



What Can We Do for the Patients With Microvascular Angina ?

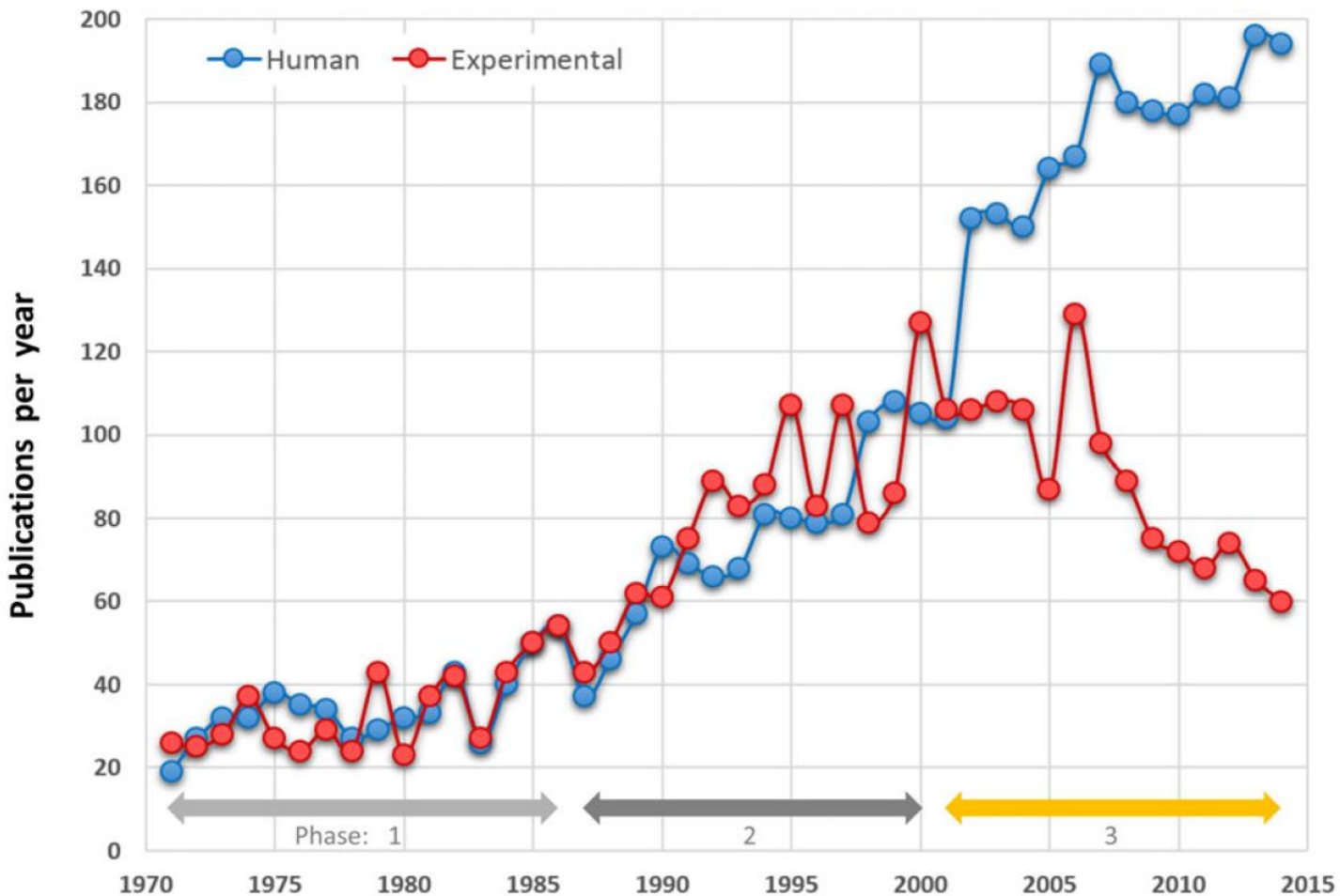
Ki Chul Sung, MD. PhD

Division of Cardiology, Department of Internal Medicine

Kangbuk Samsung Hospital

Sungkyunkwan University School of Medicine

Development of publication frequency in the area of coronary microcirculation



Treatment of MA

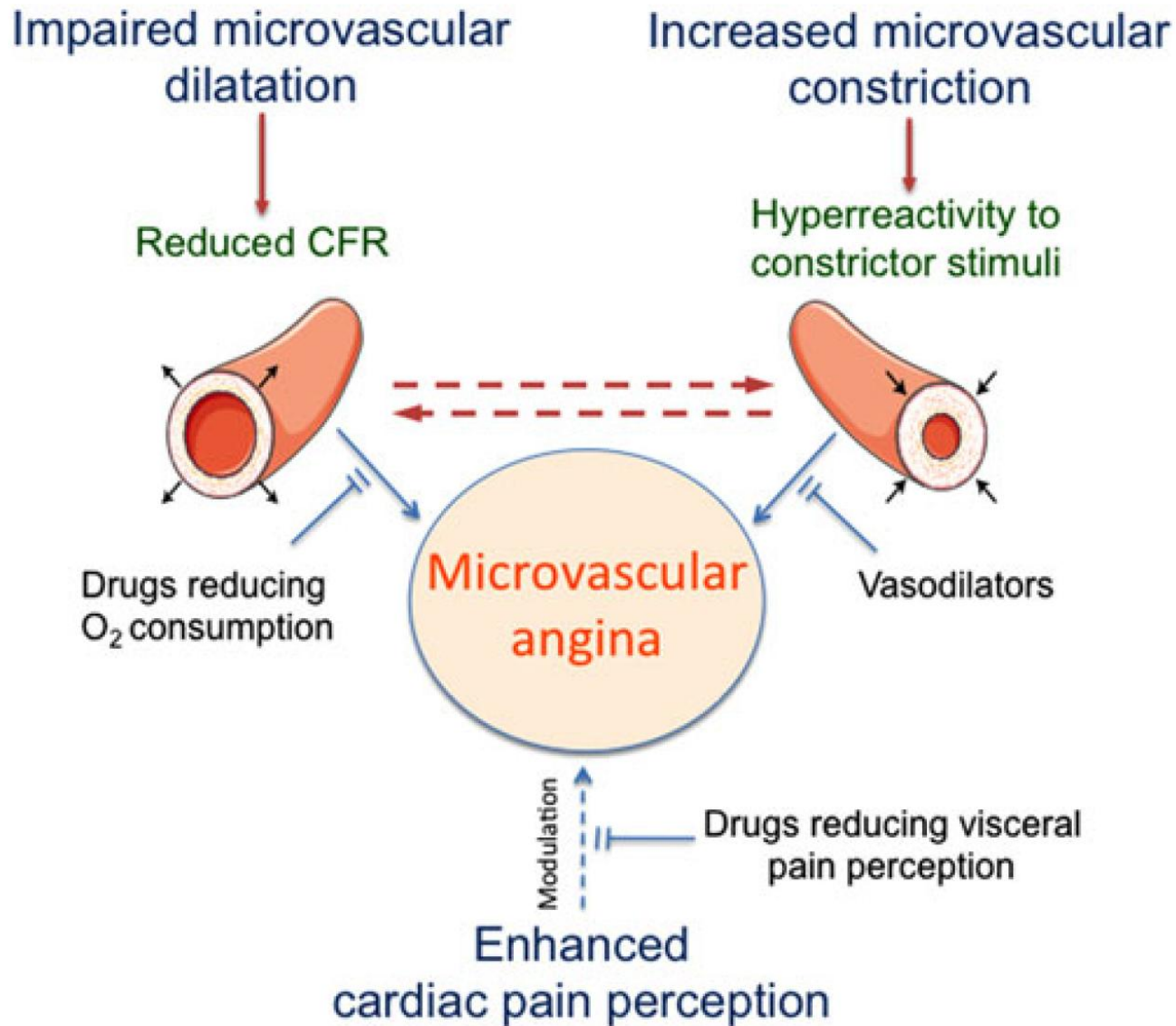
..... challenge for cardiologists.

$\frac{1}{4}$ patients Recurrent Sx

$\frac{1}{2}$ fully effective with traditional
antianginal drug.

.....Heterogeneous mechanisms

Pathophysiologic mechanism for MA



Classification of coronary microvascular dysfunction and treatment

	Clinical setting	Treatment
Type 1: in the absence of myocardial diseases and obstructive CAD	Risk factors Microvascular angina	RF control RF control, see Figure 4
Type 2: in myocardial diseases	Hypertrophic cardiomyopathy Dilated cardiomyopathy Anderson-Fabry's disease Amyloidosis Myocarditis Aortic stenosis	Alcohol septal ablation? Allopurinol Unknown Beta-galactosidase? Unknown Beta-blockers, Ivabradine?
Type 3: in obstructive CAD	Stable angina Acute coronary syndrome	Angiogenesis See Figure 5
Type 4: iatrogenic	PCI Coronary artery grafting	Statins, alpha-blockers? Statins

CAD, coronary artery diseases; SMC, smooth muscle cells; PCI, percutaneous coronary intervention.

- PHARMACOLOGIC TREATMENT

Nitrates

Release of NO from nitrite,
Activation of guanylyl cyclase
--Relaxation of blood vessels.

Observational study of 99 patients
Relieved episodes of chest pain in
42% of patients. (with calcium
blocker) (JACC Mar 1995, 807–814)

	CAD	MVA	p
Control test			
Positive	23 (96 %)	26 (90 %)	0.42
Negative	0 (0 %)	2 (7 %)	
Equivocal	1 (4 %)	1 (3 %)	
Test after ISDN			
Positive	12 (50 %)	25 (86 %)	0.001
Negative	12 (50 %)	1 (3 %)	
Equivocal	0 (0 %)	3 (10 %)	

Cardiovasc Drugs Ther 2013;27(3):229–34.

The dilator effect of nitrates on small coronary vessels is poor.
Unpredictable effectiveness, historically have been the mainstay therapy

β -Adrenergic Receptor Blockers

Blocking catecholamine-induced increases in HR, BP, myocardial contractility,
--Reducing myocardial oxygen consumption.

Improve anginal symptoms, functional capacity, and exercise testing
in up to 75% of patients with CSX.

Propranolol, Atenolol

Third generation b-blockers **nebivolol and carvedilol** .

; additional endothelium-dependent vasodilating properties ...
may be more effective...

β -Adrenergic Receptor Blockers

Nebivolol

- Increase circulating endothelial function parameters
 - asymmetric dimethylarginine(ADMA)
 - L-arginine
 - NO levels
- Improve exercise stress test parameters
 - exercise duration to 1-mm ST depression
 - total exercise duration, compared with metoprolol

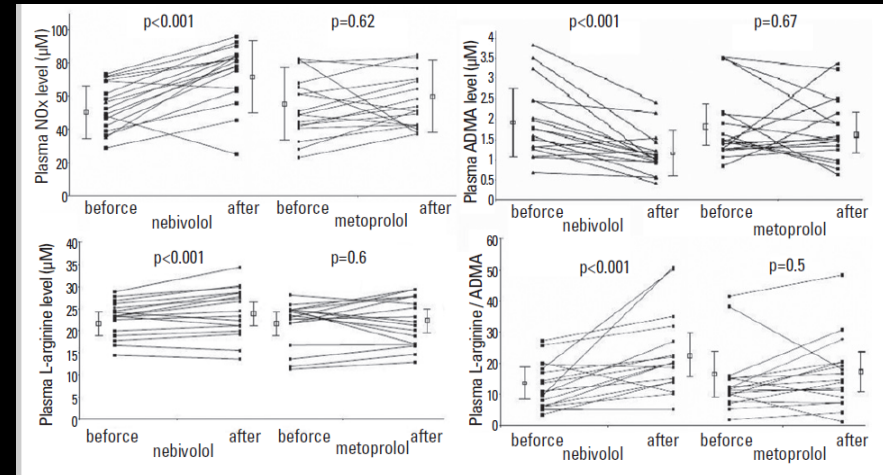


Figure 2. The changes of plasma NOx levels, ADMA levels, L-arginine levels, and plasma L-arginine / ADMA ratio after 12-week treatment with nebivolol and metoprolol in patients with syndrome X

Ana do lu Kar di yol Derg 2009; 9: 371-9

β -blockers may represent the first line of treatment of patients with CSX

Calcium Channel Antagonists

Block L-type calcium channels

- negative chronotropic
- inotropic effects
- decrease in peripheral vascular resistance.

The efficacy of CCB for treating CSX remains unclear.

B-blockers have been shown to be more effective than calcium channel antagonists.

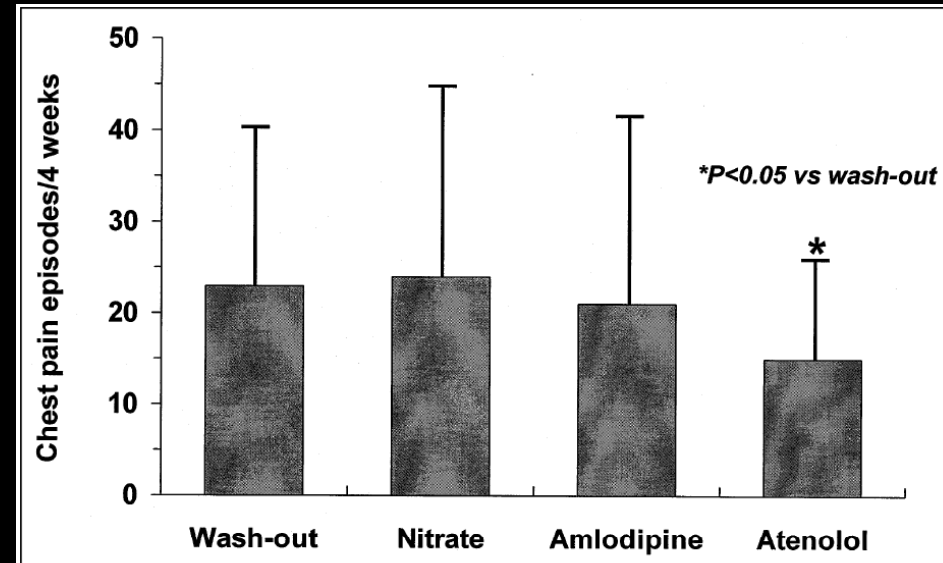


FIGURE 2. Mean number of chest pain episodes during each of the 4-week treatment periods. Lines, SD. * $p < 0.05$ versus baseline.

Am J Cardiol 1999;84(7):854-6. A858

Angiotensin-Converting Enzyme Inhibitors

- Angiotensin IIVasoconstriction

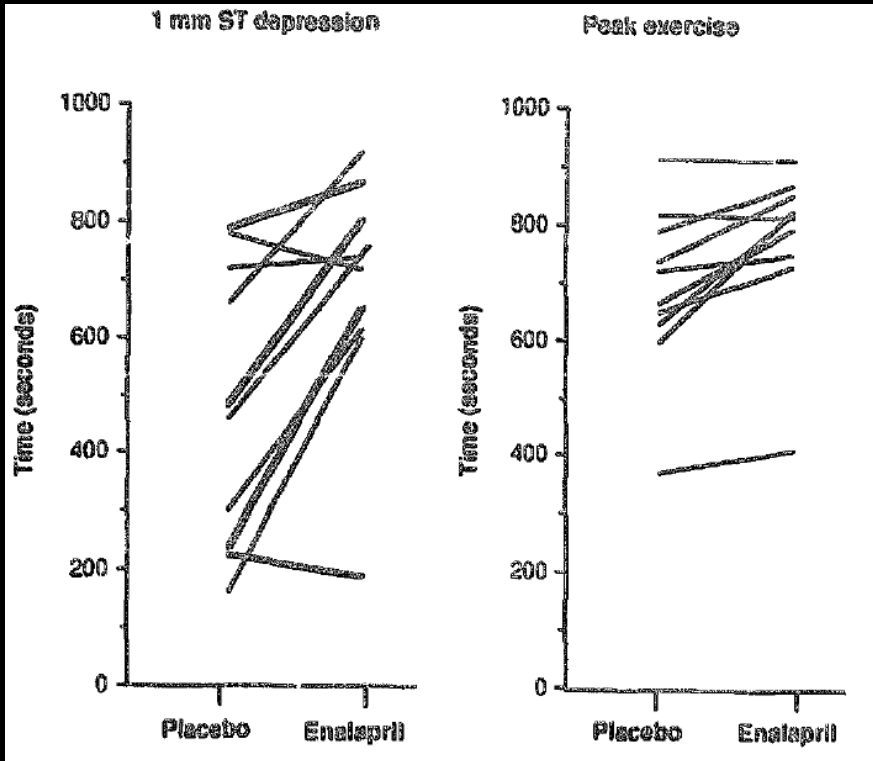
Bradykinin NO

Improve exercise tolerance
endothelial function
coronary flow rates

perindopril and indapamide ... reverse remodelling of
intramural arterioles.

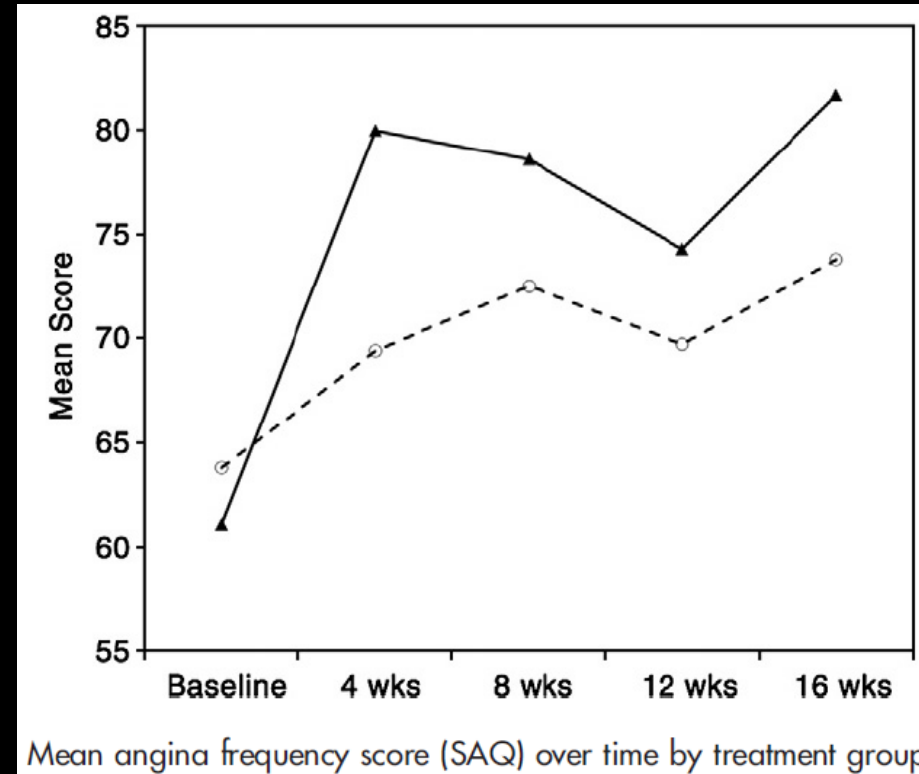
Decrease angina in patients with CSX

Angiotensin-Converting Enzyme Inhibitors



J Am Coll Cardiol 1994;23 :652-7

Enalapril increase total exercise duration, prolong time to 1 mm of ST segment depression, and decrease magnitude of ST segment depression compared with placebo



Am Heart J 2011;162:678-84

Quinapril improved anginal episode frequency as well as increased coronary flow rate

Statins

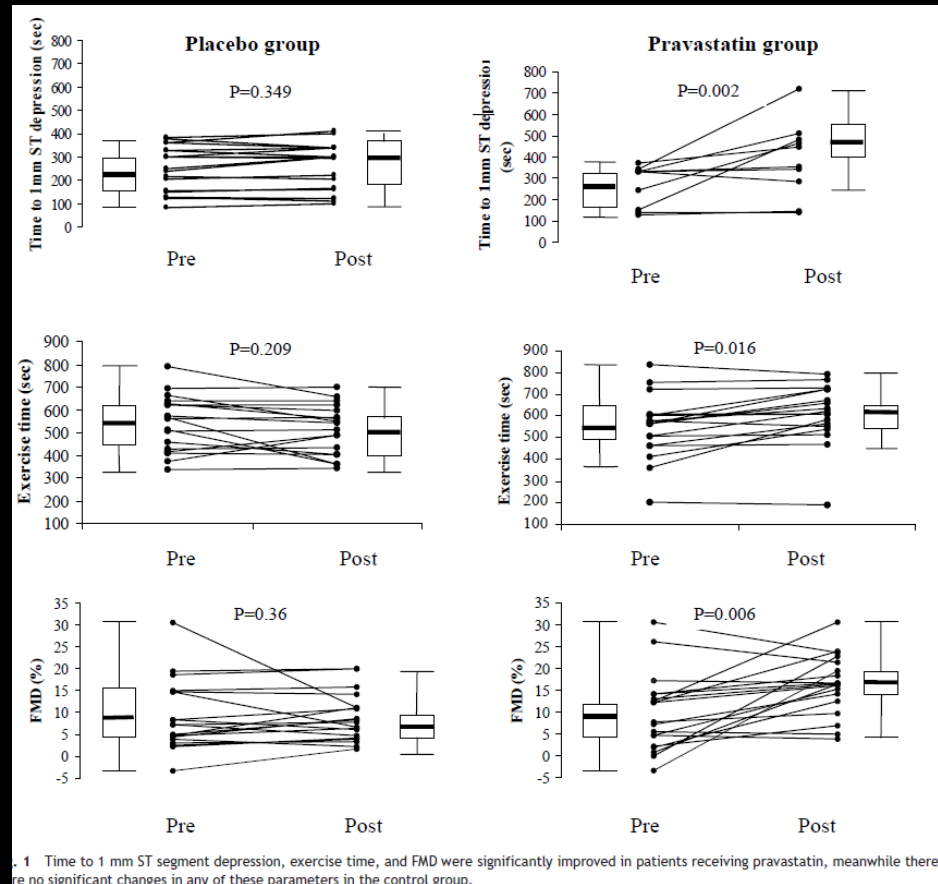
Improve endothelium-dependent vasomotion

→ may be beneficial in patients with CSX (N Engl J Med 1995;332:488-93)

Study with patients with CSX receiving pravastatin

→ significant improvement in exercise induced ischemia & brachial artery flow-mediated dilatation within 4 months

(European Heart Journal (2003) 24, 1999–2005)



Xanthine Derivatives

Adenosine receptor blockers

→ can modulate the anginal pain in CSX

Oral aminophylline for 3 weeks reported fewer episodes of chest pain, a higher exercise-induced chest pain threshold. (Heart 1997;77(6):523-6)

Xanthine derivatives may not have any acute benefit.

(G Ital Cardiol 1997;27(1):50-4)

(Heart 1997;77(6):523-6)

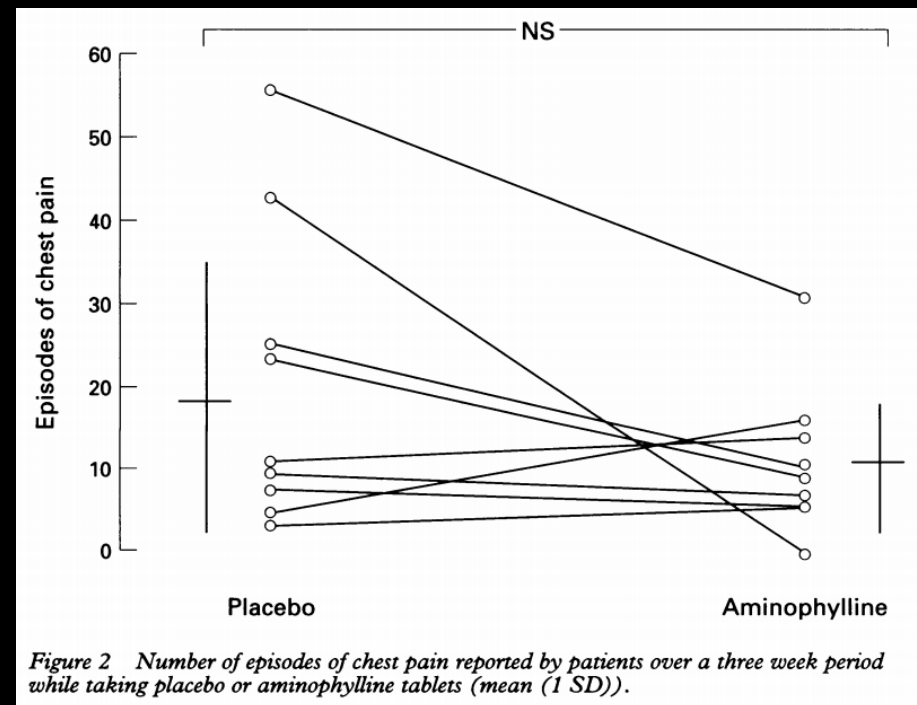


Figure 2 Number of episodes of chest pain reported by patients over a three week period while taking placebo or aminophylline tablets (mean (1 SD)).

Tricyclic Antidepressants

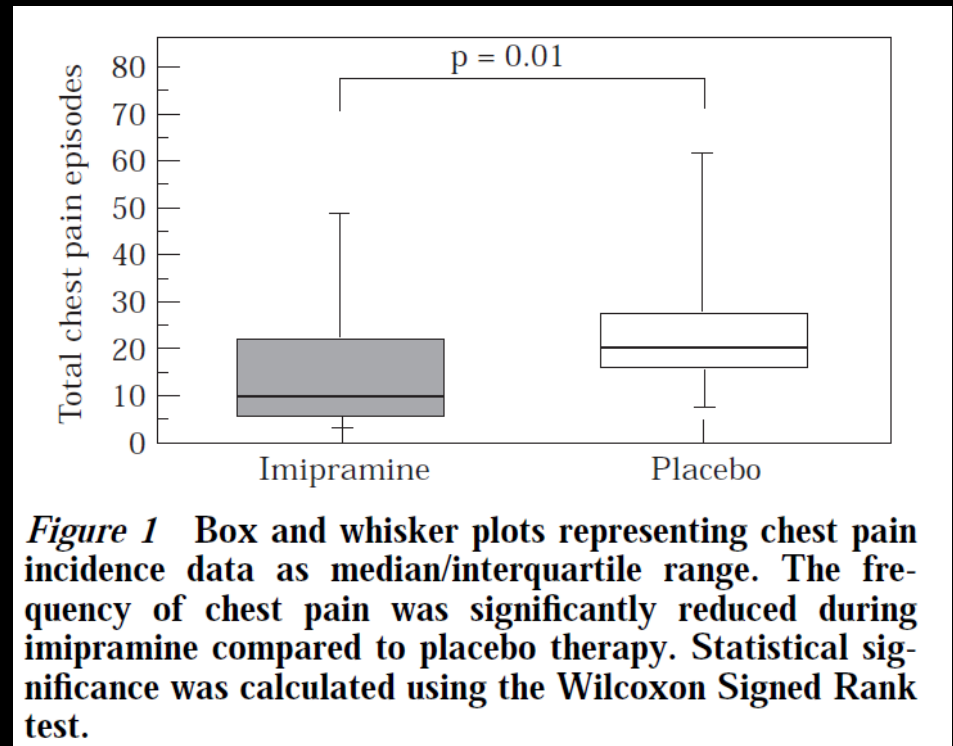
Antidepressive effects.

Analgesic activity ← balanced reuptake inhibition of the neurotransmitters serotonin and noradrenaline.

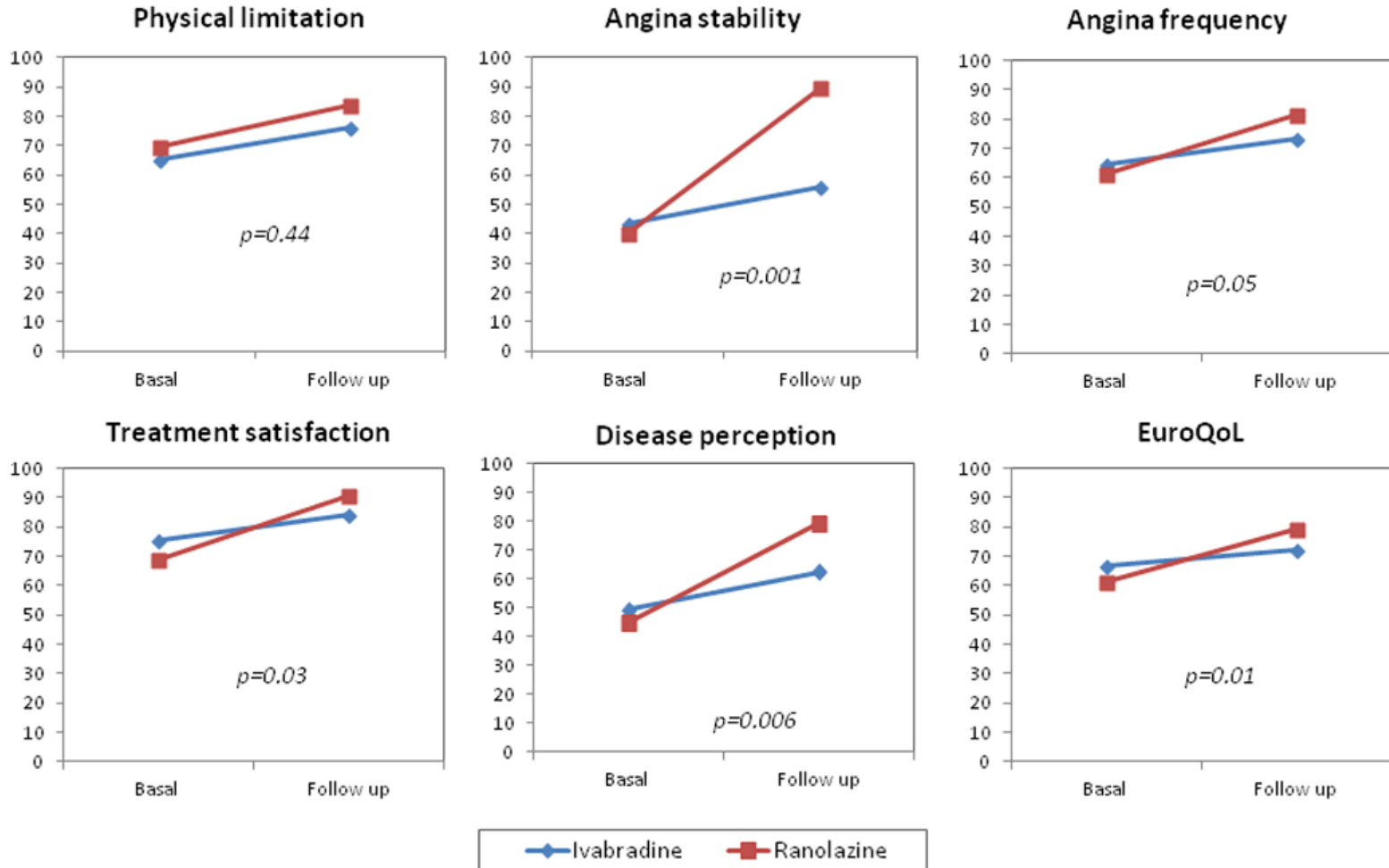
In a study of patients of CSX
→ experienced a 52% decrease
in episodes of chest pain
during the imipramine
treatment phase

(N Engl J Med 1994; 330(20):1411-7)

S/E: dry mouth, dizziness,
nausea, and constipation.



Effects of Ivabradine and Ranolazine

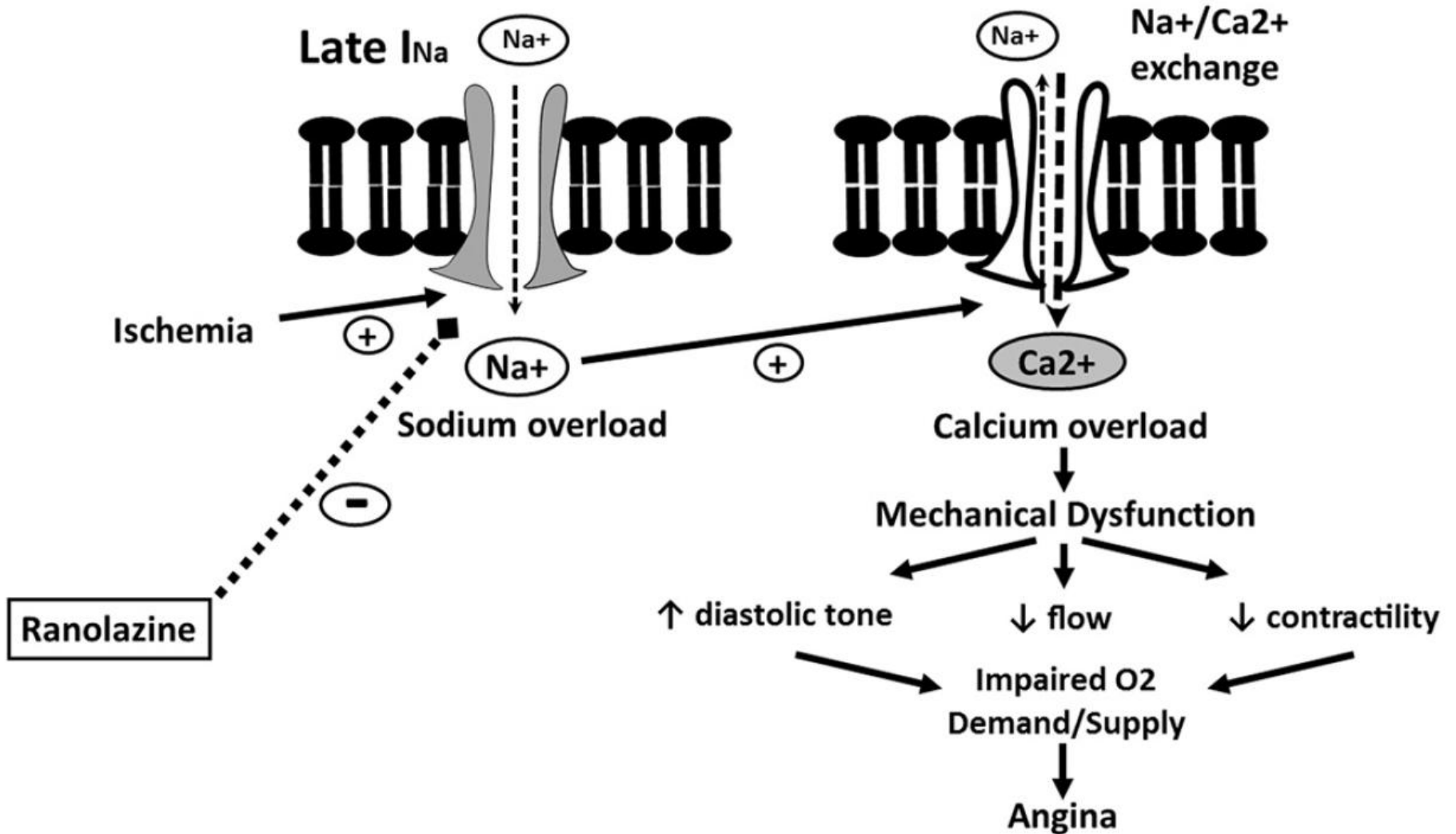


Ranolazine

2013 ESC guidelines on the management of stable coronary artery disease

Angina/ischaemia ^d relief	
Short-acting nitrates are recommended.	I
First-line treatment is indicated with β -blockers and/or calcium channel blockers to control heart rate and symptoms.	I
For second-line treatment it is recommended to add long-acting nitrates or ivabradine or nicorandil or ranolazine, according to heart rate, blood pressure and tolerance.	IIa

Ranolazine





Coronary artery disease

A randomized, placebo-controlled trial of late Na current inhibition (ranolazine) in coronary microvascular dysfunction (CMD): impact on angina and myocardial perfusion reserve

In this mechanistic trial among symptomatic subjects, no obstructive CAD, short-term late sodium current inhibition was not generally effective for SAQ angina.

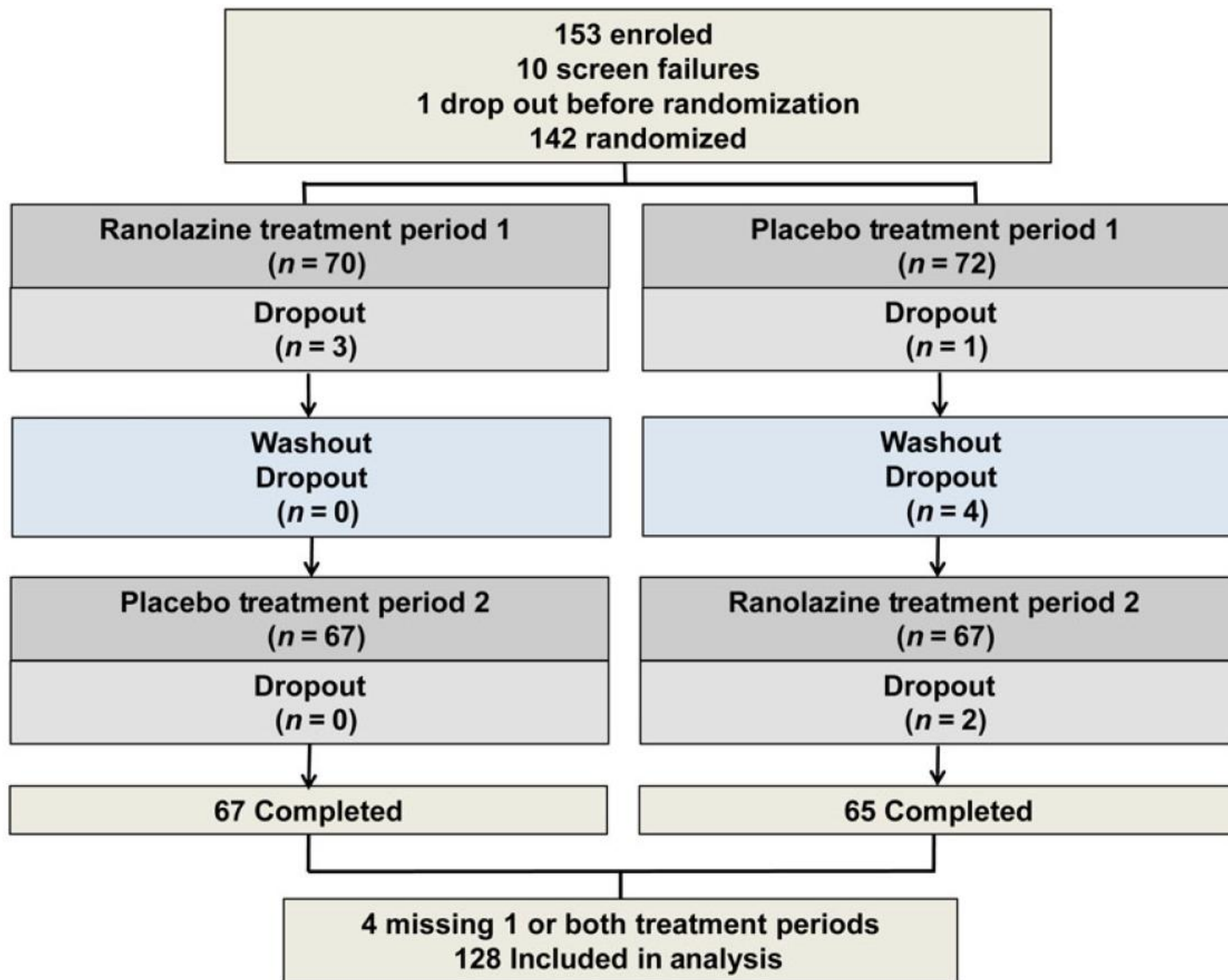
Angina and myocardial perfusion reserve changes were related, supporting the notion that strategies to improve ischaemia should be tested in these subjects.

Double-blind, placebo-controlled, crossover trial
chest pain symptoms thought to be caused by myocardial ischaemia, NO-CAD at angiography (no stenosis 50% in epicardial coronary arteries).

Evidence of CMD, at least one of the following:

1. Invasive coronary flow reserve (CFR) to adenosine < 2.5
2. No dilatation ($\leq 0\%$ change) in response to acetylcholine (Ach);
3. Myocardial perfusion reserve index (MPRI) < 2.0 at pharmacological cardiac magnetic resonance imaging (CMRI) stress test.

Ranolazine (500 mg twice a day, possibly increased to 1 g twice a day) or placebo were given in random sequence for 2 weeks each.

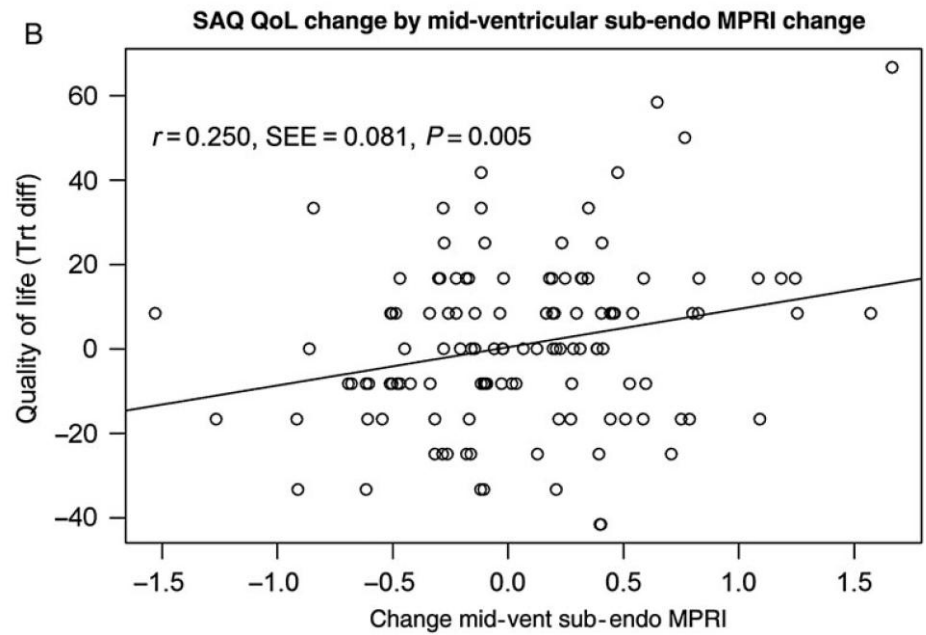
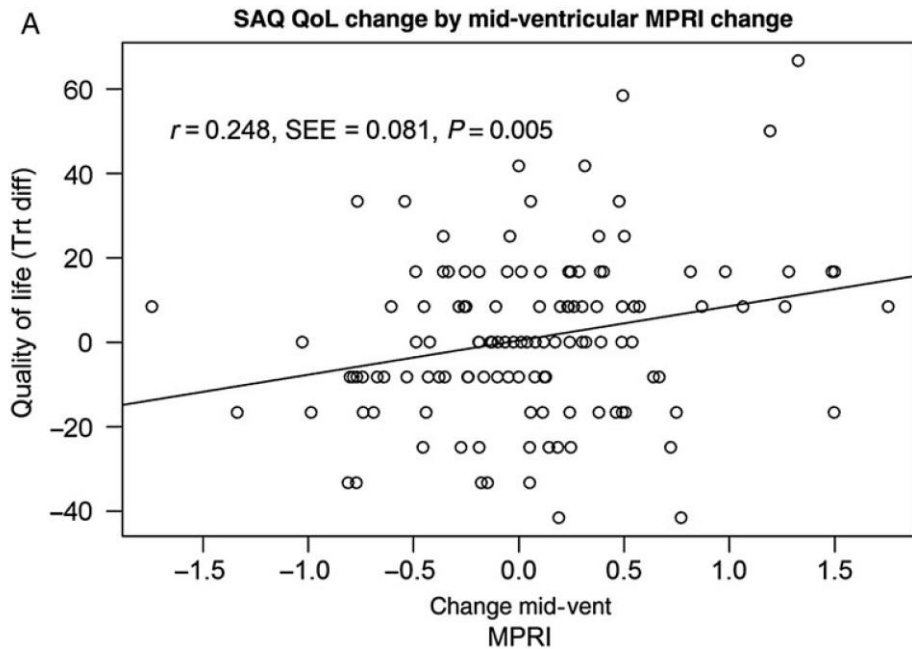


Results

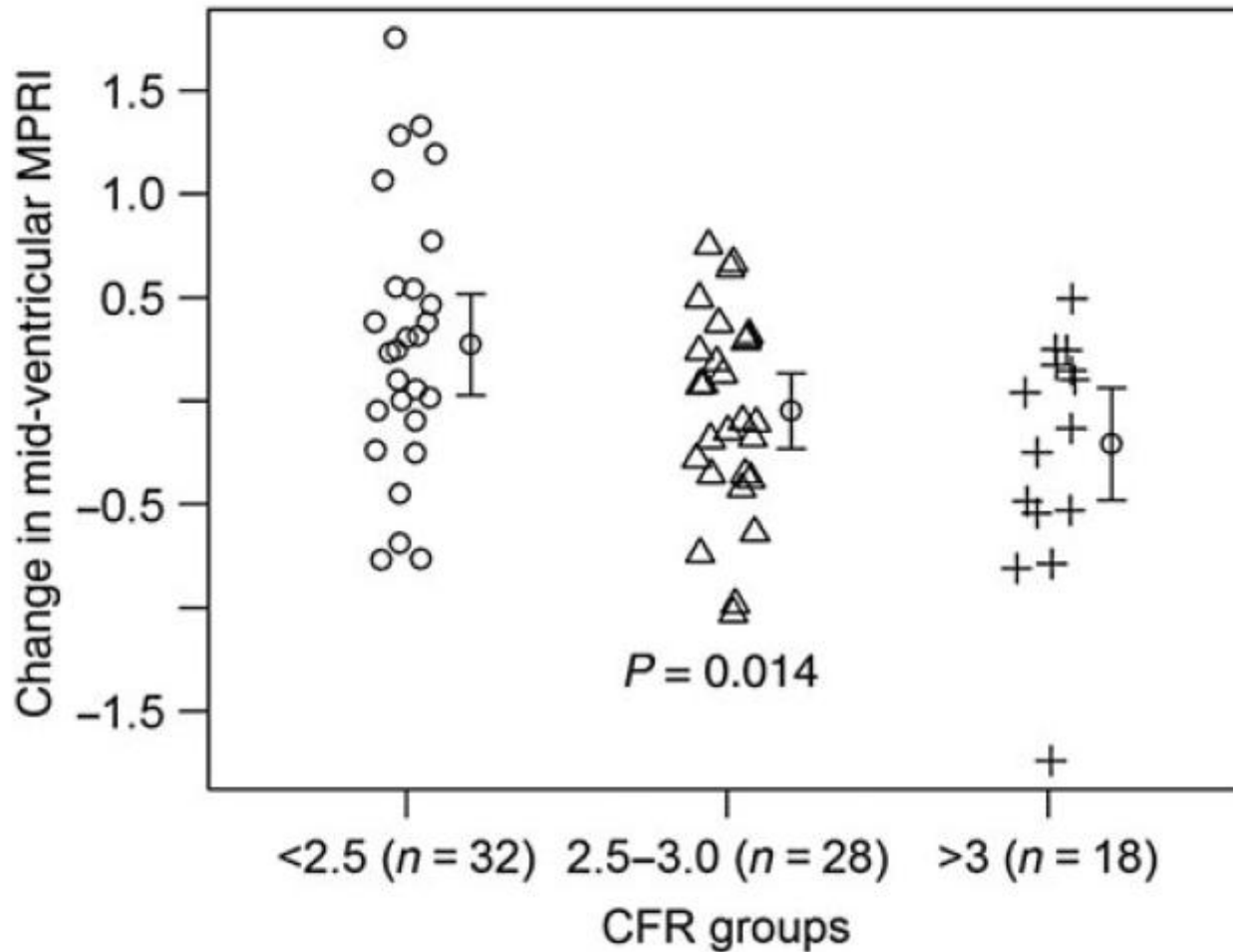
1.No differences in the effect on the primary endpoint (Seattle angina questionnaire (SAQ) scores and angina episodes or nitroglycerin use).

2.QoL depression score significantly improved with ranolazine

3.No significant effects on stress CMRI results.



Mid-ventricular and mid-ventricular sub-endocardial myocardial perfusion reserve index change vs. Seattle Angina Questionnaire quality of life change (ranolazine vs. placebo) model.



Myocardial perfusion reserve index change according to qualifying coronary flow reserve in the subset of subjects with invasive coronary reactivity testing.

Three small trials+ post-hoc analyses

Reduced CFR and evidence of exercise-induced myocardial ischaemia may have appreciable benefits.

Unlikely to be beneficial in patients with MVA caused by increased susceptibility to constrictor stimuli.

NONPHARMACOLOGIC TREATMENT

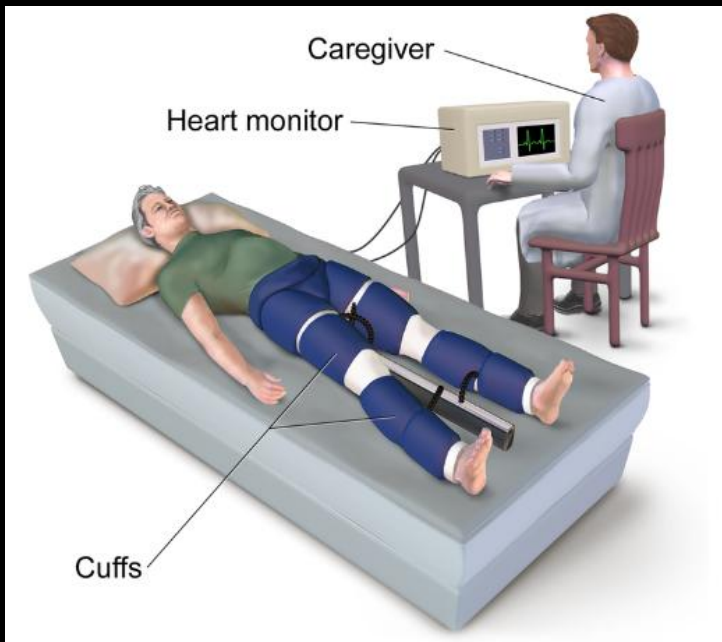
Cognitive-Behavioral Therapy

- Discuss pain and its management
 - Receive counseling and education about cardiac disease .
 - Learn stress management and relaxation techniques
- Regain exposure to activities avoided because of pain, and engage in light physical exercise.

Table 2 Pre- and post-treatment comparison (n=56)

	Before treatment	After treatment	p*
<i>Chest pain</i>			
Episodes/week	6.5	2.5	0.0001
Duration (min)	30.4	17.9	NS
Severity (1–100)	31.7	27.5	NS
GTN use (dose/week)	4	0.5	0.001
Pain-free days/week	2.4	4.5	0.0001
HAD anxiety	8	6	0.001
HAD depression	6	3	0.0001
<i>NHP problem scores</i>			
Energy	50	0	0.01
Pain	13.9	0	0.05
Emotion	10.1	0	0.05
Sleep	28.7	12.6	0.05
Social isolation	0	0	
Mobility	21.4	10.8	0.001
SIP disability	15.3	5.9	0.0001
Exercise duration (min)	7.4	9.3	0.001
ECG-positive ETT	13/54	10/53	NS ^z
Nijmegen HV score	27.5	22.0	0.001
HV-positive capnography	30/56	19/56	0.01 ^z

* Wilcoxon signed rank test, except for χ^2 test as indicated by ^z. All values are medians, except for absolute numbers as indicated.

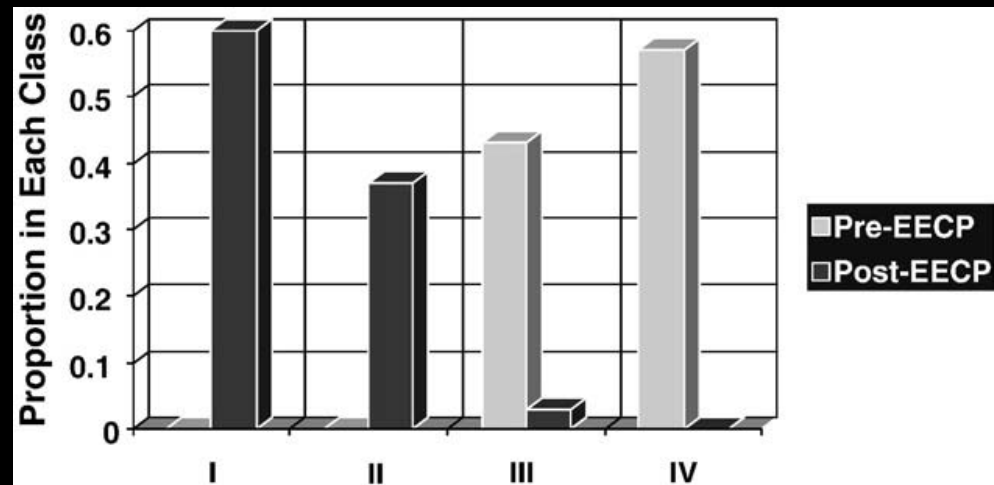


Enhanced External Counterpulsation

Change in Canadian Cardiovascular Society angina class post EECP Int J Cardiol 2009;135:256–257

Mechanisms

1. Open collaterals
2. Shear forces-Endothelium- NO
3. Regulate paracrine substances involved in vascular remodeling and reactivity



Neurostimulation

A study of 2-week trial of TENS with continued TENS for 5 years. After 5 years...
→ patients reported a 57% reduction in pain & a 30% improvement in exercise capacity. (European Journal of Pain 11 (2007) 360–365)

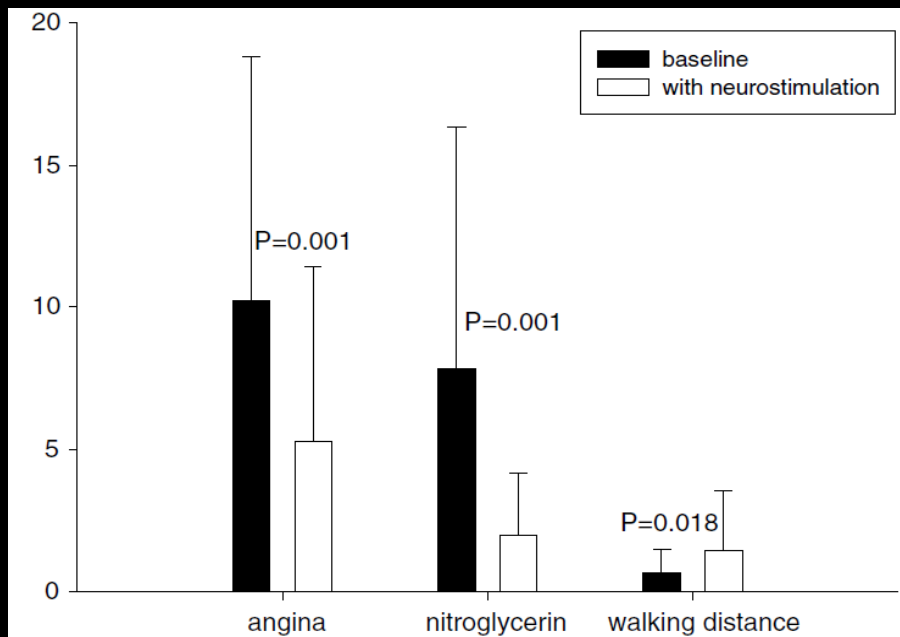
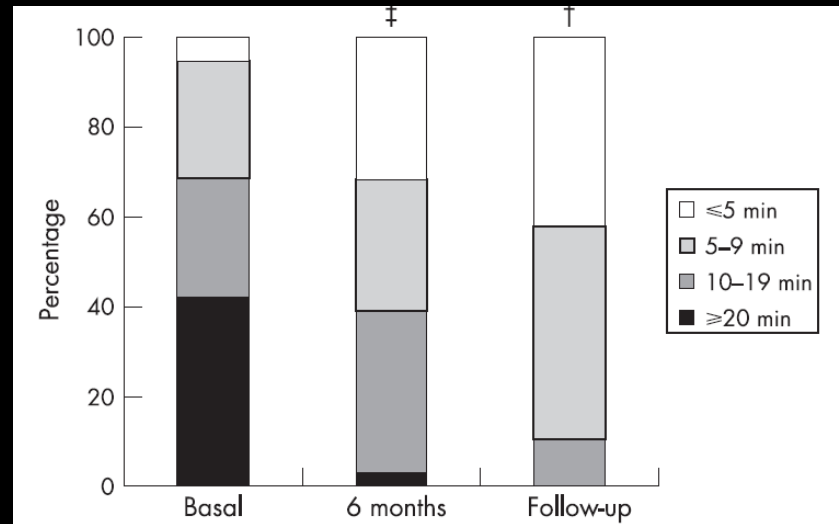
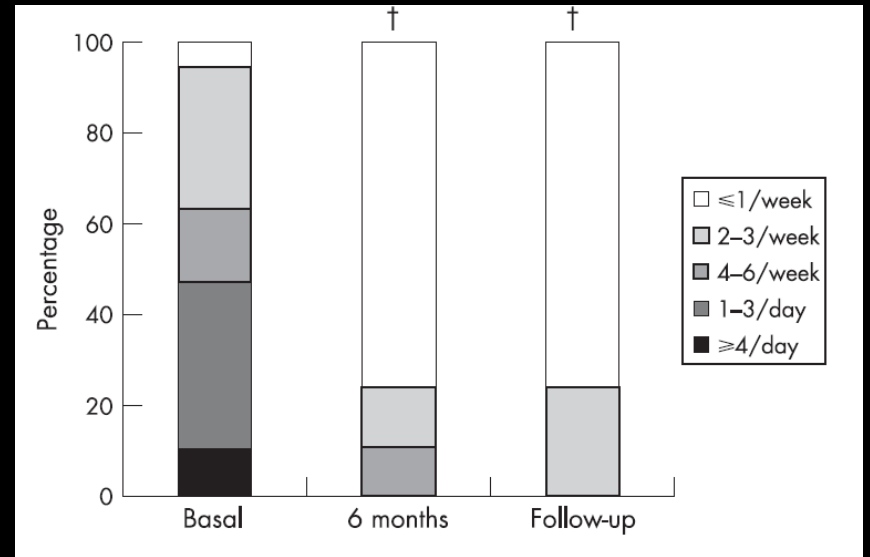
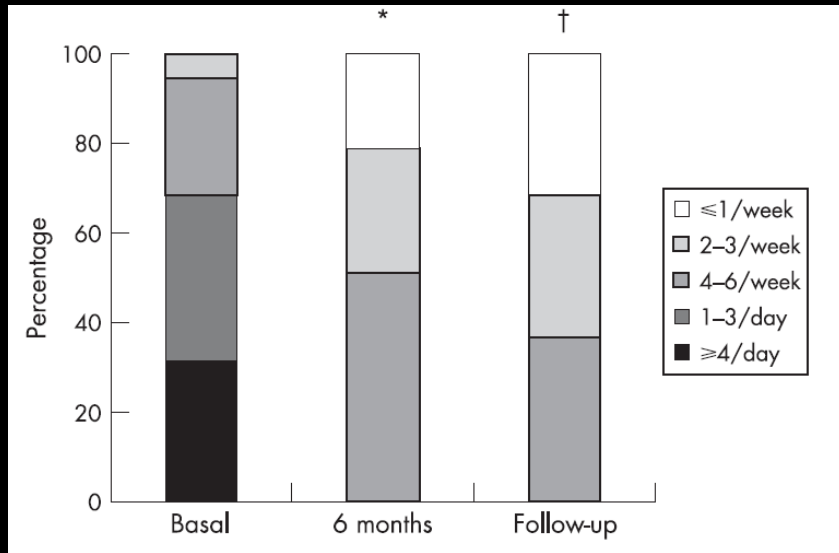


Fig. 2. Angina attacks, nitroglycerin consumption and walking distance. These outcomes are continuous variables. Angina: frequency of angina attacks (number of attacks per week); nitroglycerin: frequency of nitroglycerin use (number of doses per week); walking distance: expressed as the distance patients can walk without chest pain (kilometres).



Proportion of patients of the spinal cord stimulation (SCS) group in the different classes of frequency (upper panel) and duration (mid panel) of angina episodes, and of consumption of sublingual nitrate tablets (bottom panel) before SCS treatment (basal assessment), after 6 months of SCS treatment and the last follow-up (average 36 months). * $p = 0.005$, $p = 0.001$, $p, 0.001$.

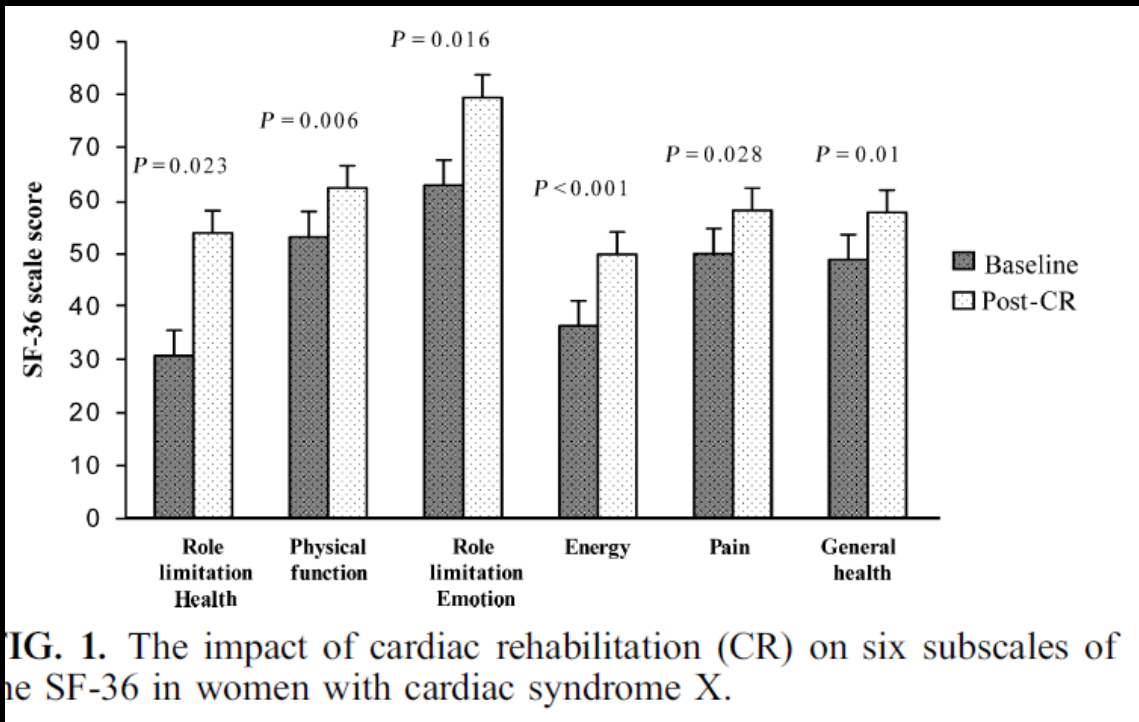
Stellate Ganglionectomy

Further research is necessary.

LIFESTYLE MODIFICATIONS

Exercise:

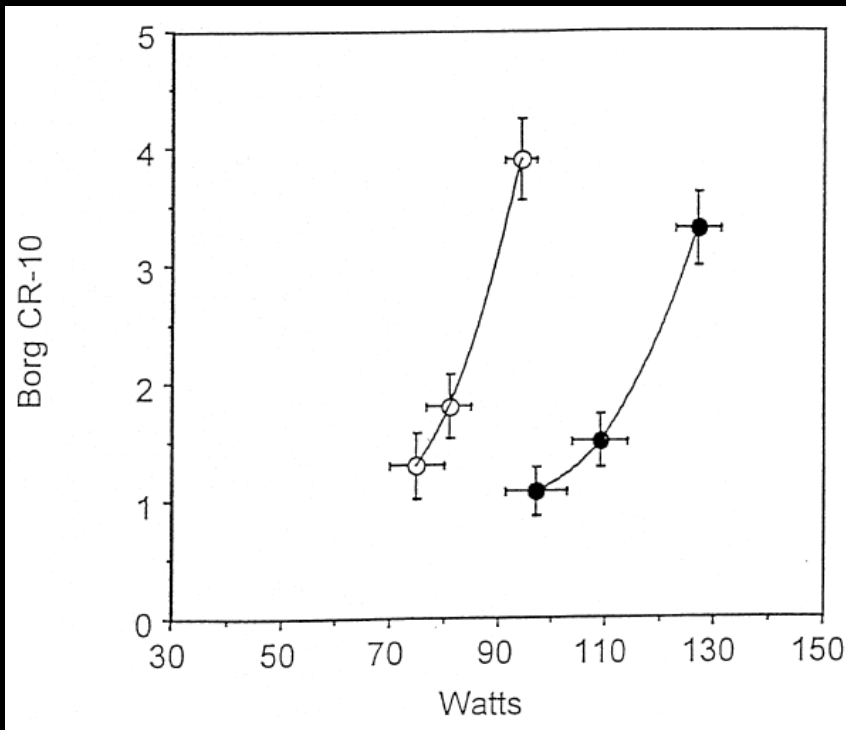
The only lifestyle modification that has been evaluated in patients with CSX



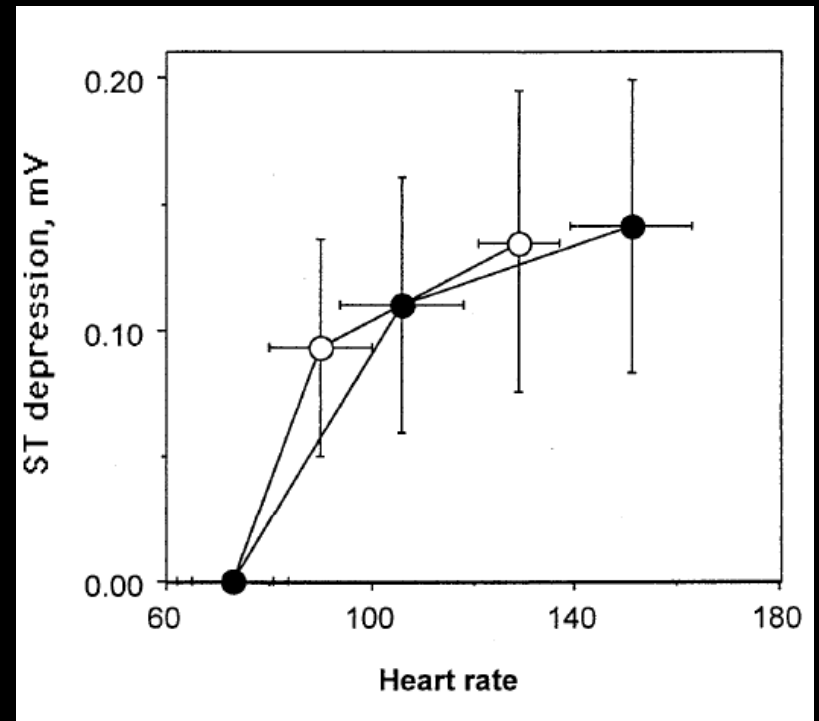
Menopause 2008;15(3):454-60.

FIG. 1. The impact of cardiac rehabilitation (CR) on six subscales of the SF-36 in women with cardiac syndrome X.

Physical Training in Syndrome X



Pain response to increased workload in the training groups (A 1 B) before (**open dots**) and after training (**solid dots**).



ST segment shifts during exercise in the training groups (A 1 B) before (**open dots**) and after training (**solid dots**).

LIFESTYLE MODIFICATIONS

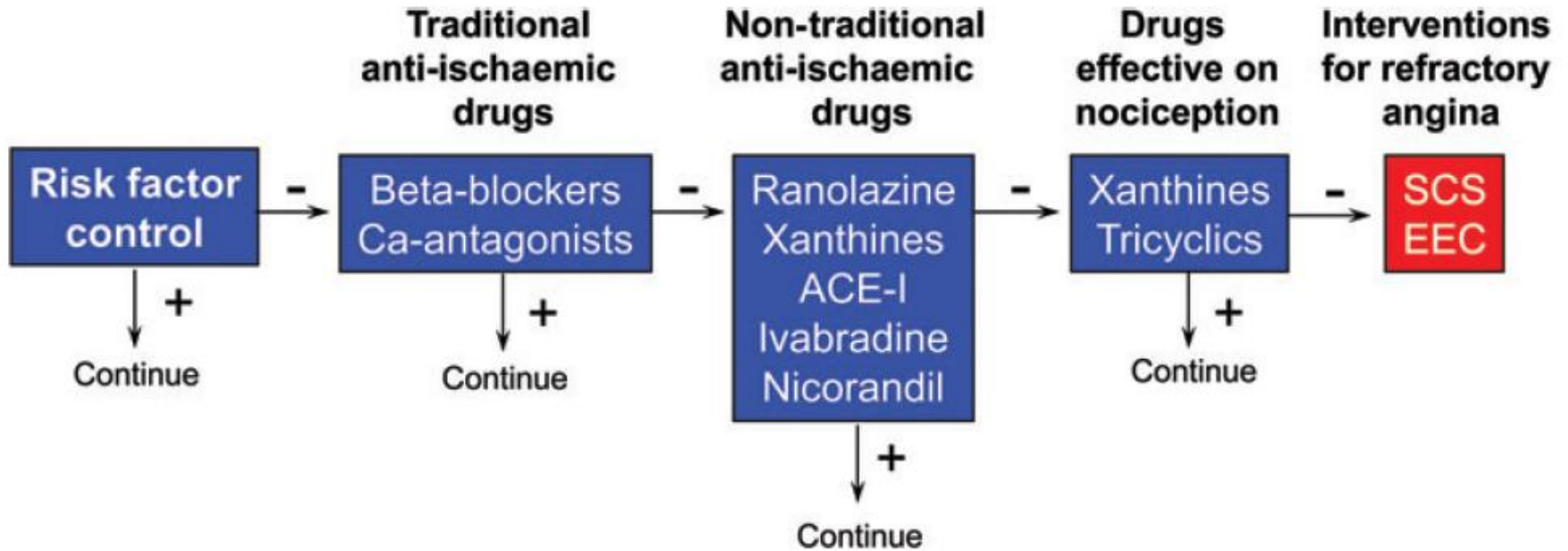
Others

Weight loss and Smoking cessation

→ Improve endothelial function

The Mediterranean diet

→ Reduces oxidative stress, inflammation, and damage to the endothelium



Treatment algorithm for patients with microvascular angina.
 SCS, spinal cord stimulation; EEC, enhanced external counterpulsation.

TREATMENT CONCLUSION

1. Combination therapeutic approach.

→ anti-ischemic & analgesic pharmacologic Tx. &
lifestyle modifications

2. Nonpharmacologic therapies .

3. Further work for the best combination of treatments
and guidelines.

감사합니다