American Heart Journal Plus: Cardiology Research and Practice 37 (2024) 100352

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Review Article

Clinical aspects of ischemia with no obstructive coronary artery disease (INOCA)

Alexander Polyak, Janet Wei, Martha Gulati, Noel Bairey Merz *

Barbra Streisand Women's Heart Center, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

ARTICLE INFO

Keywords:
Ischemia with no obstructive coronary disease (INOCA)
Coronary microvascular dysfunction (CMD)

ABSTRACT

Ischemia with no obstructive coronary arteries (INOCA) is defined as patients with evidence of myocardial ischemia without obstructive coronary artery disease. About 3–4 million people in the United States have INOCA, more commonly affecting women, and carries adverse morbidity, mortality, and relatively high healthcare costs. The pathophysiology of INOCA appears to be multi-factorial with a variety of contributing mechanisms. Diagnosis of INOCA is suggested by non-invasive or invasive testing consistent with myocardial ischemia. Due to the high prevalence of coronary risk factors and atherosclerosis in the INOCA population, current treatment strategies target angina, coronary atherosclerosis, and atherosclerotic risk factors, as well as burgeoning treatment of coronary microvascular dysfunction (CMD). Ongoing clinical trials are assessing different options.

1. Introduction: Definitions and terminology

Patients presenting with signs (abnormal stress test or troponin) and/or symptoms (angina) of ischemic heart disease usually undergo diagnostic testing. However, more than half of patients who undergo angiography have no obstructive coronary artery disease (CAD), defined as coronary stenosis >50 % [1]. This growing population of patients with evidence of ischemia and no obstructive coronary arteries (INOCA) is more common among women, and are at increased risk of adverse cardiovascular events [2,3]. The Cardiovascular Disease in Women Committee of the American College of Cardiology (ACC) summarized INOCA [4] to include patients with three findings—stable, chronic symptoms (angina) to suggest ischemic heart disease; objective evidence of myocardial ischemia on electrocardiogram or cardiac imaging with rest or at stress; and no flow limiting obstruction on angiography to suggest obstructive CAD defined as epicardial obstruction >50 % or fractional flow reserve <0.8.

Patients with acute myocardial infarction (AMI) found to have no obstructive CAD (MINOCA) make up 14 % of all AMIs and are also more common in women [5]. While there is likely overlap between MINOCA and INOCA, MINOCA is a distinct AMI presentation. Patients who present with an AMI found to have MINOCA may or may not have INOCA as well. A subgroup of INOCA and MINOCA patients have coronary microvascular dysfunction (CMD). CMD is defined as structural and functional changes in the coronary microcirculation leading to impaired coronary flow reserve (CFR), coronary blood flow (CBF), and/or coronary spasm [6,7]. CMD can be a primary cause of INOCA, but can also be found in patients with obstructive CAD, heart failure, Takotsubo syndrome and other cardiomyopathies [6]. There can be overlap among INOCA, MINOCA, and CMD, but they can also occur independently (Fig. 1). Correctly defining each presentation is important to guide clinical diagnostic and therapeutic options, as well as advancing research. This review focuses on the clinical aspects of INOCA.

2. Prevalence and costs of INOCA

Cardiovascular disease is the number one cause of death in the United States with similar rates in both men and women, however women are more likely to have no obstructive CAD than men [2,8]. The Women's Ischemic Syndrome Evaluation (WISE) studies estimate there are 3–4 million people in the United States with INOCA [3]. INOCA is diagnosed more frequently in women (50–70 %) than in men (30–50 %) among those undergoing angiography for stable angina [9]. The prevalence of CMD in the setting of suspected INOCA is 25–65 %, with different studies using different methods and cut-offs to diagnose CMD [9–11].

The INOCA population has relatively high morbidity and disability leading to repeat hospitalizations and invasive testing [12]. Women are four times more likely than men to be readmitted for angina or AMI within 180 days after angiography [13]. Patients with INOCA have

* Corresponding author at: Barbra Streisand Women's Heart Center, Cedars-Sinai Medical Center, 127 S. San Vicente Blvd, Los Angeles, CA 90048, USA.
E-mail address: merz@cshs.org (N.B. Merz).

https://doi.org/10.1016/j.ahjo.2023.100352
Received 30 November 2023; Accepted 3 December 2023
Available online 6 December 2023

frequent angina symptoms leading to decreased physical function and quality of life (QOL); a survey of the INOCA International patient support group showed that chronic symptoms led to decreased physical, mental, and social QOL [14]. The same study found that 75 % of patients had to decrease how much they worked, 50 % had to retire early, and 38 % applied for disability [14]. INOCA patients have more chronic angina symptoms and cardiac anxiety than the post-AMI and post-cardiac arrest populations [11].

INOCA leads to relatively high healthcare costs and economic burden both directly and indirectly with decreased work output and disability. The WISE study found that women with non-obstructive CAD had expected lifetime cardiovascular healthcare costs of over $750,000, comparable to $1 million for women with multi-vessel CAD [15]. An economic analysis, using QOL and work limitations questionnaires, estimated that INOCA patients have an annual healthcare cost of $21 billion in the United States, compared to $55 billion in patients with obstructive CAD [11].

3. Predictors and outcomes of INOCA

The pathophysiology of INOCA is likely multifactorial with a variety of contributing mechanisms, including atherosclerosis [16]. Atherosclerosis risk factors include age, hypertension, hyperlipidemia, active smoking and diabetes mellitus [17]. A majority of patients with INOCA and chronic angina have been shown to have some coronary atherosclerosis visualized by intravascular ultrasound (IVUS) [18]. Patients with non-obstructive CAD have an increased mortality and AMI risk compared to patients with no CAD [19].

In patients with INOCA, factors associated with increased mortality risk include age, hypertension, diabetes mellitus, and smoking, while sex, hyperlipidemia, and family history of premature CAD have not been shown to increase mortality risk [19]. Angina symptoms persisting for one year from INOCA diagnosis predicted increased major adverse cardiovascular event (MACE) in the WISE population [20].

In patients with CMD, CFR has been shown to be a continuous predictor of MACE rather than a specific cut-off value [4]. A prior study used positron emission tomography (PET) to measure CFR and found almost double the rate of MACE in patients with CFR < 2.0 [21]. A randomized, placebo controlled trial studying ranolazine in patients with angina and CMD found that anginal symptoms were directly related to myocardial perfusion reserve index, with angina symptoms improving when microvascular perfusion improved [22].

4. Diagnosis of INOCA

The 2021 ACC clinical practice guidelines on chest pain proposed an algorithm for evaluation of suspected INOCA, consisting of either an invasive or non-invasive pathway [23]. Although neither pathway was favored over the other, the guidelines noted that non-invasive testing is more prevalent, but that invasive testing may be more comprehensive [23]. A new diagnostic algorithm specific to women with suspected INOCA was proposed that favored non-invasive diagnostics based on risk factors, and if angina persists despite treatment, to then pursue invasive diagnostics [24]. The different diagnostic options are summarized in Fig. 2.

4.1. Noninvasive testing

Coronary-computed tomographic angiography (CCTA) can show obstructive coronary lesions as well as non-obstructive plaque [24]. The PROMISE trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) showed no difference between functional stress testing and anatomic CCTA in terms of clinical events overall for a 25-month follow-up [25].

Standard stress echocardiography is a Grade 1 recommendation for evaluation of stable chest pain [23], but can often be normal in patients with INOCA [26]. Stress echocardiography with doppler can measure coronary flow velocity (CFV) which was shown to be decreased in 25 % of patients with INOCA [10].

Single-photon emission computed tomography (SPECT) stress myocardial perfusion imaging (MPI) can detect myocardial ischemia [27]. However, studies have reported lower accuracy of SPECT-MPI in

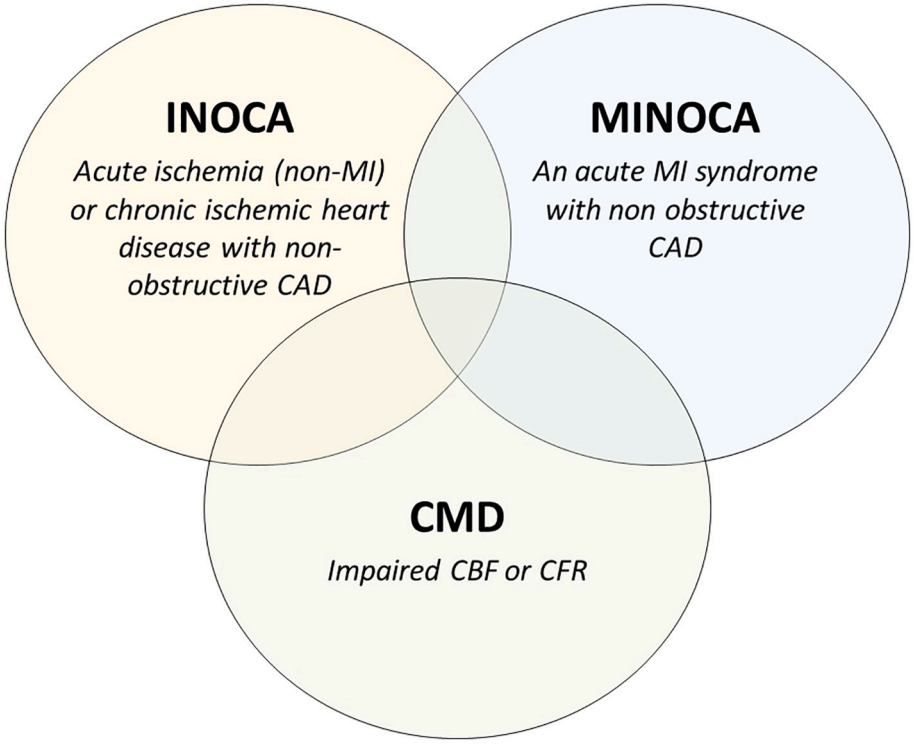

Fig. 1. Overlap exists among INOCA, MINOCA, and CMD, but they also occur independently.

Non-invasive studies	
Coronary CTA	Equivalent to stress testing (Grade 1 recommendation) for initial evaluation of stable chest pain.
Stress echo	Initial work-up of chest pain (1) or stress echo with CFV to evaluate for ischemia and CMD (2b).
SPECT perfusion scan	Lower accuracy in women, not a preferred diagnostic test in evaluation of INOCA, used as stress test in stable chest pain evaluation.
Stress PET	A preferred option (2a) for evaluation of suspected INOCA as can show ischemia and microvascular perfusion.
Stress Cardiac MRI	Complete myocardial evaluation (2a) for suspected INOCA.
Invasive studies	
Coronary Function Testing	Invasive testing in suspected INOCA that can diagnose specific circulatory issues including vasospasm and CMD. Invasive testing is equivalent (2a) to stress PET and stress cardiac MRI.

Fig. 2. Diagnostic options for INOCA, both non-invasive and invasive. Level of recommendation from the 2021 ACC guidelines on chest pain. [23]

women compared to men, likely due to smaller heart sizes and variable breast tissue attenuation [24]. SPECT-MPI has been shown to be normal in a majority of patients with CMD [28].

PET-MPI can give an accurate evaluation of coronary perfusion, left ventricular function, and CFR, with data showing improved accuracy compared to SPECT-MPI [29]. PET-MPI has less radiation compared to SPECT-MPI, and can measure myocardial blood flow and CFR to confirm diagnoses of INOCA and/or CMD [24].

Stress cardiac magnetic resonance imaging (CMRI) can demonstrate decreased perfusion in sub-endocardial myocardium in patients with INOCA, as well as identify myocardial structure, function, inflammation and ischemia [24]. Myocardial perfusion reserve index with CMRI is a semi-quantitative method to measure CFR, and at experienced centers has been shown to be able to detect CMD [30].

4.2. Invasive testing

Invasive coronary function testing (CFT) can diagnose both microvascular and macrovascular dysfunction due to either endothelium dependent mechanisms or non-endothelium dependent mechanisms. Coronary vascular function is assessed by measuring CBF with endothelium dependent probes (acetylcholine, bradykinin, substance-P, L-NMMA, shear stress) as well as measuring CFR with endothelium independent probes (adenosine, nitroprusside) [4,5]. Exercise, pacing-induced tachycardia, cold pressor test, and mental stress have also been shown to provoke abnormalities in CBF, which can suggest cardiac nociception abnormalities [4,30]. CFT results can diagnose patients with microvascular angina and help improve risk stratification of patients with INOCA [23,30].

5. Therapeutic options in INOCA

There are no evidence-based guidelines for management of patients with INOCA, however there are potential therapy strategies targeting atherosclerosis, endothelial and microvascular mechanisms that have shown benefits in smaller studies [7]. Due to the high prevalence of coronary risk factors and atherosclerosis, lifestyle modifications including diet, exercise and smoking cessation, as well as appropriate medical management of hypertension, hyperlipidemia, and diabetes mellitus are recommended for patients with INOCA [9]. Fig. 3 shows the different therapeutic options. Importantly, treatment choices may also be guided by a patient's specific diagnostic findings; for example, the Coronary Microvascular Angina (CorMicA) trial showed improvement in angina symptoms and QOL in patients whose medical management was guided by their CMD mechanism determined from invasive coronary reactivity testing [31]. The ongoing Women's Ischemia Trial to Reduce Events in Non-Obstructive CAD (WARRIOR) trial is a multicenter, randomized trial that is investigating intensive medical therapy (high intensity statins and angiotensin converting enzyme inhibitors

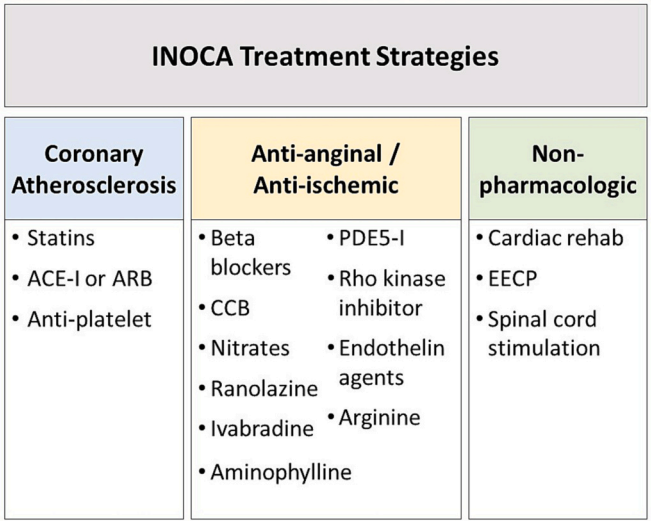

Fig. 3. Therapeutic options for management of INOCA grouped by coronary atherosclerosis, anti-angina and anti-ischemic, and non-pharmacologic options.

(ACE-I) or angiotensin receptor blockers [ARB]) and low dose aspirin versus usual care for prevention of cardiovascular disease events in symptomatic women with INOCA [32].

5.1. Statins and angiotensin-converting enzyme inhibitors

Statins can prevent progression of coronary atherosclerosis in patients with non-obstructive CAD; a prior study showed an improvement in CFR after 6 months of atorvastatin therapy [33]. Statins in combination with ACE-I may increase these benefits; patients with angina and non-obstructive CAD demonstrated improved angina symptoms and exercise tolerance after 6 months of combination atorvastatin and ramipril [34]. In women with CMD, ACE-I were shown to increase CFR and lead to improvement in angina symptoms [35]. An ARB can be substituted if an ACE-I is not tolerated [7].

5.2. Aspirin and antiplatelet options

Thromboxane A2 inhibitors (low dose aspirin and P2Y12 inhibitors) may prevent adverse outcomes in patients with INOCA [36]. This is likely through a mechanism of thromboxane A2 inhibition leading to microvascular protection against oxidative injury and reduced endothelial platelet inhibition [7].

5.3. Anti-angina options

Beta-blockers may decrease frequency of angina and improve endothelial function [4]. Nebivolol, which has vasodilatory properties via nitric oxide production, is currently being studied in women with CMD [37]. Calcium channel blockers (CCB) can be effective in patients whose symptoms are due to epicardial and coronary microvascular spasm [34]. However, a trial using diltiazem in a population of patients with angina symptoms and coronary vascular dysfunction found no improvement in CFR or angina symptoms [38]. Nitrates act as an antianginal by venodilation leading to decreased preload. Nitrates effectiveness in patients with CMD has been inconclusive, but can be used for acute angina symptoms [34].

Ranolazine, ivabradine, nicorandil, and trimetazidine are other antianginal drugs that have been studied with mixed results and may have benefit in some patients with INOCA [6,34]. An early pilot study of ranolazine in patients with INOCA showed improvement in symptoms and improved CFR, however a more recent large randomized study found no difference in symptoms or CFR with ranolazine versus placebo [22,39].

5.4. Other treatment options

In a study of INOCA patients, it was shown that aminophylline can improve exercise-induced chest pain [40]. Phosphodiesterase (PDE) type 5 inhibitors (such as sildenafil) were shown to improve CFR in women with INOCA, and were more effective in the subset of INOCA patients with CMD [7,37]. The Rho kinase pathway is involved in smooth muscle cell contraction and plays an important role in endothelial dysfunction [37]. Fasudil, a rho kinase inhibitor, can prevent acetylcholine induced coronary spasm in the macro and microcirculation [37]. L-arginine, a precursor of nitric oxide, has shown mixed results in improvement of CFR and angina symptoms [4].

Other treatment options are currently being studied. Endothelin receptor antagonists have shown benefits in microvascular angina leading to larger studies including the PRecision medicine with ZibotEntan in microvascular angina (PRIZE) [41]. A pilot clinical trial testing intracoronary CD34+ stem cell therapy in INOCA patients showed improvement in angina symptoms and QOL [42].

Non-pharmacologic treatment options can be effective in treating symptoms. Spinal cord stimulation can improve response to pain perception, angina symptoms and exercise tolerance [4]. Enhanced external counter pulsation (EECP) works by inflation and deflation of leg cuffs synchronized to the cardiac cycle and can improve angina symptoms [4]. Cardiac rehabilitation can improve exercise capacity [4].

6. Knowledge gaps

Gaps remain in our current knowledge and understanding of INOCA. To continue to advance the field, there needs to be large studies that can lead to potential evidence-based guidelines to improve prevention, diagnosis, and management. It is essential that a uniform definition is used for INOCA to further drive collaboration and research. A think tank working group summarized a standard definition of INOCA to include patients with three findings – stable, chronic symptoms (angina) to suggest ischemic heart disease; objective evidence of myocardial ischemia on electrocardiogram or cardiac imaging with rest or at stress; and no flow limiting obstruction on angiography (epicardial obstruction >50 % or fractional flow reserve <0.8) [4].

Further understanding of how different vasomotor issues impact patients with INOCA can further guide prevention, risk stratification, and management. Patients with INOCA may develop AMI (MINOCA) and further studies are needed to understand the risks and pathophysiology of this process. CMD has been found in a large portion of patients with heart failure with preserved ejection fraction (HFpEF); the PROMIS-HFpEF trial found about 75 % of patients admitted with HFpEF exacerbation had CMD without obstructive CAD [43]. The relationship between INOCA, CMD and HFpEF is being investigated, including questions of how often does INOCA progress to HFpEF and what subgroup of patients are at increased risk to develop HFpEF. Better understanding of these relationships will aid in further research design and ultimately evidence-based management guidelines for clinicians.

7. Conclusions

Patients with INOCA have relatively high morbidity, mortality and healthcare costs comparable to obstructive CAD. Diagnostic algorithms are currently IIa and IIb recommendations, but large studies are needed to develop guidelines for treatment of INOCA [23]. The current standard for management of INOCA patients is treating angina, coronary atherosclerosis, and atherosclerotic risk factors. Ongoing studies such as the WARRIOR trial will add more evidence for specific strategies for treatment of INOCA. This review of the clinical aspects of INOCA can aid clinicians in our current understanding of INOCA.

Ethical statement

All authors ensure that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association and the manuscript is in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals.

CRediT authorship contribution statement

Alexander Polyak: Conceptualization, Formal analysis, Methodology, Resources, Writing – original draft, Writing – review & editing. **Janet Wei:** Conceptualization, Data curation, Formal analysis, Investigation, Supervision, Writing – review & editing. **Martha Gulati:** Data curation, Formal analysis, Investigation, Resources, Supervision, Writing – review & editing. **Noel Bairey Merz:** Data curation, Formal analysis, Funding acquisition, Investigation, Supervision, Writing – review & editing.

Declaration of competing interest

Dr. C. Noel Bairey Merz, serves as Board of Director for iRhythm, fees paid through CSMC from Abbott Diagnostics and Sanofi. Dr. Janet Wei

served on an advisory board for Abbott Vascular.

Acknowledgements

This research was supported by the National Heart, Lung and Blood Institute (NHLBI) under grant numbers N01HV68161, N01HV68162, N01HV68163, N01HV68164, U01HL64829, U01HL64914, U01HL64924, R01HL090957, R01HL33610, R01HL56921, R01HL146158 and UM1HL087366; R03AG032631, U54AG065141, M01RR000425; UL1TR000124, UL1TR000064, UL1TR001427. This work was also supported by grants from the Edythe L. Broad, the Constance Austin Women's Heart Research Fellowships, the Barbra Streisand Women's Cardiovascular Research and Education Program, the Linda Joy Pollin Women's Heart Health Program, the Erika J. Glazer Women's Heart Research Initiative, and The Adelson Family Foundation.

References

[1] M.R. Patel, E.D. Peterson, D. Dai, et al., Low diagnostic yield of elective coronary angiography, N. Engl. J. Med. 362 (2010) 886–895, https://doi.org/10.1056/NEJMoa0907272.

[2] C.J. Pepine, K.C. Ferdinand, L.J. Shaw, et al., Emergence of nonobstructive coronary artery disease: a Woman's problem and need for change in definition on angiography, J. Am. Coll. Cardiol. 66 (2015) 1918–1933, https://doi.org/10.1016/j.jacc.2015.08.876.

[3] C.N. Bairey Merz, L.J. Shaw, S.E. Reis, et al., Insights from the NHLBI-sponsored women's ischemia syndrome evaluation (WISE) study: part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease, J. Am. Coll. Cardiol. 47 (2006) S21–S29, https://doi.org/10.1016/j.jacc.2004.12.084.

[4] C.N. Bairey Merz, C.J. Pepine, M.N. Walsh, J.L. Fleg, Ischemia and no obstructive coronary artery disease (INOCA): developing evidence-based therapies and research agenda for the next decade, Circulation 135 (2017) 1075–1092, https://doi.org/10.1161/CIRCULATIONAHA.116.024534.

[5] C. Pacheco Claudio, O. Quesada, C.J. Pepine, Noel Bairey Merz, C., Why names matter for women: MINOCA/INOCA (myocardial infarction/ischemia and no obstructive coronary artery disease), Clin. Cardiol. 41 (2018) 185–193, https://doi.org/10.1002/clc.22894.

[6] M.G. Del Buono, R.A. Montone, M. Camilli, et al., Coronary microvascular dysfunction across the spectrum of cardiovascular diseases: JACC state-of-the-art review, J. Am. Coll. Cardiol. 78 (2021) 1352–1371, https://doi.org/10.1016/j.jacc.2021.07.042.

[7] C.N. Bairey Merz, C.J. Pepine, H. Shimokawa, C. Berry, Treatment of coronary microvascular dysfunction, Cardiovasc. Res. 116 (2020) 856–870, https://doi.org/10.1093/cvr/cvaa006.

[8] C.W. Tsao, A.W. Aday, Z.I. Almarzooq, et al., Heart disease and stroke statistics-2023 update: a report from the American Heart Association, Circulation 147 (2023) e93–e621, https://doi.org/10.1161/CIR.0000000000001123.

[9] V. Kunadian, A. Chieffo, P.G. Camici, et al., An EAPCI expert consensus document on ischaemia with non-obstructive coronary arteries in collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by coronary vasomotor disorders international study group, Eur. Heart J. 41 (2020) 3504–3520, https://doi.org/10.1093/eurheartj/ehaa503.

[10] N.D. Mygind, M.M. Michelsen, A. Pena, et al., Coronary microvascular function and cardiovascular risk factors in women with angina pectoris and no obstructive coronary artery disease: the iPOWER study, J. Am. Heart Assoc. 5 (2016), e003064, https://doi.org/10.1161/JAHA.115.003064.

[11] C.L. Schumann, R.C. Mathew, J.L. Dean, et al., Functional and economic impact of INOCA and influence of coronary microvascular dysfunction, JACC Cardiovasc. Imaging 14 (2021) 1369–1379, https://doi.org/10.1016/j.jcmg.2021.01.041.

[12] L. Jespersen, S.Z. Abildstrom, A. Hvelplund, et al., Burden of hospital admission and repeat angiography in angina pectoris patients with and without coronary artery disease: a registry-based cohort study, PloS One 9 (2014), e93170, https://doi.org/10.1371/journal.pone.0093170.

[13] K.H. Humphries, A. Pu, M. Gao, R.G. Carere, L. Pilote, Angina with "normal" coronary arteries: sex differences in outcomes, Am. Heart J. 155 (2008) 375–381, https://doi.org/10.1016/j.ahj.2007.10.019.

[14] M. Gulati, N. Khan, M. George, et al., Ischemia with no obstructive coronary artery disease (INOCA): a patient self-report quality of life survey from INOCA international, Int. J. Cardiol. 371 (2023) 28–39, https://doi.org/10.1016/j.ijcard.2022.09.047.

[15] L.J. Shaw, C.N. Merz, C.J. Pepine, et al., The economic burden of angina in women with suspected ischemic heart disease: results from the National Institutes of Health–National Heart, Lung, and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation, Circulation 114 (2006) 894–904, https://doi.org/10.1161/CIRCULATIONAHA.105.609990.

[16] C.J. Pepine, Multiple causes for ischemia without obstructive coronary artery disease: not a short list, Circulation 131 (2015) 1044–1046, https://doi.org/10.1161/CIRCULATIONAHA.115.015553.

[17] P. Song, Z. Fang, H. Wang, et al., Global and regional prevalence, burden, and risk factors for carotid atherosclerosis: a systematic review, meta-analysis, and modelling study, Lancet Glob. Health 8 (2020) e721–e729, https://doi.org/10.1016/S2214-109X(20)30117-0.

[18] B.K. Lee, H.S. Lim, W.F. Fearon, et al., Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease, Circulation 131 (2015) 1054–1060, https://doi.org/10.1161/CIRCULATIONAHA.114.012636.

[19] J.K. Min, A. Dunning, F.Y. Lin, et al., Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the international multicenter CONFIRM (coronary CT angiography evaluation for clinical outcomes: an international multicenter registry) of 23,854 patients without known coronary artery disease, J. Am. Coll. Cardiol. 58 (2011) 849–860, https://doi.org/10.1016/j.jacc.2011.02.074.

[20] B.D. Johnson, L.J. Shaw, C.J. Pepine, et al., Persistent chest pain predicts cardiovascular events in women without obstructive coronary artery disease: results from the NIH-NHLBI-sponsored Women's Ischaemia Syndrome Evaluation (WISE) study, Eur. Heart J. 27 (2006) 1408–1415, https://doi.org/10.1093/eurheartj/ehl040.

[21] V.L. Murthy, M. Naya, V.R. Taqueti, et al., Effects of sex on coronary microvascular dysfunction and cardiac outcomes, Circulation 129 (2014) 2518–2527, https://doi.org/10.1161/CIRCULATIONAHA.113.008507.

[22] C.N. Bairey Merz, E.M. Handberg, C.L. Shufelt, et al., A randomized, placebo-controlled trial of late Na current inhibition (ranolazine) in coronary microvascular dysfunction (CMD): impact on angina and myocardial perfusion reserve, Eur. Heart J. 37 (2016) 1504–1513, https://doi.org/10.1093/eurheartj/ehv647.

[23] M. Gulati, P.D. Levy, D. Mukherjee, et al., 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of CHEST pain: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines, Circulation 144 (2021) e368–e454, https://doi.org/10.1161/CIR.0000000000001029.

[24] P.F. Rodriguez Lozano, E. Rrapo Kaso, J.M. Bourque, et al., Cardiovascular imaging for ischemic heart disease in women: time for a paradigm shift, JACC Cardiovasc. Imaging 15 (2022) 1488–1501, https://doi.org/10.1016/j.jcmg.2022.01.006.

[25] P.S. Douglas, U. Hoffmann, M.R. Patel, et al., Outcomes of anatomical versus functional testing for coronary artery disease, N. Engl. J. Med. 372 (2015) 1291–1300, https://doi.org/10.1056/NEJMoa1415516.

[26] P. Nihoyannopoulos, J.C. Kaski, T. Crake, A. Maseri, Absence of myocardial dysfunction during stress in patients with syndrome X, J. Am. Coll. Cardiol. 18 (1991) 1463–1470, https://doi.org/10.1016/0735-1097(91)90676-z.

[27] T.M. Bateman, Advantages and disadvantages of PET and SPECT in a busy clinical practice, J. Nucl. Cardiol. 19 (Suppl. 1) (2012) S3–11, https://doi.org/10.1007/s12350-011-9490-9.

[28] M. Saghari, M. Assadi, M. Eftekhari, et al., Frequency and severity of myocardial perfusion abnormalities using Tc-99m MIBI SPECT in cardiac syndrome X, BMC Nucl. Med. 6 (2006) 1, https://doi.org/10.1186/1471-2385-6-1.

[29] B.A. Mc Ardle, T.F. Dowsley, R.A. deKemp, G.A. Wells, R.S. Beanlands, Does rubidium-82 PET have superior accuracy to SPECT perfusion imaging for the diagnosis of obstructive coronary disease?: a systematic review and meta-analysis, J. Am. Coll. Cardiol. 60 (2012) 1828–1837, https://doi.org/10.1016/j.jacc.2012.07.038.

[30] P.K. Mehta, O. Quesada, A. Al-Badri, et al., Ischemia and no obstructive coronary arteries in patients with stable ischemic heart disease, Int. J. Cardiol. 348 (2022) 1–8, https://doi.org/10.1016/j.ijcard.2021.12.013.

[31] T.J. Ford, D. Corcoran, K.G. Oldroyd, et al., Rationale and design of the British Heart Foundation (BHF) coronary microvascular angina (CorMicA) stratified medicine clinical trial, Am. Heart J. 201 (2018) 86–94, https://doi.org/10.1016/j.ahj.2018.03.010.

[32] E.M. Handberg, C.N.B. Merz, R.M. Cooper-Dehoff, et al., Rationale and design of the women's ischemia trial to reduce events in nonobstructive CAD (WARRIOR) trial, Am. Heart J. 237 (2021) 90–103, https://doi.org/10.1016/j.ahj.2021.03.011.

[33] P. Eshtehardi, M.C. McDaniel, S.S. Dhawan, et al., Effect of intensive atorvastatin therapy on coronary atherosclerosis progression, composition, arterial remodeling, and microvascular function, J. Invasive Cardiol. 24 (2012) 522–529 (doi).

[34] P. Ong, A. Athanasiadis, U. Sechtem, Pharmacotherapy for coronary microvascular dysfunction, Eur. Heart J. Cardiovasc. Pharmacother. 1 (2015) 65–71, https://doi.org/10.1093/ehjcvp/pvu020.

[35] D.F. Pauly, B.D. Johnson, R.D. Anderson, et al., In women with symptoms of cardiac ischemia, nonobstructive coronary arteries, and microvascular dysfunction, angiotensin-converting enzyme inhibition is associated with improved microvascular function: a double-blind randomized study from the National Heart, Lung and Blood Institute women's ischemia syndrome evaluation (WISE), Am. Heart J. 162 (2011) 678–684, https://doi.org/10.1016/j.ahj.2011.07.011.

[36] M.A. Khuddus, C.J. Pepine, E.M. Handberg, et al., An intravascular ultrasound analysis in women experiencing chest pain in the absence of obstructive coronary artery disease: a substudy from the National Heart, Lung and Blood Institute-Sponsored Women's Ischemia Syndrome evaluation (WISE), J. Interv. Cardiol. 23 (2010) 511–519, https://doi.org/10.1111/j.1540-8183.2010.00598.x.

[37] F. Marchini, G. Pompei, E. D'Aniello, et al., Shedding light on treatment options for coronary vasomotor disorders: a systematic review, Cardiovasc. Drugs Ther. (2022), https://doi.org/10.1007/s10557-022-07351-x.

[38] T.P.J. Jansen, R.E. Konst, A. de Vos, et al., Efficacy of diltiazem to improve coronary vasomotor dysfunction in ANOCA: the EDIT-CMD randomized clinical trial, JACC Cardiovasc. Imaging 15 (2022) 1473–1484, https://doi.org/10.1016/j.jcmg.2022.03.012.

[39] P.K. Mehta, P. Goykhman, L.E. Thomson, et al., Ranolazine improves angina in women with evidence of myocardial ischemia but no obstructive coronary artery disease, JACC Cardiovasc. Imaging 4 (2011) 514–522, https://doi.org/10.1016/j.jcmg.2011.03.007.
[40] O. Yeşildağ, M. Yazici, O. Yilmaz, R. Uçar, O. Sağkan, The effect of aminophylline infusion on the exercise capacity in patients with syndrome X, Acta Cardiol. 54 (1999) 335–337 (doi).
[41] G.R. Abraham, A.J. Morrow, J. Oliveira, et al., Mechanistic study of the effect of endothelin SNPs in microvascular angina - protocol of the PRIZE endothelin sub-study, Int. J. Cardiol. Heart Vasc. 39 (2022), 100980, https://doi.org/10.1016/j.ijcha.2022.100980.
[42] T.D. Henry, C.N. Bairey Merz, J. Wei, et al., Autologous CD34+ stem cell therapy increases coronary flow reserve and reduces angina in patients with coronary microvascular dysfunction, Circ. Cardiovasc. Interv. 15 (2022), e010802, https://doi.org/10.1161/CIRCINTERVENTIONS.121.010802.
[43] S.J. Shah, C.S.P. Lam, S. Svedlund, et al., Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF, Eur. Heart J. 39 (2018) 3439–3450, https://doi.org/10.1093/eurheartj/ehy531.