Coronary artery disease

Pharmacotherapy for coronary microvascular dysfunction

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Coronary microvascular dysfunction (CMD) has been increasingly recognized as an important cardiac condition that can cause signs and symptoms of myocardial ischaemia in various clinical settings. The dysfunction is located at the level of the coronary microcirculation with a vessel diameter of <500 μm and can be characterized by structural alterations such as vascular remodelling, vascular rarefaction, and perivascular fibrosis but also functional alterations such as endothelial dysfunction and dysfunction of vascular smooth muscle dysfunction have been described. The underlying mechanisms are diverse, frequently overlapping, and still incompletely understood. Among others, conditions such as chronic inflammation, insulin resistance, abnormal adrenergic function, enhanced pain perception, oestrogen deficiency, and genetic predispositions have been described. A common and often underdiagnosed clinical manifestation of CMD is in patients who have angina symptoms yet no obstructive epicardial coronary artery disease nor myocardial disease but in whom cardiovascular risk factors are present. There are still very few data regarding the effectiveness of pharmacological treatments for CMD. The current ESC guidelines on the management of stable coronary artery disease suggest using aspirin and statins as well as β-blockers and/or calcium-channel blockers for the treatment of CMD. This review gives an overview of the currently available pharmacological concepts for the treatment of coronary microvascular dysfunction in patients without epicardial coronary artery disease and without myocardial disease.

Keywords
Coronary microvascular dysfunction • Angina pectoris • Pharmacotherapy

Introduction

Coronary microvascular dysfunction (CMD) has been increasingly recognized as an important cardiac condition that can be responsible for signs and symptoms of myocardial ischaemia in various clinical settings.1,2 The dysfunction is usually located at the level of the coronary microcirculation with a vessel diameter of <500 μm and can be characterized by structural alterations such as vascular remodelling, vascular rarefaction, and perivascular fibrosis but also functional alterations such as endothelial dysfunction and vascular smooth muscle dysfunction have been described. The underlying mechanisms are diverse, frequently overlapping, and still incompletely understood. Among others, conditions such as chronic inflammation, insulin resistance, abnormal adrenergic function, enhanced pain perception, oestrogen deficiency, and genetic predispositions have been described. A common and often underdiagnosed clinical manifestation of CMD is in patients who have angina symptoms yet no obstructive epicardial coronary artery disease nor myocardial disease but in whom cardiovascular risk factors are present. There are still very few data regarding the effectiveness of pharmacological treatments for CMD.3 The current ESC guidelines on the management of stable coronary artery disease suggest using aspirin and statins as well as β-blockers and/or calcium-channel blockers for the treatment of CMD. This review will focus on pharmacotherapy in patients with stable coronary microvascular disease in the absence of obstructive CAD and myocardial diseases. Non-pharmacological treatments such as spinal cord stimulation or enhanced external counterpulsation4 have shown favourable results in patients with refractory symptoms. These treatments will not be covered in this article and can be reviewed elsewhere.5 – 7

Definition of coronary microvascular dysfunction

Coronary microvascular dysfunction is defined as a mismatch of myocardial blood supply and oxygen consumption due to a dysfunction of the coronary microvessels with a diameter <500 μm [see ref. (1), Figure 1]. Structural abnormalities such as vascular remodelling, vascular rarefaction, and perivascular fibrosis as well as functional abnormalities such as endothelial dysfunction and dysfunction of vascular smooth muscle cells have been reported in this setting. The current classification of coronary microvascular dysfunction comprises four clinical scenarios (Figure 2) where type 1 is CMD in the absence of obstructive CAD and myocardial diseases, type 2 is CMD in the presence of myocardial diseases, type 3 is CMD in the presence of myocardial diseases, type 3 is CMD in the absence of obstructive CAD and myocardial diseases, and type 4 is CMD in the presence of myocardial diseases.
presence of obstructive CAD, and type 4 is iatrogenic.\textsuperscript{3} Moreover, it has been appreciated that CMD can occur in clinically stable and unstable patients.\textsuperscript{3}

**Proposed underlying mechanisms and heterogeneity in study endpoint definitions**

Various mechanisms have been described that may be responsible for the clinical presentation of angina pectoris in the absence of obstructive epicardial coronary artery disease. Among these are impaired coronary microvascular dilatation,\textsuperscript{8} enhanced vasoconstriction and spasm,\textsuperscript{9} abnormal pain perception,\textsuperscript{10} and altered adrenergic nerve function.\textsuperscript{11} In addition, all cardiovascular risk factors have shown to cause the activation of inflammatory pathways and thereby (micro)vascular dysfunction.\textsuperscript{12}

It is difficult to judge the efficacy of pharmacological treatments in this patient population. This is because the clinical studies performed so far used a variety of definitions of study endpoints and applied variable inclusion criteria. Vermeltfoort et al. analysed 57 studies on patients with angina and unobstructed coronary arteries and found that the inclusion and exclusion criteria varied substantially among these studies.\textsuperscript{13} Whereas some studies just required some form of anginal pain in the absence of coronary stenoses, others demanded exercise-induced chest pain combined with some evidence of ischaemia. This underscores the need for a thorough characterization of patients included in studies of drug therapy and for an accepted terminology and diagnostic assessment to make study results comparable.

**Available evidence for pharmacotherapy**

Regarding pharmacological therapy in CMD there are currently no large studies available. Most studies are small and not always randomized. Nevertheless, a variety of drugs have been investigated for the treatment of CMD. The latest ESC guideline on the management of stable CAD has—for the first time—addressed the issue of CMD and has recommended the use of statins, \(\beta\)-blockers, and calcium-channel blockers.\textsuperscript{2}

**Nitrates**

The efficacy of short-acting nitrates on chest pain in patients with microvascular dysfunction has been assessed in multiple studies with inconclusive results. The effectiveness in acutely relieving

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**Figure 1** Anatomical preparation of coronary arteries including coronary microvessels (Source: A. Puff, N. Zappold—Das Herz—1987).

**Figure 2** Definition of coronary microvascular dysfunction (from Crea et al.\textsuperscript{2}).
chest pain symptoms ranged from as low as 18% in a study by Day et al.14 to as high as 64% in a study by Isner et al.15 There were important differences in the inclusion criteria of these studies as well as the patient populations studied. Moreover, it has been speculated that nitrates have different effects in the epicardial coronary arteries compared with the microvessels due to different signalling pathways.16

Studies on long-acting nitrates have generally shown no positive effect and are thus not recommended as first-line drugs in these patients. This has recently been highlighted in a study by Russo et al., showing that ISDN was effective in relieving symptoms and in improving exercise stress test results in patients with stable epicardial coronary disease but ISDN was not helpful in patients with coronary microvascular dysfunction.17 According to our experience short-acting nitrates are often effective in relieving chest pain symptoms in patients with CMD, especially when administered on the background of β-blocker or calcium-channel blocker treatment. Long-acting nitrates, however, only rarely ameliorate symptoms in CMD patients although we have treated patients reacting favourably to such agents.

β-Blockers
While early studies using propranolol and acebutolol were unable to report beneficial effects,18,19 studies using atenolol reported favourable effects regarding symptoms and exercise stress test parameters.20 Atenolol was usually prescribed in doses of up to 100 mg per day. More recently, there have been reports assessing the effect of nebivolol in such patients equally showing beneficial effects21 in doses of up to 5 mg per day. β-Blockers may be especially effective in patients with high resting heart rate or increased sympathetic tone22 while they should be avoided in patients with concomitant vasospastic disorders.23 Thus, depending on the clinical presentation and concomitant diseases, β-blockers are often effective for the treatment of CMD and used as first-line drug (see Figure 3).

ACE inhibitors
Available studies assessing the effects of ACE inhibitors in these patients have generally shown beneficial results. Early studies by Kaski and Nalbantgil demonstrated improvement of exercise stress test parameters in patients with microvascular dysfunction for enalapril and cilazapril.24,25 Ozelik et al. studied 18 patients after a 2-week drug washout period. First, patients were given nisoldipine 5 mg twice daily for 4 weeks. After stopping nisoldipine and another 2 weeks of drug washout, the same patients were given ramipril 2.5 mg once daily for 4 weeks. Exercise stress test parameters, frequency of anginal attacks per week, and the need for sublingual nitroglycerin were decreased significantly with both drugs.26 In a study by Pizzi et al. 45 patients with microvascular angina were randomly assigned to receive either a combination of ramipril (10 mg/day) and atorvastatin (40 mg/day) or placebo for 6 months.27 At 6-month follow-up, patients taking atorvastatin and ramipril improved their quality of life both in terms of exercise duration and Seattle Angina Questionnaire parameters. The authors proposed that the benefits of these drugs were related to reduction of oxidative stress. In 2002, Chen et al. reported in a double-blind randomized trial that an 8-week ACE inhibitor treatment with enalapril (5 mg twice daily) improved coronary flow reserve as well as exercise parameters in patients with microvascular angina in a cohort of 20 Taiwanese patients28 compared with placebo. More recently, Pauly et al. reported in a randomized study of 61 American women with microvascular dysfunction that after 16 weeks of quinapril treatment (80 mg once daily) coronary flow reserve in response to adenosine as well as angina pectoris symptoms improved in the treatment group when compared with placebo.29 Therefore, we recommend the use of ACE inhibitors for all patients with CMD if there are no contraindications present.

Calcium-channel blockers
Calcium-channel blockers have been shown to improve symptoms and exercise stress test parameters in patients with CMD. Cannon et al. assessed the effects of verapamil and nifedipine in a randomized, double-blind, placebo-controlled outpatient study. Patients were treated for 1 month with each drug or placebo. In this study exercise stress test parameters as well as symptoms were improved by both drugs compared with placebo.30 Lanza et al. compared the effects of a β-blocker (atenolol), a calcium antagonist (amlodipine), and a nitrate (isosorbide-5-mononitrate) on anginal symptoms in 10 patients with microvascular angina (normal coronary arteries at angiography, effort angina, and ischaemic-like ST-segment changes, i.e. 1 mm horizontal or downsloping ST depression 80 ms after the J point on exercise testing) who were assessed in a crossover.

![Figure 3](image-url) "Therapeutic algorithm for microvascular angina (from Crea et al.2)."
double-blind, randomized trial. In contrast to the studies mentioned before, only atenolol significantly improved chest pain episodes. However, other studies have shown beneficial effects of nisoldipine (see above) and for diltiazem (see below) suggesting that at least a subgroup of patients with microvascular angina benefits from calcium-channel blocker treatment. Thus, calcium-channel blockers are recommended and are frequently effective in patients with CMD which is also supported by animal studies as, for example, amlodipine improves inward remodelling in CMD. We use them as first-line drug in patients with microvascular spasm and in those with mainly exercise related symptoms if β-blockers are not effective. However, some patients may paradoxically experience worsening of symptoms on calcium-channel blockers necessitating withdrawal of treatment.

**Statins**

Statins have been shown to be effective in reducing LDL levels and thereby cardiovascular risk. Moreover, they may have pleiotropic effects including a reduction of vascular inflammation and an improvement of endothelial function. In a single-blind, randomized, placebo-controlled study by Kayikcioglu et al., 40 patients with microvascular angina were randomized to pravastatin (40 mg/day) or placebo. After the treatment period of 3 months, brachial artery flow-mediated dilation improved significantly in the pravastatin group. Equally, exercise duration and time to 1-mm ST depression were significantly prolonged after statin therapy compared with placebo.

In a similar study, Fabian et al. assessed 40 patients with microvascular angina with mild hypercholesterolemia who were randomized to placebo (n = 20) or simvastatin 20 mg/day (n = 20). Brachial artery flow-mediated dilation increased significantly and the time to >1-mm ST-segment depression during stress testing was significantly prolonged by the end of the study in the treatment group.

More recently, Zhang et al. assessed the effect of a combination therapy of a statin and a calcium-channel blocker with solo treatment in patients with microvascular angina. Sixty-eight patients were divided randomly into three groups: fluvastatin (40 mg/day, n = 23), diltiazem (90 mg/day, n = 22), and combination of fluvastatin (40 mg/day) and diltiazem (90 mg/day, n = 23). After 90 days, the coronary flow reserve was improved in all three groups. In addition, the time to 1-mm ST-segment depression increased significantly in all groups. The improvement in coronary flow reserve and prolonged time to 1 mm ST-segment depression in the combination treatment group were more pronounced than in those who received mono-therapy. Based on these studies we recommend the use of statins for most patients with MVD unless there are severe side effects or contraindications present.

**Ranolazine**

Ranolazine acts via inhibiting the transmembrane late sodium current. It thereby leads to a reduced activity of the sodium-dependent calcium channels resulting in a reduction of intracellular calcium levels and prevention of calcium overload during ischaemia.

A pilot randomized, double-blind, placebo-controlled, crossover trial by Mehta et al. enrolled 20 women with angina, no obstructive CAD, and ≥10% ischaemic myocardium on adenosine stress cardiac magnetic resonance imaging. Participants were assigned to ranolazine or placebo for 4 weeks separated by a 2-week washout. Compared with placebo, patients on ranolazine had significantly better Seattle Angina Questionnaire scores and there was a trend towards an improvement of cardiac magnetic resonance myocardial perfusion reserve index on ranolazine.

In another study by Villano et al., 46 patients with stable microvascular angina (effort angina, positive exercise stress test, normal coronary angiography, coronary flow reserve <2.5), who had symptoms inadequately controlled by standard anti-ischaemic therapy, were randomized to ivabradine (5 mg twice daily), ranolazine (375 mg twice daily), or placebo for 4 weeks. The Seattle Angina Questionnaire, EuroQoL scale, and exercise stress test were assessed at baseline and after treatment. Both drugs improved questionnaire items and EuroQoL scale compared with placebo, with ranolazine achieving better results compared with ivabradine. Time to 1-mm ST-segment depression and exercise stress test duration were improved by ranolazine compared with placebo.

Finally, Tagliamonte et al. enrolled 58 patients with angina and evidence of myocardial ischaemia by Tc-99m MIBI myocardial perfusion imaging, but no obstructive coronary artery disease, in a double-blind, placebo-controlled trial. Participants were assigned to ranolazine (n = 29) or placebo (n = 29) for 8 weeks (up to 500 mg twice a day). Coronary flow reserve was determined as the ratio of hyperemic, induced by intravenous dipyridamole administration, to baseline diastolic coronary flow velocity measured by trans-thoracic Doppler in the LAD. After 8 weeks, coronary flow reserve significantly increased in the ranolazine group but not in placebo group. We mainly use ranolazine in patients in whom other drugs have proved ineffective. Thus, our experience that this drug is effective in only ~50% is possibly biased by this selection of patients with refractory symptoms.

**Metformin**

Data on the efficacy of the anti-diabetic drug metformin in patients with CMD is scarce. In the one study available, Jadhav et al. conducted a 8-week double-blind, randomized, placebo-controlled study of metformin 500 mg twice a day in 33 non-diabetic women with a prior history of normal coronary angiography but two consecutive positive (ST-segment depression ≥1 mm) exercise tolerance tests. In comparison with placebo (n = 17), metformin recipients (n = 16) showed significant reductions in weight and in homeostatic model assessment for insulin resistance. Endothelium-dependent microvascular responses to acetylcholine assessed by laser Doppler imaging in the forearm improved significantly with metformin, but responses with placebo were unchanged. Maximal ST-segment depression, Duke score, and chest pain incidence also improved in metformin relative to placebo recipients. It has been speculated that metformin may enhance nitric oxide production induced by activation of the AMP-activated protein kinase. Owing to the fact that there is currently only one study on the effectiveness of metformin in CMD patients without diabetes mellitus available the experience is limited and we do not routinely use this drug in CMD patients.

**Trimetazidine**

Trimetazidine inhibits beta-oxidation of fatty acids by blocking long-chain 3-ketoacyl-CoA thiolase, which enhances glucose oxidation and reduces ischaemia. Few studies have investigated the effect of
this drug in patients with CMD. Nalbantgil studied 35 microvascular angina patients in a placebo-controlled, double-blind study consisting of two 4-week treatment periods with 60 mg trimetazidine daily. Although heart rate and systolic blood pressure at rest, peak exercise, and the time of 1-mm ST-segment depression were not significantly different between the placebo and trimetazidine treatment group, patients in the treatment group had a prolonged total exercise time and time to 1-mm ST depression. In addition, maximum ST-segment depression was significantly less in patients with trimetazidine therapy compared with placebo.

Contrary to these findings, Leonardo et al. did not find a beneficial effect for trimetazidine in their double-blind, randomized, crossover, placebo-controlled study of 16 patients comparing trimetazidine for 2 weeks (20 mg 3 times daily), atenolol (100 mg daily), or placebo. Only patients who were treated with atenolol had a reduced number of anginal episodes as well as an increased time to 1 mm ST-segment depression during exercise stress testing after treatment. Thus, there is only limited evidence for trimetazidine in MVD patients. Moreover, due to the fact that this drug is currently not available in many countries including Germany, we do not have any personal experience with trimetazidine in our CMD patients.

Nicorandil
The effects of the vasodilator nicorandil in patients with CMD have been assessed in two studies. Yamabe et al. studied 11 patients who had a history of typical angina, positive exercise electrocardiograms, positive 201Tl scintigraphy, nearly normal coronary arteriograms, and negative coronary vasospasm. After nicorandil administration, scintigraphy results significantly improved as well as anginal symptoms and ST-depression during exercise. However, it has to be mentioned that this study had no control group. In another study, Chen et al. assessed 13 patients with microvascular angina. After a 2-week placebo run-in period, patients were randomly assigned to the first 2-week treatment with nicorandil 5 mg twice daily or placebo, then crossed over to the second 2-week treatment after a 2-week washout period. Treadmill exercise tests and 24-h ambulatory electrocardiogram monitoring were performed at the end of each treatment phase. Time to 1-mm ST depression and total exercise duration were significantly prolonged with nicorandil treatment compared with placebo. Although nicorandil is currently not licensed in Germany, it can be obtained through international pharmacies for treatment of CMD patients with refractory symptoms. In these patients we frequently found nicorandil to be effective in improving chest pain symptoms.

Oestrogen
The female sex hormone oestrogen has a strong protective vascular effect. Oestrogen levels fall in postmenopausal women explaining at least in part the increase in vascular risk in women after menopause. As many patients with CMD are postmenopausal women with oestrogen deficiency, oestrogen replacement therapy has been intensively studied, however, with conflicting results. Several studies showed that physiological levels of 17 beta-estradiol acutely and selectively potentiated endothelium-dependent vasodilation in both large coronary conductance arteries and coronary microvascular resistance arteries of postmenopausal women. However, maximum exercise duration was not uniformly found to be improved with oestrogen treatment. However, other researchers failed to demonstrate favourable effects of oestrogen treatment. These differences may be due to the different forms of oestrogen and the different routes of administration. Due to these contradictory results oestrogen treatment is not generally recommended and should only be initiated after consultation with a gynecologist to evaluate the individual pros and cons as well as side effects of such treatment.

Imipramine
Some patients with angina and unobstructed coronary arteries may suffer from enhanced pain perception. The antidepressant drug imipramine has been shown to be useful in chronic pain syndromes. Thus, Cannon et al. studied 60 consecutive patients in a randomized, double-blind, placebo-controlled 3-week trial of clonidine at a dose of 0.1 mg twice daily (20 patients), imipramine at a dose of 50 mg nightly with a morning placebo (20 patients), or placebo twice daily (20 patients); this treatment phase was compared with an identical period of twice-daily placebo for all patients (placebo phase). Only the improvement with imipramine was statistically significant and repeated assessment of sensitivity to cardiac pain showed significant improvement only in the imipramine group. The authors speculated that imipramine improved the symptoms of patients with chest pain and normal coronary angiograms, possibly through a visceral analgesic effect. The patients studied were a heterogeneous group with 23/60 (38%) of them having abnormal findings at exercise testing 10 of whom having ischaemic ST-segment depression. Effects of imipramine were not different between patients with and without objective cardiac abnormalities. A few years later Cox et al. performed a randomized, double-blind, crossover trial of imipramine 50 mg daily vs placebo in 18 women (median age 53 years; range 35–72) with chest pain and normal coronary angiograms who were suffering at least two anginal episodes per week despite conventional antianginal medication. In this trial imipramine reduced the incidence of chest pain but no improvement in quality of life parameters was seen, possibly due to the high incidence of side effects such as dry mouth, dizziness, and nausea. Therefore, we limit the use of imipramine to only those MVD patients with refractory symptoms after having tried various drugs as mentioned in Figure 3.

Xanthine antagonists
Xanthine antagonists are a class of drugs that has been investigated in patients with microvascular angina due to its favourable effects on nociception. The substances that have been assessed are aminoephedrine and bamiphylline. Both showed beneficial effects on exercise stress test parameters in various studies. Clinically, these drugs represent a bailout option in completely refractory patients before more invasive methods such as spinal cord stimulation may be considered.

Upcoming pharmacotherapies
Preliminary data suggest that endothelin-antagonists and rho-kinase inhibitors may become useful for the treatment of coronary microvascular dysfunction. Reriani et al. compared the endothelin-A-receptor antagonist atrasentan (10 mg once daily for 6 months) vs.
placebo in 47 patients looking at vascular reactivity to acetylcholine before and after the treatment. Coronary blood flow in response to acetylcholine was significantly increased in patients in the treatment arm after 6 months compared with placebo. Despite the fact that larger studies are needed to confirm the beneficial effects of atrasentan in patients with microvascular angina, it should be mentioned that the high costs of this drug currently limit the use for this indication.

Fukumoto et al. investigated the effects of fasudil, a rho-kinase inhibitor that was administered intracoronary (300 μg) in patients with coronary microvascular dysfunction compared with a control group. Fasudil reduced coronary sinus lactate production and significantly ameliorated pacing-induced myocardial ischaemia parameters such as magnitude of symptoms and maximum ST-segment depression, suggesting that it can improve the condition. However, this drug is currently not available in Europe.

**Therapeutic algorithm**

In patients with cardiovascular risk factor-related CMD (type 1), a strict and tight control of cardiovascular risk factors is recommended. Therefore, most patients receive a statin and an ACE inhibitor. β-Blockers are the first-line treatment. If this treatment does not achieve sufficient relief of symptoms or is not tolerated, calcium-channel blockers can be useful especially if patients also report symptoms at rest suggesting a vasospastic component. In patients with refractory symptoms, antianginal drugs such as ranolazine, nicorandil, or ivabradine can be tried according to local availability. Imipramine and/or bamilphylleine are alternative options in patients with refractory symptoms despite the aforementioned antianginal treatments (Figure 3).

**Clinical implications**

Coronary microvascular dysfunction is an important clinical condition that should not be overlooked since patients often continue to have symptoms leading to repeated hospital admissions and countless further investigations. In addition, the condition has been shown to be prognostically relevant. Prospective, randomized trials in well-characterized sub-cohorts are urgently needed to identify the best pharmacological management. Only then guidelines can be improved to assist the clinical community in the treatment of these patients and ultimately improve prognosis.

**Conclusion**

Patients with coronary microvascular dysfunction in the absence of epicardial coronary artery disease and/or myocardial disease should receive strict control of their cardiovascular risk factors and antianginal medication with β-blockers and or calcium-channel blockers. In addition, statins and ACE inhibitors seem to have beneficial effects in most patients. Second-line drugs are ivabradine, ranolazine, and nicorandil. However, large randomized clinical trials assessing the efficacy of pharmacotherapy in these patients are missing. Rho-kinase inhibitors and endothelin-receptor antagonists represent potential drugs that may prove useful in these patients in the future.

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**References**


