SCS endotype	Investigation	Pathophysiology	Treatment	Efficacy	Side-effects	Relevant clinical trials
Microvascular angina secondary to impaired vasodilatation	Reduced CFR and/or increased microvascular resistance	Anatomical remodelling, vascular rarefaction, disturbed coronary regulation	**ß-blockers**	Reduction in myocardial oxygen consumption	Fatigue, blurred vision. cold hands.	Bugiardini et al[1] Kayaalti et al[2]
			ACE inhibitors	Improve CFR, reduce workload, may improve small vessel remodelling	Cough, renal impairment, hyperkalaemia.	Pauly et al[3]
			Ranolazine	Improves MPRi in patients with MVA and reduced CFR	Nausea, dizziness, headache	NCT01342029[4] NCT01815957[5]
			Phosphodiesterase inhibitors	↓cGMP degradation, ↑vascular smooth muscle relaxation and ↑ CFR for those with baseline CFR <2.5	Flushing, tinnitus, headache	Denardo et al[6]
Microvascular angina secondary to abnormal vasoconstriction	Hyper-reactivity to stimuli (e.g. acetylcholine, exercise, stress)	Endothelial dysfunction, inappropriate prearteriolar vasoconstriction	**ACE inhibitors**	Improves endothelial vasomotor dysfunction	Cough, renal impairment, hyperkalaemia.	Mancini et al[7]
			Calcium antagonists	Vascular smooth muscle relaxation, reduction in myocardial oxygen consumption	Constipation, ankle swelling, flushing	Bairey Merz et al [8]
			Nicorandil	Potassium channel activator with coronary microvascular dilatory effect	Dizziness, flushing, weakness, nausea	Chen et al[9]
			Statins	Improved coronary endothelial function, pleiotropic effects including reduced vascular inflammation	Myalgia, headache, cramps	Treasure et al[10] Kayikcioglu et al[11]
			Exercise	Beneficial effect on endothelium ↓ resting blood flow and ↑ vasodilatory capacity	Muscle fatigue, myalgia	Czernin et al[12]
			Hormone-replacement therapy	Oestrogen therapy improves endothelial function short-term in CMD	↑ Risk of breast cancer, marginally ↑ risk of CVD	NCT00600106[13]
Microvascular angina secondary to abnormal pain processing	Enhanced nociception	Dysfunctional cortical pain processing	**Tricyclic antidepressants**	Improved symptom burden potentially through reduced visceral pain	Blurred vision, dry mouth, drowsiness, impaired coordination	Canon et al[14]
			Xanthine derivatives	Anti-algogenic effect (due to the direct involvement of adenosine in cardiac pain generation)	Nausea & vomiting, palpitations	Eriksson et al[15]
Epicardial and/or microvascular coronary vasospasm	Propensity to coronary vasospasm	Vascular smooth muscle hyper-reactivity	**Calcium channel antagonists**	↓ spontaneous and inducible coronary spasm via vascular smooth muscle relaxation and ↓ oxygen demand	Constipation, ankle swelling, flushing	Nishigaki et al meta-analysis[16] Johnson et al[17]
			Nitrates	↓ spontaneous and inducible coronary spasm via large epicardial vasodilation, ↓ oxygen demand. Lack of efficacy in microvascular angina with potential deleterious effect	Headaches, dizziness, flushing	Lombardi et al[18] Russo et al[19]
			Rho-kinase inhibitors	↓ Calcium sensitivity of smooth muscle by ↑ phosphatase activity reducing phosphoralated (active) myosin light chains	Rash, dizziness. Not licensed for use in Europe or USA.	Mohri et al[20]
Adjunctive non-pharmacological interventions	May be useful in all endotypes	Metabolic syndrome, endothelial dysfunction, cardiovascular risk factors, anxiety/depression	Smoking cessation, Exercise, cardiac rehabilitation, Mediterranean diet, cognitive behavioural therapy			Stampfer et al[21]

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