvastatin group, HbA_{1c} was 63 mmol/mol (7.9%) at baseline and 65 mmol/mol (8.1%) at the end of the trial (Newman et al, 2008). The effect of statin therapy on glycaemia in people with diabetes was extremely small.

Risk of new-onset diabetes

The risk of new-onset diabetes was highlighted in a meta-analysis in 2010 (Sattar et al, 2010). The researchers found 13 relevant trials, which included 91 140 people without diabetes at the start of the studies, who were followed up for an average of 4 years. The individual trials were analysed in isolation and the association between statin use and the development of diabetes was non-significant in 11 trials and significant in two. However, when the reviewers combined the results of all 13 trials in their meta-analysis, statin use increased the risk of developing diabetes by 9% overall, and this association was just significant. There were no differences in the risks between statins. The reviewers calculated that overall, treating 255 people with statins for 4 years would result in one extra case of diabetes. The conclusion was that clinical practice in people with moderate or high cardiovascular risk, or existing CVD, should not change (Sattar et al, 2010).

In their drug safety update of January 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) advised that statin use may be associated with a level of hyperglycaemia in some people where formal diabetes care is appropriate, and the risk of new-onset diabetes appears to be mainly in those already at increased risk of developing diabetes. They concluded that the overall benefits of statins strongly outweigh any risks, including in those at risk of developing diabetes or in those with pre-existing diabetes (MHRA, 2012). The cause of this association remains uncertain.

Box 1. Advice from the National Lipid Association regarding muscle pain associated with statin therapy (McKenney et al, 2006).

- Measuring baseline creatinine kinase (CK) levels is not routinely necessary but is wise in high-risk patients, in whom it provides a useful baseline since there are individual variations and ethnic differences.
- Routine CK measurements in asymptomatic patients are not necessary.
- Patients should be advised to report muscle symptoms when they occur and in this situation CK measurements should be obtained.
- Statin therapy can be continued at the same or reduced doses in patients who develop tolerable muscle symptoms or are asymptomatic with a CK level of <10 times the upper limit of normal (ULN).
- Statins should be discontinued if patients develop intolerable muscle-related symptoms with or without CK elevation or if CK is >10 times the ULN. An enquiry regarding the colour of the urine is helpful as rhabdomyolysis causes dark colouration of the urine. At this stage other causes for the symptoms and/or CK rise need to be established.

Managing muscle pain in people taking statins

There has been much media publicity about the problem of myopathy, muscle pain and rhabdomyolysis caused by statins. Approximately 1.5–3% of patients prescribed statins in randomised controlled trials, and a larger number of participants (10–13%) enrolled in prospective observational studies, develop myalgia (Scott et al, 1991; Bruckert et al, 2005; Bays, 2006; Law and Rudnicka, 2006).

In a review of research published between 1985 and 2006, the adverse effects of some statins on muscle (such as myopathy and rhabdomyolysis) were found to be rare at standard doses. Myopathy, defined as muscle pain or weakness with blood creatine kinase levels >10 times the upper limit of normal, occurred in less than 1 in 10 000 patients on standard doses. However, the risk varied between statins, and increased with higher doses and interacting drugs. Conclusions were that for most people, statins are safe and well tolerated (Armitage, 2007).

The US National Lipid Association has some sensible advice to deal with this issue (*Box 1*).

Causes of muscle pain may include: hypothyroidism, hepatic or renal disease, high alcohol intake, and drug interactions (particularly with fibrates, nicotinic acid, calcium-channel blockers, cyclosporine,

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amiodarone, thiazolidinediones, macrolide antibiotics, azole antifungals, protease inhibitors and warfarin; Sathasivam and Lecky, 2008).

Once the individual's muscle pain has settled, statin therapy, possibly with an alternative agent, can be recommenced, either at the same dose to test reproducibility or at a lower dose (McKenney et al, 2006).

If a patient is able to tolerate a lower dose of statin but is not at the LDL cholesterol goal, ezetimibe can be added to statin therapy to reduce the risk of recurrent muscle symptoms while retaining efficacy (Jacobson, 2008; Gazi et al, 2007).

The option of prescribing extended-release fluvastatin (fluvastatin XL) 80 mg/day or ezetimibe 10 mg/day or both in people with statin-induced, muscle-related adverse events was tested in a randomised controlled trial. The study found that the agents were effective and well tolerated over 12 weeks, alone or in combination (Stein et al, 2008). If a trial of fluvastatin XL 80 mg/day is unsuccessful, alternative options are to switch to low-dose rosuvastatin regimens (5–10 mg/day) or alternate-day or weekly rosuvastatin (Jacobson, 2008). This approach has only been tested in an open-label pilot study (Glueck et al, 2006).

If muscle symptoms recur with trials of multiple statins and doses, non-statin lipid-lowering therapy must be considered (Jacobson, 2008). The efficacy of ezetimibe monotherapy (Gazi et al, 2007) and ezetimibe in combination with colesevelam (Rivers et al, 2007) has been studied in statin-intolerant individuals. Lifestyle advice is clearly very important in those who cannot tolerate statins. This should include reduced intake of saturated fats and cholesterol, increased physical activity and weight control. Plant stanols and sterols are another option (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). There are several randomised trials looking at whether the addition of co-enzyme Q10 to statin therapy can reduce muscle pain and these have yielded equivocal results (Marcoff and Thompson, 2007; Young et al, 2007; Caso et al, 2007).

Barriers to statin therapy

Barriers to statin therapy include concerns about cost, increased workload and adherence to treatment, variation in treatment targets for lowering cholesterol, and concerns about perceived medicalisation, lifestyle and health behaviour. Primary prevention risk assessment tools are difficult to interpret. CVD prevention is limited by practice space and organisational issues, by problems with recording and retrieval of electronic data, and by limited doctor and nurse time. Funded nurse time, nurse-led heart disease clinics, and better use of electronic data could improve CVD prevention (Kedward and Dakin, 2003).

Adherence

Although statins are generally well tolerated, non-adherence is thought to be an important cause of reduced effectiveness (Jackevicius et al, 2001). Monitoring cholesterol concentrations seems to be useful as a way of detecting complete non-adherence to cholesterol-lowering treatment. However, as this is less accurate for detecting partial non-adherence, it should be used as an adjunct to careful questioning about problems with adherence. A practical approach is to simply ask if the individual is having problems adhering to the treatment. The question needs to be framed in a non-judgemental way that keeps the person at ease (Bell et al, 2011). For example, "I know it must be difficult to take all your medications regularly. How often do you miss taking them?" Other questions that may help assess adherence include asking individuals if they are having side effects from the drugs, why they believe they are taking them and what they believe the benefits of treatment are (Osterberg and Blaschke, 2005). As ever, how you give a drug can be just as important as what you give.

Conclusion

In people with diabetes the importance of a healthy diet, weight control and daily exercise cannot be overemphasised. Control of lipid

abnormalities is a priority and we have good agents to achieve it fairly easily. The bottom line is a multifactorial approach to include good blood pressure control and appropriate management of dysglycaemia. ■

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