INTRODUCTION

Cardiovascular disease (CVD) and Type 2 diabetes mellitus (T2DM) were once envisioned as different entities but now are thought to share common origins and pathways through insulin resistance and the cardiometabolic syndrome. Clinicians and researchers are rapidly becoming familiar with the metabolic syndrome and its presentations with the clustering of clinical syndromes and risk factors. However, the metabolic syndrome is also associated with an increased risk of T2DM, CVD (coronary-peripheral arterial disease, and stroke), chronic kidney disease (CKD), polycystic ovary syndrome (PCOS), and the metabolic hepatopathy referred to as non-alcoholic fatty liver disease or non-alcoholic steatohepatitis (NAFLD – NASH).

Thus, the term cardiometabolic syndrome (CMS) has been chosen in order to include all of these complicated metabolic disorders and the quintet of organ involvement including the cardiovascular system, pancreatic islets, kidneys, ovaries, and liver (Figure 1) [1,2].

Increased activity of the renin-angiotensin-aldosterone-system (RAAS), insulin resistance (IR), chronic low-grade inflammation, and oxidative stress – reactive oxygen species (ROS) collectively contribute to endothelial dysfunction (ED) and an accelerated atherosclerosis (atheroscleropathy), which manifest clinically as CVD. Currently, it is possible to identify and intervene in high-risk populations even before the clinical diagnosis of T2DM, CVD, CKD, PCOS, and NASH. Pharmacological interventions targeted at blocking the RAAS and improving IR have a role in the prevention of these clinical diseases and syndromes, and are avidly explored worldwide. The end-organs affected by the CMS have been included in a simple acronym named MINER in order to aid clinicians in the assessment of this high-risk population (Figure 2).

ECONOMIC IMPACT OF THE T2DM/CVD EPIDEMIC

It has been well documented that medical care cost of patients with T2DM are significantly greater than the non-diabetic population and a large proportion of this excess cost is accounted for by management of CVD. Care for patients with T2DM cost roughly double that of non-diabetics, and CVD management of diabetic patients was 2.31 times more expensive than treatment of diabetics without CVD. Costs were highest in diabetic people aged 55 to 64, underscoring the striking economic impact of cardiovascular complications related to T2DM. CVD accounts for the largest expenses in the management of T2DM, and its prevention would significantly reduce T2DM care costs [1].
The Role of Angiotensin II (Ang II) and Endothelial Dysfunction (ED) in T2DM

Angiotensin II (Ang-II) is a strong proatherosclerotic molecule with known direct and indirect vasoconstricting properties. Ang-II stimulates the potent vasoconstrictor endothelin 1 and antagonizes the actions of nitric oxide. After binding to angiotensin receptor 1 (AT-1), Ang-II induces production of reactive oxygen species (ROS) by activation of vascular NADPH oxidase [3]. In addition, there is stimulation of xantine oxidase, promotion of NADH auto-oxidation, and inhibition of superoxide dismutase (Figure 3) [4]. In conditions related to over stimulation of RAAS, such as T2DM and CVD, the normal balance between vasodilator and vasoconstricting properties of the endothelium is impaired. Increased vascular oxidative stress results in an inflammatory and proatherosclerotic vascular milieu, in which there is lipid peroxidation, cellular membranes injury, DNA damage, impairment of gene expression, and endothelial dysfunction [1].

Equally, Ang-II promotes coagulation and platelet aggregation through its effect on plasminogen activator inhibitor (PAI-1) and generates a prothrombotic environment. PAI-1 impairs matrix metalloproteinases, hampers extracellular matrix degradation, and promotes proliferation and atherosclerosis. In the kidney, Ang-II acts in concert with sustained hyperglycemia and glomerular hypertension to stimulate transforming growth factor β (TGF-β), a major regulator of vascular remodeling and a known mediator of sclerotic changes found in type 2 diabetic patients [1].

Ang-II participates in insulin resistance through interference of the phosphatidylinositol 3 kinase (PI3K) pathway and its downstream kinase Akt, implicated in the normal insulin-dependent glucose utilization and production of nitric oxide. On the other hand, Ang-II and compensatory hyperinsulinemia found in states of insulin resistance stimulate the mitogenic activated protein kinase pathway that promotes cell proliferation and migration of vascular smooth muscle cells and endothelial cells, as well as production of intracellular adhesion molecule-1 and monocyte chemoattractant protein-1. Therefore, the concept of selective insulin resistance and compensatory hyperinsulinemia is characterized in the vasculature by impairment of normal metabolic and vasorelaxing actions of insulin, while there is simultaneous stimulation of the proliferative pathway, the combined end results being ED and atherosclerosis [5].

Hyyperglycemia

Inappropriate activation of RAAS is not the only cause of endothelial injury in diabetic vascular disease. Hyperglycemia also plays a central role in the appearance and progression of atherosclerosis. Hyperglycemia promotes the formation of advanced glycation end-products (AGE), which result from non-enzymatic glycation of proteins and lipids. AGEs are formed by several pathways that coexist in hyperglycemia such as activation of polyol pathway with consequent production of AGEs and oxidative stress-induced generation of peroxynitrite. These AGEs are the ligands for the receptor for advanced glycation products (RAGE). AGEs could exert deleterious vascular effects in a receptor-dependent or independent way. AGEs cause excessive crosslinking of collagen and disruption of extracellular matrix in the vessel wall. On the other hand, ligand binding to RAGEs activates a mounting inflammatory cascade in endothelial cells,
macrophages, and smooth muscle cells with secondary overexpression of proinflammatory cytokines, adhesion molecules, and chemokines, increased production of ROS, and activation nuclear factor kappa B (NFκB). This cascade of events enhances formation of endothelial dysfunction and promotes atherogenesis [1].

**Microalbuminuria (MAU)**

MAU in diabetes is present in 20-30% of the patients and in 11-17% of hypertensive patients and is the reflection of an increased capillary permeability secondary to endothelial damage, caused by multiple endothelial insults [1]. The appearance of MAU is not an isolated event and clusters with other markers of ED and components of the CMS. It has been correlated with the production of pro-coagulant substances like activated factor VII, and in patients with type 1 diabetes, increased levels of von-Willebrand factor may precede and predict the appearance MAU.

Testing for MAU in a spot urine sample is encouraged by the American Diabetes Association and values between 30-300 mg albumin per gram creatinine on a spot urine sample is diagnostic.

T2DM patients showed that urinary albumin excretion in men is strongly associated with insulin resistance and other well-known CVD risk factors and MAU is linearly correlated with impaired endothelium-dependent, flow-mediated vasodilatation in elderly non-diabetic and diabetic individuals. Thus, MAU is a marker of endothelial damage and is clearly a predictor of CVD [1].

**Intimal Involvement in CMS and T2DM: Accelerated Atherosclerosis (Atheroscleropathy) and Atherothrombosis**

Atheroscleropathy associated with the CMS occurs within the intimal layer of the arterial vessel wall, which is constantly remodeling and may assume multiple types of plaques as outlined in the American Heart Associations classification (types I-VIII) (Figure 4) [2]. Plaque rupture and plaque erosion are the two main plaque types responsible for atherothrombosis in CMS and T2DM. Plaque rupture is commonly felt to be the most common; however, plaque erosion may be more prevalent in T2DM, smokers, and females and may be equally or more common in the CMS [2]. Recent preliminary observational studies indicate that plaque erosion may be the predominate lesion in T2DM patients who died suddenly of atherothrombosis as compared to plaque rupture (unpublished data by authors). Patients with T2DM have “vulnerable blood” due to an elevation of plasminogen activator inhibitor-1 with impaired fibrinolysis, an increase in ROS, and hyperactive platelet activity, which make all morphological plaque types, whether they rupture or erode, prone to develop diabetic atherothrombosis.

**Role of the Environment and Obesity**

The role of environment, mainly diet and physical activity, is also of paramount importance. It has been demonstrated that high levels of saturated fat and glucose found in westernized diets induce insulin resistance and endothelial dysfunction. In agreement with previous reports, a recent paper found that high-fat and refined carbohydrate diet-
induced impairment of endothelial-dependent vascular relaxation in Fischer rats, that was mediated by reduction in the production of NO, inhibition of expression of endothelial nitric oxide synthase, increased ROS, and reduced endogenous antioxidant ability [1]. In humans, a population-based prospective investigation which included 3,031 black and white young adults in the U.S. followed for 15 years, found a significant association between the frequency of consumption of fast food, weight gain, and insulin resistance measured by means of the Homeostatic Model Assessment (HOMA) technique. Indexes of IR increased approximately twofold in frequent fast food consumers (more than two visits per week) compared to low frequency consumers (less than one visit per week). Fast foods characteristically contain high-glycemic index components and a high proportion of saturated fats that have been related to IR. Importantly, this study found that fast food intake rose in particular in the participants with low frequency consumption at baseline, a finding that suggests the need of preventive public health strategies.

Adipose tissue (a major endocrine and secretory organ) may be the main site of inflammation in obesity, which increases the circulating levels of inflammatory markers reflecting spillover from an “inflamed” tissue and leads to the obesity-associated pathologies of T2DM, CVD, CMS, and the other affected end-organs.

In obesity, dysfunctional adipocytes promote inflammatory adipokines and result in chronic low-grade inflammation through activation of the NfκB pathway and enhancement of ROS production. Additionally, increased free fatty acids levels as a result of lipolysis induce ROS and are postulated to have proinflammatory effects (Figure 5) [1].

**Multifactorial Intervention: An Integral Approach TO CMS**

The Steno-2 study revealed the importance of multifactorial intervention, including diet, regular physical activity, and pharmacologic treatment with established T2DM and MAU (Figure 6) [6]. This study prospectively analyzed the effect of a multifactorial therapeutic approach (intensive intervention) on CVD risk factors in 160 patients with T2DM and MAU as a surrogate of endothelial dysfunction and predictor of CVD, as well as microvascular complications. Briefly, intensive intervention consisted of low-fat diet, light to moderate regular exercise, smoking cessation, reduction of blood pressure below 130/80 by means of ACEIs or ARBs as first line agents, multivitamin supplementation, aspirin, reduction of glycated hemoglobin below 6.5% using oral agents or insulin as needed, and pharmacologic control of hyperlipidemia (statins or fibrates), targeting blood pressure below 130/80, total cholesterol below 175 mg/dL, and triglycerides less than 150 mg/dL. The investigators randomly assigned 80 participants to intensive therapy, and 80 patients to conventional therapy, according to accepted guidelines. After a mean follow-up of 7.8 years, the intensive multifactorial intervention approach was significantly associated with a 20% absolute reduction in the risk of cardiovascular events and a relative risk reduction of 53%. The risk of developing microvascular diabetic complications (nephropathy, retinopathy, neuropathy) and MAU also decreased in the patients on intensive intervention.

RAAS blockade including angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) has been related to a delay in the development of
T2DM and along with low dose diuretics should form the cornerstone of combination therapy in hypertension and the multifactorial intervention in the CMS [5]

**Future Perspectives**

Despite previous considerations of T2DM and CVD being different entities, current knowledge indicates both involve similar mechanisms involving MAU, hypercoagulability, ED, ROS, chronic low-grade inflammation, and atheroscleropathy. Environmental factors (overnutrition and underexercise) have been shown to be of paramount importance in triggering and amplifying IR, vascular dysfunction, and atherogenesis. Prevention and management of T2DM-related CVD is the focus on key elements, which include lifestyle intervention, identification of high risk populations, traditional and non-traditional CVD risk factors, and pharmacological primary and secondary prevention. Strategies involving blockade of the RAAS have also provided valuable data demonstrating not only reduction in T2DM-related CVD, but also offer preventive effects on the incidence of T2DM. We have provided a therapeutic treatment acronym: RAAS in order to aid the clinician in considering this complicated multifactorial approach to treat patients with T2DM, CVD, and the CMS (Figure 7).

Ongoing studies, such as the ONTARGET Study, will in the near future provide avidly awaited data on RAAS interruption at single versus multiple steps. Some current ongoing trials, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Veterans Affairs Diabetes Trial (VADT), and Action in Diabetes and Vascular Disease (ADVANCE) evaluate the importance of dysglycemia and blood pressure control on CVD outcomes prevention. Other trials such as the Outcome Reduction with Initial Glargine Intervention (ORIGIN), the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR), and the Diabetes REduction Approaches with ramipril and rosiglitazone Medications (DREAM) study will evaluate combination pharmacological therapy. Collectively, a multifactorial approach involving environmental and pharmacological factors, which take into account the multiple mechanisms involved in T2DM, CVD, and CMS seems to be the best therapeutic alternative, if we are to change the global course of complications that is expected to affect more than 300 million people by 2025 (Figure 7) [1].

**References**

Figure 1. Cardiometabolic Syndrome (CMS)

A complex clinical clustering with multiple metabolic risk factors
The background X forms the 4 major arms - components of the CMS: Hyperinsulinemia (hyperproinsulinemia, hyperamylinemia), Hypertension, Hyperlipidemia - Obesity, Hyperglycemia (impaired glucose tolerance and impaired fasting glucose). Central to this syndrome are insulin resistance and the production of reactive oxygen species. It is important to note that the obesity epidemic seems to be driving the CMS. Additionally, the CMS predisposes to the development of T2DM and CVD as well as non-alcoholic steatohepatitis (MetHep), neuron- and renovascular redox stress and remodeling all associated with the MINER acronym (Figure 2). Each of the constituents of the CMS seems to be associated with oxidative stress and reactive oxygen species (ROS).
The MINER acronym of redox stress and remodeling in CMS:
The Spectrum of Diabetes Complications.

The MINER acronym may serve as a simple tool to aid clinicians in remembering those end-organ systems affected by CMS, IR, and type 2 DM. If primary care providers think of the future complications in the real and present time, they are more likely to think of various measures to prevent complications and utilize a Global Risk Reduction Team Approach.

| M | Myocardial redox stress and remodeling. **Myopathy**<br>Metabolic Hepatopathy: **NAFLD → NASH** | ROS |
| I | Islet and Intimal-vascular redox stress and remodeling: **Isletopathy and Intimopathy** | ROS |
| N | Neural redox stress and remodeling **Neuropathy and Nephropathy** | ROS |
| E | Endothelial redox stress and remodeling of the eNOS enzyme: **Endotheliopathy** | ROS |
| R | Retinal and Renal redox stress and remodeling **Retinopathy** | ROS |

Figure 2. The MINER Acronym of Diabetic Complications

ROS, redox stress, and remodeling are associated with each of the target end-organs. Each target organ will represent a combination of vascular and interstitial remodeling: Initially there is a structural change, which will evolve into a functional change and the associated diabetic complications or diabetic-opathies with multiple devastating complications and their associated morbidity and mortality.
Insulin resistance leads to the loss of hormonal homeostasis. This figure demonstrates the origin of vascular reactive oxygen-nitrogen species due to endothelial nitric oxide synthase (eNOS) enzyme uncoupling, which results in the net vascular production of superoxide and peroxynitrite instead of the vasculoprotective endothelial nitric oxide (eNO).
Figure 4. Atherothrombosis in CMS and T2DM

Top left: demonstrates vulnerable plaque rupture with eccentric plaque morphology. Top right: demonstrates vulnerable plaque erosion with concentric plaque morphology. Bottom left: demonstrates a complicated multi-layering plaque. Bottom right: demonstrates the malignant-like angiogenesis – neovascularization of the media and intima reminiscent of the neovascularization found in diabetic retinopathy. Recently the importance of plaque erosion in type 2 diabetes mellitus has been receiving increased interest and may become even more important due to the differential accumulation of PGs specifically hyaluronan and its matrix ligand CD-44.
Dysfunctional “sick” ADIPOCYTE in OBESITY:
OBESITY:A state of chronic low-grade inflammation

Elevated free fatty acid, glucose, and insulin levels enhance this NF-kappa B activation and further downstream modulates specific clinical manifestations of the CMS.

via NF kappa B

MIF
Macrophage migratory inhibitory factor

IL-6

Leptin

PAI-1

ADIPOCYTE

FFA

TNF alpha

Resistin

Angiotensinogen

“OBESITY IN THE CMS: decreased Adiponectin chronic INFLAMMATION”

The proinflammatory signals emanating from adipocytes in the obese state can have local and systemic effects that promote atherosclerosis and insulin resistance.

Figure 5. Obesity in CMS: A Chronic Inflammatory State

This figure portrays the dysfunctional adipocyte in obesity, which is responsible for the production of increased adipokines (acting in concert with NFkappaB) and free fatty acids (due to increased lipolysis), while the atheroprotective role of adiponectin is decreased. These findings place the role of obesity front and center in the CMS and it seems the obesity epidemic is driving the epidemic of T2DM and the CMS.
The Steno-2 study provides evidence that an aggressive multifactorial approach is superior to an individual approach in decreasing cardiovascular events and complications of T2DM with microalbuminuria. While this approach is a daunting task for clinicians it is well worth the time and energy to get this high-risk patient population to known therapeutic goals.
**USE OF THE RAAS ACRONYM IN CMS**

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<td>ACE-I/ARBs-SARTANS/ASA</td>
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<td>Adrenergic—beta blockade: blocks prorenin→renin</td>
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<td><strong>Antioxidant, anti-inflammatory nonselective beta blockade</strong></td>
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<td>Antipoline-felodipine—vascular antioxidant antihypertensive; favorite CCBs</td>
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<td>Aggressive control of diabetes</td>
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<td>Aggressive reduction of glucotoxicity—glycated-glyoxidated modified LDL-C</td>
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<td>Aggressive control of HTN</td>
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<td>Aggressive control of HHcy; decreasing Hcy and restoring the BH4 cofactor of the eNOS reaction with <strong>FOLIC ACID</strong></td>
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<td>recoupling the eNOS reaction and restore <strong>eNO</strong> and endothelial cell dysfunction <strong>FOLIC ACID</strong></td>
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<td>Statins: Plaque Stabilization</td>
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<td><strong>Style</strong>—lifestyle modifications: stop smoking, change the overnutrition and underexercise style</td>
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**Figure 7. Use of the RAAS Acronym as a Multifactorial Interventional Approach to CMS: Global Risk Reduction**

This figure attempts to simplify the multifactorial global risk reduction approach in order to include most all therapeutic regimens available at this time to treat and hopefully delay the multiple complications affecting the end-organs involved in the CMS.