**A practical guide to prescribing statins**

**Abstract**

Statins remain a controversial drug group and can cause problems for clinicians who are prescribing them, and/or supporting medicines concordance. This article aims to provide an update into the current thinking underpinning statin use, and to guide the clinician regarding safe and effective practice when managing patients on these drugs. Alternatives to statin therapy are briefly outlined but are not the main focus of this article.

**Introduction**

Whether you are a clinician seeing patients who are on statins, the person managing the effects of statins, or the prescribing clinician, this group of drugs has a large impact in clinical practice.

In 2017, atorvastatin was the most frequently prescribed drug in England, at over 37 million items (37,342,946 items) (NHS Digital PAC data 2018). Since NICE changed the guidelines in 2014, to reduce the threshold for primary prevention from 20% to a 10% risk of a cardiovascular event over 10 years (NICE 2014 (updated 2016)), the population captured by statins has been estimated as 12 million adults in the UK (Hawkes 2017). Nonetheless, the reputation of the statin drug group can make consultations difficult, owing to some patients' preconceived ideas, many of which are negative. The reasons for this negativity are complex and many, including:

* scepticism of global scale use
* expansion of use in the population, especially for older people.
* overtone of medicalisation of the masses.
* perceptions of a "nanny" state.
* association with multiple side effects

The reporting of side effects has also been predominantly negative; indeed, it turns out disproportionately so, when compared to the real picture.

Another issue is that statin use is prophylactic when used for primary prevention of cardiovascular disease. Patients are required to accept that while there may be a future benefit, there also may not be. This is often when patients are still at a stage of their lives when they are problem free. Unless a heart attack or stroke occurs, any advantage would never be known, (see Box 1).

In this scenario, being advised to take a drug which is widely reputed to cause side effects, can give rise to concerns among patients, particularly about its potential impact on their quality of life.

**Box 1: Statins: Risk reduction**

If patients with a 10-year cardiovascular risk of at least 10% take statins for 10 years, it would prevent at least 400 heart attacks, strokes, or vascular deaths per 10,000 treated patients.

* **NICE 2016**

If patients with a 10-year cardiovascular risk of at least 20% take statins for 5 years, it would prevent at least 450 heart attacks, strokes, or vascular deaths per 10,000 treated patients.

* **MHRA 2014**

The current guidance is that statins are recommended for patients aged 84 years and below:

* After a heart attack or stroke, as they are proven to help prevent a further episode, i.e., secondary prevention.
* If there is a known risk of cardiovascular disease, such as in the diabetic population.
* For anyone who scores a greater than 10% risk of sustaining a thrombotic event in the next 10 years on the QRISK3 calculator (updated from QRISK2)

(Clinical Knowledge Summaries (CKS) 2015)

The QRISK3 calculator was modified from the QRISK2 calculator in 2018 and the key information for both is as expected (see Table 1). More information about the medical conditions, which may help to predict heart attack and stroke, have been added in the QRISK3 formula. These now includes severe mental illness, erectile dysfunction, migraine and treatment with corticosteroids (Table 1).

**Why is lowering cholesterol important?**

The low-density lipoprotein (LDL-C) type of cholesterol is associated with atheroma formation. A high level of LDL-C is linked to cardiovascular disease, such as heart attacks, stroke and peripheral arterial disease (Prospective Studies Collaboration 2007). Conversely, high-density lipoproteins (HDL-C) confer protection from cardiovascular disease, because HDL-C complexes transport cholesterol back to the liver, lowering blood levels. However, if HDL-C levels are low, then this protection is lost (Assaman and Nofer 2003).

The total cholesterol (TC) reading can, therefore, be misleading, since a high HDL-C but a low LDL-C is protective, which together, can present as a high TC. It does provide a general guide, but the total cholesterol to HDL-C ratio is a superior indicator, because it offers a picture of cholesterol status after the protective HDL-C has been accounted for. A ratio below 4mmol/L is healthy (NHS 2018), above 6mmol/L is considered high risk (interventions to lower LDL-C should be considered), and greater than 7.5 mmol/L should prompt specialist referral (NICE 2016).

Table 1: QRISK Calculator Predictors for UK

|  |  |
| --- | --- |
| QRISK2: predictors | QRISK3: additional predictors |
| Age | Chronic kidney disease stage 3, 4 or 5 |
| Sex | Migraine |
| Ethnicity | Corticosteroids |
| Postcode | Systemic lupus erythematosus (SLE) |
| Smoking (non, ex, light, heavy, moderate) | Atypical antipsychotics |
| Diabetes (type 1 or 2) | Severe mental illness |
| Angina or heart attack in first degree relative <60 | Erectile dysfunction |
| Chronic kidney disease stage 4 or 5 | Measure of systolic blood pressure variability |
| Atrial fibrillation |  |
| On blood pressure treatment |  |
| Rheumatoid arthritis |  |
| Cholesterol/HDL ratio |  |
| Systolic blood pressure |  |
| BMI (via height and weight) |  |

<https://qrisk.org/2017/>

<https://qrisk.org/three/>

**How do statins work?**

About 80% of the cholesterol in the body is made in the liver, where it is also assembled, ready for transport (by lipoproteins) around the body. Cholesterol is essential for many functions, including cell membrane production, bile salt formation and fat-soluble vitamin production. A key step in the synthesis of cholesterol is when the enzyme HMG CoA reductase acts on HMG CoA forming mevalonate, from which cholesterol is derived. Statins inhibit this enzyme and therefore halt cholesterol production. Sensing lowered cholesterol prompts the liver cells (hepatocytes) to increase their LDL-C receptors, ready to extract more LDL-C from the blood stream. In this way, more LDL-C is removed from the circulation and, consequently, there is less atheroma formation.

Independently of LDL-C reduction, statins also lower triglycerides and can increase protective HDL-L (McTaggart and Jones 2008). Interestingly, at higher doses simvastatin and rosuvastatin increase HDL-L levels, but atorvastatin dosing is inversely related to HDL-L, with lower plasma HDL-C associated with the higher doses of 20-80mg/day (Jones et al 2004). Atorvastatin is still considered the best first-line agent, because lowering LDL-C is known to prevent cardiovascular events, whereas the effects of increasing HDL-C are less clear (Kosmas et al 2018).

**Do they cause many side effects?**

The effects of inhibiting mevalonate production are widespread. This is because mevalonate has many derivatives. One is coenzyme Q10 (CoEQ10/ubiquinone), an oily substance which assists with the generation of energy in cells. Reduced levels are associated with fatigue, and the greatest impact occurs in high energy producing tissues, such as muscle and the liver. Statin-induced myopathy has been associated with low CoEQ10 levels (Banach et al 2014), but research into the impact of CoEQ10 supplementation has failed to demonstrate improved tolerance. Therefore, this has not been approved by NICE as a co-prescribing strategy to address myopathy (NICE 2016).

Reduced levels of cholesterol in the body can affect production of vitamin D, which is essential for healthy bones and calcium homeostasis. Low levels of vitamin D are associated with a variety of non-specific symptoms, such as muscle aching, weakness and bone pain, which are all common adverse drug reactions linked to statin use. Low serum vitamin D has also been implicated in mood disorders and cognitive impairment, (Wilkins et al 2006). If these symptoms occur when on statins, low vitamin D levels might be the cause or a contributing factor (Riche et al 2016). Once again, a supplement is not routinely advised, because of weak supporting evidence (NICE 2016).

There have been many theories regarding statin induced muscle problems and the causes, which remain unclear. However, recent evidence has clarified the risk of myopathy. The MHRA (2014) published the following, which may be used to reassure patients:

* mild muscle pain: 190 cases per 100,000 patient years
* myopathy: 5 cases per 100,000 patient years
* rhabdomyolysis: 1.6 cases per 100,000 patient years

Should myalgia occur, it is important to investigate this (see Box 2). Some populations are also more at risk from muscular-skeletal problems and other ADRs, such as

* Renal impairment
* The elderly (>80)
* Hypothyroidism
* Previous of family history of muscle conditions
* Alcohol abuse
* On drug therapy which can elevate statin levels (see box 3)
* Females
* Low body mass

(Thomson et al 2016)

There is some evidence to support a genetic predisposition to myopathy, which relates to differences in the transporters, which manage cholesterol and metabolise statins. Poor metabolisers have higher levels of statins, which can predispose to adverse drug reactions (Carr et al 2013).

The most serious form of muscle disease, rhabdomyolysis, is rare (less than 2 cases per 100,000 patient years), but when it happens, the muscle tissue breaks down rapidly. The release of the myoglobulin protein in muscle into the blood stream, can lead to blockages in the kidney, acute kidney injury and renal failure.

**Box 2: What to do if muscle problems happen**

* Check LFTs and creatine kinase
* Remove statin if muscle damage indicated (see BNF and CKS Guidelines) and refer as appropriate
* Check for drug-drug interactions
* Consider dose reduction
* Consider hydrophilic statin, e.g pravastatin (only low intensity options)
* Consider statin alternative e.g ezetimibe

**(BNF 2018,CKS 2015)**

**Do statins cause diabetes?**

Statins may precipitate the onset of type 2 diabetes (Mills et al 2011) or worsen diabetes (Cui et al 2018). However, since the diabetic population is at higher risk of heart disease, controlling cholesterol levels is central to improving cardiovascular outcomes. The absolute risk of incident diabetes is small, and therefore, the benefits of statins outweigh the risk (NICE 2016). It is noteworthy that women (Mora et al 2010) and the elderly (Chogtu et al 2015) are more at risk. High dose and high intensity statins are linked to diabetes onset, when compared with a placebo, i.e.:

* 20mg/day rosuvastatin 25% risk
* 80mg/day atorvastatin 15% risk
* 40mg/day pravastatin 7% risk

(Navarese et al 2013)

The reasons for increased blood glucose are poorly understood (Thompson et al 2016), and it may be that multiple mechanisms combine to produce a diabetogenic effect. It is recommended to check HbA1c levels prior to commencing statins (NICE 2016).

**Are there other benefits in addition to improved lipid control?**

Several benefits are attributed to statins but, as yet, none have been proven sufficiently for any change to their licensed indication, which remains only for hyperlipidaemia. The reduction in mevalonate production lowers the production of elements which regulate cell turnover, e.g dolichol. Ultimately, this suppresses cell division, which can have anti-inflammatory and anti-tumour effects (Greenwood et al 2006).

Hence statins have been linked to having a favourable effect in conditions such as multiple sclerosis (Pihl-Jensen et al 2015; Zeiser 2018), and for cancer prevention and treatment (Ogura et al 2018; Hagiwara et al 2018; Zaleska and Mosenska 2018). It is noteworthy that there have been historical concerns that statins might increase cancer risk, but this has been discounted by recent large meta-trials (Taylor et al 2011; CTT Collaboration 2012).

In addition to lipid control, statins have been shown to improve cardiovascular outcomes (Rosenson 2001). This is ascribed to there being fewer ‘intermediate’ substances derived from mevalonate, such as farnesyl pyrophosphate (FPP), being available for protein modification. Suppression of proteins which regulate vascular functions means less vascular re-modelling, less atheroma formation and fewer thrombotic events (Wang et al 2008).

**Which statin?**

Although there are five statins available in the drug class, the first-line choice is atorvastatin 20mg, taken once daily for primary prevention and 80mg once daily for secondary prevention (CKS). It is noteworthy that atorvastatin is unlicensed in both these scenarios (BNF 2018). However, the evidence for these recommendations is robust (as denoted by the BNF EvGr (A) symbol) and originates from the NICE National Guidance on lipid modification (NICE 2016).

If atorvastatin is not tolerated, it should be borne in mind that any statin is considered advantageous, compared to no statin (CKS 2015). Therefore, if a dose adjustment or a different agent facilitates concordance, then non-standard treatment is recommended.

Atorvastatin does interact with some common drugs, such as clarithromycin and warfarin (Box 3) and there is the well-known interaction with grapefruit juice. Because taking the antibiotic clarithromycin (and other drugs in this class) can increase statin levels, risking side-effects, it is standard practice to stop the statin for the duration of the antibiotic therapy (BNF 2018).

Where an alternative statin is required, a high intensity replacement is preferred, that is rosuvastatin 10mg and above. At one time, simvastatin 80mg would have been an option, but this dose is associated with a higher risk of myopathy and is to be avoided if possible. Other doses of simvastatin, as well as 10mg atorvastatin, or 80mg fluvastatin, are classified as "medium intensity", which means they do not lower cholesterol to the same extent. These can be used if there is no high intensity option suitable for the patient. For reference, the CKS table can be used to review the lipid-lowering impact of all the agents and doses in the statin drug class (CKS 2015).

**Box 3: Common drug-drug interactions with atorvastatin with a ‘severe’ or ‘moderate’ effect**

* Amiodarone
* Anti-epileptics
* Azole antifungals
* Calcium channels blockers
* Ciclosporin
* Daptomycin
* Ezetimibe
* Fibrates
* Grapefruit juice
* HIV protease inhibitors
* Clarithromycin
* Warfarin

NOTE: not a full list of interactions

(BNF 2018)

**Box 4: Atorvastatin Profile**

**Advantages:**

* High intensity at low doses
* Low cost
* Can take any time of day (long half-life)
* Not affected by food intake
* Dose range 10-80
* No renal dose change (excreted in bile)

**Disadvantages**

* Unlicensed at 20mg for primary prevention
* Unlicensed for secondary prevention
* Lipophilic (crosses membranes more easily e.g muscles and blood brain barrier)
* Metabolised by the CYP450 3A4 family (propensity for drug-drug and drug-food interactions)
* Some important drug interactions
* Less effect on raising protective HDL-C (compared to simvastatin and rosuvastatin)
* Impaired insulin secretion/insulin resistance (all statins)
* May be less effective in elderly (all statins)
* Avoid in pregnancy (all statins)

**Alternatives to statins**

Ezetimibe is also licensed for hypercholesterolaemia, and its mechanism of action is to reduce the amount of cholesterol absorbed across the gut wall. It is recommended by NICE as an alternative to statins, if they are not tolerated or contra-indicated (CKS 2015). Two monoclonal antibodies, evolocumab and alirocumab, administered via subcutaneous injection, are licensed for hyperlipidaemia. NICE permits use if LDL-C is high, control by other means has not been effective and if the NHS discounted cost is applied (NICE TA393 and TA394).

**What else can be done to lower cholesterol?**

Some people prefer to try lifestyle changes first, or to do this in tandem with taking cholesterol-lowering drugs. If intake is controlled, this can contribute to lowering levels. Food of animal origin contains saturated fats, and includes fatty meat, butter and full fat cheese, as well as baked and deep-fried products. A low cholesterol diet should contain less than 300mg of cholesterol per day (NICE 2016), and a cardio-protective diet, containing wholegrains, oily fish and fruit and vegetables is recommended (NICE 2016). Smoking cessation and more exercise can also help.

However, since most of the cholesterol in the body is synthesised internally, there is a limit to how much lifestyle can influence cholesterol levels. Even if no/minimal cholesterol is ingested, the process of carbon re-cycling by the breakdown of carbohydrates, proteins and fats, allows conversion by the liver to meet cholesterol requirements.

Sometimes, a genetic propensity to produce high levels of LDL-C means the combination of lifestyle changes and statins is required. Familial hyperlipidaemia is considered to confer a risk of coronary heart disease without using any risk calculators and, usually, lipid modification using statins is considered from age 10 onwards (CKS 2015).

**Safety considerations**

Before prescribing statins, it is important to discuss the rationale for taking them, the potential side effects and to consider relevant precautions (Box 5).

**Box 5: Statins: Dos and Don’ts**

**Do**

* Employ the patient decision-aid to assist decision making (NICE 2014)
* Explain the rationale for taking statins
* Offer information about the risks, to help informed judgment
* Explore health beliefs
* Discuss cholesterol lowering lifestyle changes
* Check existing drugs
* Assess risk factors
* LFTs (at baseline and then accordingly to NICE guidelines throughout treatment)
* Undertake additional tests if high risk e.g creatine kinase
* Consider familial hypercholesterolaemia
* Safety net, e.g., advise rapid attention if muscle problems occur
* Check concordance regularly

**Don’t**

* Start or continue treatment if ALT and or AST are raised more than 3 times the upper limit
* Start or continue treatment if creatine kinase is over 5 times the normal limit
* Omit to mention that this is a long-term intervention
* Insist they must take them
* Dismiss concerns regarding side-effects
* Recommend supplementation with CoEQ10
* Recommend supplementation with vitamin D
* Stop statins if there is an increase in HbA1C or blood glucose levels

**(NICE 2016, BNF 2018, CKS 2015)**

**Conclusion**

Elevated cholesterol levels can be managed effectively by statin therapy, with associated benefits for reduced cardiovascular morbidity and mortality. Good counselling and safety- netting are essential, to foster a suitably concordant long-term relationship. Particular care should be given when prescribing for elderly patients, and for anyone with known risk factors for adverse drug reactions.

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