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REVIEW

Rosuvastatin and Atorvastatin: Comparative Effects on Glucose Metabolism in Non-Diabetic Patients with Dyslipidaemia

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Abstract: The ever increasing interventional CVD outcome studies have resulted in statins being an essential factor of cardiovascular prevention strategies. The JUPITER study in 2008, despite reducing CVD and overall mortality, highlighted an increase in new onset diabetes in the rosuvastatin treated arm. Since then there have been many meta-analyses of the RCTs and the largest carried out by Sattar et al showed a significant increase in the incidence of diabetes during the trials. The findings from the individual studies when comparing the different statins were less clear. A higher statin dosage and risk factors associated with diabetes appeared to predict this phenomenon. There have been many studies investigating the effects of statins on glycaemic control, but again no clear conclusion is apparent. Despite the increase in new onset diabetes observed, the risk is clearly out-weighed by the CVD benefits observed in nearly all the statin trials. Thus, no change is required to any of the prevention guidelines regarding statins. However, it may be prudent to monitor glycaemic control after commencing statin therapy. This review will focus on atorvastatin which is the most widely used statin worldwide and rosuvastatin which is the most efficacious. This will be against a background of the effects of other statins on glucose metabolism in non-diabetic patients.

Keywords: type 2 diabetes mellitus, statins, atorvastatin, rosuvastatin, new onset diabetes

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Introduction

As early as 1856 Rudolf Virchow suggested that atherosclerosis resulted from the accumulation of blood lipids in arterial walls.[1] Large scale epidemiological studies such as the Framingham Heart Study and PROCAM have identified several important cardiovascular disease (CVD) risk factors including dyslipidaemia (total cholesterol [TC]/high density lipoprotein cholesterol [HDL-C], low density lipoprotein cholesterol [LDL-C], triglycerides [TG]), smoking status, diabetes mellitus, hypertension, age, gender, family history of premature CVD and obesity.[2,3] In 2008, CVD alone accounted for a third of deaths in the UK (190,857 of 579,677 deaths).[4] Although the mortality rate has been steadily declining since the mid 1970s[5] a recent plateau in this downward trend has been observed; an increase in factors such as diabetes mellitus, obesity, smoking and hypertension may provide an explanation.[6–8]

The first statin developed was lovastatin in 1978 by Alberts, Chen and others at the Merck Research Laboratories in a fermentation broth of *Aspergillus terreus*. Lovastatin was approved for marketing in 1987 followed by simvastatin (1988), pravastatin (1991), fluvastatin (1994), atorvastatin (1997), cerivastatin (1998) and rosuvastatin (2003).[9] Although it was recognised that dyslipidaemia was associated with CVD it was the landmark 4S study in 1994 that demonstrated the scale of benefit in total mortality and CVD incidence that could be expected following statin therapy in a secondary prevention cohort.[10] Since then statins have formed the mainstay of lipid lowering treatment. Studies such as WOSCOPS,[11] CARE,[12] LIPID,[13] AFCAPS/TEXCAPS,[14] HPS[15] and JUPITER[16] have shown significant CVD reduction in both primary and secondary prevention. The TNT (atorvastatin 10 mg vs. 80 mg)[17] and PROVE IT-TIME 22 (pravastatin 40 mg vs. atorvastatin 80 mg)[18] trials suggested that benefit was associated with the degree of lipid lowering. Statin prescriptions in the UK have risen substantially from 295,000 in 1981 to 52 million in 2008, second in number only to anti-hypertensives; one in five prescriptions for patients with CVD were for statins.[19]

Diabetes mellitus has become a recognised global epidemic. The number of people living with diabetes in 2010 was estimated to be 285 million (6.4% of all adults worldwide) and is predicted to rise to 438 million in 2030.[20] Type 2 diabetes mellitus (T2DM) is considered to have a multifactorial aetiology consisting of genetic and environmental factors.[21] Insulin resistance and β-cell dysfunction are key factors in the pathophysiology.[22] It has been recognised that hereditary factors are important with several candidate genes shown to be associated with T2DM, their ORs ranging between 1.09 and 1.25; however, there have been suggestions that potentially over a hundred more associated genetic polymorphisms exist.[23]

In 2001 WOSCOPS, a randomised controlled trial (RCT) using pravastatin, reported a significant reduction in the incidence of diabetes.[24] The interest generated by this finding led to a number of studies evaluating the effect of statins on glycaemic control. In JUPITER, a RCT evaluating cardiovascular outcome in patients with low levels of LDL-C but high levels of high-sensitivity C-reactive protein (hsCRP) treated with rosuvastatin, a significant increase in the incidence of new onset diabetes was suggested.[16] Thus, a potential paradox may exist whereby rosuvastatin, a high intensity statin frequently prescribed in diabetes, may actually worsen glycaemic control resulting in a diagnosis of diabetes in non-diabetic patients. We will now review the literature on statins and new onset diabetes/glycaemic control with a focus on atorvastatin and rosuvastatin, the high intensity statins.

With generic atorvastatin on the immediate horizon it is reasonable to expect that it may, price depending, replace simvastatin as the first-line statin in view of superior efficacy. The National Institute for Health and Clinical Excellence (NICE) guidelines have made provision for this by stating "simvastatin or similarly priced statin" in their recommendation.[25,26] The role of rosuvastatin (which will not be a generic compound for a few more years) may be for cases when lipid targets are not reached or atorvastatin treatment is not possible in view of adverse effects/drug interactions.

Mechanism of Action, Metabolism, Pharmacokinetic Profile and Efficacy of Statins

As demonstrated in Figure 1, statins competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase which catalyses the rate limiting step in cholesterol synthesis; HMG-CoA to mevalonate.[27] This decreases de novo hepatic

Acetyl-CoA

↓

Acetoacetyl-CoA

↓

HMG-CoA

HMG-CoA reductase ↓ ⊣—— **Statins**

Mevalonate

↓

Mevalonate-PP

↓

Isopentyl-PP

↓

Geranyl-PP

↓

Farnesyl-PP ——→ Dolichols

Squalene   all-*trans* Geranylgeranyl-PP

↓   ↓   ↓
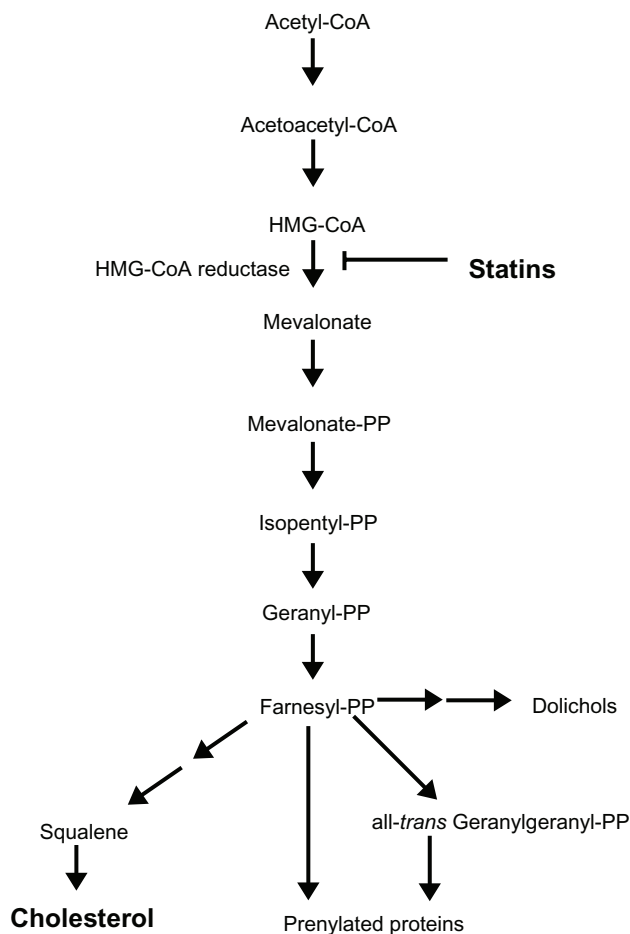
Cholesterol   Prenylated proteins

Figure 1. Cholesterol biosynthesis pathway demonstrating the step inhibited competitively by statins. From Schachter *Fundam Clin Pharmacol* 2005;19:117–25.

cholesterol synthesis and leads to an up-regulation of hepatic LDL-C receptors with subsequent increased LDL-C uptake and decreased plasma LDL-C levels. In addition to reducing LDL-C concentrations, statins can also decrease TG in some patients, perhaps by reducing the rate of very low density lipoprotein synthesis and increasing its clearance. They also increase apolipoprotein A1 (ApoA1) and HDL-C levels although the mechanisms are unclear.[27] In addition, statins are thought to have pleiotropic effects which include improvements in inflammatory responses, endothelial function and smooth muscle proliferation. These factors are considered to be important in the pathogenesis of atherosclerosis.[28,29] There has been evidence, albeit limited, that statins may also reduce inflammation[29] and be useful in countering sepsis.[30]

The British National Formulary lists 5 statins available for use in the UK; simvastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin (lovastatin and pitavastatin are not available in the UK).[31] The different statins vary considerably in origin, structure and pharmacokinetics. Statins are rapidly absorbed following administration and excepting pravastatin are extensively bound to plasma proteins. The basic structure of statins includes; analogue of the substrate, hydrophobic ring covalently bound to the substrate analogue, and side groups on the hydrophobic rings.[32] Many of the variations seen between the statins are conferred by these side chains. Figure 2 illustrates the structures of the different statins.

Simvastatin, atorvastatin and fluvastatin are relatively lipophilic while rosuvastatin and especially pravastatin are more hydrophilic.[33,34] This hydrophilicity is due to side chains consisting of the methane sulphonamide group on rosuvastatin and a hydroxyl group on pravastatin. Statins bind to the active site on the HMG-CoA reductase thus preventing its natural ligand from binding. Atorvastatin and rosuvastatin bind to the enzyme with an extra hydrogen bond and rosuvastatin also demonstrates a polar interaction; this difference in binding interaction may contribute to their superior efficacy.[35] Atorvastatin and rosuvastatin also have longer half lives. The half life of atorvastatin is approximately 14 hours[36] whilst that of rosuvastatin is about 19 hours.[37] Apart from pravastatin, statins are metabolised by hepatic cytochrome P450 enzymes.[38]

The efficacy of the statins varies within class and dose. The STELLAR trial in 2003 compared reduction of LDL-C across dose ranges of simvastatin, pravastatin, atorvastatin and rosuvastatin in 2,431 patients.[39] Across the dose range rosuvastatin was seen to be significantly more effective in decreasing LDL-C than the other statins. Dose for dose, rosuvastatin demonstrated a mean 8.2% (95% CI: 6.8%–9.7%) greater LDL-C reduction than atorvastatin. Reduction in TG was no different between the two statins, but it was observed that atorvastatin had the least effect on HDL-C.[39] The varying effect on HDL-C by rosuvastatin and atorvastatin was also noted in the VOYAGER, a meta-analysis of 37 RCTs comparing the effects of rosuvastatin, atorvastatin and simvastatin.[40] While a dose dependent increase in HDL-C (5.5%–7.9%) was noted with rosuvastatin (5 mg–40 mg), an inverse increase in HDL-C was seen with higher doses of atorvastatin (4.5% at 10 mg and 2.3% at 80 mg). Increases in apoA1 mirrored the HDL-C change in atorvastatin
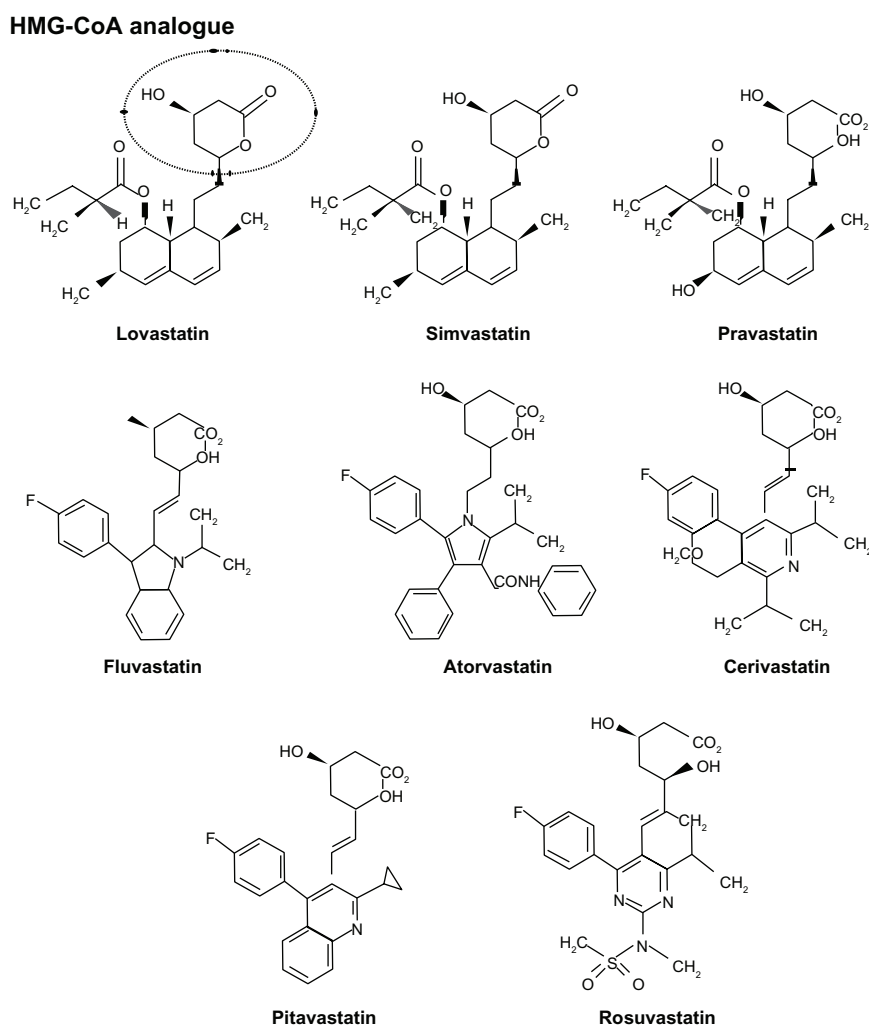
HMG-CoA analogue

Figure 2. Chemical structure of different statins. From Schachter *Fundam Clin Pharmacol* 2005;19:117–25.

treated patients. Although an apoA1 increase was observed in the rosuvastatin patients a dose response effect was lacking. The mechanism by which statins affect HDL-C is unknown. Up-regulation of peroxisome proliferator-activated receptor α (PPAR-α) by fibrates is associated with increased levels of apoA1 and HDL-C.[41] Mevalonic acid, which is reduced by statins, has been suggested in "in vitro" studies to interfere with PPAR-α.[42] However, this does not offer an explanation as to the differences observed in HDL-C following treatment with atorvastatin and rosuvastatin.

Clinical Studies Relating to Statins

Before moving onto new onset diabetes associated with statins in RCTs it is necessary to gain an understanding of the trials that have propelled statins to the position that they currently occupy. This will

hopefully lead to a balanced view of both benefit and risks seen with this class of drug. We will also briefly touch on some atorvastatin and rosuvastatin studies investigating atherosclerosis progression.

Studies with statins assessing cardiovascular disease outcomes

The best evidence of outcome is considered to be from RCTs with large numbers of patients over a lengthy period and either mortality or CVD events as primary outcomes. Several statin/placebo trials have evaluated statin effectiveness in secondary prevention. These include simvastatin in the 4S[10] and HPS[15] trials as well as pravastatin in the CARE[12] and LIPID[13] trials. Both simvastatin and pravastatin reduced the incidence of coronary events in the above trials with overall mortality also reduced in the 4S, HPS and LIPID trials. A reduction in strokes was observed

in 4S, HPS and CARE. Statins have also been seen as effective primary prevention agents. Pravastatin led to reduced coronary deaths in the WOSCOPS[11] trial. The above studies led to statins being the mainstay of cardiovascular prevention strategies and it was therefore impossible to carry out a statin/placebo trial with the newer statins; atorvastatin and rosuvastatin.

Outcome studies with atorvastatin

Prior to the CARDS trial, the role of statin therapy in diabetic patients without established CVD had not been assessed.[43] This RCT compared the effect of atorvastatin 10 mg against placebo in patients with an LDL-C ≤ 4.14 mmol/L with one of retinopathy, albuminuria, history of current smoking and hypertension. The trial had to be discontinued 2 years earlier than planned as the anticipated efficacy of CVD prevention was met prematurely. There was a 37% relative risk reduction of CVD. The individual components of CVD also showed significant event reductions; coronary heart disease (CHD) events: 36%, coronary revascularisations: 31%, strokes: 48%. Total mortality decreased by 27% albeit not significantly.

The TNT study investigated whether there would be benefit in lowering LDL-C below the then recommended LDL-C target of 2.6 mmol/L for secondary prevention patients.[17] Patients (n = 10,001) with LDL-C ≤ 3.4 mmol/L were randomised to either atorvastatin 80 mg or 10 mg. Atorvastatin 80 mg and 10 mg decreased mean LDL-C levels to 2.0 mmol/L and 2.6 mmol/L respectively. Although there was no difference in overall mortality, a significant 22% relative risk reduction in the primary end point (CVD) was observed in the atorvastatin 80 mg group. Similarly the benefit of intensive therapy versus standard therapy was evaluated in the PROVE IT–TIMI 22 study.[18] Patients hospitalised for acute coronary syndrome over the preceding 10 days (n = 4162) were allocated to either pravastatin 40 mg (standard therapy group) or atorvastatin 80 mg (intensive therapy) and outcome assessed after a mean of 24 months, both treatment groups with a median pre-treatment LDL-C of 2.74 mmol/L. A 16% relative risk reduction in the primary end point consisting of all cause mortality, myocardial infarction, documented unstable angina requiring hospitalisation, revascularisation performed at least after 30 days of randomisation and strokes, was observed in the atorvastatin 80 mg group (post

treatment median LDL-C: 1.60 mmol/L) compared to the pravastatin 40 mg group (post treatment median LDL-C: 2.46 mmol/L). Intensive and standard LDL-C lowering with atorvastatin 80 mg and simvastatin 20 mg respectively, was compared in patients (n = 8,888) with a history of myocardial infarction in the IDEAL study which involved a mean follow-up duration of 4.8 years.[44] In the atorvastatin arm LDL-C decreased from 3.11 mmol/L to 2.07 mmol/L and in the simvastatin arm from 3.11 mmol/L to 2.65 mmol/L. Although the primary endpoint of coronary death, acute myocardial infarction or cardiac arrest with resuscitation was not met (relative risk reduction 11%), major cardiovascular event reduction, a secondary end point, was lower in the atorvastatin treated group.

The effect of high dose atorvastatin on stroke prevention, the primary end-point being the time to either first non-fatal or fatal stroke following randomisation, was assessed in the SPARCL trial.[45] Patients (n = 4731) who had a stroke or transient ischaemic attack in 1 to 6 months prior to recruitment, but no history of CHD and LDL-C between 2.6 mmol/L and 4.9 mmol/L were randomised to either atorvastatin 80 mg or placebo and followed up over a median period of 4.9 years. LDL-C decreased from 3.38 mmol/L to 1.9 mmol/L in the atorvastatin group and from 3.40 mmol/L to 3.3 mmol/L in the placebo control group. A significant relative risk reduction of 16% in fatal or non-fatal strokes was seen in the atorvastatin treated patients.

Outcome studies with rosuvastatin

The JUPITER study randomised 17,802 primary prevention patients with LDL-C lower than 3.4 mmol/L and hsCRP greater than 2 mg/l to either rosuvastatin 20 mg or placebo (median LDL-C in both groups was 2.76 mmol/L) with a combined primary end point of myocardial infarction, stroke, revascularisation, hospitalisation for unstable angina and death from cardiovascular causes.[16] It was thought that statins may have a beneficial effect on patients with an elevated hsCRP, as there was some evidence that it was a marker of cardiovascular risk and statins had been shown to reduce its levels. The trial was stopped early (median follow-up: 1.9 years). Rosuvastatin was seen to lower LDL-C by 50% and hsCRP by 37%. There was significant benefit observed in

the rosuvastatin group with regards the combined primary end-point (relative risk reduction 44%) and its individual components. Many issues were raised by the JUPITER trial. For example, the role of hsCRP as a risk marker of cardiovascular disease and the role of rosuvastatin in patients with unremarkable LDL-C levels but with raised hsCRP. This caused some difficulty in placing this study with the other statin versus placebo primary prevention trials. However, it may be argued that rosuvastatin has sufficient outcome evidence given the LDL-C reduction in all the previous statin trials and the expected relative risk reduction seen in the JUPITER study.

Studies reporting on the progression of atherosclerosis

Many of these studies have smaller sample sizes and shorter follow-up periods and therefore do not carry the same weight as the RCTs described above. The REVERSAL trial compared progression of atheroma volume in patients with established CHD following randomisation to either pravastatin 40 mg or atorvastatin 80 mg.[46] Mean LDL-C (baseline: 3.89 mmol/L in both groups) was reduced to 2.85 mmol/L in the pravastatin arm and 2.05 mmol/L in the atorvastatin arm of the trial. There was a reduced progression of atheroma volume in the atorvastatin group as measured by intravascular ultrasound. The METEOR study included men aged 45 to 70 years and women aged 66 to 70 years with an LDL-C of either 3.1 mmol/L–4.9 mmol/L or 3.1 mmol/L–4.1 mmol/L, with 2 or more cardiovascular risk factors and a Framingham Risk Score <10%.[47] These patients were randomised to receive rosuvastatin 40 mg or placebo. Over a 2 year period the rosuvastatin group demonstrated a lower progression rate of atheroma as measured by carotid intima media thickness than the placebo treated group. The only study to show regression of atheroma was the ASTEROID study where 507 patients with CHD were enrolled to be treated with rosuvastatin 40 mg for 2 years.[48] Amongst these patients 292 who had one or more segments with >25% stenosis at baseline angiography had follow-up angiography assessments. The mean LDL-C on rosuvastatin treatment decreased from 3.37 mmol/L to 1.56 mmol/L and HDL-C increased from 1.10 mmol/L to 1.24 mmol/L. It was noted that rosuvastatin in this patient population decreased stenosis diameter and increased minimum lumen diameter as measured by quantitative coronary angiography.

Large statin trials and association with new onset diabetes

We have seen from trials that statins have undoubtedly been associated with postponement of cardiovascular events and in some cases overall mortality. Thus, they are at the centre of CVD prevention especially in the presence of risk factors. Diabetes is one such risk factor and it is ironic that statins have been linked with new onset diabetes. There have been conflicting results from large RCTs reporting on new onset diabetes in the statin treated cohort.[49] Sattar et al obtained data from 13 trials between 1994 and 2009 comparing standard care with statins versus placebo (7 of which had not published their data on new onset diabetes prior to their request).[50] Their meta-analysis involved 91,140 non-diabetic individuals altogether. The criteria used to diagnose diabetes varied from trial to trial and included WHO criteria, physician reported diabetes and one or two fasting glucose values ≥7.0 mmol/L. High intensity versus standard care trials and statin versus statin trials were excluded as were trials recruiting fewer than 1000 individuals. Three of the trials had published HRs for incident diabetes and these was standardised to odds ratios (OR). A previous report on WOSCOPS identified a significant reduction in new onset diabetes; relative reduction: 30%, $P = 0.04$.[24] However, the data had to be recalculated by Sattar et al, due to the use of different diabetic diagnostic criteria (the former report on WOSCOPS required glucose to increase by at least 2 mmol/L above baseline measurement). The pravastatin treated group had a lower incidence (2.5%) compared to the control group (3.1%) after a mean 4.8 years of follow-up just failing to reach statistical significance. Overall there was an increase in new onset diabetes (OR: 1.09, 95% CI: 1.02–1.17); 4.89% in the statin treated arm versus 4.5% in controls. Figure 3 demonstrates the association with diabetes by statin used, as well at the overall association with diabetes from the meta-analysis. None of the trials were associated with a reduction in risk while JUPITER[16] and PROSPER[51] were the only trials to show increased diabetes with statins treatment.

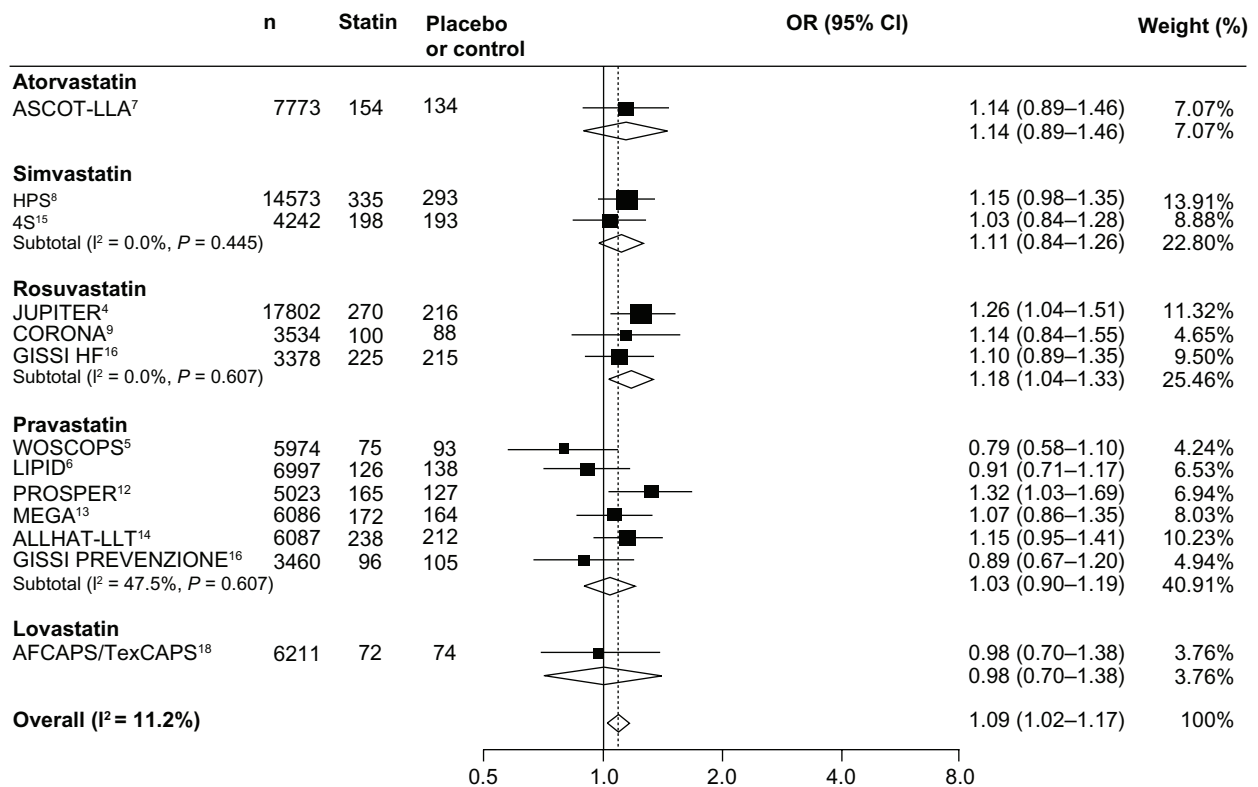|	n	Statin	Placebo or control	OR (95% CI)		Weight (%)
Atorvastatin						
ASCOT-LLA[7]	7773	154	134		1.14 (0.89–1.46)	7.07%
					1.14 (0.89–1.46)	7.07%
Simvastatin						
HPS[8]	14573	335	293		1.15 (0.98–1.35)	13.91%
4S[15]	4242	198	193		1.03 (0.84–1.28)	8.88%
Subtotal ($I^2 = 0.0\%$, $P = 0.445$)					1.11 (0.84–1.26)	22.80%
Rosuvastatin						
JUPITER[4]	17802	270	216		1.26 (1.04–1.51)	11.32%
CORONA[9]	3534	100	88		1.14 (0.84–1.55)	4.65%
GISSI HF[16]	3378	225	215		1.10 (0.89–1.35)	9.50%
Subtotal ($I^2 = 0.0\%$, $P = 0.607$)					1.18 (1.04–1.33)	25.46%
Pravastatin						
WOSCOPS[5]	5974	75	93		0.79 (0.58–1.10)	4.24%
LIPID[6]	6997	126	138		0.91 (0.71–1.17)	6.53%
PROSPER[12]	5023	165	127		1.32 (1.03–1.69)	6.94%
MEGA[13]	6086	172	164		1.07 (0.86–1.35)	8.03%
ALLHAT-LLT[14]	6087	238	212		1.15 (0.95–1.41)	10.23%
GISSI PREVENZIONE[16]	3460	96	105		0.89 (0.67–1.20)	4.94%
Subtotal ($I^2 = 47.5\%$, $P = 0.607$)					1.03 (0.90–1.19)	40.91%
Lovastatin						
AFCAPS/TexCAPS[18]	6211	72	74		0.98 (0.70–1.38)	3.76%
					0.98 (0.70–1.38)	3.76%
Overall ($I^2 = 11.2\%$)					1.09 (1.02–1.17)	100%

0.5   1.0   2.0   4.0   8.0

Figure 3. Association between different statins and development of diabetes. Reprinted from The *Lancet*, 375, Sattar et al, Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials, 735–742, (2010) with permission from Elsevier.

Sattar et al included 3 studies comparing the effects of rosuvastatin and placebo; JUPITER,[16] CORONA[52] and GISSI-HF.[53] The JUPITER study did suggest a significant increase in the risk of new onset diabetes in 2008. During the trial follow-up diabetes was diagnosed in 270 (3.0%) and 216 (2.4%) patients in the rosuvastatin and control arms respectively, both arms consisting of 8901 patients. The CORONA and GISSI HF studies, both using rosuvastatin in patients with heart failure, showed non-significant increases in new onset diabetes in the statin arms compared to placebo. ASCOT[54] was the only study included using atorvastatin (10 mg) and it revealed a non-significant increase in new onset diabetes.

As can be seen in Figure 3, only rosuvastatin showed a significant increase in incidence of diabetes when the trials were grouped by statins. Questions arise as to whether this finding relates to patient characteristics, lipid lowering efficacy, the dose of statin used or whether it is specific to the within class differences seen within statins. It was seen within the Sattar et al meta-analysis that the studies with the lowest incidence of diabetes were primary prevention studies (AFCAPS/TexCAPS[14] and WOSCOPS[11])

while those with the highest incidence included high risk patients. However, they were unable to study predictors of this apparent phenomenon. Sattar et al concluded that the increased risk of diabetes following statin treatment was small and that the benefits in cardiovascular risk clearly outweighed the increased risk of diabetes. Coleman et al published a similar meta-analysis,[55] but as all the 5 trials (WOSCOPS,[11] LIPID,[13] ASCOT,[54] HPS[15] and CORONA[52]) were included in the Sattar et al data we will not discuss it further. Similarly Ratpathak et al[56] conducted a smaller meta-analysis of trials included in Sattar et al (WOSCOPS,[11] HPS,[15] LIPID,[13] ASCOT,[54] JUPITER[16] and CORONA[52]). Analysis of all the trials together did not show a correlation between statins and new onset diabetes. Such an association was apparent however when data from WOSCOPS was removed from their original calculations.[56]

Waters et al reported a meta-analysis of 3 studies using atorvastatin.[57] SPARCL demonstrated a significant increase in the incidence of diabetes in patients on 80 mg atorvastatin; 8.71% in the atorvastatin group versus 6.06% in the placebo group.[45] The other 2 studies compared atorvastatin 80 mg and 10 mg (TNT)[17] and

atorvastatin 80 mg and simvastatin 20 mg (IDEAL).[44] Although both studies showed increases in new onset diabetes in the groups treated with atorvastatin 80 mg, this did not reach statistical significance. Waters et al inferred that the risk of developing diabetes was greater at higher doses of atorvastatin. They also evaluated factors that could have predicted diabetes in these trials. The risk of developing diabetes was associated with fasting baseline blood sugar levels >5.6 mmol/L, TG > 1.7 mmol/L; BMI > 30 kg/m² and a history of hypertension. All these factors are features of the metabolic syndrome. When all 4 of these factors were present the incidence of new onset diabetes was 25% compared to only 2% when absent.

A recently published meta-analysis by Preiss et al[58] included 5 trials (TNT,[17] IDEAL,[44] A to Z,[59] PROVE IT—TIMI22[18] and SEARCH[60]) comparing intensive dose statin therapy with moderate dose statin therapy in 32,752 non diabetic patients. An overall increase in new onset diabetes was observed in patients treated with intensive dose compared to moderate dose statin therapy (OR 1.12, 95% CI 1.04–1.22). In contrast with Waters et al, they describe higher odds of new onset diabetes for the intensive dose group with TG concentrations below the median level of distribution. Preiss et al postulated this to be a chance finding due to the multiple statistical tests involved. However, they also noted in their meta-analysis that intensive statin therapy was associated with fewer cardiovascular events (OR 0.84 CI 0.75–0.94).

Both atorvastatin and rosuvastatin increased the incidence of new onset diabetes in all studies although only in SPARCL and JUPITER respectively did this reach statistical significance.[16,57] In these trials, the doses used, baseline patient characteristics and duration of treatment all differed. Thus, it is impossible to compare their effects on new onset diabetes. We have seen that the pharmacokinetics of statins differ and even within an overall "class effect" subtle variation can be seen. A study comparing these two drugs, with outcome measures of CVD and diabetes incidence would go some way towards providing answers although the findings would only apply to the study population. There would also still remain the question of a dose response effect.

The benefits of meta-analyses include the ability to investigate variability in results, overcome small sample sizes of some of the individual trials and perhaps increase the precision of the findings. It can lead to the generation of new hypotheses and point to the next set of studies. Obviously these are limitations that affect most meta-analyses and caveats must be applied to the interpretation of these studies. Criteria for selection, the pooling of the different patient characteristics, variance in sample sizes, types of statistical analysis and measured outcomes have to be taken into account.[61]

Clinical trials investigating the pathogenesis of statin associated hyperglycaemia

Several smaller studies have examined the effect of statins on glycaemic control. With the pathogenesis of T2DM in mind we now focus on potential mechanisms by which statins may cause new onset diabetes. Insulin sensitivity, beta cell dysfunction, glucose uptake, hormonal changes leading to elevated blood sugars and changes in the effects and regulation of candidate genes associated with diabetes are potentially important factors.

Effect of statins on insulin sensitivity

Although hyperinsulinaemic euglycaemic glucose clamp is the gold standard method for the determination of insulin sensitivity, its use is limited by practical considerations.[62] Several surrogate markers have been used to evaluate insulin sensitivity. These include mathematical models such as homeostasis model assessments (HOMA) and other biochemical markers such as fasting insulin levels, adiponectin, hsCRP, insulin-like growth factor-binding protein-1, tumour necrosis factor α (TNF-α) and protein kinase C.[62] A number of studies have inversely correlated adiponectin, a protein specific to adipose tissue, with the metabolic syndrome/insulin resistance.[63,64] Features related to insulin resistance (raised TG, low HDL-C, hypertension and increased fasting plasma glucose) have also been associated with hsCRP, a marker of subclinical inflammation.[65] Similarly TNF-α has been shown to be related to insulin resistance.[66]

Baker et al conducted a meta-analysis of 16 trials comparing pravastatin (3), simvastatin (5), atorvastatin (5) and rosuvastatin (5) to placebo or controls in non-diabetic patients.[67] These studies estimated insulin sensitivity by a variety of different methods including

euglycaemic clamp, minimum model, fasting sampled intravenous glucose tolerance test, insulin suppression test, quantitative insulin sensitivity check index, HOMA, Matsuda index, Stumvoll index and Avignon index. Patient numbers and duration of follow-up ranged from 10–401 and 4–24 weeks respectively. Of these studies 14 were statin versus placebo, one comparing atorvastatin, rosuvastatin and placebo[68] and another simvastatin, pravastatin and placebo.[69] Two of the studies investigated the effects of increasing doses of simvastatin and rosuvastatin respectively. Patient characteristics in these studies varied and involved those with the metabolic syndrome, impaired fasting glucose, hypercholesterolaemia and healthy volunteers. While 10 trials were parallel in design the remaining were cross over studies with washout periods ranging from 2 to 6 weeks. The meta-analysis revealed that statins did not significantly alter insulin sensitivity compared to placebo. Baker et al then looked at within class effects and it was seen that while pravastatin significantly improved insulin sensitivity, simvastatin had an opposite effect. Atorvastatin and rosuvastatin also decreased insulin sensitivity although statistical significance was not reached. These findings are demonstrated in Figure 4. It must be stated that none of the individual studies showed any significant effect on insulin resistance. Subgroup analysis of the metabolic syndrome and non-metabolic syndrome patients did not demonstrate changes in insulin resistance. Of course, all the reservations regarding a meta-analyses described previously applies to this analysis.

Koh et al examined several studies focusing on changes in insulin sensitivity or factors associated with it (for example adiponectin) for each of the statins in both diabetic and non-diabetic patients.[70] The number of trials reviewed totalled 24; simvastatin (7), pravastatin (5), atorvastatin (10) and rosuvastatin (2). Many of these studies were included in the meta-analysis by Baker et al;[67] simvastatin (1), pravastatin (2), atorvastatin (5) and rosuvastatin (2). Although mixed outcomes were observed with simvastatin, most studies revealed worsening insulin sensitivity or changes in adiponectin reflecting it. The pravastatin related studies showed improvement in insulin sensitivity and increased adiponectin levels in patients with CHD and impaired glucose tolerance, but no change in healthy non-diabetic individuals. Interestingly, a study by Takagi et al included in the meta-analysis demonstrates that pravastatin increases insulin sensitivity and adiponectin in asymtomatic patients with hypercholesterolaemia.[71] Dose dependency was suggested by Koh et al when a significant positive relationship between the dose of atorvastatin (10, 20, 40 and 80 mg) with fasting plasma insulin and HbA1c levels and an inverse relationship with insulin sensitivity were observed when compared to either baseline or placebo. Rosuvastatin was not associated with any change in insulin sensitivity, although this may be due to the fact that only 2 studies were evaluated, one in patients with the metabolic syndrome and the other in those with familial combined hyperlipidaemia.

A study not considered by either Koh[70] or Baker[67] was performed by Ding et al[72] who observed no change in fasting plasma glucose, insulin or HOMA index after treatment with atorvastatin (10 mg–40 mg) in 27 individuals compared to 21 controls, although a decrease in adiponectin concentration was noted. Thongtang et al compared plasma insulin, adiponectin and hsCRP in 252 patients randomised to receive either atorvastatin 80 mg or rosuvastatin 40 mg.[73] Both statins significantly reduced hsCRP, but increased insulin. Glycated albumin was used as an index of glycaemia over the preceding 2–3 weeks and it was observed that atorvastatin increased it by 0.8% compared to a corresponding decrease of 0.7% with rosuvastatin. No significant difference was found between the 2 groups in adiponectin changes from baseline. Kostapanos et al investigated the effects of increasing doses of rosuvastatin (10, 20 and 40 mg) on glycaemic homeostasis (lipid profile, fasting glucose, insulin and HOMA-IR) in 72 dyslipidaemic patients with impaired fasting glucose.[74] A significant dose dependent increase was observed in plasma insulin levels and HOMA-IR values, indicating increasing insulin resistance. The best predictors of outcome were baseline HOMA-IR levels followed by the dose of rosuvastatin. These two factors also accounted for over 90% of the variability. This study was included in the meta-analysis by Baker et al[67] but not in that by Koh et al.[70]

These results do not leave us with a clear message of the effects of statins on insulin sensitivity. The weight of evidence suggests that pravastatin is least associated with worsening insulin sensitivity. With the remaining statins the effects on glycaemic homeostasis is
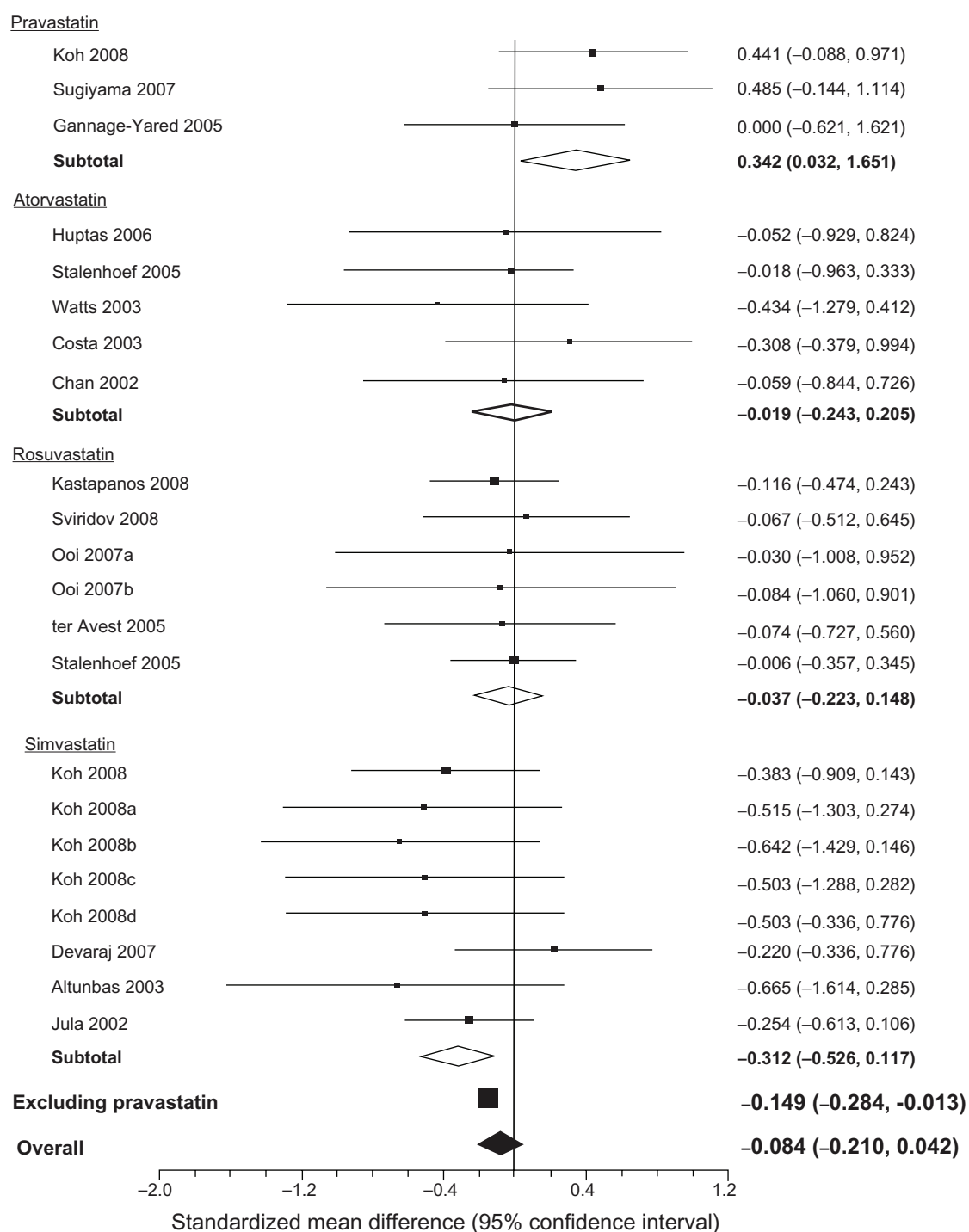
Pravastatin
Koh 2008 — 0.441 (−0.088, 0.971)
Sugiyama 2007 — 0.485 (−0.144, 1.114)
Gannage-Yared 2005 — 0.000 (−0.621, 1.621)
Subtotal **0.342 (0.032, 1.651)**

Atorvastatin
Huptas 2006 — −0.052 (−0.929, 0.824)
Stalenhoef 2005 — −0.018 (−0.963, 0.333)
Watts 2003 — −0.434 (−1.279, 0.412)
Costa 2003 — −0.308 (−0.379, 0.994)
Chan 2002 — −0.059 (−0.844, 0.726)
Subtotal **−0.019 (−0.243, 0.205)**

Rosuvastatin
Kastapanos 2008 — −0.116 (−0.474, 0.243)
Sviridov 2008 — −0.067 (−0.512, 0.645)
Ooi 2007a — −0.030 (−1.008, 0.952)
Ooi 2007b — −0.084 (−1.060, 0.901)
ter Avest 2005 — −0.074 (−0.727, 0.560)
Stalenhoef 2005 — −0.006 (−0.357, 0.345)
Subtotal **−0.037 (−0.223, 0.148)**

Simvastatin
Koh 2008 — −0.383 (−0.909, 0.143)
Koh 2008a — −0.515 (−1.303, 0.274)
Koh 2008b — −0.642 (−1.429, 0.146)
Koh 2008c — −0.503 (−1.288, 0.282)
Koh 2008d — −0.503 (−0.336, 0.776)
Devaraj 2007 — −0.220 (−0.336, 0.776)
Altunbas 2003 — −0.665 (−1.614, 0.285)
Jula 2002 — −0.254 (−0.613, 0.106)
Subtotal **−0.312 (−0.526, 0.117)**

Excluding pravastatin **−0.149 (−0.284, −0.013)**
Overall **−0.084 (−0.210, 0.042)**

−2.0   −1.2   −0.4   0.4   1.2

Standardized mean difference (95% confidence interval)

Figure 4. Association between different statins and insulin sensitivity. Reprinted from *Diabetes Research and Clinical Practice*, 87, Baker et al, Differing effect of statins on insulin sensitivity in non-diabetics: A systematic review and meta-analysis, 98–107, (2010) with permission from Elsevier.

probably dependent on the baseline characteristics of patients and the dose of statin used.

Effects of statins on insulin secretion and glucose transport

Insulin is secreted by the pancreatic β cells in response to elevated blood glucose levels.[75] This mechanism involves a change in the electrical activity of β cell ion channels and in β cell secretory function (regulated by soluble N-ethylmaleimide-sensitive factor activating protein receptor [SNARE] proteins). Glucose uptake by the β cells increases cellular ATP production with a subsequent increased ATP:ADP ratio which closes the ATP sensitive K_{ATP} channels

resulting in membrane depolarisation.[76] This in turn opens the voltage gated Ca^{2+} channels which leads to fusion of granules containing insulin with the plasma membrane; a step regulated by the SNARE proteins.[75] Specific details of this regulation by the various SNARE proteins would need a separate review article. Glucose mediated insulin secretion is biphasic consisting of an immediate first phase with limited readily available pool mobilisation followed by a second phase with larger reserve pool utilisation. SNARE proteins are involved in both these processes.[77]

Cholesterol makes up about 20% of membrane lipids and has regulatory functions. Together with sphingolipids it forms micro-domains on the cell membrane.[78] These play a part in regulating SNARE proteins in pancreatic β cells.[79] Xia et al studied the effects of reducing cholesterol synthesis by inhibiting squalene epoxidase in MIN6 (a β-cell line).[80] They found that there was inhibition of the voltage gated Ca^{2+} channels and decreased basal as well as glucose stimulated insulin release which was reversed by cholesterol repletion. It has been suggested that a mechanism for decreased insulin secretion may be related to chronic cholesterol depletion.[80]

As early as 1993 it was reported from animal studies that lovastatin may have had an inhibitory effect on glucose stimulated insulin secretion.[81] Ishikawa et al studied the effects of pravastatin, simvastatin and atorvastatin on insulin secretion using MIN6 cells.[82] Interestingly, while basal insulin secretion at low glucose concentrations was higher, output of insulin at high glucose concentrations did not increase significantly with both simvastatin and atorvastatin. Of note, these described changes to insulin secretion were much less prominent with pravastatin. The authors suggested that lipophilic statins when taken up by pancreatic β cells, either via HMG-CoA inhibition or cytotoxicity, were associated with reduced glucose mediated insulin release. These findings do not contradict the effects of insulin resistance described by some of the previously detailed clinical studies suggesting higher basal insulin secretions with atorvastatin and rosuvastatin, but not pravastatin.

It has been suggested that statins may impair insulin release via depletion of other products synthesised from the mevalonate pathway which includes ubiquinone (CoQ10) and isoprenoids, in addition to cholesterol. The depletion of CoQ10 and subsequent mitochondrial damage has been implicated in statin induced myopathy and more recently with statin related glycaemic deterioration.[83–85]

Once released, insulin activates the tyrosine kinase activity of the insulin receptor leading to phosphorylation of insulin receptor substrate 1.[86] This in turn increases the insulin sensitive solute family 2-member 4 (SLC2A4) glucose transporter in the outer cellular membrane leading to increased intake of glucose. Nakata et al investigated the effects of statins on SLC2A4 expression in NSY mice, chosen as they exhibited moderate obesity, insulin resistance and impaired insulin response to glucose.[87] Atorvastatin inhibited SLC2A4 expression, an effect reversed by addition of mevalonate or geranylgeranyl phosphate, both these isoprenoids decreased by statins. These studies point to statins potentially affecting not only insulin response, but glucose transport into cells as well.

Effect of statins on β-cell apoptosis

Histological evidence in diabetic patients has suggested a reduction in pancreatic β cell volume due to increased apoptosis with no change in neogenesis.[88] Animal studies have indicated that lipoproteins have a regulatory role in β cell survival.[89,90] It has been seen that murine β cells and β cell lines express receptors for lipoproteins, and high concentrations of LDL-C and oxidised LDL-C decrease proliferation and increase β cell apoptosis. Rütti et al exposed human and murine β cells to human plasma lipoproteins and demonstrated that LDL-C decreased β cell proliferation as well as maximal glucose stimulated insulin secretion.[91] HDL-C had the reverse effect on the survival of the islet cells. The role of free fatty acids in β cell death is also interesting. While saturated fatty acids such as palmitate are associated with toxicity, others such as oleate, a mono-unsaturated fatty acid, have been seen to protect against cell death.[92,93] In view of the findings from the above studies, there has been speculation that statins may have a protective role in relation to pancreatic β cells.[94] Although statins have been shown to induce apoptosis in several cell types by depleting isoprenoids, there does not appear to be any direct evidence of statins increasing β cell apoptosis.[95]

Effects of statins on stress hormones

Stress hormones such as corticosteroids, growth hormones and glucagon lead to increases in plasma

glucose levels. Travia et al studied basal and stimulated adrenocortical and testicular steroidogenesis following simvastatin and pravastatin treatment.[96] Baseline measurements and evaluation after 6 and 24 months of statin treatment and 2 months after discontinuation of treatment took place. They found no change in either basal or stimulated steroidogenesis. A similar finding after pravastatin treatment was observed by Böhm et al.[97] There was no evidence from studies evaluating other stress hormones of any changes that could have an impact on glycaemia.

Effect of statins on candidate genes in the pathogenesis of type 2 diabetes

Genome wide studies have identified several candidate genes associated with the pathogenesis of T2DM.[23] We have been unable to find any evidence that statins affect the regulation of any of these genes. In addition, none of them appear to have any role in the metabolism of lipoproteins.[98,99]

Adverse Effects and Safety

It has been reported that non-compliance with statins in patients with CHD can be as high as 25% to 50% after 1 year of treatment.[100] There is a belief that this non-adherence is associated with drug related adverse effects.[101] Whilst most RCTs have not shown any significant increase in adverse event rates it is well recognised that there exists a small but definite risk of musculoskeletal side effects ranging from myalgia (usually without a rise in creatine kinase) to rhabdomyolysis.[102] Nichols et al report a greater occurrence of mild statin related side effects (5%–10%) in routine practice compared to RCTs.[103] These effects appear to be a class phenomenon although within class differences can be seen.[104] Weng et al carried out a systematic review of the safety profile of statins at different doses in 75 RCTs including head to head comparisons.[105] They concluded that the incidence of major muscle related side effects was rare. When all muscle related symptoms were grouped together (including myalgia, myopathy, rhabdomyolysis) the incidence ranged between 0.01% and 11%. Variability was observed between statins. The rates varied between 3% and 4% with fluvastatin (3 studies), while the figures for atorvastatin (30 studies) and rosuvastatin (15 studies) were 0.01% to 9% and 0.8% to 11% respectively. Exercise,

lower BMI, female gender and baseline liver or renal impairment have been shown to be associated with muscle related adverse events.[106,107] Drug-drug interactions also increase the incidence of side effects with drugs metabolised by or inhibiting CYP3A4 and CYP2C9 affecting simvastatin/atorvastatin and fluvastatin/rosuvastatin respectively.[108]

Rhabdomyolysis is the most severe of the muscle related complications and entails severe muscle damage resulting in marked increases in creatine kinase often with renal impairment. The association between rhabdomyolysis and statins was observed by Graham et al who studied 252,460 patients on statin monotherapy and statin/fibrate combinations in the USA between 1998 and 2001.[109] There were 24 cases of hospitalised rhabdomyolysis. The mean incidence per 10,000 person years was 0.44 for simvastatin, atorvastatin and pravastatin (rosuvastatin was not available during this time) while the figure for cerivastatin, a statin withdrawn in 2001 was 5.34. When combined with a fibrate the incidence for simvastatin, atorvastatin and pravastatin increased to 5.98 per 10,000 patient years (rate for fibrate mono-therapy was 2.82). Interestingly the numbers needed to treat to observe one case of rhabdomyolysis was 22,727 for non-cerivastatin mono-therapy, while in older diabetics (65 years or older) it was 484 when on a statin-fibrate combination.

McAfee et al compared hospitalisation rates associated with rhabdomyolyis, myopathy, renal and hepatic dysfunction and deaths in hospital between rosuvastatin (n = 11,249) and the other statins (n = 37,282), using the database of a health insurer.[110] The incidence rate per 1000 person-years for rhabdomyolysis was 0.10 for rosuvastatin and 0.06 for the other statins with the difference not reaching statistical significance.

The solute carrier organic anion transporter family member 1B1 (SLCO1B1) gene encodes for the membrane bound Na^+ independent organic anion transporter protein 1B1 that mediates hepatic clearance of statins in addition to many endogenous substances such as bile acids.[111,112] Polymorphisms of this gene have been associated with the development of musculoskeletal side effects.[113] It has been suggested that higher plasma concentrations due to impairment of this transporter may lead to muscle related side effects. It has also been speculated that polymorphisms in the SLCO1B1 gene may not affect the pharmacokinetics of fluvastatin, a statin associated with relatively mild muscular

side effects. Pasanen et al subjected 32 patients to atorvastatin 20 mg and rosuvastatin 10 mg with a wash-out period of 1 week.[114] They observed that patients with the SLCO1B1 c.521CC genotype had a greater concentration of atorvastatin (area under the curve) than patients with the c.521TT genotype. Rosuvastatin concentrations were raised in patients with the c.521CC genotype, but not as high as with atorvastatin. Interestingly it has been reported that rosuvastatin has demonstrated a twofold increased median exposure (area under the curve and maximal concentration) in Asian patients compared to their Caucasian counterparts[115] This has seen the starting and maximum dose of rosuvastatin in Asian patients reduced to 5 mg and 20 mg respectively. At present the mechanism for this observation as well at the plasma concentration differences seen with other statins is not clear.

There has been speculation that mitochondrial dysfunction could be associated with muscle related side effects.[116,117] It has been suggested that lowering of coenzyme Q10 by statins may reduce muscle energy availability,[118,119] increase apoptosis and unmask mitochondrial defects.[120,121] However, studies relating to outcomes following coenzyme Q10 supplementation are necessary before a better understanding of this mechanism is reached.

Cognitive side effects are associated with statin treatment and are only second to muscle related problems.[122] Once again there have been views suggesting mitochondrial dysfunction being the cause of the problem.[123] Other adverse effects of statins include gastrointestinal,[124] neurological,[125] sleep,[126] erectile,[127] and psychiatric[128] complications.

Place in Therapy

Statins are now front-line agents in lowering CVD risk due to the overwhelming outcome evidence from intervention studies reviewed earlier. There are guidelines that deal with the patient group to be offered statins, the type of statin that should be used; taking into account evidence and cost-effectiveness and the lipid target for that patient population. We will briefly mention the Joint British Societies' guidelines (JBS2)[129] as well as the NICE[25,26] guidelines applicable to clinical practice in the UK. It is important to be aware of the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines that have recently been updated.[130] The Adult

Treatment Panel III/National Cholesterol Education Program guidelines in the USA (http://www.nhlbi.nih.gov/guidelines/cholesterol/) were drawn up in 2002 and reviewed in 2004 and are to be further reviewed in 2012; thus, we will not focus on them.

The JBS-2[129] define TC and/or LDL-C targets as either minimal (TC $\leq$ 5 mmol/L, LDL-C $\leq$ 3 mmol/L) or optimal (TC $\leq$ 4 mmol/L, LDL-C $\leq$ 2 mmol/L) for secondary prevention. The NICE guidelines on lipid modification (CG67)[25] and T2DM (CG66)[26] recommended simvastatin 40 mg in primary prevention for adults with a greater than 20% CVD risk as calculated by an appropriate risk calculator, in all patients with clinical evidence of CVD and patients with diabetes over 40 years of age. When simvastatin is contra-indicated either a lower dose or pravastatin is to be recommended. Should a TC target of 4 mmol/L or LDL-C target of 2 mmol/L not be met in secondary prevention patients it suggests increasing the simvastatin to 80 mg or using a statin of similar efficacy and cost; perhaps in anticipation of generic atorvastatin. A high intensity statin is recommended mainly in patients with acute coronary syndrome or patients with diabetes and CVD.

The ESC/EAS guidelines announced in 2011 as expected appear to differ in their objective.[130] They define 4 levels of cardiovascular risk, as defined by SCORE—very high, high, moderate or low CVD risk—to be used as a basis for treatment decisions. Specific LDL-C targets have been defined for each of these categories. It was stated that the clinician should base selection of the statin on the required LDL-C reduction and recommended up titration to the highest recommended dose or the highest tolerable dose to achieve target levels.

Conclusion

It is suggested by the meta-analysis of Sattar et al that a small, but significant increase in new onset diabetes is associated with some statins; approximately 4 extra patients for every 1000 patients can expect to develop diabetes.[50] There is some doubt as to whether this applies to pravastatin. It appears that patients pre-disposed to diabetes may be the individuals most at risk of new onset diabetes following statin treatment. Thus, the characteristics of the patient cohort can have an influence on this phenomenon. Studies into the influence of statins on insulin resistance and insulin secretion also suggest this association. Despite many interesting studies

investigating the causative mechanisms they are far from clear at present.

It is interesting to speculate that statins may have differing effects on the causative mechanisms of T2DM; some may increase the risk while others may be beneficial. The influence of statins on each of these mechanistic strands may be influenced by differing factors. The risk of a patient on statin therapy developing T2DM will be the sum of all these individual risks/benefits. This could provide a plausible explanation to the varying results seen in the RCTs which although not having new onset diabetes as a primary outcome, have been rigorously carried out.

There are many aspects that need further work. How does the diabetes associated with statin treatment progress? What agents should they be treated with? Why may there be within class differences? Is the lipophilic nature of the statin important? These and many more questions must be answered by designing a RCT, not just studying outcome, but also investigating the basic science of this phenomenon.

Does the data on new onset diabetes affect statin usage? For every 1000 secondary prevention patients treated with a statin for an average 4.2 years, 37 events will be postponed.[131] This benefit far outweighs the risk of diabetes. Thus, there is no need to change guidance on statin use. However, it is advisable that the glucose levels in patients treated with statins are monitored.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

Abbreviations of the Quoted Studies

A to Z, Aggrastat to Zocor; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; ASTEROID, A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; AURORA, A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis; CARDS, Collaborative Atorvastatin Diabetes Study; CARE, Cholesterol and Recurrent Events; CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure; GISSI-HF, Gruppo Italiano per lo Studio Della Sopravvivenza Nell'Infarto Miocardico Heart Failure; HPS, Heart Protection Study; IDEAL, Incremental Decrease in End Points through Aggressive Lipid Lowering; JUPITER, Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; LIPID, Long-term Intervention with Pravastatin in Ischaemic Disease; METEOR, Measuring Effects on Intima Media Thickness an Evaluation of Rosuvastatin; PLANET I, Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients with Progressive Renal Disease I; PLANET II, Prospective Evaluation of Proteinuria and Renal Function in Non-Diabetic Patients with Progressive Renal Disease II; PROCAM, Prospective Cardiovascular Münster Heart Study; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; PROVE IT—TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction Trial 22; REVERSAL, Reversing Atherosclerosis with Aggressive Lipid Lowering; SATURN, Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels; STELLAR, Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin; TNT, Treating to New Targets; WOSCOPS, West of Scotland Coronary Prevention Study.

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