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Hypolipidemic therapy for the metabolic syndrome

Andrea Cignarella [a,b,*], Stefano Bellosta [a], Alberto Corsini [a], Chiara Bolego [a]

[a] *Department of Pharmacological Sciences, University of Milan, via G. Balzaretti 9, I-20133 Milan, Italy*
[b] *Department of Pharmacology and Anaesthesiology, University of Padua, Largo Meneghetti 2, 35121 Padua, Italy*

Abstract

The metabolic syndrome appears to affect a significant proportion of the population and is associated with increased risk for development of cardiovascular disease as well as of type-2 diabetes. No single treatment for the metabolic syndrome as a whole yet exists. While the primary management of patients with the metabolic syndrome involves healthy lifestyle promotion, the atherogenic dyslipidemia is a primary target for cardiovascular disease risk reduction in these patients. Statin therapy provides effective reduction of LDL-cholesterol, which represents the primary therapeutic goal of lipid-lowering therapy in patients at risk for cardiovascular disease. Fibrates in turn are effective in normalizing lipid levels (mainly triglycerides and HDL-cholesterol) in patients with the metabolic syndrome and may improve insulin resistance. Whereas statins remain the drug of choice for patients who need to achieve the LDL-cholesterol goal, fibrate therapy may represent an alternative for those with low HDL-cholesterol and high triglyceride levels. The simultaneous use of fibrates could be indicated in patients whose LDL-cholesterol is controlled by statin therapy but whose HDL-cholesterol and/or triglycerides are still inappropriate. Such a combination, however, needs careful monitoring due to the potential hazard of adverse drug interactions. Nicotinic acid and ezetimibe may be useful agents for therapy, particularly when combined with statins. A number of emerging therapies offer potential as future options for the pharmacological treatment of metabolic syndrome.

Keywords: Atherogenic dyslipidemia; Lipid-lowering agents; Cardiovascular disease; Statins; Fibrates

1. Introduction

It has been known for a long time that the major risk factors for coronary heart disease (CHD) include hypertension, elevated levels of low-density lipoprotein cholesterol (LDL-C), smoking and type-2 diabetes. Yet, extensive research has established that several of these cardiovascular risk factors cluster to a greater degree than can be explained by chance. Recently, this clustering of symptoms has been ascribed to a specific condition: the metabolic syndrome (MetS). In fact, MetS is a cluster of the most dangerous heart attack risk factors: diabetes or prediabetes, abdominal obesity, unfavourable changes in the lipid profile (low HDL-C, increased triglycerides and small-dense LDL) and high blood pressure [1,2].

Whether or not it is accepted that MetS is a specific disease entity or just a constellation of symptoms, the prevalence of this condition is increasing worldwide and patients need to tackle these risk factors through either lifestyle or pharmacological approaches, in order to reduce the odds of developing diabetes and cardiovascular disease (CVD).

2. Evidence supporting therapeutic intervention in patients with the MetS

MetS appears to affect a significant proportion of the population. While up to 80% of the almost 200 million adults worldwide with diabetes will die of CVD, people with MetS are also at increased risk, being twice as likely to die from and three times as likely to have a heart attack or stroke compared to people without the syndrome [3]. Subjects with MetS have a five-fold greater risk of developing type-2 diabetes if not already present [4]. This puts MetS and diabetes way ahead of HIV/AIDS in morbidity and mortality terms, yet the problem is not as well recognized.

According to the NCEP definition [5], nearly one third of middle-aged men and women in most Western countries have MetS. This represents a potential public health issue, as MetS is associated with an increased risk of mortality from CHD, CVD and from all causes. In a representative prospective cohort study, 1209 Finnish men aged 40–60 at baseline, who were free of CVD, cancer or diabetes, were followed for 10 years. In this cohort, men with MetS were three to four times more likely to die of CHD than were those without the syndrome [6]. The risk of cardiovascular outcomes associated with the MetS has been also evaluated in prospective, long-term clinical trials.

* Corresponding author.
E-mail address: andrea.cignarella@unimi.it (A. Cignarella).

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Results of post hoc analyses of the Scandinavian Simvastatin Survival Study (4S) and AFCAPS/TexCAPS trials demonstrate a significant 40–50% increase in risk of major CHD events for placebo-treated patients meeting MetS criteria after excluding patients with diabetes mellitus [7].

Consistent with these observations, a recent prospective study describing the prevalence of MetS in acute myocardial infarction (MI) and assessing its impact on hospital outcomes demonstrated that almost half of all MI patients are also affected by MetS [8]. In this study, the prevalence of MetS was examined in 633 patients hospitalized with MI within 24 h of the onset of symptoms. Participants were diagnosed with MetS according to the NCEP definition and MetS was found to be more prevalent in women and older patients. Unexpectedly, analysis of the predictive value of individual MetS components for severe heart failure showed that the major determinant was hyperglycaemia. In view of the ever-increasing prevalence of MetS worldwide, this finding has important clinical implications.

3. How to treat patients with the MetS

The MetS represents a combination of underlying, major and emerging risk factors. People with MetS should be identified in clinical practice. The current clinical approach to MetS is to focus on appropriate management of accompanying risk factors. While priority should be given to management of underlying risk factors with therapeutic lifestyle changes, associated major risk factors should be treated according to evidence-based medicine goals and principles, and appropriate clinical attention should be given to the presence of emerging risk factors.

Clearly, there are multiple targets for therapy to reduce the high risk of the MetS. While no single treatment for the MetS as a whole yet exists, it is well established that lifestyle changes, for example, changes in diet and increased physical exercise, form the first-line strategy of intervention. The relevance of diet as a therapeutic strategy in MetS is emphasized in a study by Esposito et al. [9], who randomized 180 men and women with MetS to either a Mediterranean diet or a "prudent" diet. Even if the relevant cohort was limited, this study represents the first demonstration that a Mediterranean-style diet rich in whole grains, fruits, vegetables, legumes, walnuts and olive oil might be effective in reducing both the prevalence of MetS and its associated cardiovascular risk. The benefits of the diet might result from a reduction in low-grade inflammation associated with MetS.

When the lifestyle approach appears to be inadequate, it is necessary to treat the individual components of MetS so that a reduction in the individual risk associated with each component will likely contribute to reduce the overall impact on CVD and diabetes risk. Among metabolic risk factors, attention should be given to dyslipidemia. In MetS, a condition of impaired fatty acid metabolism in a adipose tissue generally results in the increased release of free fatty acids into the circulation. This in turn leads to multiple abnormalities in the circulating lipoprotein profile including low HDL, high triglycerides (TG) and VLDL remnants, with average LDL. The triad of elevated TG, reduced HDL and small dense LDL, along with concomitant increases in TG-rich remnant particles, comprises the atherogenic dyslipidemia of MetS. MetS, with or without progression to type 2 diabetes, is therefore a major atherogenic factor. CHD risk reduction in MetS requires not only aggressive LDL-C lowering but also management of each aspect of dyslipidemia, including lowering TG levels, increasing HDL-C levels, and increasing the size of the average LDL-C particle. Based on available evidence, LDL-C is the primary target of therapy in MetS [2]. In patients with atherogenic dyslipidemia with elevated TG, non-HDL-C represents a secondary target of treatment after the LDL-C goal is achieved. The tertiary goal in these patients is to raise HDL-C when it is reduced after attaining goals for LDL-C and non-HDL-C. Clinicians must understand the advantages and disadvantages of each available lipid-altering agent to provide the type and degree of treatment recommended by current guidelines. The most widely employed lipid-lowering agents for management of MetS are statins, fibrates and nicotinic acid [2], with ezetimibe being indicated as an add-on agent.

4. The mainstay of LDL-C-lowering therapy: the statins

While the primary effect of statins is to lower LDL-C, statin therapy also lowers levels of other apo B-containing lipoproteins and improves particle composition to a less atherogenic phenotype. In addition, statins lower hepatic lipase activity and small dense LDL formation [10]. Clinical trials of statin therapy have demonstrated benefit on cardiovascular morbidity and mortality, including in patients without substantially elevated LDL-C and patients with characteristics of the MetS.

Evidence supporting use of a specific statin to reduce elevated LDL-C in this group of patients is so far limited. In a pooled analysis of efficacy trials, rosuvastatin 10 mg improved the lipid profile to a similar extent in hypercholesterolaemic patients with and without the MetS [11]. The comparative efficacy of statin treatment in patients with the MetS has been newly evaluated in the prospective COmparative study with rosuvastatin in subjects with METabolic Syndrome (COMETS) study [12]. Rosuvastatin 10 mg was significantly more effective than atorvastatin 10 mg and placebo for lowering LDL-C after 6 and 12 weeks of treatment. Improvements in TC, HDL-C, and non-HDL-C were also significantly greater with rosuvastatin than with atorvastatin or placebo, whereas decreases in TG were similar in both active treatment groups. In this study, rosuvastatin was significantly more effective than atorvastatin in reducing LDL-C levels, enabling patients to achieve lipid goals and improving multiple aspects of the atherogenic lipid profile in patients with the MetS. Statins are known to reduce high-sensitivity C-reactive protein (hsCRP) levels, with a greater benefit shown for individuals with elevated hsCRP [13]. Accordingly, 28–29% reductions in hsCRP were observed after 12 weeks in all patients in this study, with more marked reductions observed in patients with elevated hsCRP values at baseline [12].

Clinical trial data concerning statin treatment in patients with MetS are discussed below and summarized in Table 1. In an analysis of the WOSCOPS trial, risk prediction increased with the number of metabolic abnormalities [14] and yet the risk reduction with pravastatin was comparable in men with and without