INOCA
WHY NAMES MATTER FOR WOMEN?

Cardio_Cast

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OVERVIEW OF THIS PODCAST

- **DEFINITION AND EPIDEMIOLOGY**
- **PATHOGENESIS OF INOCA**
- **DIAGNOSTIC CRITERIA FOR INOCA**
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DEFINITION AND EPIDEMIOLOGY OF INOCA AND MINOCA

- Cardiac ischaemia caused by vascular dysfunction in the setting of non-obstructive coronary atherosclerosis has been defined INOCA. In this condition, the mismatch between blood supply and myocardial oxygen demands may be caused by structural or vasomotor disorders at a microcirculatory level and/or epicardial coronary artery spasm. At least 10% to 30% of patients presenting with signs or symptoms of angina have no significant coronary artery disease (CAD) on invasive coronary angiography.
- Potential explanations for the apparent increasing prevalence of stable INOCA include more sensitive diagnostics, including advanced cardiac imaging and high-sensitive troponins.
- The association between traditional cardiovascular risk factors and INOCA is not well established. Diabetes is not frequently found in this category of patients, while hypertension and dyslipidaemia are relatively more prevalent. Smoking habits has been associated with coronary microvascular dysfunction (CMD).

DEFINITION AND EPIDEMIOLOGY OF INOCA AND MINOCA

- In all studies, there is a strong female preponderance for the condition. Compared with men, women have a higher incidence of signs and symptoms of myocardial ischemia, yet 30% to 50% of women who undergo coronary angiography do not have obstructive CAD.
- Myocardial infarction in the absence of obstructive coronary artery disease (MINOCA) is diagnosed in patients with features of acute myocardial infarction (AMI) with non-obstructive coronary arteries on angiography. The diagnosis can be made in case of no coronary artery stenosis ≥ 50% in any potential infarct-related artery, in the absence of a specific alternate diagnosis for the clinical presentation.
- The prevalence of MINOCA in large AMI registries ranges from 5% and 25%, depending on the population examined

Reis SE, Holubkov R, Conrad Smith AJ, Kelsey SF, Sharaf BL, Reichek N, Rogers WJ, Merz CN, Sopko G, Pepine CJ; WISE Investigators. Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: results from the NHLBI WISE study. Am Heart J. 2001 May;141(5):735-41. doi: 10.1067/mhj.2001.114198. PMID: 11320360.

DEFINITION AND EPIDEMIOLOGY OF INOCA AND MINOCA

- MINOCA patient characteristics differ from those of other AMI and Chronic Coronary Syndrome (CCS). MINOCA subjects are younger, are more often female, and tend to have fewer traditional cardiovascular risk factors. In the Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study, women were disproportionately represented and had 5-fold higher odds of presenting with MINOCA than men.
- The prevalence of traditional CAD risk factors and clinical features also varies among patients with MINOCA versus AMI with obstructive CAD coronary artery disease. All traditional cardiovascular risk factors are less frequent in MINOCA than in their counterparts with CAD; however consistent data have been observed only for dyslipidaemia.

https://doi.org/10.1161/circulationaha.117.031650

PATHOGENESIS OF INOCA

- **CORONARY MICROVASCULAR DYSFUNCTION – MICROVASCULAR ANGINA**
- **EPICARDIAL CORONARY ARTERY SPASM – VASOSPASTIC ANGINA**

> FOCUS BOX 1
>
> - In the setting of INOCA two distinctive mechanisms play a central role (alone or in combination with CAD), defining different endotypes: CMD and epicardial vasospasm.
> - In INOCA the main mechanisms of CMD are structural microcirculatory remodelling or vasomotor disorders caused by arteriolar dysregulation, the latter much related to endothelial dysfunction. The clinical manifestation of CMD in INOCA is MVA.
> - Epicardial vasospasm originates from enhanced vessel reactivity to vasoconstrictor stimuli. The clinical manifestation of CMD is VSA.

Figure 1 Mechanisms of myocardial ischaemia.

doi:10.1093/eurheartj/ehaa503

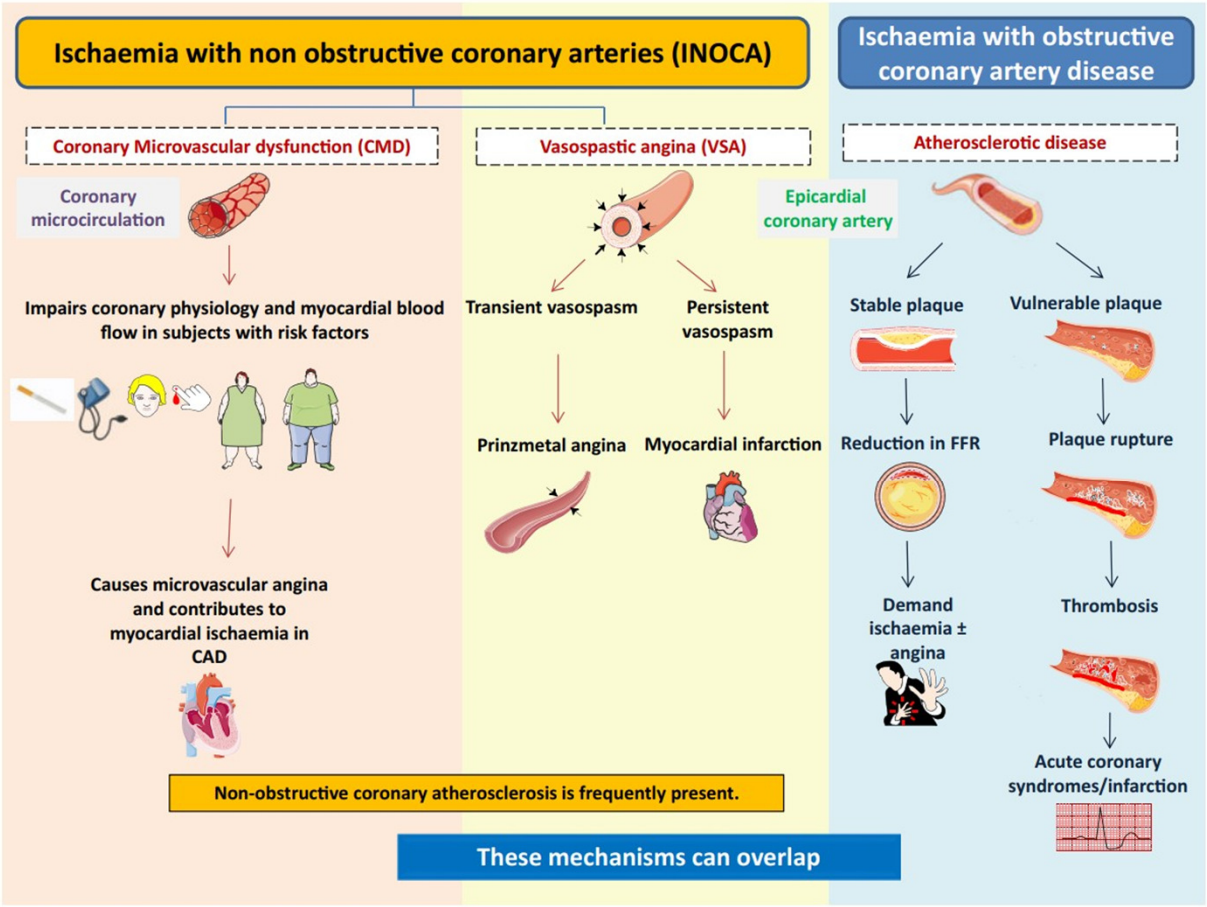

Figure 2 Mechanisms of myocardial ischaemia in INOCA and obstructive coronary artery disease. CAD, coronary artery disease; FFR, fractional flow reserve.

doi:10.1093/eurheartj/ehaa503

Table 1 **Diagnostic criteria for microvascular angina**

Criteria	Evidence	Diagnostic parameters
1	Symptoms of myocardial ischaemia[a]	Effort or rest angina
		Exertional dyspnoea
2	Absence of obstructive CAD (<50% diameter reduction or FFR >0.80)	Coronary CTA
		Invasive coronary angiography
3	Objective evidence of myocardial ischaemia[b]	Presence of reversible defect, abnormality or flow reserve on a functional imaging test
4	Evidence of impaired coronary microvascular function	Impaired coronary flow reserve (cut-off <2.0), invasive or noninvasively determined
		Coronary microvascular spasm, defined as reproduction of symptoms, ischaemic ECG shifts but no epicardial spasm during acetylcholine testing
		Abnormal coronary microvascular resistance indices (e.g. IMR ≥25)

Definitive microvascular angina is only diagnosed if criterias 1, 2, 3 and 4 are present.
CAD, coronary artery disease; CCTA, coronary computed tomographic angiography; ECG, electrocardiogram; FFR, fractional flow reserve; IMR, index of microcirculatory resistance.
[a]Many patients with heart failure with preserved ejection fraction would fulfil these criteria: dyspnoea, no obstructive CAD and impaired CFR. For this reason, consider measuring LV end-diastolic pressure (normal ≤10 mmHg) and NT-proBNP normal <125 pg/mL.[16]
[b]Signs of ischaemia may be present but are not necessary. However, evidence of impaired coronary microvascular function should be present.

doi:10.1093/eurheartj/ehaa503

TABLE 1

Clinical criteria for microvascular angina (MVA)*

MICROVASCULAR ANGINA CLINICAL CRITERIA
(1) Symptoms of myocardial ischemia: (a) Effort and/or rest angina (b) Angina equivalents (i.e. shortness of breath) *(2) Absence of obstructive CAD (<50% diameter stenosis or FFR >0.80) by:* (a) Coronary CTA (b) Invasive coronary angiography *(3) Objective evidence of myocardial ischemia:* (a) Ischemic ECG changes during an episode of chest pain (b) Stress-induced chest pain and/or ischemic ECG changes in the presence or absence of transient/reversible abnormal myocardial perfusion and/or wall motion abnormality *(4) Evidence of impaired coronary microvascular function:* (a) Impaired coronary flow reserve (cut-off values depend on methodology use between ⩽2.0 and ⩽2.5) (b) Coronary microvascular spasm, defined as reproduction of symptoms, ischemic ECG shifts but no epicardial spasm during acetylcholine testing (c) Abnormal coronary microvascular resistance indices (e.g. IMR >25) (d) Coronary slow-flow phenomenon, defined as TIMI frame count >25
Definitive microvascular angina: is only diagnosed if all four criteria are present. **Suspected microvascular angina:** is diagnosed if symptoms of ischemia are present (criteria 1) with no obstructive coronary artery disease (criteria 2) but only (a) objective evidence of myocardial ischemia (criteria 3), or (b) evidence of impaired coronary microvascular function (criteria 4) alone. *Clinical criteria from the Coronary Artery Vasospastic Disorders Summit (COVADIS)

EPICARDIAL CORONARY ARTERY SPASM – VASOSPASTIC ANGINA

- Epicardial vessel spasm typically has an origin in a hyper-reactive epicardial coronary segment that undergoes maximal contraction
- hen exposed to a vasoconstrictor stimulus.55 Among such triggering stimuli are smoking, drugs, peaks in blood pressure (BP), cold exposure, emotional stress, and hyperventilation. Severe coronary vasospasm may also occur in the context of allergic reactions (Kounis syndrome). Coronary segments adjacent to implanted drug-eluting stents may also become prone to undergo coronary spasm.
- The substrate of coronary spasm can be found in abnormal function of both vascular smooth muscle and endothelial cells. A primary and non-specific hyper-reactivity of coronary vascular smooth muscle cells has been consistently demonstrated in patients with variant angina and appears to be a key component of epicardial vessel spasm. Available evidence suggests that endothelial dysfunction facilitates the induction of spasm in predisposed coronary segments

Lanza GA, Careri G, Crea F. Mechanisms of coronary artery spasm. Circulation 2011;124:1774–1782.

TABLE 2

Diagnostic criteria for vasospastic angina (VSA)*

VASOSPASTIC ANGINA DIAGNOSTIC CRITERIA
(1) Nitrate-responsive angina – during spontaneous episode, with at least one of the following: (a) Rest angina – especially between night and early morning (b) Marked diurnal variation in exercise tolerance – reduced in morning (c) Hyperventilation can precipitate an episode (d) Calcium channel blockers (but not beta-blockers) suppress episodes *(2) Transient ischemic ECG changes – during spontaneous episode, including any of the following in at least two continuous leads:* (a) ST segment elevation ≥0.1 mV (b) ST segment depression ≥0.1 mV (c) New negative T waves. (3) Coronary artery spasm – defined as transient total or subtotal coronary artery occlusion (≥90% constriction) with angina and ischemic ECG changes either spontaneously or in response to a provocative stimulus (typically acetylcholine, ergot, or hyperventilation)
Definitive vasospastic angina: nitrate-responsive angina during spontaneous episodes and either transient ischemic ECG changes or coronary artery spasm criteria are fulfilled. **Suspected vasospastic angina:** nitrate-responsive angina during spontaneous episodes but transient ischemic ECG changes are equivocal or unavailable and or coronary artery spasm criteria are equivocal.
*Diagnostic criteria from the Coronary Artery Vasospastic Disorders Summit (COVADIS)

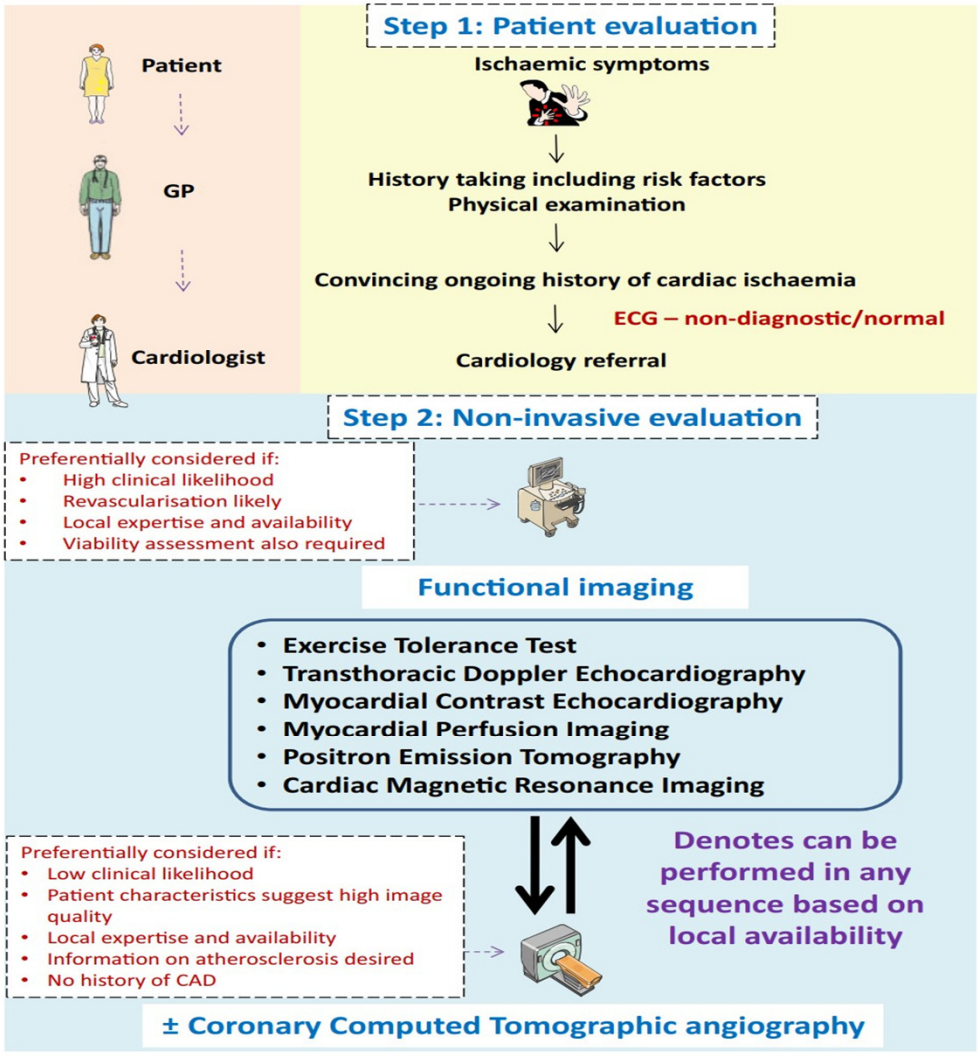

Figure 3 Non-invasive evaluation of INOCA. GP, general practitioner.

doi:10.1093/eurheartj/ehaa503

Table 2 **INOCA endotypes diagnostic criteria**

	INOCA endotypes	Pathophysiology	Diagnostic criteria
1	Microvascular angina[a]	CMD	Diagnostic guidewire and Adenosine test • FFR > 0.8 • CFR < 2.0 • IMR ≥ 25[b] • HMR ≥ 1.9[b] Vasoreactivity (acetylcholine test) • No or <90% diameter reduction • + angina • + ischaemic ECG changes
2	Vasospastic angina	Epicardial spasm	Diagnostic guidewire and Adenosine test • FFR > 0.8 • CFR ≥ 2.0 • IMR < 25 • HMR < 1.9 Vasoreactivity (acetylcholine test) • ≥ 90% diameter reduction • + angina • + ischaemic ECG changes
3	Both microvascular and vasospastic angina	Both CMD and epicardial spasm	Diagnostic guidewire and Adenosine test • FFR > 0.8 • CFR < 2.0 • IMR ≥ 25 • HMR ≥ 1.9 Vasoreactivity (acetylcholine test) • No or <90% or ≥90% diameter reduction • + angina • + ischaemic ECG changes

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Table 2 **INOCA endotypes diagnostic criteria**

4	Non-cardiac chest pain	None	Diagnostic guidewire and Adenosine test • FFR > 0.8 • CFR ≥ 2.0 • IMR < 25 • HMR < 1.9 Vasoreactivity (acetylcholine test) • No or <90% diameter reduction • No angina • No ischaemic ECG changes
5	Non-flow-limiting CAD[c]	Diffuse coronary artery atherosclerosis	Diagnostic guidewire and adenosine test • FFR > 0.8 • CFR ≥ 2.0 • IMR < 25 • HMR < 1.9 Vasoreactivity (acetylcholine test) • No or <90% diameter reduction • No angina • No ischaemic ECG changes

CAD, coronary artery disease; CFR, coronary flow reserve; FFR, fractional flow reserve; HMR, hyperaemic myocardial velocity resistance; IMR, index of microvascular resistance.

[a]Non endothelial dependent microvascular angina may be diagnosed non-invasively by the methods described.

[b]IMR and HMR values shown in table as alternative *measures* of microcirculatory resistance (based on thermodilution or Doppler, respectively).

[c]<50% stenosis severity by visual assessment.

doi:10.1093/eurheartj/ehaa503

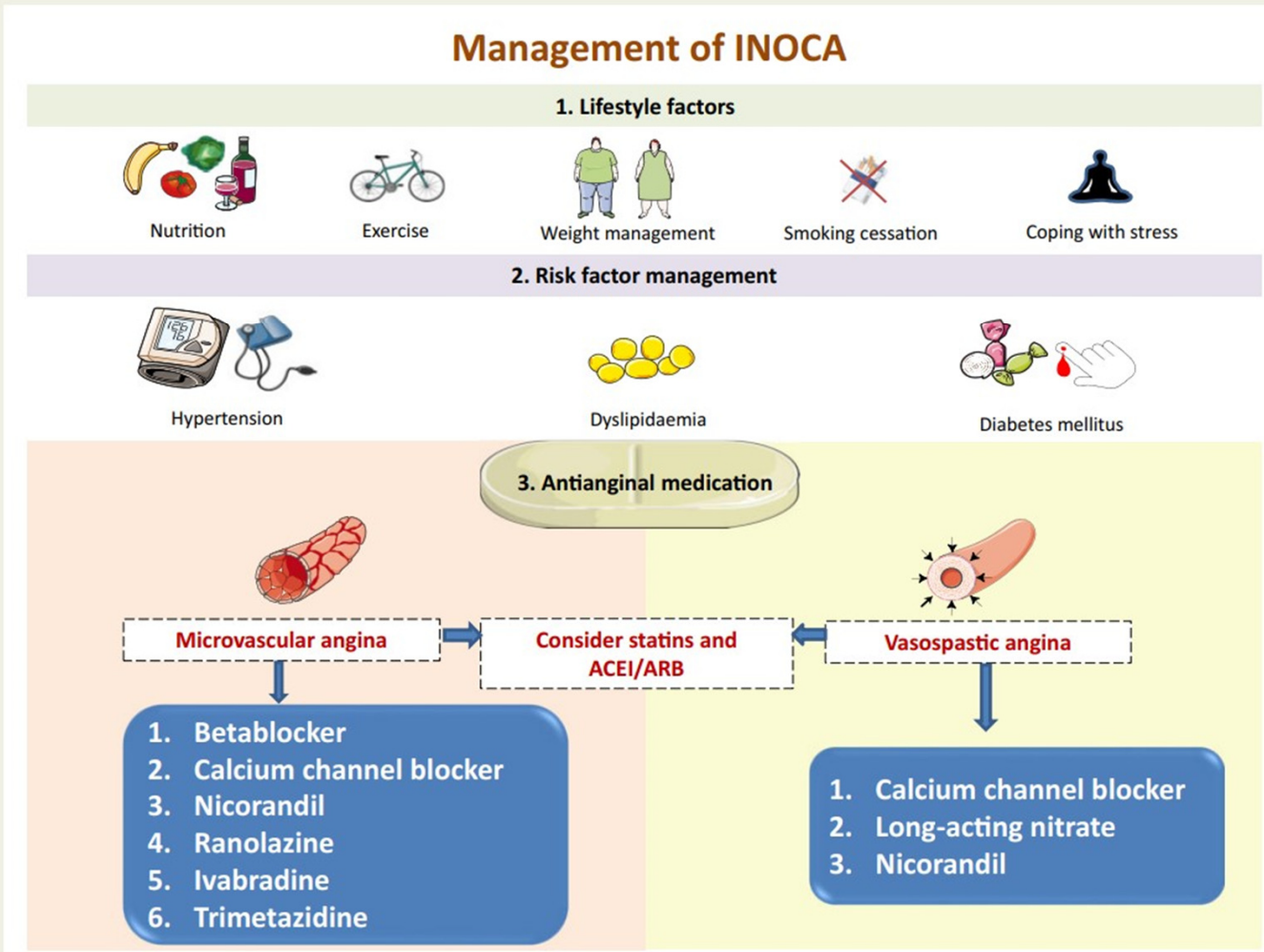


Figure 5 Management of INOCA. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

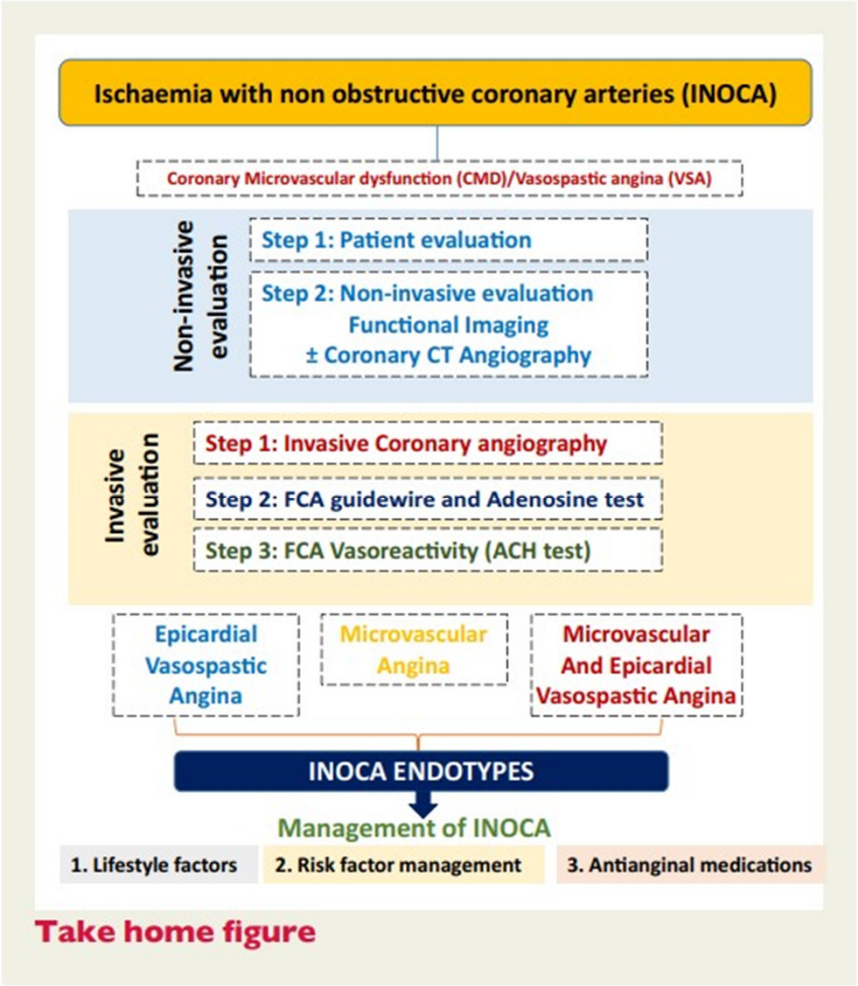
doi:10.1093/eurheartj/ehaa503

Table 3 Medical therapy in the management of INOCA

Diagnosis	Treatment	Mechanisms of effect
MVA	Beta-blockers (Nebivolol 2.5–10 mg daily)	• ↓ Myocardial oxygen consumption • Antioxidant properties
	Calcium channel blockers (Amlodipine 10 mg daily)	• Vascular smooth muscle relaxation • ↓ Myocardial oxygen consumption
	Ranolazine (375–750 mg twice daily or 500 mg–1 g twice daily in the USA)	• Improves microvascular perfusion reserve index in patients with MVA and reduced CFR
	Trimetazidine (35 mg twice daily)	• Increases cell tolerance to ischaemia by maintaining cellular homeostasis
	ACE inhibitors (Ramipril 2.5 - 10mg), ARBs	• Improve CFR • ↓ Workload • May improve small vessel remodelling
VSA	Calcium channel blockers (Amlodipine 10 mg or Verapamil 240 mg SR or Diltiazem 90 mg twice daily or 120–360 mg single or divided doses)	• ↓ Spontaneous and inducible coronary spasm via vascular smooth muscle relaxation • ↓ Oxygen demand
	Nitrates (Isosorbide mononitrate XL 30 mg)	• ↓ Spontaneous and inducible coronary spasm via large epicardial vasodilation • ↓ Oxygen demand
	Nicorandil (10-20 mg twice daily)	• Potassium channel activator with coronary microvascular dilatory effect
Both MVA + VSA	Calcium channel blockers (Amlodipine 10 mg or Verapamil 240 mg SR or Diltiazem 90 mg twice daily or 120–360 mg single or divided doses)	• Vascular smooth muscle relaxation • ↓ Myocardial oxygen consumption
	Nicorandil (10-20 mg twice daily)	• Potassium channel activator with coronary microvascular dilatory effect
	Trimetazidine (35 mg twice daily)	• Increases cell tolerance to ischaemia by maintaining cellular homeostasis
	ACE inhibitors (Ramipril 2.5 -10mg), ARBs	• Improve CFR • ↓ Workload • May improve small vessel remodelling
	Statins (Rosuvastatin 10–20 mg)	• Improve coronary endothelial function • Pleiotropic effects including reduced vascular inflammation

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CFR, coronary flow reserve; MVA, microvascular angina; VSA, vasospastic angina.

doi:10.1093/eurheartj/ehaa503



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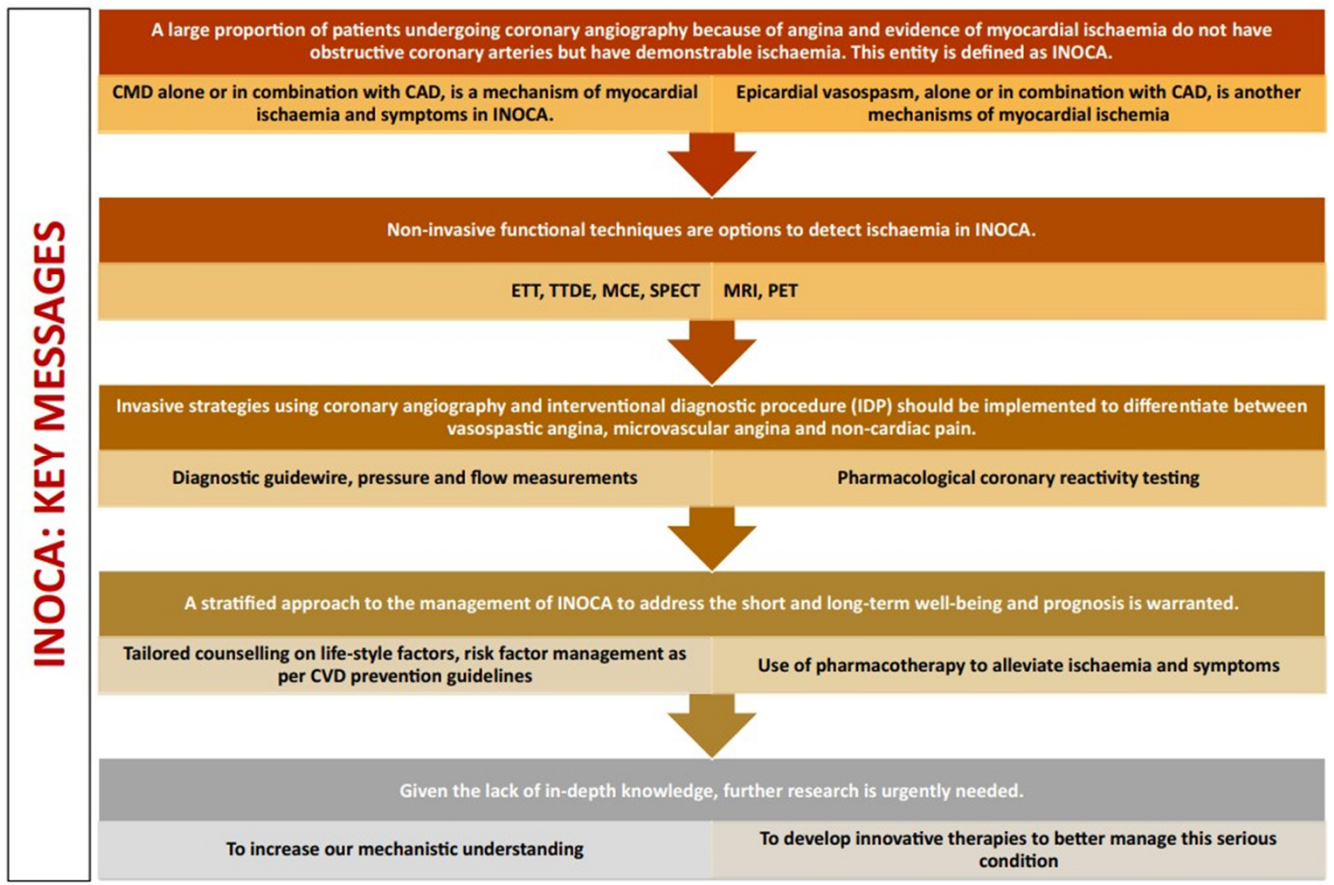

Figure 6 Key messages.

doi:10.1093/eurheartj/ehaa503

PROGNOSIS OF INOCA

- Current evidence indicates that INOCA is not a benign condition, as these patients have impaired quality of life, higher risk of disability and higher incidence of MACE including death, non-fatal myocardial infarction, heart failure, re-hospitalization and repeated coronary angiography for recurrent angina.
- The incidence of all-cause death and non-fatal myocardial infarction has been shown higher in patients with non-obstructive CAD as compared to those with angiographically normal coronary arteries. When ischemia is documented through the demonstration of CMD or endothelial dysfunction, the prognosis is further impaired. Epicardial vasospasm is associated with major adverse events including sudden cardiac death, acute myocardial infarction and syncope which may unfortunately occur before the diagnosis is established.
- Almost two thirds of women undergoing clinically indicated coronary angiography for suspected ischemic heart disease in the original cohort of the WISE study were diagnosed with INOCA.

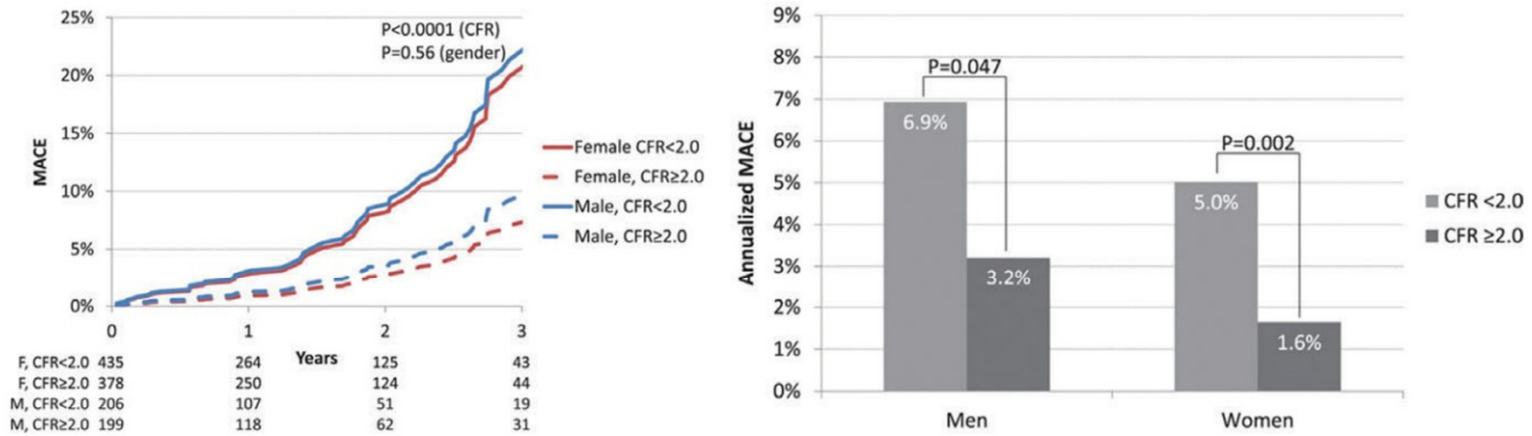

FIGURE 1 Annualized major adverse cardiac event (MACE) rates by sex and coronary flow reserve (CFR).[90] Abbreviations: CAD, coronary artery disease; CMD_{PET}, coronary microvascular dysfunction positron emission tomography; ds, days; HF, heart failure; MI, myocardial infarction (Reprinted with permission.)

DOI: 10.1002/clc.22894

TABLE 1 Natural history studies of patients with coronary microvascular dysfunction[13] (Reprinted with permission.)

Author, Year	No.	Population	Method	Outcome Measure	Follow-up	CMD Outcome Predictor	
						Univariate	Multivariate
Britten, 2004[81]	120	Post-PCI/mild CAD	Intracoronary papaverine or adenosine CFR Doppler flow wire	Cardiac death, ACS, revascularization, stroke	6.5 ± 3 years (14–125 months)	Yes	Yes
Schindler, 2006[82]	72	CAD risk factors without flow-limiting stenosis	CPT-MBF increase with ^{13}N-NH_3 PET	CV death, ACS, MI, PCI/CABG, stroke, PTA	66 ± 8 months	Yes	No
Rigo, 2007[83]	86	CAD, LAD 51%–75% stenosis	Vasodilator LAD CFR, Doppler/TTE	Nonfatal MI	30 months, 14 median	Yes	Yes
Nemes, 2008[84]	397	Hospitalized, angina, mostly severe CAD, TEE for AA	Vasodilator LAD CFR, Doppler/TEE	CV death, HF, thrombosis	41 ± 12 months	Yes	Yes
Herzog, 2009[85]	229	Suspect CAD/66% had severe CAD	Vasodilator CFR with ^{13}N-NH_3 PET	CV death, nonfatal MI, hospitalization, PCI/CABG	5.5 ± 2.1 years	Yes	Yes
Tio, 2009[86]	344	Severe CAD, not revascularized, LV systolic dysfunction	Vasodilator CFR with ^{13}N-NH_3 PET	Cardiac death	85 months (1–138 months)	Yes	Yes
Cortigiani, 2010[87]	1660	Chest pain, normal DSE	Vasodilator LAD CFR, Doppler/TTE	Death, MI, revascularization	19 months median	Yes	Yes
Pepine (WISE), 2010[88]	189	Women, angina/ischemia, most with obstructive CAD	Intracoronary Ado-CFR, Doppler flow wire	Death, nonfatal MI, nonfatal stroke, HF hospitalization	5.4 years (mean)	Yes	Yes
Ziadi, 2011[34]	677	Most had severe CAD	Vasodilator CFR with ^{82}Rb PET	CV death, nonfatal MI	387 days (375–416 days)	Yes	Yes
Balazs (SZEGED study), 2011[89]	45	Women, angina/ischemia, no obstructive CAD	Vasodilator CFR, Doppler/TEE, TTE	Death, CV hospitalization	102 ± 26 months, 113 median	Yes	Yes
Murthy, 2014[90]	1218; 813 women, 405 men	No obstructive CAD (excluded by CTA or PET)	Stress Perfusion, imaging (PET)	CV death, MI, late revascularization (>90 days) or HF hospitalization	3 years	Yes	Yes

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CPT, cold pressor test; CTA, computed tomography angiography; CV, cardiovascular; DSE, dobutamine stress echo; HF, heart failure; LAD, left anterior descending; LV, left ventricular; MBF, myocardial blood flow; MI, myocardial infarction; PCI, percutaneous coronary intervention; PET, positron emission tomography; PTA, percutaneous transluminal angioplasty; SZEGED, SummariZation of long-tErm prognostic siGnificance of coronary flow rEserve in special Disorders; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; WISE, Women's Ischemia Syndrome Evaluation.

DOI: 10.1002/clc.22894