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Review

Differential Effects of Different Statins on Metabolic Syndrome

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Abstract

Low-density lipoprotein (LDL) is established as the primary causal factor of atherosclerotic cardiovascular disease and blood level of LDL cholesterol (LDL-C) is directly related to cardiovascular events. Statins have been established as the primary mode of treatment to lower LDL-C. However, metabolic syndrome (MeS) is also identified as closely associated with atherosclerotic cardiovascular disease (ASCVD). The defining characters of MeS, however, are triglyceride (TG), high-density lipoprotein (HDL), small-dense LDL (and not total LDL), blood pressure, body weight and blood sugar level. MS is also associated with pro-inflammatory and pro-thrombotic states. Statins vary in their effects on these parameters of MeS. Thus, while treating dyslipidaemia in presence of MeS, the choice of statin does matter. This article reviews these differing effects of different statins on the individual characters that define MeS.

Keywords: Metabolic syndrome, statins, differential effects

Introduction

Metabolic syndrome is a constellation of diverse atherosclerotic cardiovascular disease (ASCVD) risk factors arising primarily from insulin resistance and glucose intolerance.

As per the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III of 2005, clinically MeS is diagnosed if an individual is positive for three or more of the following measurements.[1]

- Abdominal obesity (waist circumference ≥40 inches in men or ≥35 inches in women)
- High blood pressure (≥130/85 mm Hg) or under treatment
- High fasting blood glucose (≥100 mg/dL) or under treatment
- Elevated TGs (≥150 mg/dL) or under treatment
- Low high-density lipoprotein cholesterol (HDL-C) (males <40 mg/dL; females <50 mg/dL) or under treatment

Atherogenic dyslipidaemia in MeS is characterized by low plasma level of HDL-C, increased level of TG and a preponderance of small-dense (sd) particles of low-density lipoprotein cholesterol (LDL-C). The fundamental lipid abnormality may be a high level of very-low-density lipoprotein (VLDL).[2]

Multiple factors are associated with MeS including physical inactivity, atherogenic diet, tobacco use, family history of premature coronary heart disease (CHD), ageing, insulin resistance, glucose intolerance, pro-inflammatory state like elevated blood levels of high sensitive C-reactive protein (hs-CRP), tumour necrosis factor-alpha (TNF-a), interleukins (IL-6, IL-8), and pro-thrombotic state like high fibrinogen or plasminogen activator inhibitor-1 (PAI 1).[3]

Collectively or independently, all these factors endanger the risk for cardiovascular disease (CVD), type 2 diabetes mellitus (T2D), and vascular or neurological complications including stroke.

Framingham risk score estimates the 10-year risk of CHD based on cigarette smoking, blood pressure, total cholesterol, HDL-C, and age thus considering two components of MeS and triages patients into 3 risk categories based on a 10-year risk of CHD, while patients with ASCVD or diabetes are already in a high-risk category without need of Framingham risk scoring.

Recently, SCORE system has been used to assess ASCVD risk by the European Society of Cardiology (ESC) which considered age, gender, systolic blood pressure, total cholesterol and smoking status to calculate the future cardiovascular risk.[4]

Management of MeS aims to reduce both a short-term and lifetime risk with lifestyle changes, primarily aiming at weight loss, diet, and exercise and appropriate use of pharmacological agents to reduce the specific risk factors including optimizing the lipid levels.[5]

Statins are the most effective and best-tolerated agents widely used for treating dyslipidaemia with additional pleiotropic effects to reduce oxidative stress and modulation of inflammatory responses (e.g., decrease in hs-CRP). They also improve endothelial function, stabilise atherosclerotic plaques, decrease platelet activation, and inhibit thrombogenicity and smooth muscle cell proliferation. Statins are universally recognized to reduce cardiovascular morbidity and mortality in large outcome trials in various populations including patients with MeS.[2]

Though the effects of statins are generally ascribed to as a class effect, there are some intraclass variations, particularly relevant while dealing with cases of MeS. **Table 1** summarizes the effects of different statins on the main components of metabolic syndrome. It must be noted that the purpose of this table is to give a gross idea as to the differential effects of statins, but it is no way conclusive. It may also be noted that the effects also vary according to the dose of a statin.

Table 1. Effects of different statins on the components of metabolic syndrome

Name of statin	Abdominal obesity	Serum uric acid	New onset diabetes	Triglyceride (reduction)	HDL-C (increase)
Atorvastatin	? Increase	-6.5%	+13%	23% - 33%	5% - 9%
Pitavastatin	-	+3.5%	-26%	32%	29%
Pravastatin	-	-	+4%	12% - 15%	3% - 7%
Rosuvastatin	-	-3.6%	+24%	22% - 34%	8% - 11%
Simvastatin	-	-	+21%	15% - 23%	8% - 10%

Variable Properties of Statins

Statins competitively inhibit hydroxymethylglutaryl coenzyme A (HMG-CoA), thereby decrease cholesterol biosynthesis, reciprocally upregulate hepatic LDL receptors, and enhance the clearance of apo B-containing lipoproteins; thus, regulating lipoprotein metabolism.

Synthetic statins (atorvastatin, cerivastatin, fluvastatin, pravastatin, pitavastatin, and rosuvastatin) inhibit HMG-CoA reductase more; e.g., rosuvastatin is the most potent statin to reduce HMG-CoA, by more than 50%. Natural statins (fungal derived lovastatin, pravastatin, and simvastatin) are weaker in this regard.[6]

Hydrophilic statins (pravastatin and rosuvastatin) target the liver more efficiently because their uptake is carrier-mediated, while lipophilic statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin and simvastatin) are less hepatoselective and diffuse in extrahepatic tissues, thus showing a higher incidence of adverse effects. Hydrophilic statins, on the other hand, maybe less pleiotropic. Though a head-to-head comparison is lacking, meta-analyses suggest that lipophilic statins have more beneficial effects on heart failure and related clinical outcomes compared to hydrophilic statins (rosuvastatin). But the subject is nowhere near conclusive.[7]

The side chains of statins determine their pharmacokinetic (PK) and pharmacodynamic (PD) properties as well as their pleiotropic effects and drug-drug interactions.

Statins Effects on Lipids in Metabolic Syndrome

The efficacy of statins for reductions in LDL-C, reductions in TG, and increases in HDL-C is well documented by a multitude of clinical studies, observational studies and meta-analysis including patients with MeS.

Subgroup analyses in 893 patients who fulfilled the criteria for the MeS in the Scandinavian Simvastatin Survival Study (4S), showed, compared to placebo treatment, simvastatin significantly reduced LDL-C (- 35.3% reduction), TG (- 21.1 % reduction), total cholesterol and non-HDL cholesterol and increased HDL-C (+8.7% increase) after 1 year.[8]

Simvastatin (20 or 40 mg/d) produced a 37.5% versus a 36.0% decrease in LDL-C, 24.1% versus 6.7% decrease in TG, and a 10.3% vs. a 0.6% increase in HDL-C in MeS patients compared with patients not having MeS.[6]

Ballantyne CM *et al*. analysed data from 5 trials in 580 patients with the metabolic syndrome completing 12 weeks treatment with rosuvastatin 10 mg daily. It decreased LDL-C (-47%), non-HDL cholesterol (-43%), non-HDL cholesterol/HDL cholesterol ratio (-47%), apolipoprotein B (-37%), apolipoprotein B/apolipoprotein A-I ratio (-40%), triglycerides (-23%), and increased apolipoprotein A-I (+7%), and HDL-C (+10%).[9]

Post hoc analysis of data from a 6-week, randomized comparative trial assessed effects of rosuvastatin, atorvastatin, simvastatin, and pravastatin across dose ranges in 811 hypercholesterolemic MeS patients as per the NCEP ATP III criteria for MeS (body mass index >30 kg/m^2 substituted for waist circumference). Rosuvastatin showed the highest efficacy in reducing LDL-C, reducing TG and increasing HDL-C compared to all other statins although all statins had a favourable effect in hypercholesterolemic patients on the atherogenic dyslipidaemia associated with MeS. Percent reductions in LDL-C ranged from 20% in the pravastatin 10-mg group to 55% in the rosuvastatin 40-mg group; TG reductions were 22% to 34% with rosuvastatin, 23% to 33% with atorvastatin, 15% to 23% with simvastatin, and 12% to 15% with pravastatin. HDL-C increased by 8% to 11% with rosuvastatin, 5% to 9% with atorvastatin, 8% to 10% with simvastatin, and 3% to 7% with pravastatin.[10]

There are no consistent differences in HDL responses between the upper and lower starting doses of each statin. Rosuvastatin appears to increase both HDL-C and apolipoprotein (apo) A-I to a greater extent compared to other statins. Average increases of HDL-C by different statins have been calculated to as follows: rosuvastatin 8.5%, pravastatin 6.5%, simvastatin 6.4%, atorvastatin 5.5%.[11]

One meta-analysis found that, with exception of atorvastatin, statin-induced increases in HDL-C occurred in parallel with reductions in LDL-C. It subscribes to the view that the main mechanism of statin-mediated increases in HDL-C is reduced cholesterol ester transfer into VLDL and LDL, secondary to reduced levels of these lipoproteins. The reason atorvastatin does not conform to this pattern and the potential clinical significance is unknown.[12]

Although most statins increase HDL-C levels to some extent, pitavastatin consistently produces significantly greater HDL elevations that are maintained, or increased, over time.[13] Moreover, pitavastatin appears to improve HDL-C function and to slow the progression of atherosclerotic plaques by modifying HDL-C-related inflammation and oxidation, both of which are common in patients with MetS and T2D.[14]

In a trial comparing low and high doses of rosuvastatin, it was found that high-dose statin therapy significantly reduced the sd-LDL and malondialdehyde-modified LDL-cholesterol MDA-LDL in comparison with low-dose statin therapy.[15]

Statins on Chronic Heart Disease Events in Metabolic Syndrome

Three large trials of statin treatment for CHD prevention: the West of Scotland Coronary Prevention Study (WOSCOPS), the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), and the 4S clearly showed that metabolic syndrome at baseline was an important risk for CHD event (the increase was 1.8- fold in the WOSCOPS, 1.4-fold in the AFCAPS/TexCAPS, and 1.5-fold in the 4S).[8]

In a recently published large trial of 27000 patients, it has been shown that MeS is associated with 60% cases of ASCVD. This group of patients draw maximum benefit from the aggressive treatment of dyslipidaemia including evolocumab on top of maximally tolerated doses of statins.[16]

Patients with MeS experienced greater reductions in coronary events than did patients with isolated LDL cholesterol elevations. In 4S study, compared with placebo, treatment with simvastatin significantly reduced atherosclerotic events; relative risk reduction seemed to be greater with simvastatin in the subgroup of patients with the metabolic syndrome (31–61%) across all endpoints.[8]

MeS continued to predict CHD events as per the post hoc analysis of the WOSCOPS wherein 1691 subjects having the MeS, treatment with pravastatin decreased CVD events by 27%. Men with MeS had a significantly higher risk for CHD (3.7-fold increase) and diabetes (24.5-fold increase) compared with men with no MeS. Pravastatin had similar risk reduction for CHD in men with or without MeS (HR, 0.73 and 0.69; pravastatin versus placebo).[17]

Statins on Inflammatory Markers in Metabolic Syndrome

Data indicate that CRP, a marker of systemic inflammation and atherogenesis, predicts cardiovascular risks like myocardial infarction, stroke and sudden death in healthy as well as in established CHD patients and patients with acute ischemia. Statins have shown to reduce CRP levels independent of their action on lipids. The CRP-lowering effect of statins is a class effect shared by all.[18]

CRP also enhanced prognostic information in WOSCOPS for both outcomes of CHD and diabetes in MeS patients.[17]

In the AFCAPS/TexCAPS study, treatment with lovastatin also resulted in 37% reduction ($p< 0.001$) in the risk for first acute major coronary events; in fact, the benefit of statin therapy in reducing coronary events in MeS patients was only evident in those with CRP >1 mg/L. If the baseline CRP was less than 1 mg/L, whether MeS was present or not, there was no benefit of statin therapy. In primary prevention setting for low-risk population, CRP may be used to decide initiation of statin therapy in subjects with MeS.

In Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial (n=17,802), rosuvastatin 20 mg per day significantly reduced the incidence of the major cardiovascular event despite lipid levels below the threshold for treatment according to prevention guidelines. Rosuvastatin reduced CRP levels by 37% (to mean of 2.2 mg/L) and LDL by 50% (to mean of 55 mg/dL). In this study, 41.4% of the subjects who had MeS also showed similar significant benefit as in those without MeS.[19]

The production of pro-inflammatory cytokines in MeS leads to the inhibition of the fibrinolytic/antithrombotic pathways. Through their anti-inflammatory effect, statins inhibit IL-1 and TNF-α production and improve endothelial function, and thus may help reverse the hypercoagulability associated with MeS.

One study showed that pitavastatin progressively normalised the triglycerides-to-cholesterol ratio within 6 months of treatment, without modifying glucose metabolism or significantly changing HDL levels. Furthermore, the study suggested that pitavastatin enhances plasmalogen production, and, although the biochemical mechanism is not completely understood, this might be clinically relevant in reducing oxidative stress and inflammation. Moreover, an effectiveness analysis showed that pitavastatin treatment resulted in a significant decrease of high-sensitivity C-reactive protein (CRP) levels in patients with metabolic syndrome, whereas high-molecular-weight adiponectin levels did not change.[20]

Statin and Risk of Diabetes in Metabolic Syndrome

An increased risk of developing new-onset T2D after long-term statin treatment is well documented in several observational studies, clinical trials and meta-analyses implicating almost all statins (pravastatin, simvastatin, atorvastatin and rosuvastatin). Data indicate that different statins have varying effects on the risk of T2DM and an excess risk ranging from 9% to 13%, with the highest risk of T2D seen in patients taking high-intensity statin therapy.

Risk of T2D and hyperglycaemia deterioration were assessed in the MeS in men (METSIM) in a 6-year follow-up cohort; wherein statin therapy was associated with a 46% increased risk of T2D and was attributable to statin (both simvastatin and atorvastatin) induced dose-dependent decreases in insulin sensitivity and insulin secretion.

The JUPITER study compared rosuvastatin with placebo (20 mg/day) over a median of 1.9 years, and showed a small but significant increase in diabetes incidence rates (an absolute increase of 0.6%; relative increase of 24%; $p=0.01$); the risk may increase by 10% with higher statin doses. Subjects with one or more major diabetes risk factor were at higher risk of developing T2D. Another study of the effectiveness of additional reductions in cholesterol and homocysteine found that the simvastatin treatment was associated with a dose-dependent increased risk of diabetes, with diabetes found in 11.6% participants who received 80 mg simvastatin compared to 10.9% in participants receiving 20 mg simvastatin.[21]

A meta-analysis of 29 trials (1,63,039 participants of which 1,41,863 were non-diabetics) showed that statins, as a class, significantly increased the likelihood of developing diabetes by 12%. Atorvastatin 80 mg was associated with the highest risk of T2D, followed by rosuvastatin and simvastatin 80 mg, indicating that statins have varying effects on the risk of T2D. The odd ratio (95% CIs) for simvastatin 80 mg, simvastatin 20 mg, atorvastatin, pravastatin, lovastatin and pitavastatin were 1.21 (0.99-1.49), 1.13 (0.99-1.29), 1.13 (0.94-1.34), 1.04 (0.93-1.16), 0.98 (0.69-1.38) and 0.74 (0.31-1.77), respectively. Notably, pitavastatin reduced the rate of new-onset T2D by other trials as well.[22,23]

Most importantly, despite the increase of T2DM, it is important to emphasize the benefits of statin administration in reducing myocardial infarction, stroke and cardiovascular deaths in high CVD risk patients.

Statin and Uric Acid in Metabolic Syndrome

Elevated serum uric acid (SUA) is a strong risk factor of increased cardiovascular disease (CVD) in patients with MeS. Differential effects of statins on plasma uric acid levels could be featured basis physicochemical variations, metabolism, and pharmacokinetics of each statin.

Atorvastatin significantly lowers serum uric acid. It may augment urine uric acid excretion due to decline in proximal tubular reabsorption of uric acid and being lipophilic, it may have better tissue effects, including improving endothelial function and regulating renal vasculature, thus improving renal blood flow and glomerular filtration rate (GFR), thus decreasing serum uric acid levels.

In the ATOrvastatin and ROSuvastatin (ATOROS) study, SUA levels decreased in the atorvastatin-treated group but did not significantly change from baseline after rosuvastatin treatment.[24]

In another trial, however, SUA level compared after few months with the baseline levels was significantly decreased in the atorvastatin and rosuvastatin groups by 6.5% and 3.6%, but in pitavastatin group, the SUA level increased by 3.7%.[25]

Statins and Body Weight

There is some anecdotal evidence that atorvastatin increases body weight. In early days of statin use, it was promoted as a panacea against heart disease, and as such, people resorted to dietary indiscretion (the "Tony Roma" effect). Reality soon set in and emphasis on lifestyle management was reinforced with the result of weight reduction in statin users as they were already labelled as high-risk for ASCVD.

In some patients, statins, particularly high intensity statins, do cause reduction of abdominal visceral fat, thereby addressing MeS parameters.

Summary

Statins are the drug of choice for treating dyslipidaemia, with or without MeS. Most of their effects and side effects are related to the class. However, due to differing structures and pharmacokinetic and pharmacodynamic properties, they differ to some extent in their actions. In Mes, these variations become somewhat more relevant. Their main difference lies in the drug-drug interaction, which is beyond the scope of this discourse. Special attention needs to be given to the effects of different statins on the TG and HDL-C levels and also to their diabetogenic potentials while dealing with MeS patients.

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