Role of statin therapy in the management of patients with the metabolic syndrome

Ewa Dembowski, Michael H. Davidson

Abstract

Patients with the metabolic syndrome (MS) have an increased risk of developing cardiovascular disease (CVD) and diabetes. Treatment goals to reduce this risk include aggressive lipid lowering. However, despite aggressive management with statins, there remains a high residual risk in patients with MS. Clinical trials continue to provide evidence that more aggressive risk factor modification results in improved CVD outcomes, but implementation and achievement of the myriad of goals frequently requires multiple therapeutic approaches. The addition of combination therapy with statins is emerging as the optimal therapeutic approach to further lower the risk of CVD in patients with MS.

Key words: metabolic syndrome, statins, lipids, dyslipidemia, risk factors.

The metabolic syndrome (MS) describes a clustering of modifiable risk factors associated with an increased risk of developing cardiovascular disease and diabetes [1-4]. These risk factors include various combinations of hypertension, abdominal obesity, glucose intolerance, and atherogenic dyslipidemia [4-7]. The prevalence of the MS represents a growing public health problem, following the global increasing trends in obesity, diabetes and aging of the population. Lifestyle change directed toward weight reduction and increased physical activity is essential and considered to be the first-line approach to reducing the risk factors associated with the MS. However, patients with the MS often require pharmacologic intervention for the management of dyslipidemia, hypertension, and hyperglycemia to further reduce their risk for coronary heart disease (CHD) [8].

The major abnormalities that constitute the atherogenic dyslipidemia associated with the MS include low levels of high-density lipoprotein (HDL) cholesterol, high levels of triglycerides (TG), as well as elevated numbers of small, dense, low-density lipoprotein (LDL) particles [9]. The LDL cholesterol levels may be increased however may also remain within the normal range. In fact, studies have shown that the risk of CHD in patients with MS is increased irrespective of absolute LDL levels [4]. It is the increased density and decreased size of the LDL particles in the MS that is believed to enhance their atherogenicity.

It is well accepted that statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, lower LDL cholesterol levels and reduce the risk of cardiovascular events in many high-risk patients [7, 8, 10]. Statins have also been shown to increase HDL and lower TG levels. In addition,
although of unknown clinical significance, statins have been reported to have effects independent of lipid level alterations. These “pleiotropic” effects include among others: vasodilation, plaque-stabilization, as well as antioxidant, anti-inflammatory and anti-thrombotic effects [11].

The clinical significance of the high residual risk in patients with the MS or diabetes on statin therapy is of growing importance because of the increasing prevalence of obesity and the associated comorbidities in the world. Therefore, new strategies are emerging to better define the therapeutic targets and the implementation of therapies to achieve these more aggressive goals.

Patients with the MS have become an increasingly complex management challenge for cardiologists and other clinicians. Clinical trials continue to provide evidence that more aggressive risk factor modification results in improved cardiovascular disease (CVD) outcomes, but implementation and achievement of the myriad of goals frequently requires multiple therapeutic approaches.

**Targets of therapy for patients with metabolic syndrome**

Relative risk reduction is most frequently mentioned to describe the benefits of lipid lowering therapy. In statin trials, a 1% decrease in LDL-C is generally associated with a 1% relative risk reduction in cardiovascular (CV) events [12-16]. In the subgroup of patients with type 2 diabetes, the relative risk reduction is similar to that in the non-diabetic population, but there is generally a greater absolute risk reduction, especially in patients with documented CVD, because of the much higher baseline risk of CV events [15]. Therefore, in patients with type 2 diabetes and/or MS, absolute risk reduction, which determines the number needed to treat to reduce events and thereby drives the cost and benefits of therapy, represents the better term to evaluate the overall benefits of treatment. In general, relative risk reduction is driven by the percent reduction in LDL-C whereas absolute risk reduction is determined by the baseline risk for CV events. In addition, since the patients with type 2 diabetes have a much higher baseline risk for CV events, the residual risk remains elevated despite statin therapy (Figure 1) [1, 16].

Based on the concept of treating the patients with the greatest absolute risk most aggressively, the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) identified treatment goals for patients at high risk for cardiovascular events: including those with cardiovascular disease, diabetes mellitus, or a 10-year coronary heart disease risk of >20%. The recommendations established an LDL cholesterol goal of <100 mg/dL and a non-HDL cholesterol goal <130 mg/dL for this high risk population [4]. The NCEP ATP III report also recognized the importance of treating metabolic risk factors as a secondary target of cardiovascular risk reduction, after LDL cholesterol reduction.

According to NCEP ATP III [4] the definition of high-risk includes patients with clinical atherosclerosis, diabetes, or those without these conditions, but with an adapted Framingham 10-year absolute risk of CAD of >20% [4]. There are already 2 accepted modifications of the guidelines based on the HPS [17]. NCEP ATP III allows clinical judgment in the initiation of lipid-lowering therapy for patients at high risk with an LDL-C level between 100 and 130 mg/dL [4]. Based on the HPS results demonstrating a benefit regardless of the baseline LDL, the clinical judgment zone at 100 to 130 mg/dL should no longer exist; for patients with baseline LDL <100 mg/dL, consideration should be given for the initiation of treatment. Although this high-risk group is already estimated to be 20 million people in the United States, and it is likely to grow as the population ages and becomes more obese, there is increasing interest in identifying a higher-risk primary prevention population to target for more aggressive lipid-lowering goals. Hs-CRP is a laboratory blood test that is very highly correlated with the presence of MS [18]. The AHA/CDC recommendation to utilize hs-CRP screening in patients with a Framingham 10-year risk of 10 to 20% may identify another significant portion of the population that requires the more aggressive LDL-C goal of <100 mg/dL as opposed to the present goal of <130 mg/dL [18]. Based on the hs-CRP observational data, a Framingham 10-year risk of ≥5% in conjunction with an hs-CRP level in the borderline risk range (1.0-3.0 mg/L) confers a substantially higher relative risk. This data would support a high-risk classification for patients with a Framingham 10-year risk of ≥5% in conjunction with an hs-CRP level of ≥2.0 mg/L [19]. Because an hs-CRP of 2.0 mg/L is approximately the median level for adults in the United States, this strategy could potentially result in a significant increase in the US population that would be classified as high risk for more aggressive treatment. An alternative
strategy is the screening of patients with any of the 5 criteria for the MS (visceral obesity, low HDL, hypertriglyceridemia, hypertension, or impaired fasting glucose) for elevated hs-CRP. This strategy would approximate the screening of patients with a Framingham score of ≥5%, but because the score is so influenced by age or sex, this approach would probably incorporate younger US patients. In patients with the MS, hs-CRP remains an important predictor of CV events [20]. Therefore, rather than a blanket recommendation to treat all patients with the MS to an LDL-C goal of <100 mg/dL, regardless of the risk classification, perhaps a more cost-effective approach would be to consider patients with the MS as high risk only if they have an hs-CRP level ≥2.0 or a Framingham score of ≥20%. It is hoped that the JUPITER trial will provide important insights into the utility of hs-CRP level as a screening measure to identify patients who require more aggressive risk modification [21]. The issue of risk classification of MS patients remains a difficult challenge because >40% of the older adult population have the MS and this figure is likely to grow significantly over the next decade. Evidence-based trials, which include cost-effectiveness evaluations, will likely be necessary to establish the appropriate treatment recommendations for this growing at-risk population.

Lipoprotein subfraction testing has also been advocated as a means to further define risk beyond that determined by a standard fasting lipid profile. The evidence supporting the use of lipoprotein subfraction testing to assess LDL-C particle number, distribution, and size to more accurately predict CV risk is generally positive, but some data suggest otherwise [19, 22]. The presence of high levels of both small, dense LDL-C and hs-CRP correlate with the MS. The hs-CRP appears to predict CV events better than small, dense LDL-C [22], and it is unclear whether LDL-C particle size continues to correlate with increased risk if non-HDL-C or total cholesterol/HDL-C goals are achieved. With these limitations, it is unlikely that guideline recommendations will be modified to include lipoprotein subfraction testing to enhance CV risk detection.

Apolipoprotein B: Apolipoprotein (apo) B levels have been advocated as a better measure of CVD risk than either LDL or non-HDL and have the advantage of providing a target for a single parameter as opposed to multiple targets of LDL and non-HDL, if triglycerides exceed 200 mg/dL [23]. Apo B reflects all the atherogenic lipoproteins and has consistently been demonstrated to predict CV risk better than LDL in outcome trials [24]. An apo B level <90 mg/dL has been proposed as an alternative to the NCEP ATP III goal of LDL-C <100 mg/dL and non-HDL-C <130 mg/dL [25]. On the basis of an evaluation of >22,000 patients receiving statin therapy in clinical trials, if apo B was <90 mg/dL, almost all the patients were at the dual goal of LDL-C <100 and non-HDL-C <130 mg/dL [23]. Alternatively, many high-risk patients at the NCEP ATP III LDL and non-HDL goals had apo B levels >90 mg/dL. An optional apo B target of <80 mg/dL would be the potential goal for very high risk patients [23]. The apo B-apo A1 ratio has been shown to have the greatest predictive value in epidemiologic and outcome trials, and a goal of <0.7 has been proposed for high-risk patients [24].

Triglyceride-HDL ratio, LDL particle number and LDL particle size: In patients with type 2 diabetes and MS, there is a high prevalence of elevated triglycerides, low HDL, and an increase in the number of small, dense LDL particles. This clustering of lipid abnormalities has been given multiple names, including, recently, the atherogenic index of plasma, defined as log(triglyceride-HDL), with a ratio of ≥3.5 reflective of a high prevalence of insulin resistance [25-27]. An elevated triglyceride-HDL ratio has been demonstrated to be a good indication of outcome benefits with fibrates and therefore may help guide the choice for lipid-altering therapy in addition to statin treatment. In addition, pioglitazone has been shown to significantly reduce the atherogenic index of plasma in patients with type 2 diabetes [28]. Alternatively, more precise measurements of LDL particle size are available to access increased residual risk in patients with type 2 diabetes.

Inflammatory markers

High sensitivity C-reactive protein (hs-CRP) has been shown in multiple trials to enhance risk prediction independently and additively to LDL-C [29]. In both the PROVE-IT and A to Z trials with acute coronary syndromes, the dual goal of LDL-C <70 mg/dL and hs-CRP <20 mg/L was associated with the lowest risk for recurrent CVD events [30]. Because hs-CRP is reflective of an increased risk factor milieu, this inflammatory marker, if elevated, may help guide the intensification of risk factor modification. In the PROVE-IT trial, in the cohort of patients with all the major risk factors corrected, the hs-CRP was low, and the event rates were also concurrently reduced. Lipoprotein-associated phospholipase A2 has been proposed as an inflammatory marker that has been implicated in a causative role in the development of atherosclerosis and may enhance risk prediction in addition to hs-CRP [31].

In 2004, based on several trials published after its 2001 recommendations [17, 32] the NCEP ATP III revised its recommendations, suggesting an LDL goal of <70 mg/dL and non-HDL goal of <100 mg/dL for those patients at the highest risk of CHD, including those with multiple risk factors of the MS [33]. The value of lowering LDL to levels below 100 mg/dL in patients with stable coronary disease
was subsequently validated in the Treating to New Targets (TNT) trial [34]. TNT showed that lowering LDL cholesterol to mean levels of 77 mg/dL with atorvastatin 80 mg/day reduced the rate of major cardiovascular events by 22% compared with atorvastatin 10 mg/day (p=0.026) over a median follow up of about 5 years.

A post hoc analysis of the TNT study investigated a subgroup of patients with CHD and the MS [35]. Consistent with previously described lipid profiles in the MS, the overall cohort of patients in this analysis had similar baseline mean levels of LDL and total cholesterol, but slightly lower HDL and slightly higher TG levels compared to patients without the MS. However, despite similar baseline LDL levels, patients with CHD and the MS were found to be at significantly higher cardiovascular risk (a 44% increase in absolute risk) than those with only CHD.

The increased risk for cardiovascular events in the MS cohort was reduced by aggressive LDL lowering. After three months of treatment, patients treated with atorvastatin 80 mg had a mean LDL of 72.6 mg/dL compared to 99.3 mg/dL in the atorvastatin 10 mg group. After a median follow up of about 5 years, major cardiovascular events occurred in 13% of patients receiving atorvastatin 10 mg compared with 9.5% receiving atorvastatin 10 mg. This post-hoc analysis demonstrated that the more components of the MS, the greater the absolute benefit from more aggressive LDL-C reduction. In fact, if patients had no MS components, there was no benefit for 80 mg of atorvastatin. This supports the concept that all the benefit of more aggressive LDL-C reduction is driven by the patients with the greater absolute risk, which is characterized by any of the five components of the MS. Patients with the MS and CHD have a favorable number needed to treat (NNT) to reduce cardiovascular events (Figure 2). This finding represented a 29% relative risk reduction in events for the high dose statin treatment arm. Thus, subgroup analysis of TNT for patients with the MS support the idea that this group of patients is at increased risk for cardiovascular events and provides a compelling rationale for more intensive LDL lowering therapy.

Efficacy of statins in metabolic syndrome

The efficacy of statins in achieving reduction of LDL and improvement of lipid profiles in patients with the MS has been suggested in numerous post hoc analyses of large outcome trials [36-39]. The first prospective study of the efficacy of statin therapy in the MS was The COMparative study with rosuvastatin in subjects with METabolic Syndrome (COMETS) trial [40]. COMETS randomized patients with the MS (as well as LDL levels >130 mg/dL and a 10-year coronary heart disease risk score of >10%) to receive rosuvastatin 10 mg, atorvastatin 10 mg or placebo for 6 weeks. Patients were then treated with an additional 6 weeks of either rosuvastatin 20 mg (rosuvastatin and placebo groups) or atorvastatin 20 mg (atorvastatin group). Both treatment groups were found to have a significant LDL lowering compared to placebo. Treatment with rosuvastatin 10 mg, however, resulted in significantly greater reduction in LDL lowering than atorvastatin 10 mg (41.7 vs. 35.7%, p<0.001) after 6 weeks of treatment. The percentage reduction from baseline after 12 weeks of treatment remained significantly better in the rosuvastatin group (48.9 vs. 42.5%, p<0.01). The rosuvastatin group also had significantly greater improvements in HDL (9.5 vs. 5.1%, p<0.01) but similar reductions in TG (19.1 vs. 20.9%) [40]. COMETS provides direct evidence for the benefit of statin therapy in lowering LDL levels for patients with the MS.

High residual risk in patients with the metabolic syndrome

But despite aggressive LDL lowering therapy, there remains a significant residual risk of morbidity and mortality in patients with the MS. In review of patients with low HDL in most statin event trials, there is an elevated rate of residual events even with statin treatment. In fact, the event rates in subgroups of high risk patients, such as those with diabetes and features of the MS, are often found to be higher in the statin treatment group than the placebo group [17, 41-43].

In the Heart Protection Study (HPS) [17] subgroup analysis of patients with low levels of HDL cholesterol (<35 mg/dL), simvastatin had an event rate of 22.5% vs. an event rate of 20.9% for patients...
receiving placebo. Patients with hypertriglyceridemia (TG >254 mg/dL) had an event rate of 23.2 vs. 23.7% for patients receiving placebo (TG <177 mg/dL). Therefore patients with low levels of HDL and high levels of TG on statin therapy have a residual risk of cardiovascular events comparable to placebo-treated patients with normal levels of HDL cholesterol and triglycerides.

In TNT, patients taking atorvastatin 80 mg had a 29% relative risk reduction in cardiovascular events compared to atorvastatin 10 mg group [35]. Therefore, approximately 70% of the events were not avoided in patients with MS despite significant LDL reduction. This study highlights the fact that even with a LDL <70 mg/dL, a patient with CHD who has the MS is likely to have a high recurrent event rate.

**Combination therapy to reduce residual risks in metabolic syndrome**

Recognizing this high residual risk of cardiovascular events in patients with MS, there is an emerging need for additional strategies to achieve the treatment goals. Notably, less than one-half of patients in the atorvastatin 80 mg arm of TNT achieved an LDL goal of <70 mg/dL. This suggests that statin therapy alone is often not sufficient in achieving target goals in the patients with the MS. The NEPTUNE II survey demonstrated this difficulty [44] 75% of the cardiovascular disease population surveyed were classified as high risk and therefore eligible for LDL cholesterol goals of <70 mg/dL. However of this group, only 18% of patients achieved this LDL goal.

Aggressive statin therapy should still be considered the cornerstone of initial therapy in patients with the MS. Clinical trial evidence in statin trials have demonstrated both safety and event reduction of higher statin doses. Although statins have a 40% higher rate of adverse effects than placebo, the rates of significant musculoskeletal and hepatic toxicity are very low in high dose statin therapy [45]. This increased risk of liver enzyme elevations or myopathy does not correlate with level of LDL cholesterol reduction. Rather, plots of LDL reduction by dose of statin indicate that the toxicity rate increases once a specific dose threshold is exceeded [46]. In general, statin doses are very safe until the 40 mg dose, and the titration from 40 to 80 mg is associated with a 3-fold increase in liver toxicity or myopathy [15]. This suggests that combination therapy for patients on a 40 mg dose, rather than an increase in that statin dose, may be more effective in achieving LDL goals while remaining at an acceptable safety profile.

Ezetimibe, a cholesterol absorption inhibitor, added to statin therapy results in an additional 15 to 20% reduction in LDL [47]. This addition does not increase the risk of myopathy or liver toxicity beyond that of statin therapy alone. Furthermore the addition of ezetimibe to statin therapy has been shown to be significantly more effective in lowering LDL cholesterol and achieving LDL target goals than doubling the statin monotherapy dose.

However, in patients with the mixed lipidemia of the MS, levels of LDL alone do not adequately represent the risk associated with atherogenic lipoproteins. The NCEP ATP III guidelines have recommended a non-HDL goal of <100 mg/dL in addition to an LDL goal of <70 mg/dL as a secondary target of therapy in patients with serum TG levels >200 mg/dL. Statin treatment alone is often insufficient to achieve the non-HDL targets. In patients with persistent hypertriglyceridemia while on statin therapy, the addition of a TG-lowering agent is recommended as a therapeutic option to reduce levels of non-HDL.

Addition of fibrates to statins has been shown to improve lipid profiles in patients with mixed hyperlipidemia [48]. The Triglyceride Reduction in Metabolic Syndrome (TRIMS) study confirmed the improvement of several lipid markers for cardiovascular event risk in patients with hypertriglyceridemia and the MS after treatment with 8 weeks of fenofibrate [49]. These favorable changes were noted in decreased levels of non-HDL as well as increased levels of HDL in the fenofibrate treatment group. In addition, treatment with fenofibrate produced a shift toward larger LDL particle size.

Historically, however, fibrate and statin combination therapy has been a source of safety concerns. In the NEPTUNE survey [44], 25% of patients receiving treatment for dyslipidemia had a TG >200 mg/dL. Only 27% of patients with hypertriglyceridemia and CHD had achieved their non-HDL treatment goals. In addition, only 5% of those surveyed were receiving combination antilipidemic therapy. The major reason combination therapy with fibrates is seldom clinically used is the perception of adverse safety associated with combining a statin and fibrate. Although there is an increase in reports of rhabdomyolysis with statin and fibrate combined therapy, this risk appears to be about 15× higher with gemfibrozil than for fenofibrate when used with statins [15]. Data from recent the FIELD trial suggests that combining fenofibrate with statins does not significantly increase the risk of myopathy in a cohort of patients with diabetes [50].

Another approach to patients with persistent hypertriglyceridemia while receiving statin therapy is to combine prescription omega-3 acid ethyl esters (P-OM3) with the statin. In a recent study, coadministration of P-OM3 with simvastatin 40 mg was associated with a significantly greater reduction in non-HDL and TG levels compared with simvastatin alone [51]. Thus combining statins with P-OM3s is another potential therapeutic approach to the patients with the MS.
In conclusions patients with the MS are at high risk for cardiovascular events. Treatment goals to reduce this risk include lowering the LDL to <70 mg/dL and non-HDL to <100 mg/dL. Aggressive high-dose statins are the initial therapy for patients with the MS. However, statin treatment alone is often insufficient to achieve these targets. The addition of combination therapy with statins is emerging as the optimal therapeutic approach to lower the risk of cardiovascular events in patients with the MS.

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