The cardiovascular metabolic syndrome
Rana, J.S.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Cardiovascular Metabolic Syndrome – an Interplay of Obesity, Inflammation, Diabetes and Coronary Heart Disease
1. Introduction

Superbia, invidia e avarizia sono
le tre faville c’hanno i cuori accesi
Arrogance, envy and avarice
are the three sparks that have all hearts inflamed.
Inferno Canto VI, The Divine Comedy, by Alighieri Dante

It was around 1.8 million years ago when *Homo erectus* became the first hominid to apply fire to food, thus enkindling the first hunting-and-gathering economy in which animals became a significant part of the diet and resources were shared (1). Presently, at the advent of the third millennium, human society is ever evolving, and along with it the disease patterns that afflict different populations and continue to go through paradigm changes. Only a century ago infectious disease was a major cause of mortality, whereas today chronic diseases are the largest cause of death in the world, led by cardiovascular disease (CVD) with 17 million deaths in 2002, mainly from ischemic heart disease and stroke (2). The global prevalence of all the leading chronic diseases is increasing, with the majority occurring in developing countries and projected to increase substantially over the next two decades (3). Cardiovascular disease is to date already the leading cause of mortality even in developing countries (2). Between 1990 and 2020, mortality from ischemic heart disease in developing countries is expected to increase by 120% for women and 137% for men (4).

The global number of individuals with type 2 diabetes in 2000 was estimated to be 171 million (2.8% of the world’s population), a figure projected to increase in 2030 to 366 million (6.5%) (5). The prevalence of obesity is increasing in virtually all populations and age groups worldwide. Obesity predisposes patients to a large number of co-morbidities and increased mortality rates (6,7). Chronic diseases have not simply displaced infectious afflictions in developing countries, rather such countries now experience a polarized, double burden of disease (6).

The causes of the pandemic of chronic disease are complex and include political,
demographic, and lifestyle factors. What is more disturbing is the ever increasing overlap of chronic diseases such as obesity, type 2 diabetes and coronary heart disease. In the last decade there has been escalating evidence recognizing metabolic disorders such as type 2 diabetes and obesity as major risk factors for cardiovascular disease, along with the previously well established factors such as lipoprotein disorders and hypertension.

2. Obesity

The prevalence of obesity has doubled or even risen threefold in less than two decades. At least 1.1 billion adults are overweight, including 312 million who are overtly obese (7). The prevalence of obesity and increased weight is estimated to range from 40 to 60%, in industrialized and many developing countries (7). At the same time, over 50% of adults in Western Europe are considered overweight or obese, which represents a dramatic increase of 10–40% in European countries alone in the last decade.

The economic costs of obesity are estimated to be in the range of 2 to 7% of total healthcare costs (7). In some developing countries it presents a double burden alongside enduring problems of under-nutrition. Furthermore, the incidence of CVD goes up with increasing body weight (8) and total mortality for CVD is higher for higher quintiles of body mass index (BMI) (9).

Another disturbing issue is the increase in rates of obesity in children of up to 2- to 4-fold increase over the last 2 decades (10). Excess weight in childhood and adolescence is associated with increased risk of hypertension, adverse blood lipid profiles, and early atherosclerotic lesions (10), indicating that these children are likely to inflate the number of adults with CVD in the future. Studies in American children and adolescents have also revealed an alarming increase in the incidence of type 2 diabetes (11). Substantial evidence suggests that overweight children and adolescents are more likely to have insulin resistance, abnormal plasma lipid profiles, and hypertension later in life (10). Thus, in addition to the growing number of children found to have type 2 diabetes, many more of these overweight youngsters can be expected to develop the disease as adults.
3. Type 2 diabetes and the metabolic syndrome

It is projected that between 1995 and 2025, the number of individuals with type 2 diabetes is expected to increase 170% in developing countries compared with 42% in developed nations (12). Individuals with type 2 diabetes are at increased risk not only for CVD but also for greater cardiovascular mortality. Age adjusted death rates of patients with type 2 diabetes are twice those of non-diabetic individuals, and 75% of the excess mortality in men and 57% of the excess mortality in women is this disorder is attributable to CVD (13). Indeed, an estimated 25% to 46% of patients with type 2 diabetes die of ischemic heart disease. Individuals with type 2 diabetes who have had a prior myocardial infarction (MI) also experience increased rates of re-infarction, congestive heart failure, and death (14).

The risk of developing type 2 diabetes is strongly correlated with excess weight (15). Increase in weight gives rise to early metabolic abnormalities that include hyperinsulinemia, insulin resistance, and glucose intolerance. The constellation of these risk factors is now recognized as “Metabolic Syndrome”.

The prevalence of metabolic syndrome is estimated to be around 20–25% of the population (16). People with metabolic syndrome are twice as likely to die from coronary heart disease and three times as likely to have a heart attack or stroke compared with people without the syndrome (17). In addition, almost 200 million people globally have diabetes and 80% of these may die from cardiovascular disease (18), so there is a tremendous medical and moral imperative to identify individuals with metabolic syndrome early, so that lifestyle interventions and treatment may prevent the development of diabetes and cardiovascular disease. Existing guidelines have been put forward by the World Health Organization (WHO) (19) and National Cholesterol Education Program—Third Adult Treatment Panel (NCEP ATP III) (20). It has proven difficult to make direct comparisons between the data from studies where different definitions have been used to identify the syndrome (21). Considering the need for a single, universally accepted diagnostic tool that is easy to use in clinical practice, the International Diabetes Federation (IDF) has come up with a definition (Table 1) (21). The new IDF definition addresses both clinical and research needs, providing an accessible, diagnostic tool suitable for
### Table 1. Definitions of Metabolic Syndrome

<table>
<thead>
<tr>
<th>WHO clinical criteria for the metabolic syndrome</th>
<th>ATP III clinical identification of the metabolic syndrome</th>
<th>The new International Diabetes Federation (IDF) definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one of the following</td>
<td>Three or more of the following five risk factors required:</td>
<td>Patient must have:</td>
</tr>
<tr>
<td>1. Fasting glucose &gt; 110 mg/dL (6.1 mmol/L)</td>
<td>1. Central obesity</td>
<td>1. Central obesity.</td>
</tr>
<tr>
<td>2. Known or newly diagnosed type 2 diabetes</td>
<td>Waist circumference</td>
<td>Waist circumference</td>
</tr>
<tr>
<td>3. Impaired glucose tolerance (IGT) (2-h glucose ≥ 1.88 mmol/l)</td>
<td>Men &gt; 102 cm (&gt; 40 in)</td>
<td>Men: ≥94 cm for White/African American</td>
</tr>
<tr>
<td></td>
<td>Women &gt; 88 cm (&gt; 35 in)</td>
<td>≥90 cm for Hispanic/Chinese</td>
</tr>
<tr>
<td>together with two or more of the following:</td>
<td>2. Triglycerides &gt; 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality</td>
<td>≥285 cm for Japanese</td>
</tr>
<tr>
<td>1. Triglycerides (&gt; 1.7 mmol/L; 150 mg/dL) and/or low HDL cholesterol (&lt; 0.9 mmol/L; 35 mg/dL men; &lt; 1.0 mmol/L; 39 mg/dL women)</td>
<td>Men &lt; 40 mg/dL (1.03 mmol/L)</td>
<td>Women: ≥80 cm (except ≥90 for Japanese)</td>
</tr>
<tr>
<td>2. Microalbuminuria</td>
<td>3. HDL cholesterol</td>
<td>2. HDL cholesterol:</td>
</tr>
<tr>
<td>(urinary albumin excretion rate &gt; 20 mg/min or albumin: creatinine ratio &gt; 30 mg/g)</td>
<td>Men &lt; 50 mg/dL (1.29 mmol/L)</td>
<td>Men &lt; 40 mg/dL (1.03 mmol/L)</td>
</tr>
<tr>
<td></td>
<td>Women &lt; 50 mg/dL (1.29 mmol/L)</td>
<td>Women &lt; 50 mg/dL (1.29 mmol/L)</td>
</tr>
<tr>
<td></td>
<td>(or specific treatment for this lipid abnormality)</td>
<td>(or specific treatment for this lipid abnormality)</td>
</tr>
<tr>
<td>3. Blood pressure: systolic BP ≥ 140 or diastolic BP ≥ 90 mm Hg or treatment of previously diagnosed hypertension</td>
<td>4. Blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension</td>
<td>3. Blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension</td>
</tr>
</tbody>
</table>

Worldwide use. It is important to recognize that the metabolic syndrome may not only lead to type 2 diabetes and to subsequent CVD, it may also result in CVD without clinically evident type 2 diabetes (11).

Finally, socio-cultural factors also play an important role in the pathophysiology of type 2 diabetes and CVD. As other populations increasingly adopt the dietary patterns and physical inactivity characteristic of a Western lifestyle, they show a corresponding increase in
markers of the metabolic syndrome, type 2 diabetes, and CVD (11). Given the great overlap in prevalence of obesity, type 2 diabetes and CVD, it has become increasingly clear that people with obesity are more prone to type 2 diabetes and vice versa, and such a vicious cycle of metabolic abnormalities is proving to be a major risk factor for CVD.

4. Inflammation

4.1 Inflammation and coronary heart disease
Research in recent years has shown that atherosclerosis is a low grade inflammatory disorder, and not merely the passive accumulation of lipids within artery walls (22,23). Oxidative components of modified low-density lipoprotein (LDL) induce a chronic inflammatory process that involves the arterial endothelium and ultimately results in the complications of atherosclerosis (22). The association of inflammation with the initiation and progression of atherosclerosis suggests that markers of inflammation, eg, such as C-reactive protein (CRP), are useful in predicting an increased risk of CVD and inflammatory processes may also be potential targets of therapy in preventing or treating CVD (23).

Atherosclerosis is a multi-step disease that involves chronic inflammation from initiation to progression and, eventually, plaque rupture (24). In atherosclerosis, the normal homeostatic functions of the endothelium are altered, promoting an inflammatory response (22). Adhesion molecules expressed by inflamed endothelium recruit leukocytes, including monocytes, which then penetrate into the intima, predisposing the vessel wall to lipid accumulation. Inflammatory mediators enhance uptake of modified lipoprotein particles and formation of lipid-laden macrophages. T-lymphocytes migrating with the monocytes continue to release cytokines that help to perpetuate the inflammation (25). Cytokines released from dysfunctional endothelial cells weaken the protective fibrous cap by limiting the collagen production by vascular smooth muscle cells that stabilize the smooth muscle cap. Such plaque instability ultimately can cause unstable angina, acute coronary syndromes, and myocardial infarction. (22,23,26)

Recent data have revealed that the plasma concentration of inflammatory mediators, such as TNF-alpha, interleukin-6, CRP, fibrinogen, and plasminogen activator inhibitor-
Chapter 1

1 (PAI-1) levels are increased in the insulin resistant states of obesity and type 2 diabetes (27,28). Also, an increase in inflammatory mediators has been shown to predict the future development of obesity and type 2 diabetes (27.28).

4.2 Inflammation and endothelial glycocalyx

One interesting pathway by which chronic inflammation can accelerate formation of atherosclerotic lesions could be through loss of endothelial glycocalyx. The endothelial glycocalyx is a negatively charged, organized mesh, consisting of membranous glycoproteins, proteoglycans, glycosaminoglycans and associated plasma proteins, and is situated at the luminal site of all blood vessels (29). Its major constituents comprise hyaluronic acid (HA) and the negatively-charged heparan sulphate proteoglycans. Using electron and intravital microscopy it was demonstrated that this layer can reach up to 0.5 - 3 μm intraluminally, thus exceeding the dimensions of the endothelium itself several fold (30). To date, most observations of glycocalyx modulation have been limited to the microvasculature. Since atherosclerosis is confined to the macrovasculature direct visualisation using electron/confocal microscopy suitable for large vessels was recently developed (31). Using these methodologies, it was confirmed that glycocalyx dimensions were also diminished in the macrovasculature at sites prone for atherosclerosis development, such as the carotid bifurcation (32).

Due to its strategic position between the vessel wall and the flowing blood, the endothelial glycocalyx has been shown to exert many vasculo-protective effects such as attenuating vascular permeability and modulating leukocyte interactions with the endothelium (33). More recently the glycocalyx has also been shown to serve as mechano-shear sensor determining flow-mediated NO-release by the endothelium (34). In recent years, several atherogenic stimuli such as oxidative stress, oxLDL and TNF-α all were shown to have a detrimental impact on the glycocalyx within as little as 30 minutes after exposure (35,36). This perturbation is characterized by increased shedding of hyaluronan into the plasma resulting in loss of protective properties of the vessel wall, such as increased glycocalyx permeability for atherogenic lipoproteins, increased adhesiveness of platelets and leukocytes to the endothelium. In diabetes mellitus most of these disturbances causing glycocalyx perturbation have been described and proposed to be caused by
impaired NO-availability following increased oxygen radical formation due to hyperglycemia (37). Data from our department show that increased glucose levels indeed induce loss of endothelial glycocalyx in humans and the full plethora of pro-atherogenic effects could be reproduced in-vivo (38).

4.3 Inflammation, obesity and diabetes

The state of chronic inflammation typical of obesity and type 2 diabetes occurs at metabolically relevant sites, such as the liver, muscle, and most interestingly, adipose tissue. It is well established that defective insulin receptor signaling is instrumental to the pathogenesis of type 2 diabetes (39). Increased inflammatory state IL-6, associated with obesity and type 2 diabetes, might interfere with insulin action by suppressing insulin signal transduction. This in turn might interfere with the anti-inflammatory effect of insulin. One such pathway that involves phosphorylation and signaling is mediated through the members of the insulin-receptor substrate (IRS) family of proteins, since it is relevant to insulin-mediated glucose metabolism and crosstalk with inflammatory pathways (40). Among several serine phosphorylation sites on IRS-1, ser-307 appears to be of major importance and targeted by c-Jun N-terminal kinase (JNK) (41). JNK might be a key molecule leading to insulin resistance and type 2 diabetes, since human mutations in the gene coding for JNK-binding protein (a natural inhibitor of JNK activity) causes type 2 diabetes (42).

Research in recent years suggests that adipose tissue may function as potent endocrine organ (43). The nuclear receptor peroxisome proliferator-activated receptor-gamma plays an important role in the regulation of gene expression and the differentiation in adipose tissue (44). It stimulates adipogenesis and modulates the storage of fatty acids. Elevated levels of adipocytokines such as leptin, resistin, and TNF-α worsen insulin sensitivity, increase insulin resistance, and stimulate atherogenesis (45-47). Novel data have shown that the concomitant presence of promoter polymorphisms of TNF-α (G-308A), which is associated with increased plasma TNF-α concentrations, and IL-6 (C-124G) associated with increased the risk for insulin resistance, in obese subjects with impaired glucose tolerance, carry twice the risk of conversion to type 2 diabetes when compared with other genotypes (48).
In contrast, adiponectin, another cytokine produced by the adipocyte, seems to have a favorable effect on metabolic disturbance (49). Lower levels of adiponectin have been associated with the metabolic syndrome (50), whereas higher levels of adiponectin have been associated with decreased risk of type 2 diabetes and myocardial infarction (51,52). Consistent with these observations is the fact that plasma adiponectin levels have an inverse relationship with adiposity, insulin resistance, diastolic pressure, triglyceride concentration and TNF-α receptor concentration (53). Recently it has been suggested that adiponectin might be the missing link between insulin resistance and obesity (54). Leptin, another adipocyte specific protein, is elevated in the obese, has pro-aggregatory effect on platelets and might also regulate immune function through a stimulation of responses to inflammatory challenges (55).

Inflammation and anomalous free fatty acid metabolism in obesity in turn contribute to the increasing insulin resistance and beta-cell dysfunction that precipitate type 2 diabetes (56). Type 2 diabetes begins with peripheral insulin resistance and ends in complete loss of insulin secretion if the disease progresses through its entire natural history (57). Whereas, pancreatic beta cells initially are able to compensate for insulin resistance by increasing insulin secretion, compensation fails as beta cells exhaust their capacity to react appropriately to rising glucose concentrations leading to development of glucose intolerance and type 2 diabetes (58).

Type 2 diabetes in turn causes endothelial dysfunction, thus increasing the risk of both microvascular and macrovascular disease (59,60). Within the endothelium, the oxidative stress of hyperglycemia inhibits nitric oxide production, affecting endothelial function (61). Whereas concentration of nitric oxide is reduced, the production of vasoconstrictors, such as endothelin-1, angiotensin II, and prostanoids is increased (62,63). Also, in a state of atherosclerotic vascular disease, hyperglycemia promotes plaque instability (64).

So, inflammation seems to play a role across the full spectrum, of the pathophysiology of obesity, metabolic syndrome, type 2 diabetes as well as coronary artery disease (65-67) (fig 1).
5. Dylypidemia of diabetes and metabolic syndrome

Data from the Framingham Heart Study (68) show that twice as many diabetic than non-diabetic individuals have low plasma levels of HDL-C and elevated triglycerides. By comparison, the proportions of men and women with increased total and LDL-C are similar in diabetic and non-diabetic patient groups. Data from the Prospective Cardiovascular Münster (PROCAM) Study and the UKPDS are consistent with these findings (69,70). Although plasma levels of LDL-C in patients with type 2 diabetes and the metabolic syndrome are either normal or only modestly elevated, there is an increase in the number of small, dense LDL particles. These small, dense LDL particles are thought to be highly atherogenic because of their increased susceptibility to oxidation and their association with insulin resistance, high triglycerides and low HDL-C (71). Together this dyslipidaemic profile – elevated triglycerides, low HDL-C and an increase in small, dense LDL particles - is often referred to as the 'lipid triad.'

The risk of atherosclerosis is reflected by the balance between apolipoprotein B (apo B), the major protein component of cholesterol-rich LDL and very low-density lipoprotein (VLDL) particles, and apolipoprotein A (apo A, the main constituent of HDL). Apo B is linked to the transfer of cholesterol to the peripheral tissues or so
called "forward cholesterol transport", and is also associated with the assembly of triglyceride- and cholesterol-rich lipoprotein particles. By contrast, apo-A-containing HDL particles promote cholesterol efflux from peripheral cells and facilitate its transport to the liver for excretion or "reverse cholesterol transport". In addition, HDL may be atheroprotective because of its anti-inflammatory and anti-oxidant actions, and as a result of its ability to reverse endothelial dysfunction. A recently published report from the INTERHEART Study (72), which assessed the relative importance of different risk factors for CHD in 52 countries worldwide showed that an increased apo B to apo A ratio was associated with a population attributable risk that exceeded a stunning 30%.

In patients with type 2 diabetes and metabolic syndrome, presence of insulin resistance increases lipolysis and breakdown of triglycerides in adipocytes, leading to increased free fatty acid levels. The increased flux of free fatty acids to the liver increases triglyceride levels and promotes the secretion of large VLDL particles (73). Central (or visceral) obesity appears to be particularly closely associated with the increased flux of free fatty acids to the liver. The increased secretion of VLDLs in turn leads to a rise in fasting and postprandial triglycerides and drives the transfer of triglyceride from VLDL to HDL in exchange for cholesteryl esters via the action of cholesteryl ester transfer protein (CETP). As a result, VLDL becomes more cholesterol-rich while HDL gains triglyceride and becomes susceptible to the lipolytic action of hepatic lipase which turns it into smaller, denser particles (73), less able to accept cholesterol for transfer to the liver and excretion from the body. CETP may also promote the exchange of triglycerides from VLDL to LDL; these triglyceride-rich LDL subsequently undergo lipolytic hydrolysis resulting in small, dense LDL particles. In addition, the reduced affinity of small dense LDL particles for the LDL receptor extends their lifetime in the plasma, again facilitating their likelihood of infiltrating the arterial wall, becoming deposited there and thus contributing to plaque formation.

5.1 Targeting the Lipid Triad

Current treatment recommendations for management of dyslipidaemia associated with type 2 diabetes and the metabolic syndrome focus on statin therapy, in addition to
Table 2. Reduction in CHD risk overall and for diabetic patients treated with statins in major intervention trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Statin</th>
<th>No. of patients with diabetes</th>
<th>CHD risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total Population</td>
</tr>
<tr>
<td>Primary prevention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>Lovastatin</td>
<td>155</td>
<td>37%</td>
</tr>
<tr>
<td>HPS</td>
<td>Simvastatin</td>
<td>2912</td>
<td>24%</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>Atorvastatin</td>
<td>2532</td>
<td>36%</td>
</tr>
<tr>
<td>CARDs</td>
<td>Atorvastatin</td>
<td>2838</td>
<td>-</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARE</td>
<td>Pravastatin</td>
<td>586</td>
<td>23%</td>
</tr>
<tr>
<td>4S</td>
<td>Simvastatin</td>
<td>202</td>
<td>32%</td>
</tr>
<tr>
<td>LIPID</td>
<td>Pravastatin</td>
<td>782</td>
<td>25%</td>
</tr>
<tr>
<td>4S reanalysis</td>
<td>Simvastatin</td>
<td>483</td>
<td>32%</td>
</tr>
<tr>
<td>HPS</td>
<td>Simvastatin</td>
<td>3051</td>
<td>-</td>
</tr>
<tr>
<td>ALLHAT-LLT</td>
<td>Pravastatin</td>
<td>3638</td>
<td>9%</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>Atorvastatin</td>
<td>2532</td>
<td>29%</td>
</tr>
</tbody>
</table>

Abbreviations: AFCAPS/TexCAPS Air Force/Texas Coronary Atherosclerosis Prevention Study; HPS Heart Protection Study; ALLHAT-LLT Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Treatment; ASCOT-LLA Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm; CARDs Collaborative Atorvastatin Diabetes Study; CARE Cholesterol and Recurrent Events Trial; 4S Scandinavian Simvastatin Survival Study; LIPID Long-term Intervention with Pravastatin in Ischaemic Disease

dietary and lifestyle adaptation, even though plasma levels of LDL-C per se may be only slightly elevated in such patients (74,75). These recommendations are based on data from most of the major statin intervention studies, which demonstrated that LDL-C lowering with statin therapy was effective in reducing CHD risk in patients with type 2 diabetes in both primary and secondary settings (Table 2).

While there is no doubt that statins significantly reduce the CHD risk in patients with type 2 diabetes (and metabolic syndrome), subgroup analyses from the Heart Protection Study (76) showed that the residual risk of a coronary event in diabetic patients remained twice that observed in non-diabetic patients treated with statins. Thus, although diabetic patients gained as much relative benefit from statins as non-diabetic patients, treatment did not push their absolute risk down to the same value as in non-diabetics. These findings were consistent across all statin intervention studies irrespective of the nature of the statin. The high level of residual risk in patients with type 2 diabetes and the
metabolic syndrome treated with statins highlights the need to target other lipids, specifically low HDL-C and elevated triglycerides characteristic of the atherogenic dyslipidaemia associated with both conditions.

While statins are effective in reducing plasma levels of LDL-C, they have only modest effects on reducing triglycerides (by 15-35%) and raising HDL-C (by typically less than 10%) (74). Even with aggressive statin therapy, such as high dose atorvastatin (77,78), the increase in HDL-C was no more than 10%, and triglycerides were reduced by only 20%. Moreover, the results of the STENO-2 study (79) demonstrated that although intensive statin therapy resulted in a significant increase in the proportion of diabetic patients who achieved cholesterol treatment goals (70% vs. 20% in patients treated with conventional therapy, p<0.001), there was little change in the proportion of patients who achieved triglyceride treatment goals (58% vs. 43%, p=0.19). There are a number of agents that raise HDL-C and lower triglycerides, which could potentially be used in combination with a statin. These include the peroxisome proliferator-activated receptor (PPAR) agonists, fibrates and nicotinic acid.

5.1.1. Peroxisome proliferator-activated receptor (PPAR) agonists

PPAR\_\gamma\_ agonists such as the thiazolidinediones are oral anti-diabetic drugs, and offer potential for the treatment of both glucose and lipid metabolism. These agents have variable effects on the lipid profile as well as improving insulin sensitivity and blood glucose levels in patients with type 2 diabetes. Summary analysis based on data from 19 placebo-controlled studies showed that treatment with pioglitazone was associated with 18.7% reduction in triglycerides and 9.9% increase in HDL-C, whereas rosiglitazone produced an overall increase in triglycerides (by 4.4%) and only raised HDL-C by 5.2% (80).

Additionally, the thiazolidinediones have a range of anti-inflammatory properties that may contribute to an improved cardiovascular risk profile in patients with type 2 diabetes and potentially oppose the progression of atherosclerosis (81). For example, treatment with rosiglitazone has been shown to reduce plasma levels of CRP in patients with type 2 diabetes, as well as reducing levels of the matrix metalloproteinase-9 (MMP-
suggesting that treatment may help to stabilise atherosclerotic plaques from rupture as well as countering the inflammatory processes associated with the early stages of atherosclerosis (82). In addition, thiazolidinedione treatment can suppress the production of pro-inflammatory cytokines in obese, non-diabetic individuals (83). Thus, stimulation of the PPAR\_\gamma receptor, which is found in fat and muscle tissue, not only mediates the anti-diabetic effects of the thiazolidinediones, but also is implicated in the anti-inflammatory actions of these agents (81).

### 5.1.2. Fibrates (PPAR\_\alpha agonists)
The clinical benefits of raising HDL-C and lowering triglycerides with fibrates or PPAR\_\alpha agonists therapy in patients with type 2 diabetes have been established in VA-HIT (84,85), Helsinki Heart Study (86) and the Type 2 diabetes Atherosclerosis Intervention Study (DAIS) (87). Patients included in VA-HIT had a high prevalence of characteristics of the metabolic syndrome; 33\% had high triglycerides, 63\% had low HDL-C, 57\% had hypertension, 25\% had type 2 diabetes and 13\% had impaired fasting glucose (84). Overall, treatment with gemfibrozil for 5 years reduced nonfatal MI and CHD death by 22\%; moreover, treatment was more effective in patients with hyperinsulinaemia and type 2 diabetes (85). In the DAIS, patients with type 2 diabetes treated with fenofibrate for 3 years exhibited reduced angiographic progression of localised coronary stenoses and also tended to have fewer cardiovascular events (87). Therefore, a combination statin/fibrate therapy may be often necessary to control all lipid abnormalities in patients with diabetes and metabolic syndrome. The potential clinical benefit of fenofibrate will be specified by the ongoing Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (88).

### 5.1.3. Nicotinic acid
Data for both the thiazolidinediones and fibrates suggest that the extent of HDL-C raising with either treatment is less than that required for optimal cardiovascular risk reduction in patients with type 2 diabetes and metabolic syndrome. In contrast, nicotinic acid is the most potent agent available for raising plasma levels of HDL-C (by up to 26\% at clinically recommended doses) as well as substantially lowering triglycerides (by up to 50\%) and LDL-C (by up to 25\%) (89). Nicotinic acid also favourably alters
the LDL composition, shifting the subclass distribution of LDL from small, dense particles to larger, more buoyant (and hence less atherogenic) particles, as well as enhancing the cardioprotective larger HDL particles. Additionally, nicotinic acid is the only agent available that reduces Lp(a) (75).

Nicotinic acid also inhibits oxidation of LDL-C, one of the critical early steps contributing to atherosclerosis, and reduces vascular inflammation (as indicated by a reduction in CRP levels), thereby improving endothelial function (90). Studies have shown that nicotinic acid appears to activate nuclear transcription factors such as the PPARγ, possibly via prostaglandin metabolism, and this may in part explain its anti-inflammatory effects (91). The Coronary Drug Project showed that treatment with nicotinic acid for 15 years continued to demonstrate a significant reduction in mortality in patients treated with nicotinic acid (11% vs. placebo, p<0.001) (92). Subgroup analysis suggested a greater reduction in non-fatal MI in patients with the highest fasting blood glucose (≥126 mg/dl [7 mmol/l]) (93).

5.1.4. Combining nicotinic acid with a statin
Combining nicotinic acid and a statin would be a logical approach to therapy as it addresses the metabolic abnormalities associated with type 2 diabetes and metabolic syndrome. Studies have shown that addition of nicotinic acid to primary statin therapy produces additional lipid-modifying benefit (94,95). HDL-Atherosclerosis Treatment Study (HATS) (96) showed that treatment with simvastatin and nicotinic acid led to a 26% increase in HDL-C, 38% reduction in triglycerides and 42% reduction in LDL-C. These lipid changes were associated with a 60-90% fall in the frequency of major coronary events. Furthermore, post hoc analysis of the HATS study data showed that such combined treatment reduced progression of atherosclerosis by 90% in patients with the metabolic syndrome compared when compared to placebo group (97).

Recently reported results from the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER 2) Study (98), provide further support for the atheroprotective effect of the combination of nicotinic acid and a statin in patients with established CHD and low HDL-C (< 45 mg/dl [1.17 mmol/l]),
27% of whom had type 2 diabetes and over 50% of whom had features of the metabolic syndrome. The Arterial Disease Multiple Intervention Trial (ADMIT) (99), which included a subgroup of 125 patients with type 2 diabetes showed that nicotinic acid daily significantly improved diabetic dyslipidaemia (increasing HDL-C by 29% and decreasing triglycerides and LDL-C by 23% and 8%, respectively) without any significant deterioration in glycaemic control.

Taken together, the available data suggest that combination lipid-modifying therapy aimed at LDL-C reduction (with a statin) as well as raising HDL-C and reducing triglycerides is an important strategy to further reduce cardiovascular risk in patients with type 2 diabetes and metabolic syndrome.

5.1.5. Novel therapies

The possible use of CETP inhibitors in the treatment of dyslipidemia is under study. Two pharmacological small-molecule inhibitors of CETP, JTT-705 and torcetrapib, have recently been shown to effectively raise HDL cholesterol in humans without serious side effects when either used as a monotherapy or combined with statins that lower low-density lipoprotein cholesterol (100). Data from the DAIS furthermore show that elevated CETP concentration is associated with increased progression of coronary atherosclerosis in patients with type 2 diabetes. Long-term studies will have to be performed to show whether CETP inhibition decreases the risk of atherosclerotic disease in dyslipidemic patients.

Recently a novel class of drugs aimed at tackling obesity and related metabolic and cardiovascular disorders by selectively antagonising the cannabinoid type 1 receptor (CB1) was studied. Van Gaal and colleagues reported the results of a 1-year blinded randomised clinical trial of rimonabant, the first drug of this class, in obese and overweight patients. Rimonabant was reported to cause a pronounced reduction in bodyweight, along with a parallel decrease in waist circumference, and a sustained amelioration of the metabolic profile (101). This compound therefore holds great promise for the prevention and treatment of the metabolic syndrome and the associated cardiovascular disease risk.
6. Cardiovascular metabolic syndrome

We are victims of our own evolutionary success, having developed a high caloric diet while minimizing the amount of maintenance energy expended on physical activity (1). As a consequence obesity and type 2 diabetes has reached epidemic proportions. Today the biggest killers in the world are not infectious diseases; rather it is chronic afflictions such as cardiovascular disease, obesity and type 2 diabetes that affect populations across the globe (102).

The role of inflammation in the pathogenesis of obesity, metabolic syndrome, type 2 diabetes and coronary heart disease (65-67) has provided a possible common pathological link between these diseases. Complex inter-relationships exist and therefore it is exceedingly difficult to delineate the direction of the causal pathways between these disorders. Given the overlap in prevalence of these metabolic disorders, and an alarming increase in risk for cardiovascular disease due to presence of them, novel approaches to prevention and therapy of patients with heart disease are called for (66).

Given the characteristic atherogenic dyslipidaemia of low HDL-C, elevated triglycerides and increase in small dense LDL associated with both type 2 diabetes and metabolic syndrome, there is need for targeted therapy. The current evidence base supports the use of combination therapy with a statin and nicotinic acid or a fibrate, in addition to diet and lifestyle intervention, to further reduce cardiovascular risk. Novel drug therapies like CETP inhibitors and CB1 antagonists seem to hold a lot of promise (100,101).

Concerted effort is needed to prevent the onslaught of this “Cardiovascular Metabolic Syndrome”. Along with the study of the enormity of this disease burden and epidemiological risk patterns, novel therapeutic and broader prevention strategies are required. Simple life style modification of eating healthy and increased physical activity (103) are important tools for primary and secondary prevention for all these diseases. Various treatment options are currently available (104) (table 3). Continued research, awareness and implementation of practical steps is essential at individual, institutional and governmental levels to tackle this pandemic.
### Table 3. Approach to Treatment

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Treatment</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity and Overweight</td>
<td>Weight loss via caloric restriction and exercise</td>
<td>BMI of $&lt; 25 \text{ Kg/m}^2$ or waist circumference of $&lt; 40$ inches in men and $&lt; 35$ inches in women.</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Lifestyle modifications; insulin or medical therapy for patients with diabetes, no indication for medical therapy for among people with metabolic syndrome without diabetes.</td>
<td>$&lt; 7.0$ hemoglobin A1c for those diabetes; $&lt; 100$ mg/dl fasting glucose for those with metabolic syndrome and without diabetes.</td>
</tr>
<tr>
<td>Lipids</td>
<td>Lifestyle modifications for all; Statins alone or in combination with nicotinic acid or a cholesterol absorption inhibitor.</td>
<td>$&lt; 100$ mg/dL or $&lt; 70$ mg/dL if known CHD or CHD equivalent.</td>
</tr>
<tr>
<td>1. LDL-cholesterol</td>
<td>Nicotinic acid or a fibrate; Statins alone or in combination with nicotinic acid or a cholesterol absorption inhibitor.</td>
<td>$&gt; 40$ mg/dL (men) and $&gt; 50$ mg/dL (women).</td>
</tr>
<tr>
<td>2. HDL-cholesterol</td>
<td>Nicotinic acid or a fibrate; Certain statins.</td>
<td>$&lt; 150$ mg/dL.</td>
</tr>
<tr>
<td>3. Triglycerides</td>
<td>Nicotinic acid or a fibrate; Certain statins.</td>
<td>$&lt; 150$ mg/dL.</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>Lifestyle modifications; Medical therapy choice per JNC VII guidelines.</td>
<td>$&lt; 130/80$ mm Hg.</td>
</tr>
<tr>
<td>Prothrombotic state</td>
<td>Low-dose aspirin.</td>
<td></td>
</tr>
<tr>
<td>Proinflammatory state</td>
<td>Aspirin, statins, fibrates, insulin and thiazolidinediones (TZDs) have shown to have anti-inflammatory effect.</td>
<td></td>
</tr>
</tbody>
</table>

JNC VII = the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

### References


Chapter 1


