Cardiovascular Syndrome X and Endothelial Dysfunction
Eugenia Vázquez-Rey and Juan Carlos Kaski

Up to 30% of patients with chest pain who undergo coronary arteriography, have completely normal coronary angiograms. The subgroup with typical angina and a positive response to stress testing is generally included under the diagnosis of cardiovascular syndrome X. Several causes and mechanisms have been investigated in the past twenty years, to explain both chest pain and ischemic angina-like ST segment depression that are commonly observed in these patients. Clinical and pathogenic heterogeneity appears to be the main features of the syndrome. Among the suggested pathophysiological mechanisms, endothelial dysfunction of the coronary microcirculation features prominently.

In this review, we present the available evidence regarding endothelial dysfunction in cardiovascular syndrome X.

Key words: Syndrome X. Endothelial dysfunction. Myocardial ischaemia.

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INTRODUCTION

Angina in the setting of normal coronary arteries is a heterogeneous entity, both clinically and pathophysiological. The most accepted definition of the syndrome includes chest pain with coronary characteristics, a positive stress test (typical ST segment depression), and coronary arteries that appear normal on angiography, with possible extracardiac causes of the chest pain, coronary spasm, arterial hypertension (AHT), and ventricular hypertrophy ruled out.1 Over the last 30 years, multiple pathogenic mechanisms have been considered as possible causes; it is likely that these vary from patient to patient (Table 1).2,3

Since Kemp introduced the term «syndrome X»4 in an editorial published in 1973, many groups have studied the possibility of a decrease in the coronary reserve being the cause of this syndrome; it has been noted that at least some of the patients classified as having

### TABLE 1. Physiopathological mechanisms in the cardiac X syndrome

<table>
<thead>
<tr>
<th>Endothelial dysfunction</th>
<th>microvascular dysfunction</th>
<th>ischemia</th>
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<tbody>
<tr>
<td>Change in the perception of chest pain</td>
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<td>Change in the perception of cardiac pain</td>
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<td>Metabolic changes in cardiac muscle</td>
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<td>Hyperfunction of the Na+/H+ pump</td>
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<td>Increase in sympathetic tone</td>
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this syndrome have a limited increase in coronary fluid in response to stimuli such as high-frequency atrial pacemakers or microvascular vasodilators such as acetylcholine, papaverin, adenosine, or dipiridamol. Cannon and Epstein\textsuperscript{1} termed this entity, characterized by a decrease in the coronary reserve, «microvascular angina.» Later, several studies identified endothelial dysfunction as one of the pathogenic mechanisms of this type of microvascular dysfunction,\textsuperscript{6-8} and even more importantly, some researchers have found, in patients with syndrome X, not only coronary circulation but also peripheral circulation, indicating that the syndrome may involve a generalized vascular disturbance.\textsuperscript{9,12}

**PHYSIOPATHOLOGY OF MICROVASCULAR ANGINA**

Coronary microcirculation is responsible for regulating coronary flow. It is reasonable to assume, therefore, that a decrease in the coronary reserve may cause myocardial ischemia. Many researchers have questioned, nevertheless, the existence of myocardial ischemia in the cardiac X syndrome due to the absence of hemodynamic or metabolic evidence of ischemia in most patients studied.\textsuperscript{13-18}

In patients with heart disease, ischemia is frequently associated with transient abnormalities in myocardial contractility as is shown on echocardiography or isotopic techniques. In patients with the X syndrome, however, only a few studies performed with isotopic techniques have shown a decrease in the ejection fraction during exercise (approximately 30% of patients).\textsuperscript{19,20} Some authors have described an association between the perfusion defects evident on gammography and the presence of coronary endothelial dysfunction.\textsuperscript{21,22} These changes may be an expression of ischemia or a reflection of the heterogeneity of myocardial perfusion in these patients, which has also been observed in studies performed with positron emission tomography (PET).

Masera et al\textsuperscript{23} proposed the hypothesis that patients with the X syndrome may present with functional and structural abnormalities in microcirculation, prearteriolar in nature, consistent with diffuse or patchy microvascular vasoconstriction (or the absence of appropriate vasodilatation), which would lead to myocardial ischemia that was undetectable by the usual techniques or that was compensated for by hypercontractility in the adjacent territories, which are normally perfused. These changes may help explain the broad spectrum of symptoms that occur in these patients. When greater numbers of vessels are involved, the decrease in the coronary reserve is greater, and the ischemia is greater. When, on the other hand, the involvement is restricted to a few vessels, the freeing of adenosine in the arterioles distal to the diseased prearteriolar vessels could cause chest pain in the absence of ischemia, given the algogenic properties of adenosine, and may even be responsible for changes observed on electrocardiogram (ECG) since adenosine produces a decrease in the action potential duration of myocytes and has a negative chronotropic effect.

Recent studies performed with stress echocardiography, both transthoracic and transesophageal, have established the absence of contractility abnormalities triggered by stress in these types of patients.\textsuperscript{14,24-26} In contrast to the echocardiographic data, changes have been identified in \textit{O}_2 saturation, pH, and the production of lactate in coronary chest blood, indicative of ischemia in the subgroup of patients with the X syndrome.\textsuperscript{27-29} In a study of 9 patients with the X syndrome and 5 controls who underwent stress testing (induced atrial tachycardia), production of lipid peroxidation products (indicative of ischemia) was documented in the syndrome X patients but not in the controls.\textsuperscript{30}

Recently, Buchthal et al\textsuperscript{31} studied 35 women with angina whose coronary arteries showed no significant stenosis on angiography (20% or less) and 12 controls, using magnetic resonance (MR) imaging with P-31, which allows direct assessment of high energy phosphates in the myocardium and the metabolic identification of ischemia. The authors found a decrease in the percentage of phosphocreatinine/ATP greater than 2 standard deviations from the mean in 20% of patients during a stress test (handgrip exercise). This result provides new evidence of myocardial ischemia in at least some of the patients with syndrome X (Table 2).
**Coronary endothelium. The physiopathological role of nitric oxide**

The vascular endothelium is responsible for important functions, including regulation of capillary permeability, vascular tone, and blood flow. The endothelium has a dual role in the control of vascular tone by segregating, in response to hemodynamic and chemical stimuli, both vasodilatory substances (such as nitric oxide [NO] and prostacycline), and vasoconstrictive substances (endothelin-I [ET-1] and angiotensin II [AT-II]). An adequate balance between these elements, vasoconstrictors and vasodilators, is essential for maintaining vascular homeostasis. When this balance is upset, the result is an increased predisposition to vasoconstriction of the vessels, leukocyte adherence, plaque activation, mitogenesis, and increases in the oxidative state, thrombosis, activation of coagulation, vascular inflammation, and atherosclerosis. 32-35

NO plays a key role in the regulation of vascular tone. In addition to being the principal determining factor of the basal tone of smooth vascular muscle, it counteracts the action of AT-II and ET-1. In addition, NO also inhibits the activation of plaque and leukocytes, and has an antiproliferative effect on smooth vascular muscle. NO is synthesized from the amino acid L-Arginine by the NO-synthetase enzyme. The activation of the endothelium by shearing forces or by the binding of bradykinin (BK) or acetylcholine (Ach) to their respective receptors results in a calcium entrance current that stimulates endothelial nitric oxide synthetase (eNOS). The NO that is formed from the L-arginine diffuses to the adjacent muscle cells, stimulating in them the soluble form of the guanylate cyclase (sGC) enzyme, which produces an increase in cyclic guanosine monophosphate (cGMP) which regulates the relaxation of muscle cells (Figure 1).

Initially, eNOS was described as not inducible, but it was later shown that certain stimuli, such as hypoxic,
xia, vigorous exercise, and stages of growth are associated with an increase in the expression of the enzyme in endothelial cells. Certain cytokines, such as tumor necrosis factor alpha (TNF-α), reduce the expression of eNOS because of the increase of a cystolic protein, called eNOS binding protein (EBP), which binds to the mRNA of the stabilized eNOS.

**Microvascular endothelial dysfunction in syndrome X**

Patients with cardiovascular syndrome X present with increased resistance of coronary flow, which is attributed to endothelial dysfunction in microcirculation. In humans, coronary microcirculation can be studied indirectly by measuring the myocardial flow in response to various vasodilator stimuli. The so-called vasodilatory reserve, or coronary flow reserve, is expressed as the quotient of maximum flow, obtained in response to vasodilators, and basal flow. Among the techniques used to perform these measurements is PET, intracoronary Doppler, blood flow measurement by thermodilution in the coronary chest and, more recently, by MR imaging.

Egashira et al reported on endothelial dysfunction in patients with syndrome X and noted that the administration of L-arginine (a precursor of NO) improved endothelium-dependent vasoilation, which indicates a defect in NO synthesis in these patients.

Previously, Bellamy et al showed that the oral administration of L-arginine for 4 weeks improved exercise tolerance and reversed the endothelial dysfunction in patients with syndrome X.

Quyyumi et al evaluated the response to Ach and to high-frequency atrial pacemaker in 51 patients with syndrome X, and found a correlation between both responses, indicating that endothelial dysfunction may contribute to a decrease in the coronary reserve during stress and anginous pain in these patients. Nevertheless, the authors also observed that some patients had a normal reaction to Ach.

Endothelial dysfunction can be also evaluated with serological markers, which are cellular components that are freed into the bloodstream when endothelial cells are damaged or activated. Among these are the von Willebrand factor (vWF), fibrinogen, fibronectin, and alfa-2-macroglobulin. Another type of marker for endothelial activation is the VCAM-1 and ICAM-1 markers, which mediate leukocyte adhesion to the vascular endothelium. Tousoulis et al showed that there is a significant increase in the plasma concentrations of VCAM-1 and ICAM-1 both in patients with syndrome X and in patients with heart disease as compared to healthy controls. Bøtker et al performed a study that compared the vWF values in 3 groups of patients, 1 group with heart disease, 1 with syndrome X, and a control group. The authors found significantly higher vWF values in the patients with heart disease, but not in the other 2 groups. Nevertheless, the considerable overlap of the results from the syndrome X group and the group of patients with heart disease reported in the study by Bøtker et al points out, once again, that the patients with syndrome X are a heterogeneous group; some patients in this group do have elevated concentrations of vWF factor. This heterogeneity may be also be explained by the fact that studies have shown systemic endothelial dysfunction only in some patients with syndrome X, including those patients who had no elevated concentrations of vWF factor. Therefore, some researchers have found a decrease in the endothelium-dependent vasodilatory response on echo-Doppler or plethysmography of the forearm in patients with syndrome X and healthy controls in whom they evaluated the response of myocardial flow to dipiridamol using PET and systemic vasoreactivity using ultrasound of the brachial artery, and in whom they studied the structure and function of subcutaneous resistance vessels in the biopsy specimen obtained from the glutes. These findings confirmed the presence of both reduced coronary and peripheral vasodilatory capacities; however, they did not find functional or structural abnormalities in the arteries that they isolated.

**The role of endothelin**

The endothelins are a family of peptides consisting of 21 amino acids (ET-1, ET-2, ET-3) codified by 3 distinct genes. Endothelins are expressed in various tissues, where they act as moderators of vasomotor tone, cell proliferation, and hormone production. ET-1 is the only one that is produced in endothelial cells, although it is also produced in the smooth muscle cells of the vascular wall. It was isolated for the first time by Yanagisawa et al in 1988 from the endothelial cells of pig aorta. ET-1 is a vasoconstrictor and neuromodulator peptide. Recent studies suggest it has an important role in the regulation of basal coronary arterial flow and it has been associated with the pathogenesis of processes such as ischemia-reperfusion damage, cardiac insufficiency, hypertension, and atherosclerosis. Endothelin is the most powerful vasoconstrictor known at the present time (100 times more powerful than noradrenalin). Two receptors (ETA and ETB) have been identified. The ETA receptor is the predominant subtype and is present in vascular wall myocytes. Stimulating the receptor results in vasoconstriction. The ETB receptor is present in the endothelial cells, which produce a vasodilation effect, and also in the vascular myocytes, where it exerts a vasoconstrictor effect.

ET-1 is not stored in secretory granules in the interior of the cell. Stimuli such as ischemia, hypoxia, and shear stress induce transcription of the gene...
(Figure 2) and the synthesis and secretion of ET-1 within minutes. Its half-life is 4 to 7 minutes and 80% of it is cleared by the lungs. Nevertheless, after binding to the receptor, the vasoconstrictor effect may last more than 60 minutes. Although its secretion is 75% albumin, acting in a predominantly paracrine manner on the vascular myocytes, its plasma concentrations correlate well with the severity and degree of heart disease, unstable angina, and cardiac insufficiency, and thus have prognostic value. Elevated ET-1 values have also been reported in patients with coronary spasm. Nevertheless, the available evidence shows that vasoconstriction mediated by ET-1 occurs predominantly at the microvascular level, most likely due to the distribution of the various types of receptors in the coronary vasculature. These findings have lead to speculation that increases in ET-1 activity may be implicated in the physiopathology of microvascular angina. In a study by Kaski et al plasma ET-1 values were measured in 40 patients with syndrome X and 21 healthy controls; the authors found that plasma concentrations of ET-1 were significantly higher in patients with syndrome X than in the controls. Even more important, they observed that in patients with syndrome X, the plasma levels of endothelin had a negative correlation with the levels of ischemic pain. In another study, the same group showed an inverse correlation between basal artery ET-1 levels and the coronary reserve in women with syndrome X. In a later study of larger series of patients with syndrome X, the same authors observed that those patients who presented with a left branch block of the His bundle (LBBHB) or who had suffered a previous infarct in particular had the highest ET-1 levels.

Lanza et al measured plasma concentrations of ET-1 in overall circulation and in the coronary chest in 13 patients with syndrome X and 8 controls, at baseline and after stimulation with high-frequency atrial pacemaker. The baseline ET-1 levels, both in the samples obtained from the femoral artery and from the coronary chest, were significantly greater in the patients with syndrome X than in the controls. After stimulation with the atrial pacemaker, the authors found an increase in the ET-1 values in the coronary chest in the patients with syndrome X but not in the control patients. Other authors, however, have not been able to detect higher plasma concentrations of ET-1 in patients with syndrome X. Newby et al did not observe differences in the ET-1 levels between patients with syndrome X and healthy controls, but found that the peripheral vasoconstrictor response to the infusion of ET-1 had an inverse correlation with its plasma concentrations. This phenomenon may reflect hyperactivity of the ET-1 system and an increase in the number of type A receptors. Desideri et al did not find any differences at baseline in the plasma values of ET-1 or in VCAM-1 or in nitrate values. They did, however, observe significantly higher concentrations of ET-1 in patients with syndrome X than in control patients after glucose overload, which may indicate the endothelium is more susceptible to certain stimuli.

These findings raise important questions regarding the role of ET-1 in the physiopathology of syndrome X. Opherk et al showed that the presence of LBBHB...
on ECG is associated with a subgroup of patients with syndrome X who had an increased risk of developing left ventricular dysfunction at a later date. In addition, it has been reported that patients with syndrome X and LBBHB have abnormalities in lactate metabolism during stress. Based on these observations, it has been proposed that patients with LBBHB and syndrome X may have a type of dilated myocardial infarction associated with microvascular ischemia. It has been suggested that the elevated ET-1 values in patients with syndrome X may contribute to the development of microvascular myocardial ischemia, which in serious cases could produce conduction abnormalities and progressive left ventricle dysfunction. A study by our group indicated that among patients with syndrome X who underwent repeated coronary angiography due to the instability of their symptoms, patients with LBBHB had a higher likelihood of a developing coronary angiography disease than patients who had conduction anamolies.

Microvascular spasm

The mechanism of microvascular spasm was proposed more than 10 years ago by several researchers. Recently, Mohri et al investigated the response to intracoronary Ach in 117 patients with angina and normal or nearly normal coronary arteries (stenosis <50%). The majority of the patients presented with angina at rest, indicative of coronary spasm. During angiography, 29 of the patients presented with typical angina or ischemic changes on ECG, or both, without evidence of spasm in the epicardial coronary arteries. In 11 of the 29 patients in this group the production of lactate, measured in the coronary chest, was also detected. On the other hand, Murakami et al published findings on 3 patients with transient ST segment irregularities and normal coronary angiogram during episodes. All the patients had a positive electric ergometry by ST segment depression; however, coronary stenosis was present on angiogram and testing to provoke coronary spasm was negative. A decrease in the endothelium-dependent coronary reserve was detected in 1 of the 2 patients in whom the test could be performed. The underlying mechanism in this case would be constriction of the arterioles to less than 200 mm in diameter.

ETIOLOGY OF ENDOTHELIAL DYSFUNCTION IN SYNDROME X

There are a variety of causes that may contribute to endothelial dysfunction in patients with syndrome X, including risk factors such as diabetes, smoking, arterial hypertension (AHT), hypercholesterolemia, and other factors that have recently been implicated in atherogenesis such as homocysteine, O2 free radicals, infections, inflammatory mechanisms, and estrogen deficits.

Several authors have shown that coronary risk factors, such as AHT, hypercholesterolemia, and diabetes are associated with a reduction in NO availability, both at baseline and after stimulation (Ach), in patients with normal coronary arteries on angiogram. Even more importantly, other authors have shown that the amelioration of these risk factors, as well as angiotensin converting enzyme inhibitors (ACEI), can normalize endothelial function. Similarly, various studies have shown that endothelial dysfunction, produced by classic coronary risk factors, affects not only the epicardial coronary arteries, but also microcirculation and peripheral circulation.

Based on the observation that many patients with syndrome X are menopausal and postmenopausal women, an estrogen deficit has been proposed as a possible factor in the pathogenesis of this syndrome. A relationship has been found between endothelial dysfunction and estrogen deficits, both in asymptomatic and hypertensive women and in women with documented heart disease. Rosano et al performed a study of 107 women with chest pain and normal coronary arteries on angiogram, of whom 95 developed the illness following menopause. Forty-three of the women had undergone a hysterectomy, which is an incidence 4 times higher than that in the general population. In addition, a notable improvement in endothelial function in coronary microcirculation was observed after hormone replacement therapy in women with syndrome X, and improved peripheral endothelial function is observed after estrogen treatment or combined hormone treatment in women with and without heart disease. Webb et al showed that the administration of estradiol achieved a notable decrease of ET-1 in postmenopausal women with heart disease; however, they did not observe a change in vasomotor function, in spite of the reduction in ET-1.

There is another syndrome X, a metabolic type that is defined by its epidemiological association with insulin resistance, AHT, dyslipemia, and atherosclerotic heart disease.

Studies have found that patients with angina and normal coronary arteries have insulin resistance, and an increase in the secretion of proinsulin, increased concentrations of triglycerides, and decreased HDL, which also occur in patients with metabolic syndrome X. On the other hand, an increase in plasma concentrations of ET-1 has been observed in patients with metabolic syndrome X. Both syndromes are also characterized by endothelial dysfunction and an increase in the Na+–H+ exchange in cell membranes (Table 3).

It has been suggested that insulin resistance in patients with angina and normal coronary arteries may result from endothelial dysfunction, due to variations.
in microvascular fluid in the skeletal muscle, given that glucose capture is stimulated by insulin by means of an increase in local fluid mediated by NO.\textsuperscript{129} Researchers have observed that the response to insulin is associated with capillary density in the skeletal muscle and can be improved by interventions such as physical exercise, which increases the capture of glucose and blood flow. On the other hand, the pancreatic islet beta cell dysfunction, evident in the increase in pancreatic islet beta cells observed in patients with insulin resistance, type 2 diabetes mellitus, and arterial hypertension (AHT)\textsuperscript{130,131} as well as in patients with cardiac syndrome X, may be the result of the effect of pancreatic microcirculation perfusion. Nevertheless, although endothelial dysfunction has been associated with the presence of insulin resistance in different phases of atherosclerosis,\textsuperscript{132} it is not clear whether it is the direct cause.\textsuperscript{133}

It has been suggested that a defect in glucose transport in the cell membrane is the most likely mechanism of insulin resistance in patients with cardiac syndrome X.\textsuperscript{134} The hyperinsulinemia that is associated with insulin resistance may also be a cause of endothelial dysfunction. Recently, Arcaro et al\textsuperscript{135} showed, in a study of healthy volunteers, that moderate hyperinsulinemia, at the same level as that present in patients with insulin resistance, causes serious endothelial dysfunction in macrocirculation. In the same study, the authors reported that a regimen of vitamin C prevented the development of endothelial dysfunction, which indicates a possible mechanism of action that increases oxidative stress. It has been shown that insulin in microcirculation activates both the production of NO and ET\textsubscript{1}.\textsuperscript{136} Endothelin induces the expression of NO\textsubscript{EP}H oxidase in endothelial cells, with the consequent generation of superoxide anion.\textsuperscript{137} On the other hand, it has been noted that hyperinsulinemia of exogenous origin activates NO\textsubscript{EP}H oxidase in rat aortic endothelium.\textsuperscript{138} Based on these findings, the authors suggested that insulin may cause endothelial dysfunction after an increased availability of ET\textsubscript{1} and a subsequent increase in oxidative stress. In the opinion of some authors, all these changes observed in metabolic syndrome X lead to a vicious circle in which endothelial dysfunction contributes to insulin resistance and vice versa.\textsuperscript{139}

A recent study by García-Soriano et al\textsuperscript{140} reported that the activation of the (ADP-ribose) polymerase (PARP) enzyme is an important factor in the pathogenesis of endothelial dysfunction in diabetes mellitus. PARP is a nuclear enzyme that has been implicated in the response to AND lesion. These authors found that the destruction of pancreatic islets with streptozotocin in mice induces a state of intense hyperglycemia, the intravascular production of oxidative substances, activation of the PARP, and endothelial dysfunction. In addition, the authors showed that endothelial dysfunction in mice is dependent on PARP. Experiments in vitro on pulmonary endothelial cells showed that increased concentrations of glucose are a potent stimulus for the activation of PARP following formation of superoxidized radicals. It has also been shown that the endothelial cells exposed to elevated concentrations of glucose generate oxygen free radicals.\textsuperscript{141}

In accordance with the association observed between insulin resistance and endothelial dysfunction, it has been suggested that agents that increase sensitivity to insulin may also improve endothelial function. Pasceri et al\textsuperscript{142} showed that troglitazone (activator of the proliferator-activated receptor gamma) inhibits in vitro the expression of VCAM-1 and ICAM-1 in activated endothelial cells. Based on this and other studies,\textsuperscript{143-146} clinical trials were performed to study the nonhypoglycemic effects of these new oral antibodies that showed a beneficial effect on endothelial function,\textsuperscript{147-149} at least in the short term. Nevertheless, at present, there is no agreement among all researchers, as one well-designed study has yielded conflicting results in this regard.\textsuperscript{150}

### CONCLUSIONS

Although the long-term prognosis for patients with syndrome X is generally benign, their quality of life frequently deteriorates for years due to the persistence of episodes of precordial pain. In addition, hospital readmissions and repeated diagnostic tests result in a significant consumption of resources.

The physiopathology of syndrome X involves a variety of mechanisms that vary from patient to patient. Among these, microvascular endothelial dysfunction may explain the precordial pain and the electrocardiographic changes in at least 1 subgroup of patients. More importantly, it has recently been shown that endothelial dysfunction in patients with non-obstructive heart disease is a marker for the risk of acute episodes.\textsuperscript{151} Nevertheless, the question as to whether this endothelial dysfunction is the cause of myocardial ischemia continues to be controversial, as is whether the ischemia plays a role in the physiopathology of the

### TABLE 3. Common characteristics of the metabolic and cardiac syndromes X

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<tr>
<th>Insulin resistance</th>
<th>Hyperinsulinemia</th>
<th>Hypertriglyceridemia</th>
<th>Decrease in HDL</th>
<th>Increase in ET-1</th>
<th>Endothelial dysfunction</th>
<th>Increase in Na&quot;\textsuperscript{+}-H&quot;\textsuperscript{+} exchange</th>
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ET-1 indicates endothelin 1; HDL, high density lipoproteins
syndrome. A number of authors have investigated the reversibility of endothelial function. It has been shown that short-term treatment with ACEI improves endothelial function in patients with known atherosclerosis. In patients with type 2 diabetes with insulin resistance, studies that evaluated improvement in endothelial function with ACEI have yielded conflicting results. Likewise, in patients with hypercholesterolemia with and without heart disease, an improvement in endothelial function has been reported following hypolipemic treatment. Replacement hormone therapy and new antidiabetic drugs may also be useful in the treatment of endothelial dysfunction in the cardiovascular syndrome X.

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