Therapy of patients with cardiac syndrome X

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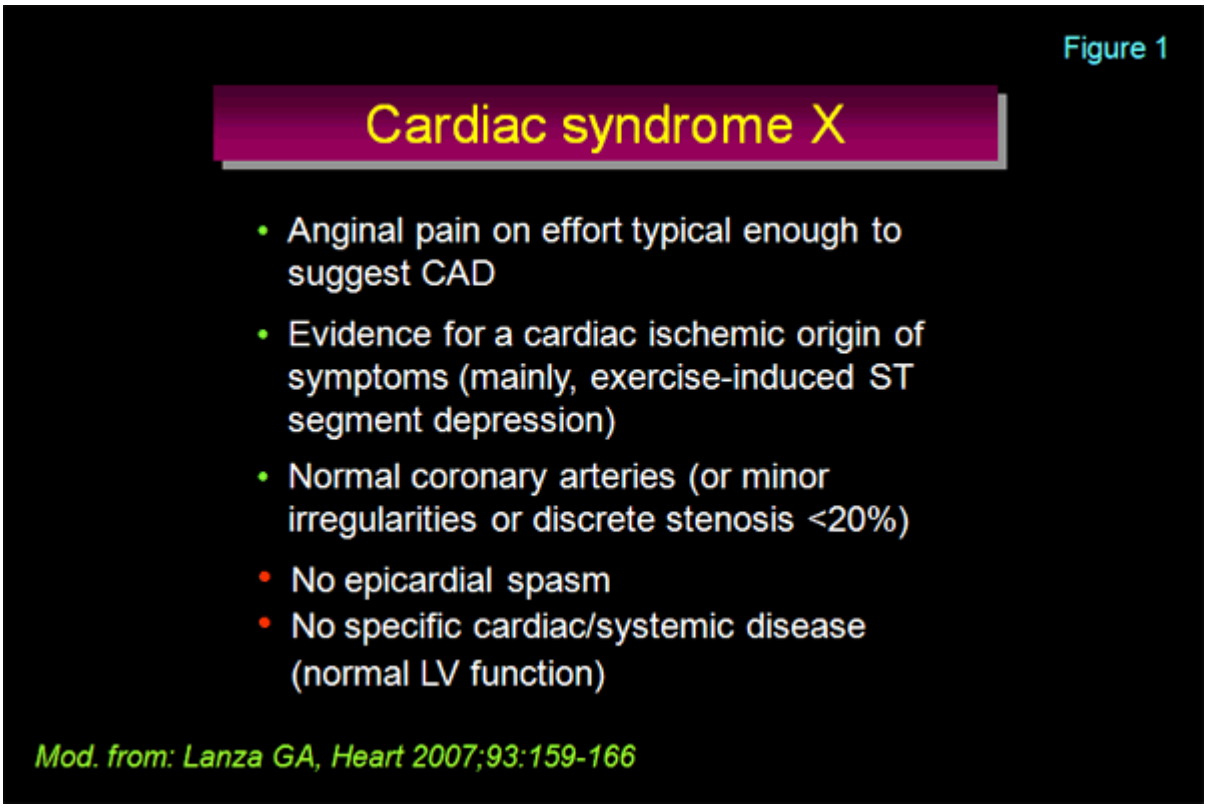
Introduction

Cardiac syndrome X (CSX) is usually characterized by: 1) angina episodes predominantly related to efforts, typical enough to suggest obstructive coronary artery disease; 2) ST-segment depression compatible with myocardial ischemia during spontaneous or provoked angina; 3) normal coronary arteries at angiography (although very mild abnormalities can be acceptable for the diagnosis); 4) no evidence for epicardial coronary artery spasm and other specific cardiac disease **(Figure 1)**.



Following theoretical plausible hypotheses, the numerous studies performed to support the microvascular origin of SX and clarify the mechanisms responsible for its occurrence have been directed, in variable ways, to two main objectives, that is

1) to provide evidence of abnormalities of coronary microvascular vasomotion, which can only be obtained indirectly by measuring CBF or CVR, as obviously coronary resistence vessels cannot be assessed visually on coronary angiography, and

2) Individuation of potential mechanisms responsible for the microvascular dysfunction.

Obviously several studies assessed these objectives togetether, whereas others wre focused on only one of these aspects.

Coronary microvascular dysfunction (CMVD), as indicated by the blunted response of coronary blood flow (CBF) to vasodilator drugs, but also an impaired CBF in response to vasoconstrictor stimuli, was suggested by most studies to be responsible for the syndrome. The mechanisms of CMVD, however, are likely heterogeneous and can variably involve abnormalities in endothelial and in vascular smooth muscle cell function. Furthermore, several abnormalities have been described in CSX able to cause CMVD, including insulin resistance, low-grade inflammation, abnormal adrenergic function, increased endothelin-1 release and membrane Na^+-H^+ exchanger activity, and (in women) estrogen deficiency. Furthermore, traditional cardiovascular risk factors (including hypertension, hypercholesterolemia, diabetes, smoking) might also contribute to CMVD.

However, in a relevant group of CSX patients, an increased painful perception of cardiac stimuli has been described and can significantly influence frequency and clinical characteristics of chest pain episodes.

Long-term prognosis of CSX patients has consistently been shown to be excellent. However, studies have also consistently shown that a significant number of patients have persistent symptoms at follow-up, which may considerably impair usual daily activities and quality of life. These patients often undergo hospitalization for recurrent chest pain, and repeat non invasive and also invasive diagnostic tests, with relevant individual and social economical issues.

Thus, the primary goal of treatment in CSX patients is control of symptoms and improvement of quality of life. Accordingly, interventions reported to have beneficial effects on chest pain episodes should be preferred to those shown to improve only surrogate clinical end-points, including ischemic ECG changes or CBF abnormalities.

According to the pathophysiological mechanisms of the syndrome, most treatments are directed at improving CMVD and myocardial ischemia through either aspecific or specific mechanisms, whereas some therapies are directed to increase cardiac pain threshold.

It should be stressed that indications about management of CSX patients derive from studies which suffer from some important limitations, including a usual small number of patients enrolled, the lack, in some cases, of appropriate randomization and control, and heterogeneity of end-points, which often do not allow adequate comparisons among proposed treatments and robust conclusions about the magnitude of their efficacy.

Anti-ischemic drugs

Traditional anti-ischemic drugs remain the first-option medical treatment in CSX patients and are sufficient to control chest pain in most cases.

Beta-blockers. Beta-blockers are the cornerstone therapy of patients with stable angina and obstructive coronary artery disease (CAD) and have been reported to have beneficial effects also in CSX **(Figure 2)**. Atenolol, in particular, was shown to improve short-term symptoms in a small randomized, controlled trial **(Figure 3)**. Beta-blockers act mainly by contrasting the negative effects of the nervous sympathetic system. In particular, they reduce myocardial oxygen demand during efforts, but may also improve vascular motility in some patients. In general, ß-blocking agents should probably constitute the first-option drug therapy in most CSX patients, particularly in those with evidence of increased adrenergic tone (e.g., high heart rate or decreased heart rate variability during 24 hour Holter monitoring, or rapid increase of heart rate and/or blood pressure during exercise).

Calcium-antagonists. A summary of studies on calcium-antagonists in CSX is shown in **Figure 4.** Calcium antagonists could act mainly through improvement of coronary microcirculation. Furthermore non dihydropyridine drugs may reduce heart rate and myocardial oxygen consumption. Stimulation of adrenergic activity, following significant hypotension, however, may constitute a limitation. Nifedipine was shown to improve CBF, but no significant effects could be demonstrated on coronary microvascular function for diltiazem in a study. A reduction of angina symptoms and improvement of exercise test results were variably reported with several calcium-antagonists. In some patients, however, nifedipine was associated with worsening of symptoms, whereas amlodipine failed to achieve beneficial effects on anginal symptoms in our small study **(Figure 3)**.

Nitrates. Nitrates have coronary vasodilator effects and reduce cardiac preload. However, the effects of nitrates on coronary microcirculation are limited, and hypotension and reflex tachycardia may reduce their beneficial actions. Short-acting nitrates can be used to treat chest pain attacks, as in obstructive CAD, but they achieve consistent effects in about 50% of CSX patients only **(Figure 5)**. Long-acting nitrates, on the other hand, were assessed only in our study, in which we failed to show significant effects on symptoms **(Figure 3)**.

Figure 2

Main results of trials with beta-blockers In patients with cardiac syndrome X

	Drug	Symptoms	ExT	Holter	CBF
Bugiardini 1989	Propranolol			+	
Romeo 1990	Acebutolol		+/-		
Borghi 1991	Propranolol	+	+		
Wiedermann 1995	Propranolol				+/-
Fragasso 1997	Atenolol	+	+		
Lanza 1997	Atenolol	+			

(+) = positive effect; (-) = no effect

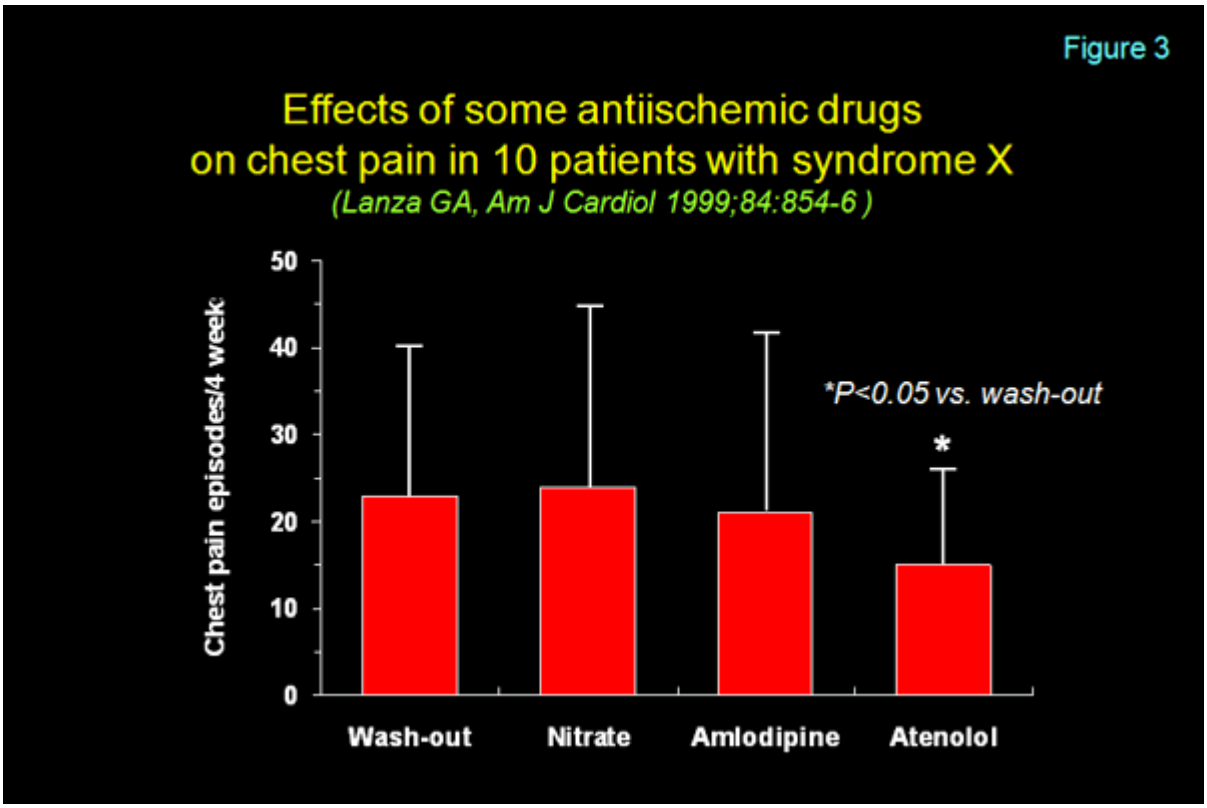


Figure 3
Effects of some antiischemic drugs
on chest pain in 10 patients with syndrome X
(Lanza GA, Am J Cardiol 1999;84:854-6)
Chest pain episodes/4 week
50
40
30
20
10
0
*P<0.05 vs. wash-out
*
Wash-out
Nitrate
Amlodipine
Atenolol

Figure 4

Main results of trials with calcium-antagonists In patients with syndrome X

	Drug	Symptoms	ExT	Holter	CBF
Cannon 1985	Verapamil Nifedipine	+	+		
Bugiardini 1989	Verapamil			-	
Cannon 1990	Lidoflazine	-	+		+
Romeo 1990	Verapamil		+		
Montorsi 1990	Nifedipine		+		+
Borghi 1991	Verapamil	-	+		
Sutsch 1995	Diltiazem				-
Lanza 1997	Amlodipine	-			
Ozçelik 1999	Nisoldipine	+	+		

(+) = positive effect; (-) = no effect

Figure 5

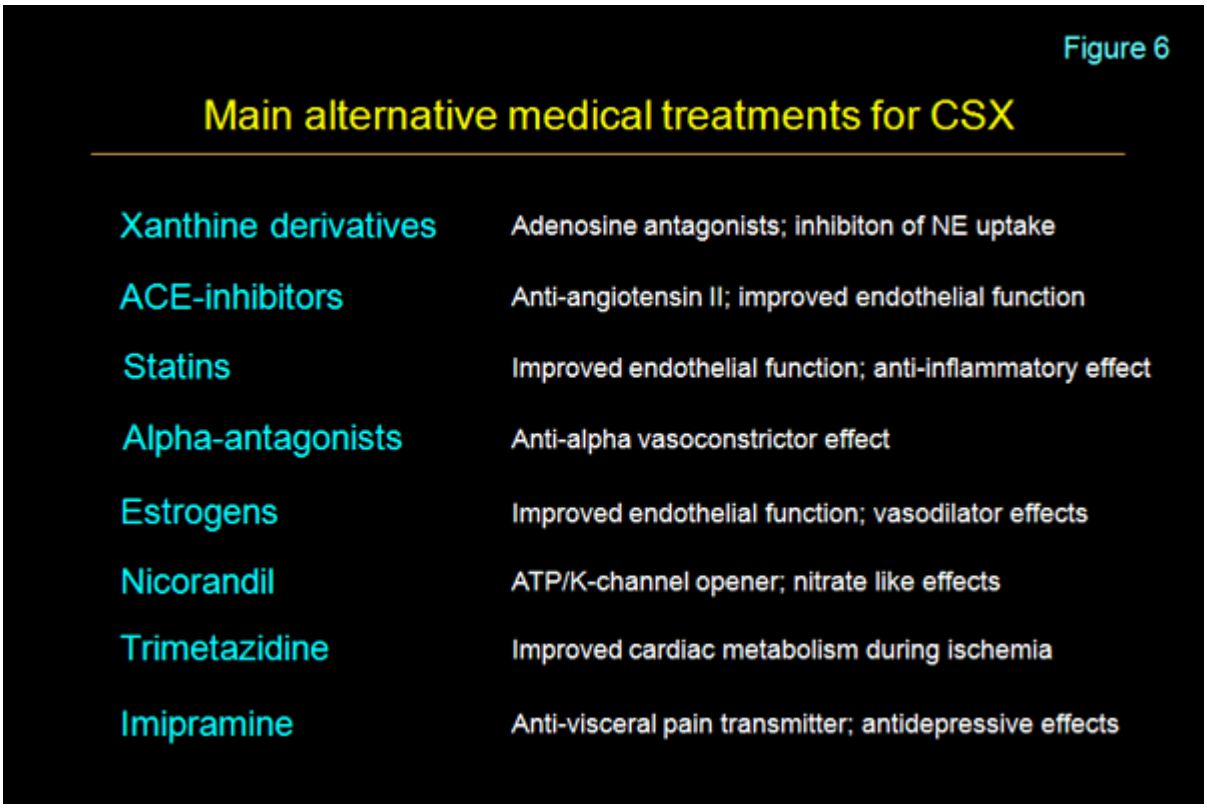
Efficacy of short-acting nitrates on chest pain In patients with angina and normal coronary arteries

	No. Patients	Efficay (%)
Waxler 1971	86	47
Kemp 1973	200	41
Day 1976	45	18
Pasternak 1980	159	41
Isner 1981	109	64
Bass 1983	46	19
Romeo 1993*	30	33
Kaski 1995*	99	42
Lanza 2007*	153	52

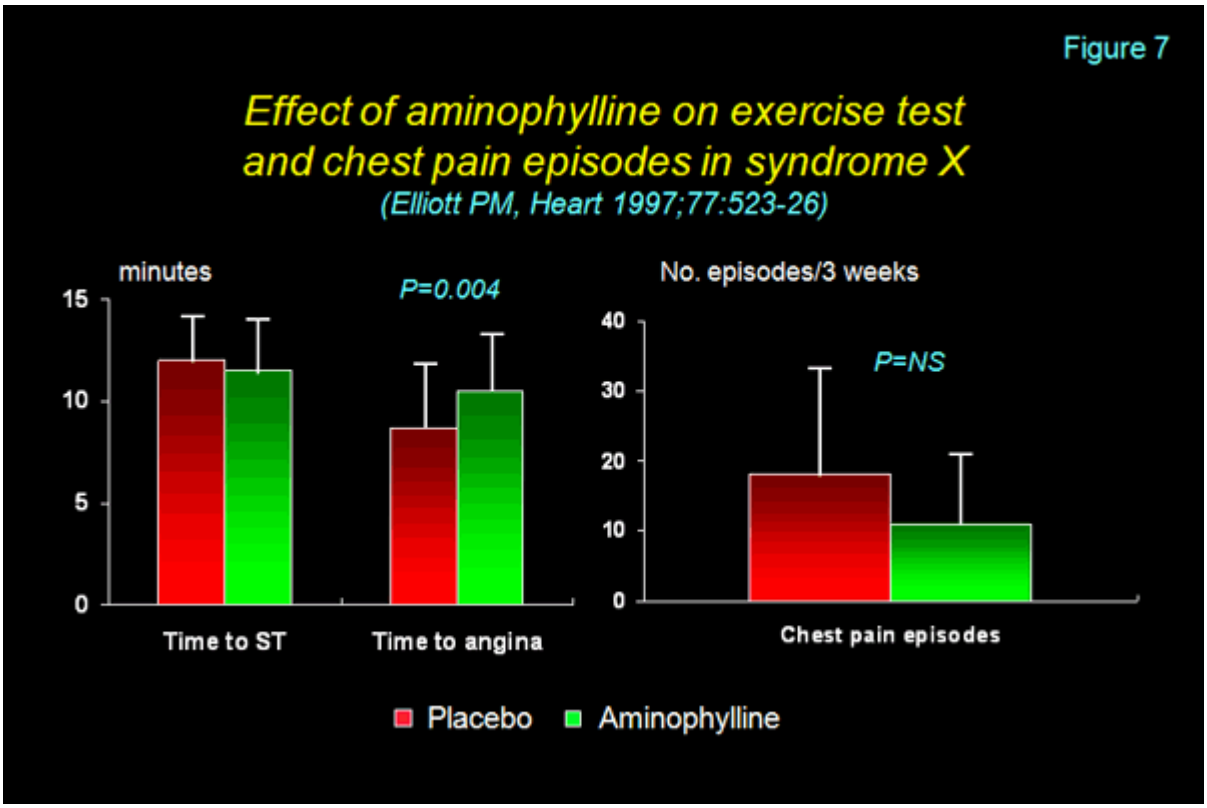
*Typical CSX patients

Other forms of treatment

Several other forms of treatment have been proposed for CSX patients who remain symptomatic for angina episodes despite optimal anti-ischemic drug therapy **(Figure 6)**.



Xanthine derivatives. These drugs have been assessed in several studies. They may act mainly through their adenosine receptor blocking action, which may result in a direct anti-algogenic effect (due to the involvement of adenosine in ischemic cardiac pain generation), but also in an anti-ischemic effect, related to a favourable redistribution of coronary blood flow. The latter can be also facilitated by the inhibition of norepinephrine uptake by sympathergic nerve fibres. Beneficial effects of aminophylline and bamiphylline have been reported by several studies on exercise stress test results **(Figure 7)**, although the effects on angina symptoms have not been adequately investigated.



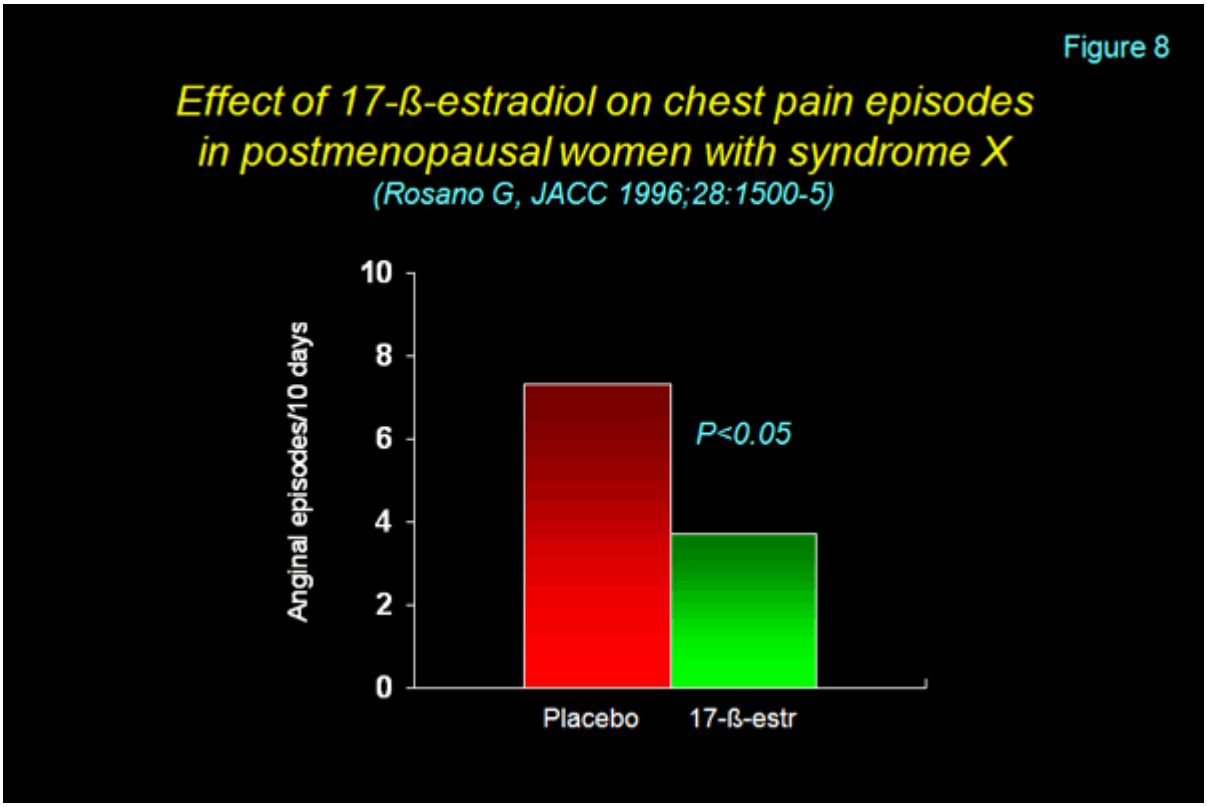
Angiotensin converting enzyme (ACE)-inhibitors. ACE-inhibitors have been proposed due to a possible involvement of the renin-angiotensin-aldosterone system in CMVD. Angiotensin II, in particular, may have vasoconstrictor effects on small coronary arteries and also facilitate endothelial dysfunction through its pro-oxidant effect. ACE-inhibitors have variably been reported to have favourable effects on symptoms and on exercise stress test results in small controlled trials. Furthermore, enalapril was found to increase NO availability in CSX patients in a study. These drugs can be particularly indicated in patients with evidence of hypertension.

Hydroxy-methyl-glutaryl coenzyme A reductase inhibitors. Statins have also been reported to have beneficial effects on angina symptoms and exercise tolerance in some recent controlled studies in CSX patients, likely because of the improvement of endothelial vasodilator function mediated by a reduction of oxidative stress. The usefulness of statins can be particularly significant in patients with increased blood cholesterol levels and/or biomarkers of inflammation (e.g., C-reactive protein), which can significantly contribute to endothelial dysfunction.

Alpha-antagonist drugs. These drugs might act by decreasing alpha-mediated vasoconstriction in coronary microcirculation. However, studies with prazosine

and doxazosine (peripheral action) or clonidine (central action) achieved inconsistent results.

Estrogens. Most patients developing CSX are post-menopausal women, which suggests that estrogen deficiency may have a pathogenic role in the genesis of the syndrome in several cases. Accordingly, estrogens have been proposed as a form of therapy in this group of CSX patients. Estrogens improve coronary endothelial function and may also act favourably on cardiac pain perception. In a small randomized controlled trial, 17ß-estradiol determined a mild to moderate reduction of angina episodes in postmenopausal CSX women **(Figure 8)**. Some concerns about possible negative effects, however, may limit long-term use of estrogens for CSX therapy.



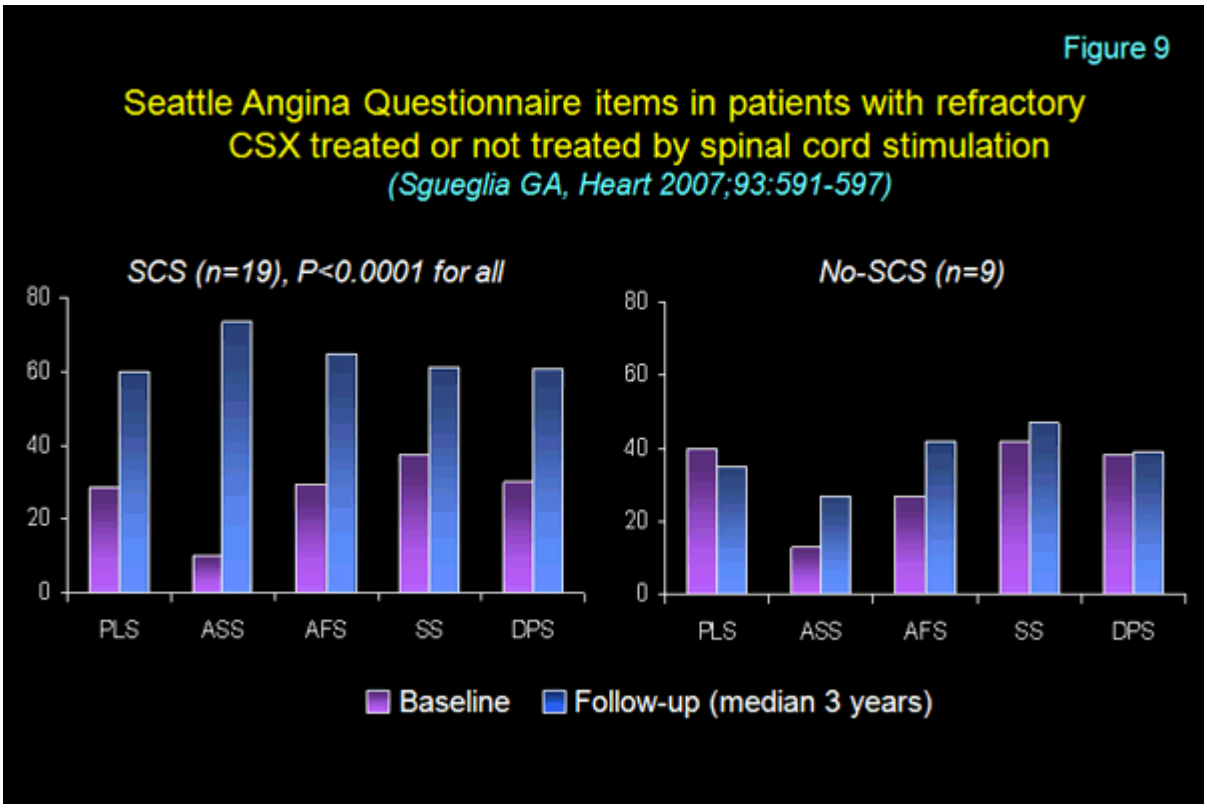
Nicorandil. Nicorandil is an adenosine triphosphate (ATP) dependent potassium channel opener, also with nitrate-like effects, which might act mainly through a direct vasodilator effect on coronary microcirculation. Intravenous and oral nicorandil was shown to have some beneficial effects on exercise induced signs of myocardial ischemia, but its effects on symptoms are unknown.

Trimetazidine. This drug is believed to improve tolerance for ischemia of myocardial cells by switching cell metabolism from free fatty acid toward glucose oxidation during exercise and stress

conditions. The drug was reported to have beneficial effects on exercise test results in a CSX patients in a study, but no effects were observed on symptoms and exercise results in another study.

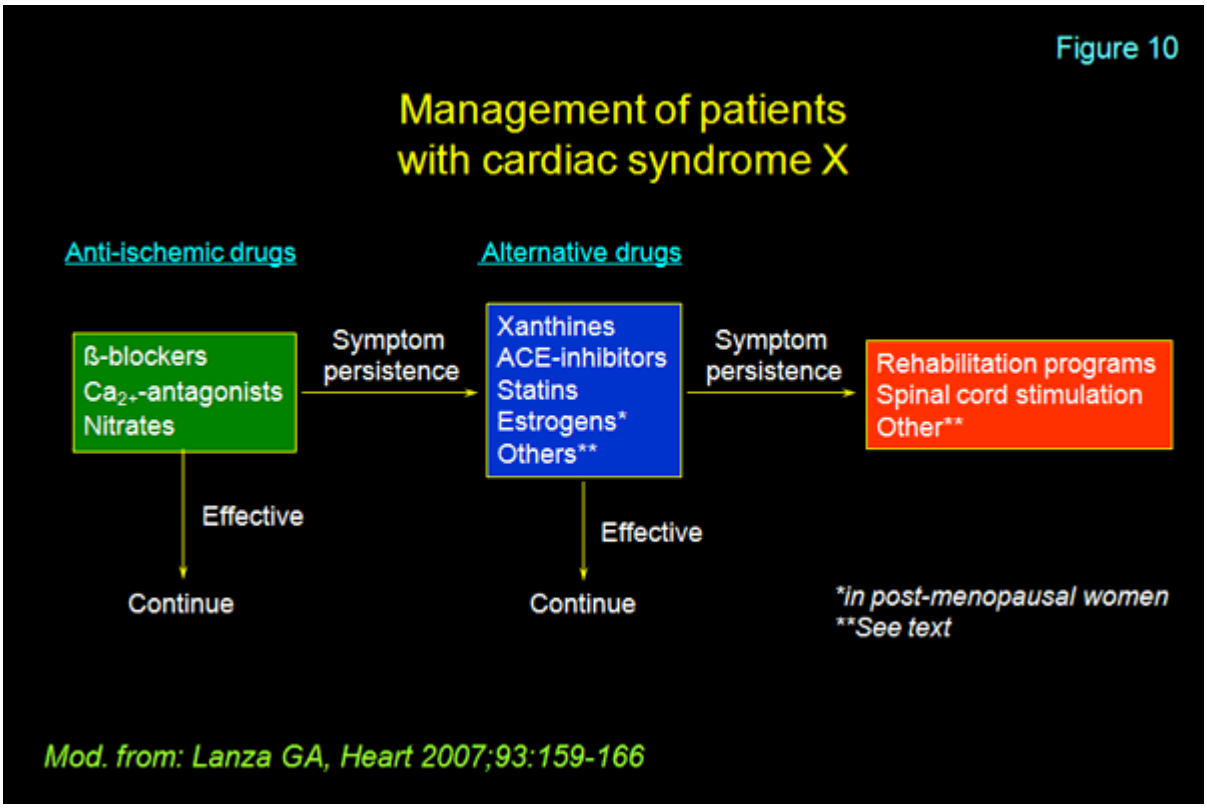
Imipramine. Imipramine, an anti-depressive drug that inhibits pain transmission from visceral tissues, was found to reduce chest pain episodes in patients with angina and normal coronary arteries in two studies. However, quality of life was not significantly improved in another study, mainly because of the occurrence of unpleasant side effects. Clonidine might also act through similar mechanisms, but it failed to achieve significant control of symptoms.

Electrical neuromodulation. A small group of patients with CSX present severe chest pain symptoms that cannot be controlled effectively with maximally tolerated medical therapy. In these patients, with refractory CSX, beneficial effects have been shown on angina symptoms and quality of life, both at short-term and long-term follow-up, by spinal cord stimulation **(Figure 9)** and other neuromodulatory techniques (i.e., transcutaneous electrical nerve stimulation, TENS). These therapeutic techniques might act by modulation of pain transmission from the heart to the brain, but also by improving coronary microvascular function and reducing myocardial ischemia, possibly mainly through modulation of sympathetic tone.



Conclusions

A scheme of the therapeutic approach and management of CSX patients is shown in **Figure 10**. A beta-blocker or a non dihydropiridine calcium antagonist are usually the first-option therapy in these patients. A combination of the two drugs is possible in case of insufficient results. A dihydropiridine calcium antagonist and/or a long-acting nitrate can be added based on the assessment of individual patients.



In case of insufficient benefits of anti-ischemic drugs, ACE-inhibitors and statins can be variously added, in particular when hypertension and hypercholesterolemia, respectively, are present. In women with menopause, estrogens may be helpful, in particular in case of concomitant post-menopausal symptoms. Xanthine derivatives and alpha-blockers are further choices if symptoms persist, while imipramine should be reserved to the most symptomatic patients or to patients with some evidence of depressive symptoms. In patients who remain symptomatic despite multiple drug therapy, spinal cord stimulation can be effective in controlling symptoms in more than 50% of patients.

Finally, it should be stressed that therapeutic management of CSX always requires an optimal interaction between the caring physician/cardiologist and the patient in the attempt to achieve optimal symptom control, in particular because psychological abnormalities in several cases contribute significantly to the chronic chest pain and disability of these patients. Thus adequate medical support can be crucial for patients with debilitating symptoms. An *exercise rehabilitation program*, and also *relaxation techniques*, can also be helpful to improve effort tolerance and quality of life in significantly symptomatic patients.