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SPOTLIGHT REVIEW

Treatment of coronary microvascular dysfunction

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Abstract

Contemporary data indicate that patients with signs and symptoms of ischaemia and non-obstructive coronary artery disease (INOCA) often have coronary microvascular dysfunction (CMD) with elevated risk for adverse outcomes. Coronary endothelial (constriction with acetylcholine) and/or microvascular (limited coronary flow reserve with adenosine) dysfunction are well-documented, and extensive non-obstructive atherosclerosis is often present. Despite these data, patients with INOCA currently remain under-treated, in part, because existing management guidelines do not address this large, mostly female population due to the absence of evidence-based data. Relatively small sample-sized, short-term pilot studies of symptomatic mostly women, with INOCA, using intense medical therapies targeting endothelial, microvascular, and/or atherosclerosis mechanisms suggest symptom, ischaemia, and coronary vascular functional improvement, however, randomized, controlled outcome trials testing treatment strategies have not been completed. We review evidence regarding CMD pharmacotherapy. Potent statins in combination with angiotensin-converting enzyme inhibitor (ACE-I) or receptor blockers if intolerant, at maximally tolerated doses appear to improve angina, stress testing, myocardial perfusion, coronary endothelial function, and microvascular function. The Coronary Microvascular Angina trial supports invasive diagnostic testing with stratified therapy as an approach to improve symptoms and quality of life. The WARRIOR trial is testing intense medical therapy of high-intensity statin, maximally tolerated ACE-I plus aspirin on longer-term outcomes to provide evidence for guidelines. Novel treatments and those under development appear promising as the basis for future trial planning.

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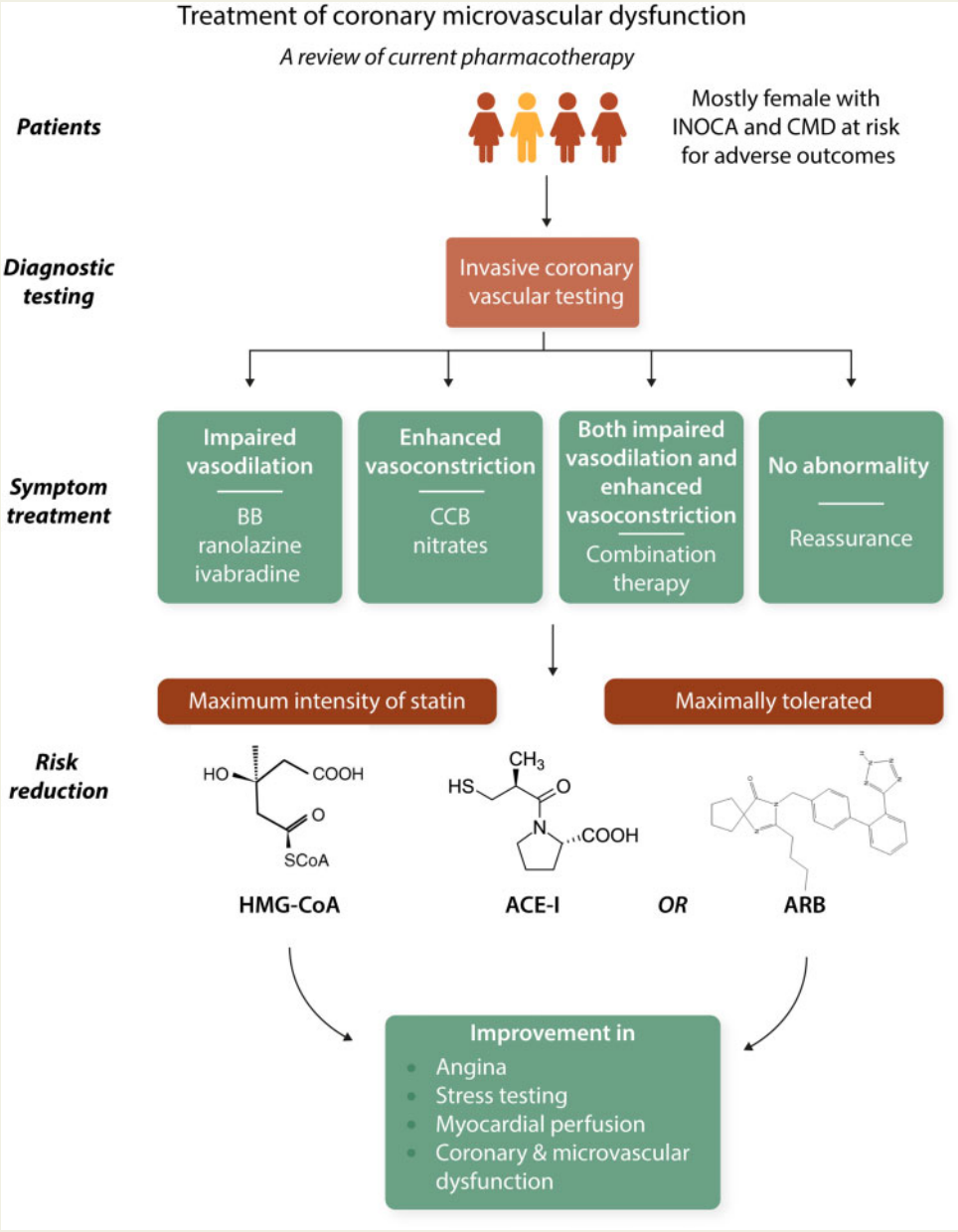
Graphical Abstract



Keywords INOCA • CMD • Women • Angina • Ischaemia

This article is part of the Spotlight Issue on Coronary Microvascular Dysfunction.

1. Introduction

Older reports suggested the prognosis of angina with evidence of ischaemia and non-obstructive coronary artery disease (INOCA) was benign.[1–3] Now, considerable contemporary data support the conclusion that these patients often have coronary microvascular dysfunction (CMD) and are at higher risk for adverse outcomes vs. reference subjects.[4–9] Nevertheless, INOCA patients currently remain under-treated, because management guidelines do not address this population due to the absence of evidence-based data.[10]

Mechanistically, coronary endothelial (constriction with acetylcholine) and/or microvascular [limited coronary flow reserve (CFR) with adenosine] dysfunction (*Figure 1*) are well-documented and associated with adverse prognosis.[11] Furthermore, diffuse non-obstructive atherosclerosis with 'compensatory' coronary remodelling is well documented in women.[12,13] Persistent angina, ischaemia on stress testing, multiple risk

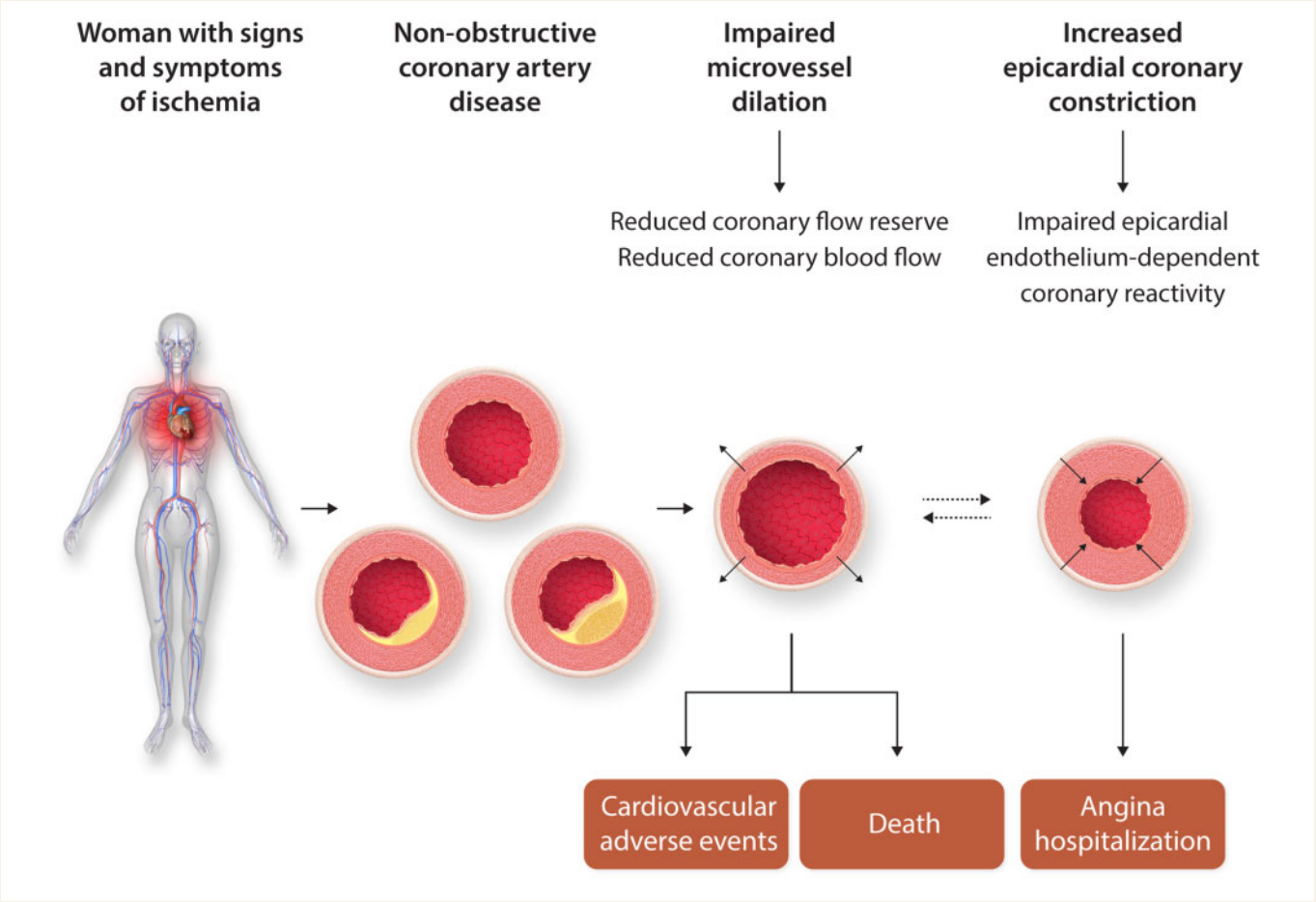


Figure 1 CMD reactivity testing and prognosis. Women with no obstructive coronary artery disease and the potential role of coronary reactive testing to identify those at higher risk for adverse events. Permission granted to reproduce figure from AlBadri *et al.*[11]

factors, and more extensive non-obstructive plaque (multi-vessel) predict higher risk for adverse events.[14–17]

Relatively small sample-sized, short-term pilot studies of INOCA subjects, mostly women, using intense medical therapies targeting endothelial, microvascular, and/or atherosclerosis mechanisms suggest symptom, ischaemia, and coronary vascular functional improvement,[18] however, randomized, controlled major outcome trials testing treatment strategies have not been completed. We review the evidence regarding the treatment of CMD.

2. Review of pharmacotherapy

2.1 Conventional therapy—anti-atherosclerosis treatment

Statins, angiotensin-converting enzyme inhibitor (ACE-I) or receptor blockers (ARB), and low-dose aspirin are secondary prevention anti-atherothrombosis treatments that beneficially impact many mechanisms summarized above that likely contribute to symptoms and outcomes in INOCA patients; they counteract oxidative stress, are anti-inflammatory, improve both endothelial and microvascular function,[19,20] and rebalance sympathetic dysregulation (*Table 1*).[19–22] These treatments improve angina, stress testing, myocardial perfusion, coronary endothelial function, and microvascular function in small-size trials. Statins reduce plaque lipid-rich core, inflammation, macrophage, and foam cell formation, promote fibrous cap thickening, and decrease platelet reactivity.[23] Drug combinations (e.g. statins plus ACE-I) appear to amplify some benefits.[20]

Thromboxane A2 (TXA2) inhibitors (low-dose aspirin and P2Y12 platelet inhibitors) are also likely useful in preventing adverse outcomes of INOCA patients.[12] They minimize platelet-rich microemboli and related downstream events. Activation of thromboxane A2 synthase (TXAS)/TXA2/thromboxane prostanoid (TP) receptors leads to arterial constriction, platelet aggregation, and vascular injury. Microvascular dysfunction was characterized in ischaemia/reperfusion injury using genetically modified knock-out (TXAS-/-, TP-/-, and TXAS-/-TP-/-) mice.[24] Activation of TXAS/TXA2/TP receptors led to microvascular constriction, platelet aggregation, and vascular injury; aspirin reduced endothelial platelet adhesion. Thus, inhibiting TXAS/TXA2/TP signalling confers microvascular protection against oxidative injury in the microcirculation.

2.2 Conventional therapy—anti-anginal treatment

Calcium antagonists fail to ameliorate CFR limitations in CMD patients[25] but can prevent epicardial coronary vasospasm. Few controlled long-acting nitrate studies have been reported and beta-blockers are effective only for some.[26] Notably, a highly selective beta-1 blocker with vasodilatory effects via nitric oxide (NO) production, nebivolol, has effects on

Table 1 Pharmacotherapy of coronary microvascular dysfunction mechanistic trials

Conventional treatments	Intermediate outcome impact
Anti-atherosclerosis treatment	
Statins	+
ACE-I, angiotensin renin blockers	+
Low-dose aspirin	+
Anti-angina treatments	
Calcium antagonists	+
Alpha beta-blockers	+
Beta-blockers	+
Nitrates	+
Ranolazine	+/-
Exercise	+
Enhanced external counter-pulsation	+
Imipramine, amitriptyline, nortriptyline	+
L-arginine	+
Spinal cord stimulation	+
Novel treatments	
RAAS active agents	
ACE-I quinapril	+
Mineralocorticoid inhibition-eplerenone	-
PDE	
PDE type 3 inhibition—cilostazol	+
PDE type 5 inhibition—sildenafil	+
Calcium channel antagonism—benidpine	+
Selective If-channel blockade—ivabradine	+/-
Rho-kinase inhibition—fasudil	+
Endothelin receptor antagonists—darusentan and atrasentan	+
Adenosine active agents—dipyridamole, caffeine, aminophylline, paraxanthine, pentoxifylline, theobromine, and theophylline	+/-
Myocardial metabolic active agents	
Dichloroacetate	-
Carnitine analogues—acetyl-L-carnitine, propionyl-L-carnitine, and L-carnitine	-
Perhexiline	-
Trimetazidine	+
Metformin	+
Amiodarone/dronedarone	+
Anti-inflammation agents	
IL-1b inhibition-canakinumab, rilonacept	-
Methotrexate	-
Hormone therapy	-
IL-1a-anakinra	-
IL-6-Tocilizumab	-
TNF-α inhibitors	+
Glycaemic active agents—SGLT 1 and 2 inhibitors, GLP-1 agonists	-
Androgen analogues—testosterone (T), low-dose T (transdermal patch), and T undecanoate injection	+
Oestrogen analogues—norethindrone/ethinyl oestradiol, CEOs and medroxyprogesterone acetate, and CEO	+/-
Nervous system active agents—neuropeptide Y and selective serotonin reuptake inhibitors (escitalopram)	+/-
Gene and cell-based therapies—autologous CD34 cells	-
Small-molecule targets	-

+, benefit; +/-, no benefit; -, mixed benefit and no benefit; ACE-I, angiotensin-converting enzyme inhibitor; CEO, conjugated equine oestrogen; GLP-1, glucagon-like peptide 1; PDE, phosphodiesterase inhibition.

angina and exercise capacity and is being studied in women with CMD.[27] Intracoronary nebivolol increases CFR either due to reduction in resting flow (controls) or increase in maximal coronary flow [coronary artery disease (CAD) patients] as collateral flow index decreased parallel to reduction in myocardial oxygen consumption.[28] Importantly, nebivolol improved left ventricular (LV) filling pressure and CFR in uncomplicated arterial hypertension suggesting myocardial stimulation of NO release and improvement in coronary microvascular function.

Ranolazine is an antianginal that inhibits the late sodium channel and reduces intracellular calcium in cardiomyocytes, leading to improved ventricular relaxation which should facilitate microvascular function.[29] Results on CMD are conflicting. One pilot study showed improved symptoms in women with INOCA, and patients with low CFR improved CFR with treatment.[30] A similar sized study showed some symptom improvement but no effect on CFR.[31] A large randomized-crossover trial of ranolazine vs. placebo found no difference in symptoms or cardiac magnetic resonance imaging (cMRI)-myocardial perfusion reserve.[32] But stratification by baseline invasive CFR suggested that those with reduced CFR improved with ranolazine.[33]

Other treatments include exercise training, which beneficially modulates adrenergic and NO pathways,[34] but training trials are problematic for patient compliance and expense. Enhanced external counterpulsation therapy can improve angina.[35] Tricyclics (e.g. imipramine, amitriptyline, and nortriptyline) block multiple receptors, including muscarinic acetylcholine receptors, H1 and H2-histamine receptors, sodium and calcium channel receptors, and inhibit serotonin and norepinephrine reuptake. In a randomized, placebo-controlled trial of patients with INOCA, imipramine improved angina, possibly through visceral analgesic effects[36] but not quality of life (QoL).[37] Specific mechanism(s) for improvement require(s) additional investigation. L-arginine improved angina and vascular function,[38] but increased myocardial infarction in obstructive CAD patients. Hormone therapy improved chest pain symptoms, menopausal symptoms, and quality of life, but did not improve ischaemia or endothelial dysfunction.[39] Spinal cord stimulation normalizes abnormal pain perception,[40] improves angina, and increases exercise tolerance.[41]

2.3 Novel therapies

RAAS active agents including ACE-I in a randomized, double-blind, placebo-controlled trial, of women with INOCA and CFR <3.0, found quinapril (80 mg/d) significantly improved CFR over placebo. Both ACE-I treatment and CFR increased significantly contributing to angina improvement. Furthermore, effects on CFR concentrated among women with CFRs <2.5, consistent with the overall WISE hypothesis.[42]

Other randomized controlled trials of ACE-I in CMD using intracoronary Doppler coronary flow measurements confirmed benefit with enalapril.[21] CFR improved with ACE-I in subjects with diabetes,[43] and coronary microvascular function improved with ACE-I using positron emission tomography imaging in patients with hypertension,[44] although no effect was detected in two very small studies.[45,46] Several non-randomized studies using different methods to assess coronary microvascular function in small patient samples, further confirmed ACE-I improved coronary microvascular function.[47–50] Finally, ACE-I, with either a calcium antagonist or indapamide, also appeared beneficial.[51,52] A small study including patients with diabetes also showed an effect.[53]

Whether the effect of ACE-I on coronary microvascular function is indirectly mediated via blood pressure (BP) reduction is uncertain, but it is unlikely the only mechanism of benefit given the critical role of angiotensin II in vascular function. Additional evidence suggests ACE-I is associated with improvement in markers of endothelial function, and several circulating biomarkers.[25,26,54–56]

Mineralocorticoid inhibition (eplerenone) added to ACE-I, in another randomized double-blind, placebo-controlled trial of women with INOCA, provided no additional angina reduction or improvement in CFR.[57]

2.4 Phosphodiesterase inhibition

Phosphodiesterase (PDE) type 3 inhibition-(cilostazol) is used for intermittent claudication and prevention after stroke, coronary stent restenosis, and percutaneous coronary intervention (PCI). PDE-3 receptors are subdivided into PDE-3As and PDE-3Bs; the former in platelets, vascular smooth muscle cells, and cardiomyocytes; the latter in adipocytes, hepatocytes, pancreatic β-cells, and macrophages. Inhibiting PDE increases intracellular cyclic adenosine monophosphate with antiplatelet, anti-inflammatory, and vasodilatory effects. Benefits in renal and retinal microvascular complications of diabetes were suggested.[58] Cilostazol reduces superoxide anion, improves the production of local hepatocyte growth factor, and motility and morphogenesis of epithelial and endothelial cells.

Effects of cilostazol were assessed on coronary responses in patients with vasospastic angina (VSA, acetylcholine provocation). CFR, coronary volumetric flow, and diameter changes by N(G)-monomethyl-L-arginine were all significantly increased with cilostazol.[59] In a prospective, multicentre study of patients with spontaneous or ergonovine-provoked VSA refractory to calcium antagonists and nitrates, addition of cilostazol appeared effective.[60] In a multicentre randomized, double-blind, placebo-controlled trial of VSA patients refractory to amlodipine, cilostazol reduced angina frequency and intensity without serious adverse effects.[61]

PDE type 5 inhibition (sildenafil) improved perfusion of hypoperfused myocardium during exercise in a canine model.[62] In CAD patients, a single dose of sildenafil, without a placebo comparison, dilated coronary arteries and improved endothelium-dependent vasodilatation.[63] Others suggested continuous sildenafil infusion, in double-blinded placebo-controlled crossover design, did not reverse endothelial dysfunction in obstructive CAD patients.[64]

In women with INOCA, sildenafil acutely improved CFR using open, repeated measures design.[65] The observed improvement concentrated among women with CFR <2.5 (i.e. CMD).

These encouraging preliminary findings support the need for additional larger, randomized, double-blind trials with these agents, particularly the longer-acting preparation vardenafil.

Calcium Channel Antagonism is widely used for VSA. Benidipine, a long-acting dihydropyridine, showed a beneficial prognostic impact in VSA patients.[56] Additionally, with the hope of improving reduced vasodilator capacity of the coronary microcirculation and reducing cardiac afterload, calcium antagonists are often used for patients with CMD. However, they have shown variable results in trials of INOCA patients.[25,26,54,55] It has been reported that intracoronary diltiazem does not improve CFR in patients with microvascular angina (MVA).[25] Furthermore, no significant improvement in angina was observed with amlodipine in INOCA patients,[55] and verapamil failed to reduce spontaneous episodes of ischaemic ST-segment changes in another study.[26] Patients with abnormal vasodilator reserve can have improved symptoms, less nitrate use, and improved exercise tolerance with verapamil or nifedipine.[54] Furthermore, long-acting nifedipine also exerted cardiovascular protective effects through inhibition of vascular inflammation and improvement of endothelial function in INOCA patients. Thus, long-acting L-type calcium channel blockers appear to be more favourable for the coronary microcirculation compared with short-acting ones.

Selective If-channel blockade using ivabradine is a specific bradycardic agent that selectively reduces sinus node activity through inhibition of the If-current.[66] In contrast to β-blockers, ivabradine does not cause vasoconstriction or negative inotropic effects.[66] Beneficial effects of

ivabradine in ischaemic heart disease (IHD) are mediated by indirect effects to improve exercise tolerance, prolong time to ischaemia during exercise, and reduce angina severity and frequency vs. other antianginal agents in patients with stable angina.[66,67] Ivabradine improved angina in patients with MVA but coronary microvascular function did not change, suggesting that symptomatic improvement could be attributed to heart-rate-lowering effect.[31] However, others have found that ivabradine improves CFR in non-obstructed coronary arteries of patients with stable CAD both at the intrinsic heart rate and at paced heart rate identical to that before treatment.[68] Thus, ivabradine improves CFR in patients with stable CAD. These effects persist even after heart rate correction indicating improved microvascular function.[69] Thus, it is possible that ivabradine and/or perhaps some of the several other If-channel inhibitors have a role in CMD patients, although further studies are needed.

Rho-kinase inhibition impacts small guanosine triphosphate-binding protein Rho that enhances myosin light chain phosphorylation through inhibition of myosin-binding subunit of myosin phosphatase, leading to vascular smooth muscle hypercontraction.[70] Rho-kinase has a key role in the pathogenesis of coronary vasomotion abnormalities and associated VSA where its activity in circulating neutrophils is a biomarker for diagnosis, assessment of activity, and long-term prognosis.[71] Fasudil, a specific Rho-kinase inhibitor, is highly effective in preventing acetylcholine-induced coronary spasm and resultant myocardial ischaemia.[72] The Rho-kinase pathway has been shown to be substantially involved in endothelial dysfunction, vascular smooth muscle hypercontraction, and vasospasm as well as inflammatory cell accumulation in blood vessel adventitia,[73] and a pathogenetic mechanism in patients with chest pain and non-obstructive CAD.[74] Intracoronary fasudil is effective not only for patients with epicardial coronary spasm[72] but also for approximately two-thirds of patients with MVA.[75] Fasudil may be effective in CMD when Rho-kinase plays a role of the disorder. In models, myocardial hypertrophy induced by pressure overload leads to myocardial dysfunction, CMD, and ischaemia possibly due to oxidative stress, enhanced vasoconstriction to endothelin-1 (ET-1), and compromised endothelial NO function via elevated Rho-kinase signalling.[76]

Endothelin receptor antagonists (ERA) address ET-1, which increases peripheral and coronary vascular tone via ETA-activation.[77–79] ET-1 contributes to coronary endothelial dysfunction[78] and its tonic inhibitory effect on myocardial perfusion is related to atherosclerosis risk factor burden.[80] In patients with MVA, ET-1 is increased and linked with reduced time to onset exercise angina.[81] Additionally, some suggest increased ET-1 activity is associated with reduced CFR in women.[82] An abnormal pattern of diffuse, heterogeneous myocardial perfusion was associated with ET-1 in CMD[83] and the ERA antagonist, darusentan, improved myocardial perfusion and increased the homogeneity perfusion. These findings imply that in patients with CMD, ET-1 caused regional reductions in myocardial perfusion that can be improved with ERA receptor blockade. In a randomized placebo-controlled trial of the ERA antagonist, atrasentan for 6 months, in patients with CMD, chronic ERA antagonism improved microvascular coronary endothelial function.[84] This was accompanied by reductions in BP and plasma glucose. The Coronary Microvascular Angina (CorMicA) investigators found peripheral arterioles from patients with INOCA showed enhanced constriction to ET-1 and the thromboxane agonist U46619, compared with reference subjects.[85] These findings support the hypothesis that patients with INOCA are at risk of developing more generalized small vessel dysfunction. Two small randomized trials of an ET-1 receptor antagonist in MVA suggested benefit[83,84] and larger trials are needed. To this end, the Precision Medicine With Zibotentan in Microvascular Angina (PRIZE) study is a randomized, double-blind, placebo-controlled, crossover trial of zibotentan, an oral endothelin A receptor-selective antagonist, in MVA (ClinicalTrials.gov Identifier: NCT04097314). A total of 356 patients will be enrolled and at least 100 will be randomized in multiple centres across the UK. The primary outcome is exercise duration on the Bruce treadmill protocol. Secondary outcomes include patient-reported outcome measures, and a cMRI sub-study will provide information on the effects of treatment on myocardial blood flow.

Adenosine active agents include dipyridamole which was proposed to increase CBF by selective coronary vasodilatation without systemic haemodynamic effects,[86] and is useful to evaluate CMD in patients without obstructive coronary stenoses.[87,88] However, it is limited as an antianginal agent.[89] Although additional studies are needed, dipyridamole may be an effective in CMD patients without coronary obstruction. Xanthine derivatives (e.g. caffeine, aminophylline, paraxanthine, pentoxifylline, theobromine, and theophylline) may have beneficial effects for CMD patients related to several mechanisms.[90,91] They inhibit arteriolar dilation of adenosine by inhibition of vascular smooth adenosine-A2 receptors, which may redistribute CBF in CMD patients towards ischaemic regions where adenosine release is increased.[90] Xanthines may exert an analgesic effect, antagonizing stimulation of cardiac nerve pain fibres by adenosine, a major mediator of ischaemic chest pain.[91] However, in a randomized trial, oral aminophylline did not improve exercise-related ischaemic electrocardiogram (ECG) changes in MVA subjects, although angina improved.[92] In another study of INOCA patients,[93] intravenous aminophylline (total dose 6 mg/kg within 15 min) demonstrated benefit for time to onset ischaemia and exercise-induced chest pain. Disparate effects on symptoms and ST-segment changes of ischaemia warrant additional study as it is possible that xanthines may improve exercise tolerance in MVA, especially if pain sensitivity is the issue.

Myocardial metabolic active agents improve the efficiency of myocardial metabolism and substrate handling. Dichloroacetate (DCA), inhibits all isoforms of pyruvate dehydrogenase (PDH) kinase (PDK), the 'gatekeeping' enzyme in glucose oxidation. Myocardial metabolic reprogramming in ischaemia, infarction, and hypertrophy shares similarities with chronic hypoxia. Activation of PDH with DCA during chronic hypoxia maintains myocardial adenosine triphosphate (ATP) and glycogen improving hypoxic tolerance. In a type 2 diabetes model, DCA restored PDH activity, reversed LV diastolic dysfunction and normalized blood glucose.[94] A first-in-human trial of DCA in idiopathic pulmonary arterial hypertension (iPAH) suggests that PDK is 'a druggable target' for microvascular improvement in 'genetically susceptible' patients.[95] iPAH is a progressive vascular disease with occlusive vascular remodelling due to pro-proliferative and antiapoptotic environment in the wall of resistance pulmonary arteries. If similar changes occur in coronary resistance vessels in CMD, these findings could lead the way for novel precision medicine approaches to CMD. These findings suggest that PDK activation can improve myocardial function during hypoxic conditions such as ischaemia due to CMD and clinical trials appear warranted.

Carnitine analogues include acetyl-L-carnitine (ALC), propionyl-L-carnitine (PLC), and L-carnitine (LC) which are naturally occurring carnitine derivates formed by carnitine acetyltransferase. Beneficial cardiovascular (CV) effects of ALC and PLC have been extensively evaluated in animal models and humans. Multiple clinical trials have suggested ALC and PLC as potential strategies in management of peripheral arterial disease, myocardial ischaemia, cerebral ischaemia, and heart failure as well as type 2 diabetes, an independent risk factor for cardiovascular disease development. However, as attractive as these carnitine analogues appear, no

adequately powered randomized, controlled studies are available in English language searches that focus on INOCA patients or CMD.

Perhexiline, classed as a coronary vasodilator, binds to mitochondrial carnitine palmitoyltransferase (CPT)-1 and CPT-2 to shift myocardial substrate utilization from long-chain fatty acids to carbohydrates through inhibition of CPT-1 and, to a lesser extent, CPT-2. This increases glucose and lactate utilization, per unit oxygen consumption and results in an oxygen-sparing effect to explain remarkable antianginal efficacy.[96] This increases ATP production for the same O_2 consumption and potentiates platelet responsiveness to NO. Most recently, this agent has been shown to be a KLF14 activator independent of its function in mitochondria.[97] Perhexiline reduces leucocyte-endothelial adhesion *in vivo* and this is a KLF14-dependent protective effect on endothelial cell inflammatory activation.[98] Due to hepatic and peripheral nerve toxicity in poor metabolizers (~10% of exposed), development was discontinued in the USA, but it is used elsewhere with dose modification in poorly metabolizing patients identified through plasma monitoring that can eliminate significant side effects.[96] Data with perhexiline from patients with hypertrophic cardiomyopathy, where CMD is prevalent, are encouraging.[99]

Trimetazidine (TMZ), monotherapy and in combination with other antianginal agents, improved angina and exercise time in 12-double-blind, randomized trials of patients with stable angina.[100] In INOCA patients, TMZ improved angina and stress testing results vs. conventional therapy. Moreover, there was an improvement in silent ischaemia, nitrate consumption, functional class, myocardial perfusion, and endothelial function probably related to reduced ET-1 and increased antioxidant status.[101] A single TMZ dose increased exercise duration, total work, and improved ECG signs of ischaemia. An ongoing, randomized trial could provide definitive evidence of metabolic cardioprotection for chronic stable angina or acute coronary syndrome in patients post-PCI.[102]

Metformin prevents diabetes and may reduce adverse outcomes, but effects on microvascular function and angina are unclear. A double-blind, randomized, placebo-controlled study[103] of metformin in non-diabetic women with INOCA found metformin reduced weight and insulin resistance, improved endothelium-dependent microvascular function and responses to acetylcholine, exercise-induced ST-segment depression, Duke treadmill score, and chest pain. However, the mechanism is unclear and larger controlled trials of longer duration are warranted.

Amiodarone was introduced as an antianginal in 1967 and used in Europe for stable, unstable, and variant angina.[104] Combining amiodarone with multiple conventional antianginal drugs was well-tolerated. In addition to decreased myocardial oxygen demand, amiodarone increased myocardial oxygen supply, improved CFR and prevented coronary constriction.[105,106] Intracoronary amiodarone confirmed potent coronary vasodilation with decreased coronary resistance and increased coronary flow.[107] In a placebo-controlled trial[108] of stable angina patients receiving 'triple' antianginal therapy, amiodarone increased exercise duration, rate-pressure-product and reduced ST-segment depression.[108] Its iodine-free derivative, dronedarone with better side-effect profile and multichannel blockade, has favourable coronary microcirculatory, myocardial protectant, and remodelling effects in experimental models.[109] Dronedarone's good safety profile and decreased angina hospitalizations support testing in INOCA patients without heart failure.

Anti-inflammation agents block associated endothelial dysfunction that plays a key role in CMD pathogenesis. Specific approaches to modify inflammation and assess-related effects on CMD are difficult since essentially all effective anti-ischaemic and anti-atherosclerosis agents modify inflammation, to some degree.[110] Interleukin (IL)-1β is central to the inflammatory response that drives IL-6 signalling. There is considerable interest to test anti-inflammatory agents in CMD. Low-dose methotrexate was ineffective in the Cardiovascular Inflammation Reduction Trial among subjects with obstructive CAD. Colchicine in the LoDoCo2 and COLCOT trials, as well as proposed trials involving other modulators of IL-1, IL-6, and the NLRP3 inflammasome offer promise. IL-1a-anakinra, in rheumatoid arthritis (RA) patients improved myocardial contractility and relaxation, CFR, and brachial fibromuscular dysplasia (FMD).[111] IL-6-tocilizumab, an IL-6 receptor antagonist, improved brachial FMD and aortic stiffness in RA.[112] Whether these arterial changes are direct effects of IL-6/IL-6 receptor pathway inhibition, maintained over-time, and translate into better outcomes warrants further studies. In revascularized NSTEMI patients, tocilizumab attenuated inflammation and cardiac troponin T release but did not influence coronary microvascular or endothelial function.[113]

IL-1b inhibition—rilonacept and canakinumab bind IL-beta before it binds to its receptor complex. Canakinumab, a monoclonal antibody targeting IL-1β, reduced CV events independent of lipid-lowering and other treatments in the CANTOS trial.[114] Another report suggested beneficial effects on carotid intimal media thickness and arterial stiffness.[115] In chronic kidney disease patients, not on dialysis, rilonacept was well-tolerated and improved brachial FMD without changing conduit vessel stiffness as it reduced indices of systemic inflammation.[116] Multiple studies suggest that anti-tumour necrosis factor alpha (TNF-α) treatment improves endothelial function in patients with RA, psoriasis and psoriatic arthritis.[117,118]

SGLT2 channel inhibition—multiple studies demonstrate that blocking endothelial sodium-glucose cotransporter-2 improves endothelial function in diabetes.[119] If this improves ischaemia and outcomes in patients with CMD remains to be determined. Also, the effect of SGLT1 and 2 inhibition is unknown. Because these agents improve cardiovascular outcomes in diabetes trials, they offer promise for CMD.

Hormones—androgen analogues—in men with stable angina low-dose testosterone (T, transdermal patch) increased androgen levels two-fold as time to exercise-induced ischaemia increased.[120] A placebo-controlled trial in men with angina and low plasma T found T undecanoate injection improved exercise time.[80] Larger and longer studies are needed to clarify testosterone treatment in INOCA.[100] Oestrogen analogues—post-menopausal oestrogen may be effective[121] and in a placebo-controlled trial, there was less-frequent angina with 1 mg norethindrone/10 μg ethinyl oestradiol, fewer hot flashes/night sweats and less avoidance of intimacy.[39] But no differences in ischaemia, brachial FMD, compliance, or adverse events between treatments were observed. However, recruitment was limited by safety concerns prompted with Women's Health Initiative (WHI) hormone trial early results. However, recent WHI data concluded conjugated equine oestrogens (CEO, 0.625 mg/day) plus medroxyprogesterone acetate (2.5 mg/day) for 5.6 years or CEO alone for 7.2 years was not associated with increased all-cause, CV, or cancer mortality during 18 years follow-up.[122] These safety data may make it possible to better clarify the role of oestrogen in post-menopausal-women with CMD.

Nervous system active agents are considered since INOCA patients may experience ischaemia with mental stress and transient coronary constriction, which is also reflected in the peripheral microvasculature.[123] Catecholamines, acetylcholine, histamine, serotonin, neuropeptide Y (NPY), and other molecules have been proposed. NPY is co-stored with norepinephrine in perivascular sympathetic nerves and released after sympathetic stimulation. This potent vasoconstrictor and inhibitor of cardiac vagal activity induces transient ischaemia by microvascular constriction, and increases during exercise in angina

patients.[124] A randomized study found NPY inhibition lowered systolic BP during and after exercise,[125] however, did not affect exercise-induced ischaemia in CAD patients. NPY also stimulates endothelial differentiation of mesenchymal stem cells and may contribute to myocardial repair by increasing differentiated cardiomyocytes in ischaemia-damaged myocardium.[126] This provides a novel possibility for cell-based cardiac repair and remodelling with CMD and after myocardial injury. Further studies are needed to elucidate dose–responses and effects of NPY inhibitors in coronary microvasculature. Selective serotonin reuptake inhibitors—escitalopram reduced platelet serotonin receptor transporters and altered transporter binding affinity density of 5-hydroxytriptan uptake sites and LV diastolic dysfunction and measures of psychological functioning improved without effecting exercise-induced ischaemia.[127]

Gene and cell-based therapies—including cellular injections with bone-marrow-derived CD34+ cells have shown promise, in refractory angina, some of which is likely related to CMD. Increasing evidence indicates that paracrine factors, or growth and differentiation factors, from

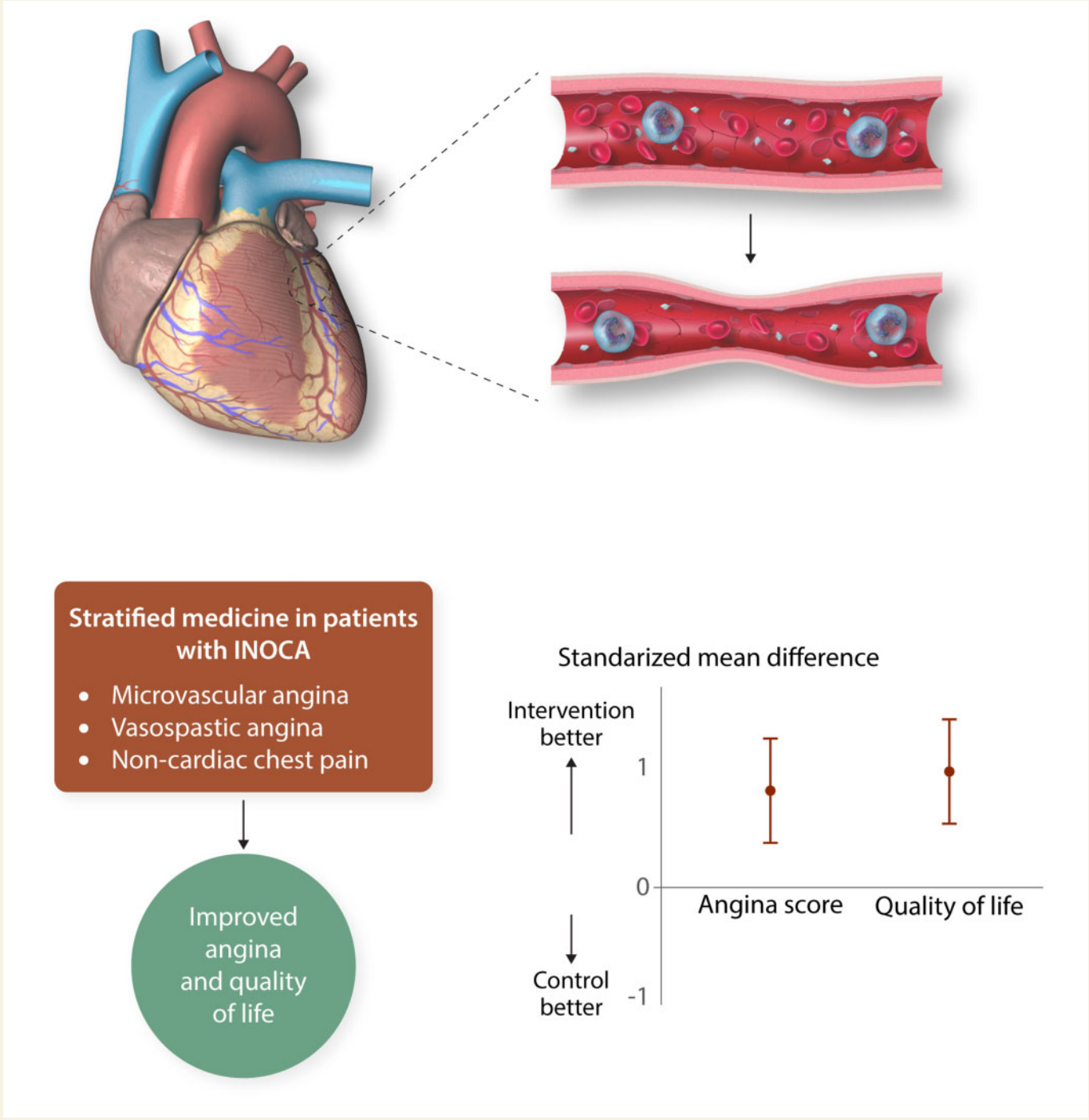


Figure 2 CorMicA. Stratified medical therpay guided by an interventional diagnostic procedure (IDP) improves health status of patients with symptoms and/or sings of angina but no ischaemia and non-obstructive coronary artery disease (INOCA). Permission granted to reproduce figure from Ford *et al.*[130]

transplanted cells and/or reactive immune cells modify healing processes including neovascularization, inflammation, fibrosis, contractility, bioenergetics, and endogenous repair.[128] This knowledge, should foster development of novel small-molecule pharmacological strategies derived from these paracrine factors to stimulate endogenous mechanisms and provide alternatives to current therapies for CMD.

Small molecules directly target agents that decrease BP and heart rate, oxidative metabolism, antioxidant, and antiapoptotic activities. These small molecules need to be tested in INOCA experimental models. One such small molecule, fluorine substituent (TT-10), a fluorine-containing biologically active compound, promotes cardiomyocyte proliferation with antiapoptotic and antioxidant effects *in vitro* and *in vivo*. In mice with experimental myocardial ischaemia and infarction, TT-10 improved cardiac function attenuating infarct size and fibrosis.[129] If these small molecules modified experimental IHD in animal models and showed acceptable safety and effectiveness in acute and chronic CMD, clinical trials could advance this field.

3. Diagnostic Testing Management

Much is known about the diagnostic value of invasive tests of coronary vascular function, but these tests are rarely used in clinical practice. Due to lack of evidence for patient benefit, therapy should be altered based on coronary function testing. The CorMicA trial[130] (*Figure 2*) addressed this evidence-gap hypothesizing that stratified medicine, combining an interventional diagnostic procedure (IDP) with guideline-linked medical therapy, would be feasible and lead to improvements in angina and QoL in INOCA patients. Accordingly, patients with INOCA (~3/4 women, age 61) had an IDP, which measured CFR, index of microcirculatory resistance, and fractional flow reserve (intravenous adenosine and intracoronary acetylcholine according to guidelines[131]) as an adjunctive procedure following angiogram acquisition. Patients were then randomized to either 'IDP-with results disclosed and ESC guideline-based management' or 'sham-with results not disclosed and standard of care'. Among those randomized to IDP recommendations included, for 'CMD'—a beta-blocker (nebivolol), life-style changes, consider ACE-I and statin; for 'coronary vasospasm'—calcium antagonist with or without long-acting nitrate, life-style changes; and for 'non-cardiac chest pain'—stop antianginal drugs, discharge from cardiology, consider non-cardiac investigation. At 6 months, the IDP patients had less angina ($P = 0.001$), less often and less severe, with improved QoL ($P < 0.001$) and none required treatment change. No serious adverse events occurred during testing and there were no differences in major adverse cardiac events at 6 months.

This 'first trial' to investigate a coronary function testing strategy for INOCA, found the majority of INOCA patients have an underlying diagnosis amenable to diagnosis in the catheter laboratory and angina improved when therapy was tailored for a specific coronary disorder. Future trials are anticipated to determine the wider external validity of this approach.

4. Current clinical guidelines

The European Society of Cardiology specifies treatment of MVA and coronary vasospasm (*Table 2*),[132] while the Japanese Circulation Society outlines treatment of VSA.[133] Both guidelines confirm relatively low levels of evidence for treatment and no large randomized outcome trials. Recent USA stable IHD guidelines do not directly address angina treatment,[134] while prior guidelines do not specifically address CMD or VSA (*Figure 3*),[135] thus are potentially relevant/useful as evidenced in the CorMicA trial.[130]

Table 2 Adapted European Society of Cardiology microvascular angina guidelines

Recommendations	Class[a]	Level[b]
Guidewire-based CFR and/or microcirculatory resistance measurements should be considered in patients with persistent symptoms, but coronary arteries that are either angiographically normal or have moderate stenoses with preserved iwFR/FFR	IIa	B
Intracoronary acetylcholine with ECG monitoring may be considered during angiography, if coronary arteries are either angiographically normal or have moderate stenoses with preserved iwFR/FFR, to assess microvascular spasm	IIb	B
Transthoracic Doppler of the LAD, CMR, and PET may be considered for non-invasive assessment of CFR	IIb	B

Adapted from Bairey Merz *et al.*[32]
CFR, coronary flow reserve; CMR, cardiac magnetic resonance; ECG, electrocardiogram; FFR, fractional flow reserve; iwFR, instantaneous wave-free ratio; LAD, left anterior descending; PET, positron emission tomography.
[a]Class of recommendation.
[b]Level of evidence.

5. Knowledge gaps and evidence needed for guidelines

Several knowledge gaps should be addressed to further our understanding of CMD and develop treatment strategies (*Figure 4*). Population natural history for identification of higher risk phenotypes can provide evidence for at-risk populations to enrol in trials, as well to develop treatment targets. Evidence regarding which antianginal treatments are most effective for angina in INOCA with CMD is needed. Investigation regarding relations between reduction in angina and reductions in adverse cardiovascular events and recurrent hospitalization should be sought.

Multiple, relatively small, intermediate outcome trials in subjects using conventional secondary prevention and novel treatments offer promising targets for major outcome trials. There is need for larger randomized outcome trials given the CMD prevalence and lack of evidenced-based guidelines. A large randomized multicentre, prospective, randomized, blinded outcome study evaluating intensive medical therapy (high-intensity statin, ACE-Is or ARBs, and aspirin) vs. usual care in 4422 symptomatic women with INOCA is underway [Women's Ischaemia Treatment Reduces Events In Non-Obstructive CAD (WARRIOR)-NCT03417388] (*Figure 5*).

6. Summary and conclusions

Currently, treatment for patients with INOCA centres on symptom and primary risk factor therapy and the prevailing practice is largely

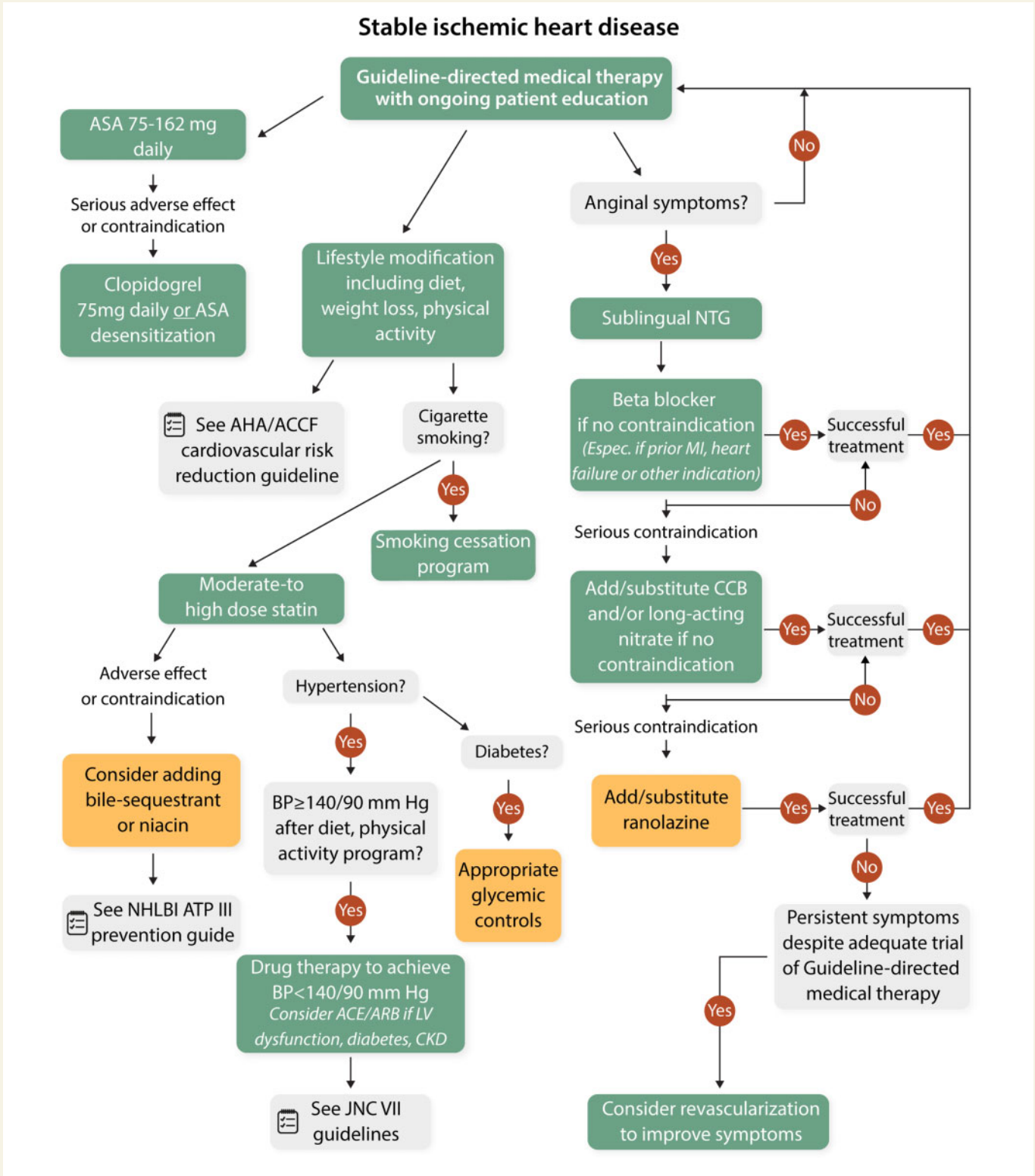


Figure 3 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS stable ischaemic heart disease guidelines. Colours respond to the class of recommendations in the ACCF/AHA. The algorithms do not represent a comprehensive list of recommendations. The use of bile acid sequestrant is relatively contraindicated when triglycerides are ≥200 mg/dL and is contraindicated when triglycerides are ≥500 mg/dL. Dietary supplement niacin must not be used as a substitute for prescription niacin. ACCF, American College of Cardiology Foundation; ACE-I, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin-receptor blocker; ASA, aspirin; ATP III, Adult Treatment Panel 3; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; HDL-C, high density lipoprotein cholesterol; JNC VII, Seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure; LDL-C, low density lipoprotein cholesterol; LV, left ventricular; MI, myocardial infarction; NHLBI, National Heart, Lung and Blood Institute; NTG, nitroglycerine.

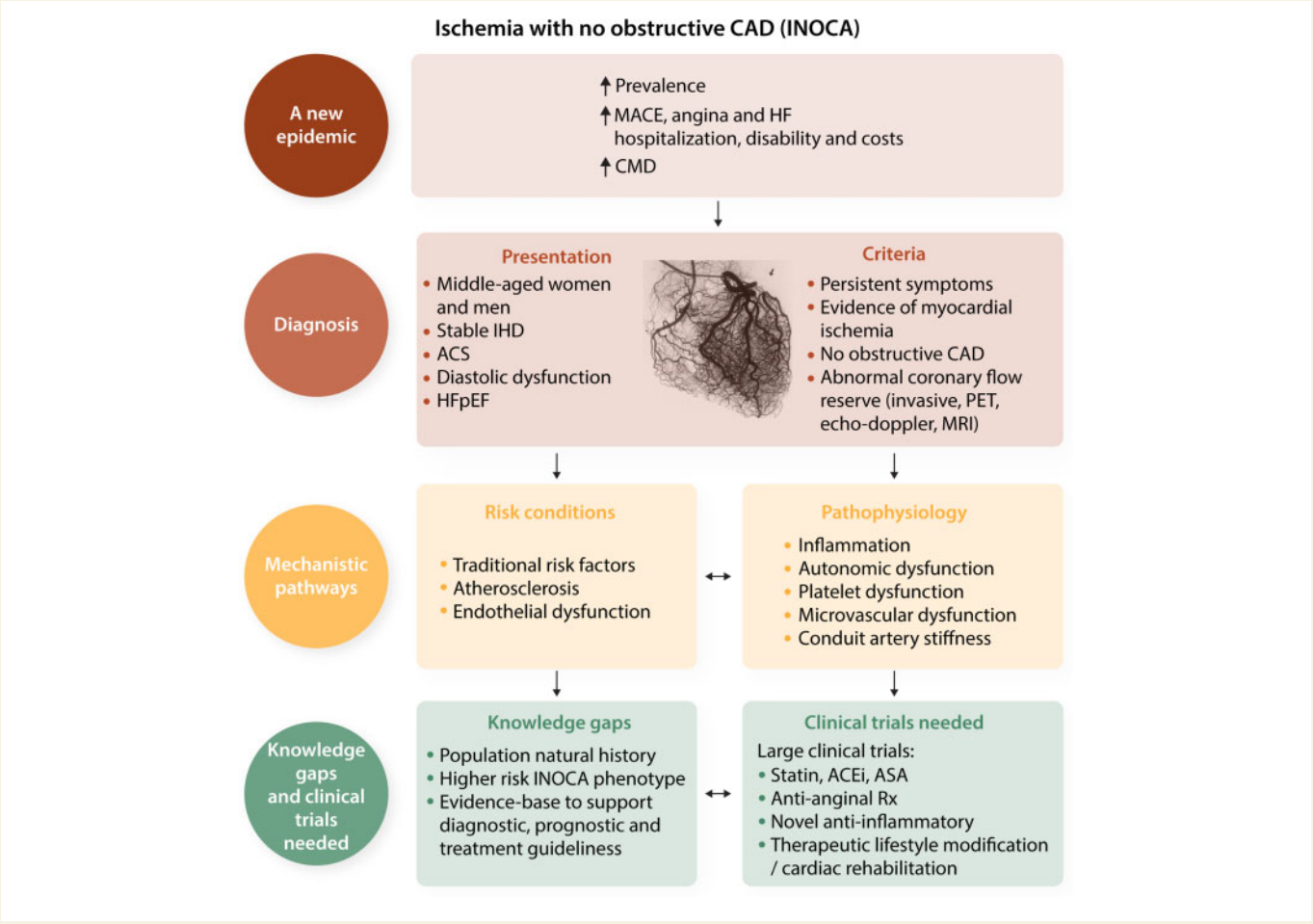


Figure 4 CMD and INOCA knowledge gaps.

reassurance, often with repeated testing. This increasingly appears unacceptable because of the documented presence of CMD in most patients, the ischaemia-related symptoms that frequently limit functional status, the relatively high major adverse cardiovascular event rates, and healthcare resource consumption. Prior, small sample size, short-term pharmacologic probe studies in similar subjects suggest symptom/functional improvement. Specifically, potent statins in combination with ACE-Is or if intolerant ARBs, at maximally tolerated doses appear effective for improved angina, stress testing, myocardial perfusion, coronary endothelial function, and microvascular function. Several novel therapies also appear promising and serve the basis for future trial planning. Recent data support benefit of invasive diagnostic testing and specific therapy to improve symptoms and QoL. The ongoing WARRIOR trial (*Figure 5*) is testing intense medical therapy of high-intensity statin, maximally tolerated ACE-I, and aspirin on longer-term outcomes to gather evidence for CMD management guidelines.

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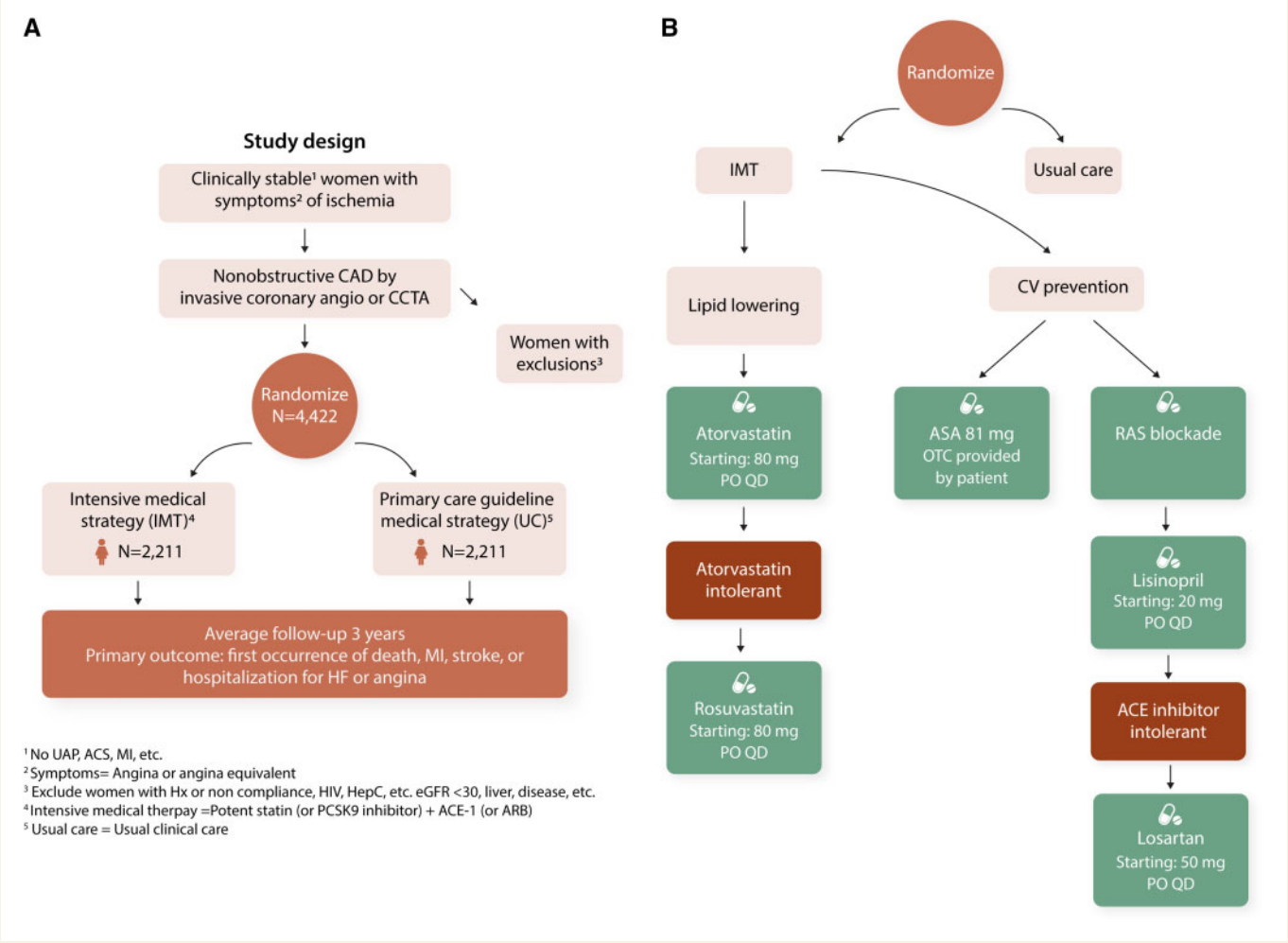

Figure 5 WARRIOR trial.

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