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## **Microvascular angina – an abstruse path to diagnose and to treat – a review of literature.**

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## **Abstract**

### **Introduction**

Chronic coronary syndrome is predominantly related to the atherosclerotic obstruction of the coronary artery or arteries. However, this phenomenon is not the only causative factor in this disease. It is usually forgotten, that there is a possibility of ischemia of the cardiac muscle with no obstruction found in the main vessel. The trigger of such pathology might be underlying in the microcirculatory system and the inappropriate dilation or constriction of those small vessels, which results in insufficient blood supply to the cardiomyocytes, similarly to the typical obstructive coronary artery disease. In this article we are willing to show that such dysfunction poses a great danger to the health and life and therefore we should be able to properly diagnose and treat it.

### **Purpose of the work**

The aim of this review of up-to-date literature is to raise awareness among both doctors and patients about the phenomenon of coronary artery disease but with no significant obstruction in the vessels supplying the cardiac muscle. The common cause of such condition is coronary microvascular dysfunction, that leads to a disease called microvascular angina. Our purpose was to reveal, how dangerous to the health of the patients this could be and therefore how essential it is to provide a proper diagnose and management. In addition, we have noticed a need for a summary of what has already been discovered on this topic, available therapeutic methods and future perspectives.

### **Materials and methods**

The search of English and Polish language literature up to December 2023 has been done using the PubMed database, Google Scholar database and several international guidelines. The search regarded the topics of microvascular angina, coronary microvascular dysfunction, cardiac syndrome X and chronic coronary syndrome.

## **Summary**

Microvascular angina, like any chronic coronary syndrome, means a chest pain developed when the cardiac muscle is insufficiently supplied with blood, although in this case the symptoms usually occur untypically, since there is no obstruction in the main epicardial arteries. The pathology arises in the smallest of vessels: arterioles, capillaries and venules. They might be minuscule, but they play a crucial role in the distribution of local blood flow and an exchange between cardiomyocytes and red blood cells or plasma. We must be aware of that and stop underestimating the implications that it brings. The diagnosis of the impaired microcirculation is challenging but not impossible. There still a lot to develop in this field, we especially should keep seeking new methods of targeted treatment for this condition. Doctors must be able to properly care about their patients suffering from microvascular angina. It is essential to stratify their cardiovascular risk, propose different therapeutic strategies, since the treatment may frequently be fruitless, and to monitor their mental health.

## **Keywords**

‘microvascular angina’; ‘coronary microvascular dysfunction’; ‘cardiac syndrome X’; ‘microcirculation’; ‘chronic coronary syndrome’

## **1. Introduction**

Heart disease and cancer are nowadays known to be the main causes of mortality and morbidity. Heart diseases are the leading culprit of death in the majority of populations throughout the world, with coronary artery disease (CAD) as its most common type[1]. CAD means a disease affecting coronary (epicardial) arteries supplying the cardiac muscle, therefore this condition leads to the insufficient delivery of oxygen or nutrients to cardiomyocytes resulting in ischemia, predominantly manifested as a chest pain, discomfort, which is called ‘angina’. The most common root of the process affecting epicardial arteries is an atherosclerotic disease causing an obstruction of the vessel – obstructive CAD (OCAD). This is the type of the disease that most patients know, heard about and the most scientists are focusing on in their researches. However, the CAD might be also due to a non-obstructive or minimally obstructive disease of the vessels. CAD can be present as an acute form (acute coronary syndrome, ACS) or chronic (chronic coronary syndrome, CCS)[4] which was

described as a stable angina (pectoris) or a stable ischemic heart disease (IHD) in the past. In this article we have focused on a type of CCS, which is considered as special due to lack of a significant obstruction in any of the coronary arteries – nonobstructive CAD. There are different factors proven as the culprit of this phenomenon, by and large this could be a consequence of a coronary microvascular dysfunction (CMD) or a vasospasm. For the majority of patients and physicians, a typical CCS is manifested with chest pain related to physical activity and as a main trigger of this condition, atherosclerotic obstruction of an epicardial artery or arteries is believed. It is correct in most of the cases, but there is another group of individuals developing such angina, which also results in myocardial ischemia, but the main cause of this condition is different, hence the nonobstructive CAD is frequently underdiagnosed or mistreated. We have noticed the challenges and the struggle that the diagnosis and management could cause, for that reason we have decided to provide this review of an up-to-date literature focused on CCS caused by CMD, for the sake of a better understanding of this condition and consequently an improvement in a process of patient care.

## **2. Materials and methods**

This is a narrative type of review, no statistical calculations were performed. The search of independent English and Polish language literature has been done using the PubMed database, Google Scholar database, international guidelines provided by the European Society of Cardiology (ESC), American Heart Association (AHA), British Cardiovascular Society (BCS) and the statistics published by the Centers for Disease Control and Prevention (CDC). We used a query containing the keywords related to our topic: ‘microvascular angina’, ‘coronary microvascular dysfunction’, ‘cardiac syndrome X’, ‘microcirculation’ or ‘chronic coronary syndrome’.

## **3. Results**

The selective search retrieved 72 records. After review of the abstracts and full texts, 34 articles were included in the analysis. The reason why we have rejected this number of articles was in most of the cases focus on microcirculatory dysfunction but secondary to other cardiovascular diseases, like hypertension or diabetes. In our review we were willing to provide up-to-date information on primary CMD of unknown triggering factor. We have also noticed a need to gather the most recent guidelines on the topic of microvascular angina (MVA) in this article.

## 4. Discussion

### 4.1. Definition

MVA, a condition formerly known as a 'cardiac syndrome X' is defined as a CCS with no evidence of obstruction or no significant obstruction (meaning a presence of obstruction but not greater than 50% of the arterial diameter[2, 3]) in any of the vessels supplying the cardiac muscle, the main cause of chest pain in MVA is developed due to CMD, hence MVA belongs to a special subtype of CAD – Ischemia with Nonobstructive Coronary Arteries (INOCA)[2], together with vasospastic angina (VSA). The microcirculation, which consists of small vessels – arterioles, capillaries and venules – with diameters not greater than 150  $\mu\text{m}$ [10], or according to other sources not greater than approximately 300  $\mu\text{m}$ [32], although a better criterium for this definition is their physiological response (meaning a constriction of their lumen) to the blood pressure increase, is liable for the regulation of blood flow, pertinently to the current demands of the supplied organ[9]. The main topic of interests of this review is only one but very important part of the microcirculation – the vessels regulating the flow to the cardiac muscle. These small vessels and their thin walls formed predominantly by endothelial cells (EC) enable the transport of oxygen from red blood cells (RBC), hormones and nutrients from plasma to cardiomyocytes. EC in response to fluctuations of blood pressure are able to deliver various mediators locally, causing either constriction or dilation of smooth muscle cells located in the walls of arterioles and therefore EC play the most important role in the regulation of local microcirculatory blood flow and exchange of oxygen and metabolites, they additionally take part in maintain the balance between thrombogenesis and fibrinolysis. The pathology of regulation of coronary blood supply might be due to the dysfunction of the release of the mediators by the EC, which results in a disturbed constriction and relaxation of smooth muscle cells and therefore arteriolar dysregulation, to the remodelling of microvessels which later causes impaired microcirculatory conductance or both of these mechanisms simultaneously, that is why it has been challenging for researchers around the world, to detect and properly understand them, although over the recent years a huge progress of the scientific knowledge about this phenomenon has been made. When such dysfunction occurs, it is the reason of insufficient blood flow and oxygen delivery to cardiomyocytes, hence it leads to the ischemia of the cardiac muscle. In addition, CMD is a first part of the atherosclerotic process[33] and also poses a higher risk of developing cardiovascular events. It is observed not only in MVA, but also in several other cardiac

diseases, such as: heart failure with preserved ejection fraction, reperfusion injury after ischemia or hypertrophic cardiomyopathy[12].

#### 4.2.Epidemiology

MVA occurs more frequently in female than male[4, 6, 11, 27]. This phenomenon was proven in many international studies, although the reasons for the gender differences are still unclear. Even half of the women manifesting angina suffer from CMD[29]. An analysis performed on the first patients enrolled to the Coronary Microvascular Disease Registry in the USA revealed similar conclusions[27]. In addition, the characteristics of population that suffered from MVA in their study showed that they tended to have a lower BMI than the subjects without CMD. Approximately 82% of participants, who were diagnosed with CMD, suffered from hypertension, 77% from hyperlipidaemia. The mean age was 62,4 years old. The patients were most commonly African American and Caucasian.

Recently, especially in the context of a global pandemic of COVID-19, there have been ongoing discussions on the impact of mental stress on multiple organ systems in the human body, including cardiovascular system, with a focus on endothelial dysfunction and vascular inflammation[34]. Decades ago, several studies with monkeys have revealed that in the group exposed to psychosocial, chronic stress, the endothelium-dependent vasodilation was impaired[35]. This is one of the mechanisms in which CMD occurs among people suffering from angina. More alternative trials are necessary to be conducted on this topic, nevertheless we can suspect that an exposure to stress may be a risk factor for developing MVA.

Diagnosis of CMD is related to a poor prognosis, to the higher risk of MI or death and a worse or incomplete response to the pharmacotherapy for CAD. A comparative study aiming at better diagnosis and understanding of IHD among women conducted by the National Heart, Lung and Blood Institute – sponsored WISE (Women's Ischemia Syndrome Evaluation)[30] showed that among women with suspected ischemia, enrolled to the study population, CMD diagnosed as coronary microvascular reactivity in a response to intracoronary adenosine (in a stenosis-free area) equalled more frequent major adverse outcomes, meaning: death, myocardial infarction (MI), stroke, hospitalization for chronic heart failure, after years of observation (the mean observation time was 5,4 years).

#### 4.3. Clinical manifestation

Patients undergoing MVA present mostly chest pain, which is also the leading symptom among the patients with OCAD. However, angina pectoris in individuals with MVA occurs in relation to exercise or also at rest or in association with exposure to cold temperature or under stress, which is different from a typical symptom of CCS. Patients with OCAD develop exercise – related chest pain which is relieved at rest or after sublingual administration of nitrates[4]. Angina caused by CMD often occurs not only during exercise but also in a post-exercise period[28] and the relief after nitrates is not as visible as it is among individuals suffering from OCAD. This is the main reason why MVA is so frequently underdiagnosed and not treated properly.

#### 4.4. Diagnosis and its obstacles

Any patient presenting angina pectoris should be referred to a coronary angiography, to detect life-threatening obstructions in epicardial arteries. However, among many of them, even up to 70% of such patients, according to a recent Expert Consensus Document published by the European Association of Percutaneous Coronary Interventions (EAPCI)[13] , no clinically significant obstruction can be found. The results of one American study were similar. Only approximately one third of the patients who manifested CAD symptoms and later underwent coronary angiography were diagnosed with OCAD. Therefore the researchers have noticed a need for new better strategies of risk stratifications and diagnostic methods for such individuals[25]. Majority of subjects with no significant obstruction in epicardial arteries may suffer from INOCA but their diagnostic process often ends at the standard stage – coronary angiography, with a non-cardiac cause of their symptoms taken for granted. That is a misdiagnose and therefore poses a threat to the health and life to the patients.

The results of the CorMicATrial (British Heart Foundation Coronary Microvascular Angina)[14] published in 2018 have proven that coronary angiography may only provide the diagnosis of OCAD and selection of patients undergoing angina with no significant obstruction is crucial because such individuals are most likely to suffer from vasospastic angina or MVA, the conditions that cannot be diagnosed as easily as OCAD. In this trial, the researchers have chosen individuals with no significant obstruction according to angiography results and later divided those people into an intervention group, which consisted of 76 subjects who later underwent comprehensive, graded diagnostic procedure – invasive assessment of coronary flow reserve (CFR), index of microcirculatory resistance (IMR),

fractional flow reserve (FFR) and a vasoreactivity testing with acetylcholine, followed by appropriate to the discovered condition pharmacotherapy and life-style changes, and a control group, which consisted of 75 subjects and who only received standard diagnostic procedure – coronary angiography. The results after a time period of 6 months have showed an improvement in both: angina severity (measured with thanks to the Seattle Angina Questionnaire summary score) and quality of life (measured by EQ-5D index and visual analogue score) in the intervention group comparing to the control group. Lack of OCAD cannot be equal to a non-cardiac cause of angina.

To diagnose MVA, more than a standard coronary angiography is required, according to the most recent ESC guidelines, released in 2019[4], that we nowadays follow. After exclusion of OCAD in angiography, it is essential to consider the possibility of non-obstructive CAD, especially if the patients present the above mentioned symptoms and have documented signs of ischaemia in non-invasive functional tests, predominantly in electrocardiography (ECG) or echocardiography. The tests enabling to discover MVA include: measuring IMR (in the catheterization laboratory by intracoronary thermodilution or Doppler flow velocity) and measuring CFR (non-invasively with transthoracic Doppler echocardiography, magnetic resonance imaging (MRI) or positron emission tomography (PET) or invasively by the same methods as while measuring IMR), the measurements usually require intravenous administration of vasodilators, most commonly adenosine is used. If  $IMR \geq 25$  or  $CFR < 2.0$  is measured, MVA in a mechanism called ‘impaired microcirculatory conductance’ can be diagnosed, which means that CFR is limited and the vasodilation in microcirculation is impaired. MVA could also be developed in a different mechanism called ‘arteriolar dysregulation’ and is related to enhanced vasoconstriction. This pathology might be discovered in an invasive test, after administration of acetylcholine directly to the coronary vessels, during angiography. In individuals undergoing arteriolar dysfunction, acetylcholine is most likely to cause vasoconstriction and therefore clinical symptoms of angina and ischaemic changes in ECG. Detecting the mechanism of MVA is a crucial part of the diagnosis, because further treatment and management is different, depending on the mechanism of CMD. These are the standard and the only recommended methods to detect MVA. However, they are invasive and may pose a danger to the health of some of the patients. That is why, the search of new methods of discovery of this condition is held among the world. The Coronary Vasomotion Disorders International Study Group (COVADIS)[3] presented international standardized criteria for the diagnosis of this condition: symptoms of myocardial



ischemia; absence of obstructive CAD; objective evidence of myocardial ischemia; evidence of microvascular dysfunction.

A prospective study published in 2022 has showed, that in a selected group of 38 patients with non-obstructive CAD, measuring haemodynamic indicators of arteriolar dysregulation non-invasively enabled the detection of arteriolar dysregulation, which normally, according to the 2019 ESC guidelines, could only be assessed after administration of adenosine invasively to the cardiac vessels[15]. The indicators were assessed by hyperventilation to induce vasospasm (microvascular dysfunction), which was later followed by supine bicycle exercise test. During these tests, stress echocardiography with Doppler measurements of coronary flow were made and at the end of the tests, the response, which meant coronary flow velocity in distal left anterior descending artery (LAD), was also measured thanks to transthoracic Doppler echocardiography. An abnormal response to hyperventilation was defined as coronary flow velocity ratio (stress vs. at rest)  $<1.0$ . The test with administration of adenosine was also done, to estimate vasodilatation independent on endothelium. An abnormal response to this substance was defined as coronary flow velocity reserve  $<2.0$ . More research on this topic is required, nevertheless this result could be a promising alternative method, to make the diagnosis of MVA with vasospastic component easier and more accessible to all of the individuals suffering from non-obstructive CAD.

#### 4.5.Treatment

The official recommendations on the treatment of MVA are similar to the available methods for CCS treatment. However, up to 25% of patients suffering from MVA do not respond to such management or do not satisfactorily respond, their symptoms are not entirely relieved[16]. To this day, there is no high-quality, large study on the management of this condition. Current guidelines on pharmacotherapy are dependent on the mechanism in which CMD occurred. To present the most important differences, we have included a short summary (Table 1.). One must not forget, that these pathologies might coexist, in such case the therapeutic approach should be a mixture between the two strategies.

Coronary Microvascular Dysfunction		
Mechanism	Impaired Microcirculatory Conductance	Arteriolar dysregulation
Dysfunctional process	Vasodilation (restricted)	Vasoconstriction (enhanced)
Differential diagnosis	CFR <2.0 or IMR $\geq$ 25 measured invasively in the catheterization laboratory, although CFR only could be measured non-invasively	Positive testing after intracoronary administration of acetylcholine with ECG monitoring, during angiography
Treatment recommended by the ESC[4]	<ul style="list-style-type: none"> <li>○ BB</li> <li>○ ACE-I or ARB</li> <li>○ Statins</li> <li>○ Life-style changes</li> </ul>	<ul style="list-style-type: none"> <li>○ CCB</li> <li>○ Long acting nitrates</li> <li>○ Life-style changes</li> <li>○ If necessary, depending on individual cardiovascular risk factors: ACE-I or ARB, statins</li> </ul>

Table 1. A brief summary of the mechanisms of CMD.

If the impaired microcirculatory conductance (limited CFR) was detected, but the result of the test with acetylcholine was negative (the vasospastic component of CMD was not discovered), treatment with beta-blockers (BB), angiotensin-converting enzyme inhibitors (ACE-I) or receptor blockers (ARB) and statins is advised by the ESC[4], which is a conventional anti-atherosclerotic therapy. The pharmacotherapy should be accompanied by appropriate life-style changes, such as smoking cessation or physical activity. The effect of exercise training on anginal pain was tested. The group suffering from angina in this study was characterized by physical deconditioning and a lower threshold of pain, comparing to reference, healthy subjects. Therefore, the scientists have advised a physical training as a part of therapeutic process for angina[20]. Nebivolol, a highly selective BB that in addition stimulates the production and the release of nitric oxide (NO) causing local vasodilation, was proven to increase CFR significantly, thanks to the study published in 2007, in which the researchers measured Doppler-flow wire derived coronary flow velocity first at rest, and then after the intracoronary administration of nebivolol in a group of patients with CAD and in a control group of subjects without CAD[18]. The study group presented lower values of CFR at rest comparing to the healthy individuals. After nebivolol there was a significant increase in CFR in both of the groups. Neglia et al.[24] have studied a group of 20 patients and animal models (rats) with arterial hypertension. The researchers knew that this condition usually results in

microcirculatory remodelling and therefore causes CMD. They investigated the impact that the combination of drugs: perindopril (ACE-I) and indapamide (a thiazide-like diuretic) might have on the process of such remodelling and coronary flow. The results after 6 months of treatment indicated that in the patients the myocardial flow was improved and in rats the researchers noticed that the improvement of coronary flow was due to a reverse remodelling of the microvessels. This shows us the possible role of these substances in the treatment of CMD. What the ESC guidelines did not include are ranolazine and phosphodiesterase type 5 (PDE-5) inhibitors. Ranolazine, the late sodium channel inhibitor, is worth to consider in the management of the patients. There was a randomized, placebo-controlled trial published in 2011 that gathered women suffering from angina but with no evidence of OCAD. Women were randomly selected to a group receiving ranolazine and a group on placebo. Mehta et al. have proven that ranolazine helped to improve the symptoms of angina in the study group. The improvement of symptoms was measured thanks to the Seattle Angina Questionnaire score[19]. However, the evidence of the influence of this substance on individuals with CMD are mixed, there is a need for more scientific research on this topic. PDE-5 inhibitors, such as sildenafil, were tested in the management of women suffering from non-obstructive CAD as a part of a multicenter study – WISE[21]. The study group included 23 women without OCAD but presenting anginal pain, their CFR before the test was  $\leq 3.0$ . The participants received sildenafil and 45 minutes after the administration, CFR was measured. The results presented an acute increase of CFR after PDE-5 inhibitor. However, further outcomes of such treatment were not investigated. Calcium channel blockers (CCB) are not recommended in this condition, for many years they have been known to have no impact on CFR. It was already proven in a large clinical trial in the year 1995[17].

CCB are on the contrary strongly recommended in MVA with the vasospastic component (normal CFR and a positive result of the test with acetylcholine). Treatment of this mechanism of CMD is similar to the therapy methods for VSA[4], hence long acting nitrates may be included together with CCB. Reducing the cardiovascular risk with statins and ACE-I or ARB and life-style changes were also recommended. In the management of this condition not only CCB are used, but also phosphodiesterase type 3 (PDE-3) inhibitors, such as cilostazol. This substance is known to be included in the therapy for intermittent claudication, but it has been proven to be beneficial for the patients suffering from VSA in several studies[22, 23]. And if so, cilostazol could be considered in CMD triggered by arteriolar dysfunction (enhanced vasoconstriction).

A study on the effects of canagliflozin on coronary microvasculature, myocardial blood flow and angiogenesis was conducted by Banerjee et al[26]. They used small (rat) and large animals models (swine). Canagliflozin is a sodium-glucose cotransporter-2 (SGLT-2) inhibitor, primarily used as a treatment for diabetes mellitus type 2. The researchers have come to the results that the use of canagliflozin leads to an increase of myocardial blood flow accompanied by no significant increase in proangiogenic signalling. In addition, SGLT-2 inhibitor caused an improvement in coronary microvascular vasodilation and a decrease in vasoconstriction. These conclusions are very promising as maybe in the future this medication could be used in patients with CMD, also non-diabetic. Nevertheless, more study on this topic is necessary before canagliflozin could be registered as a part of a treatment for MVA.

#### 4.6. Impact on the quality of life

It has already been proven in the recent decades, on the contrary to what had been believed beforehand, that this disease, even though there is no obstruction in the main epicardial arteries so at first such condition might seem not so dangerous, leads to MI with all of its consequences, as well as to an increased risk of mortality of any cause compared to healthy individuals, just like the typical OCAD[5, 6, 7]. In a Danish retrospective study[6], a study group consisting of patients aged 20 years and more, who underwent coronary angiography due to manifested symptoms of stable angina pectoris, was formed and it was additionally divided into: patients with normal coronary arteries, with diffuse non-obstructive CAD and with OCAD. As a reference group, patients without any symptoms of angina, randomly selected to the Copenhagen City Heart Study[8], also aged 20 years or more, were chosen. Individuals with prior cardiovascular disease or missing data were excluded from the study. Both populations were later divided by the sex. The results of the observation after 7,5 years have showed, that for both genders in the groups with normal coronary arteries and with non-obstructive CAD there was a statistically significant increase in major cardiovascular events, defined as: cardiovascular mortality, hospitalization for MI, heart failure or stroke, and an increased risk of all-cause mortality, compared to a reference, asymptomatic group. Such results, together with many other studies[30] that have been completed on this topic, show us the threat that MVA poses to health and life of patients suffering from it and the importance of providing a successful treatment of this condition.

Another part of the National Heart, Lung and Blood Institute – sponsored WISE study compared the relationship between depression and its severity with cardiovascular risk factors, survival and major adverse outcomes among 505 women presenting angina, enrolled to the

WISE[31]. After the observation period, the researchers have come to the conclusions that the individuals with elevated depression symptoms or a history of treatment for depression have a higher risk of developing major cardiovascular events (MI or death). Severity of depression could be an important predictor of an increased CAD risk profile. That is why the scientists suggested the need to evaluate mental health of the patients who were diagnosed with CAD, since depression seems to occur frequently in this group.

## **5. Conclusions**

Diagnosis of CCS thus far equals OCAD in the thoughts of many patients and physicians. One must never forget about the possibility of non-obstructive CAD, among which CMD is a frequent causative factor. The diagnosis of MVA might seem untypical and complicated, nevertheless it is a duty of a doctor to provide a search for evidence of this condition and if detected, to ensure a proper treatment, according to the recent scientific data and guidelines. It is necessary for individuals suffering from CMD, since such diagnosis means a higher risk of death or MI and an impaired quality of life. The therapeutic methods that we have nowadays are not enough, because many of the patients are not satisfied with the control of the symptoms they achieve even with the appropriate pharmacotherapy, hence it is also essential that we keep searching for new management methods.

## **Abbreviations and Acronyms**

ACE-I angiotensin-converting enzyme inhibitors

ACS acute coronary syndrome

AHA American Heart Association

ARB receptor blockers

BB beta-blockers

BCS British Cardiovascular Society

CAD coronary artery disease

CCB Calcium channel blockers

CCS chronic coronary syndrome

CDC Centers for Disease Control and Prevention

CFR coronary flow reserve

CMD coronary microvascular dysfunction

COVADIS Coronary Vasomotion Disorders International Study Group

EAPCI European Association of Percutaneous Coronary Interventions

EC endothelial cells

ECG electrocardiography

ESC European Society of Cardiology

FFR fractional flow reserve

IHD ischemic heart disease

IMR index of microcirculatory resistance

INOCA Ischemia with Nonobstructive Coronary Arteries

LAD left anterior descending artery

MI myocardial infarction

MRI magnetic resonance imaging

MVA microvascular angina

NO nitric oxide

OCAD obstructive coronary artery disease

PDE-3 phosphodiesterase type 3

PDE-5 phosphodiesterase type 5

PET positron emission tomography

RBC red blood cells

SGLT-2 sodium-glucose cotransporter-2

VSA vasospastic angina

## **Statements and declarations**

### **Authors' contribution:**

Conceptualization: UM. Methodology: KB, AK. Software: BB. Check: AN, AP. Formal Analysis: DB. Investigation: AK. Resources: UM, AN. Data Curation: KB. Writing-Rough Preparation: BB. Writing-Review and Editing: UM, DB, AP. Visualization: AK. Supervision: AN, KB. Project Administration: DB, BB.

All listed authors discussed the results. All authors have read and agreed with the published version of the manuscript.

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## **References**

1. Heart Disease Facts | CdC.gov. Centers for Disease Control and Prevention. <https://www.cdc.gov/heartdisease/facts.htm>. Published May 15, 2023.

2. Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients with Chronic Coronary Disease: A report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation*. 2023;148(9). doi:10.1161/cir.0000000000001168.
3. Ong P, Camici PG, Beltrame JF, et al. International standardization of diagnostic criteria for microvascular angina. *International Journal of Cardiology*. 2018;250:16-20. doi:10.1016/j.ijcard.2017.08.068.
4. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *European Heart Journal*. 2019;41(3):407-477. doi:10.1093/eurheartj/ehz425.
5. Herrmann J, Kaski JC, Lerman A. Coronary microvascular dysfunction in the clinical setting: from mystery to reality. *European Heart Journal*. 2012;33(22):2771-2783. doi:10.1093/eurheartj/ehs246.
6. Jespersen L, Hvelplund A, Abildstrøm SZ, et al. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. *European Heart Journal*. 2011;33(6):734-744. doi:10.1093/eurheartj/ehr331.
7. Gulati M, Cooper-DeHoff RM, McClure C, et al. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease. *Archives of Internal Medicine*. 2009;169(9):843. doi:10.1001/archinternmed.2009.50.
8. The Copenhagen city heart study. *European Heart Journal Supplements*. 2001;3:H1-H83. doi:10.1016/s1520-765x(01)90110-5.
9. Patel B, Fisher M. Therapeutic advances in myocardial microvascular resistance: Unravelling the enigma. *Pharmacology & Therapeutics*. 2010;127(2):131-147. doi:10.1016/j.pharmthera.2010.04.014.
10. Gryglewska B. The microcirculation and hypertension. *Gryglewska | Arterial Hypertension*. [https://journals.viamedica.pl/arterial\\_hypertension/article/view/12857](https://journals.viamedica.pl/arterial_hypertension/article/view/12857). Published 2001.
11. Civieri G, Kerkhof PLM, Montisci R, Iliceto S, Tona F. Sex differences in diagnostic modalities of coronary artery disease: Evidence from coronary microcirculation. *Atherosclerosis*. 2023;384:117276. doi:10.1016/j.atherosclerosis.2023.117276.



12. Sechtem U, Brown DL, Godo S, Lanza GA, Shimokawa H, Sidik N. Coronary microvascular dysfunction in stable ischaemic heart disease (non-obstructive coronary artery disease and obstructive coronary artery disease). *Cardiovascular Research*. 2020;116(4):771-786. doi:10.1093/cvr/cvaa005.
13. Kunadian V, Chieffo A, Camici PG, 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. *Eurointervention*. 2021;16(13):1049-1069. doi:10.4244/eijy20m07\_01.
14. Ford T, Stanley B, Good R, et al. Stratified medical therapy using invasive coronary function testing in angina. *Journal of the American College of Cardiology*. 2018;72(23):2841-2855. doi:10.1016/j.jacc.2018.09.006.
15. Dedić S, Bošković N, Giga V, et al. Haemodynamic indicators of arteriolar dysregulation during combined hyperventilation and exercise test in patients with ANOCA (SESPASM). *European Heart Journal*. 2022;43(Supplement\_2). doi:10.1093/eurheartj/ehac544.082.
16. Ullrich-Daub H, Daub S, Olschewski M, Münzel T, Gori T. Diseases of the coronary microcirculation: diagnosis and treatment. *Deutsches Arzteblatt International*. November 2023. doi:10.3238/arztebl.m2023.0205.
17. Süttsch G, Oechslin E, Mayer I, Hess OM. Effect of diltiazem on coronary flow reserve in patients with microvascular angina. *International Journal of Cardiology*. 1995;52(2):135-143. doi:10.1016/0167-5273(95)02458-9.
18. Togni M, Vigorito F, Windecker S, et al. Does the B-Blocker Nebivolol increase coronary flow reserve? *Cardiovascular Drugs and Therapy*. 2007;21(2):99-108. doi:10.1007/s10557-006-0494-7.
19. Mehta PK, Goykhman P, Thomson L, et al. Ranolazine improves angina in women with evidence of myocardial ischemia but no obstructive coronary artery disease. *JACC: Cardiovascular Imaging*. 2011;4(5):514-522. doi:10.1016/j.jcmg.2011.03.007.
20. Eriksson BE, Tyni-Lenné R, Svedenhag J, et al. Physical training in Syndrome X. *Journal of the American College of Cardiology*. 2000;36(5):1619-1625. doi:10.1016/s0735-1097(00)00931-1.
21. Denardo SJ, Wen X, Handberg EM, et al. Effect of phosphodiesterase type 5 inhibition on microvascular coronary dysfunction in women: A Women's Ischemia Syndrome

- Evaluation (WISE) Ancillary study. *Clinical Cardiology*. 2011;34(8):483-487. doi:10.1002/clc.20935.
22. Yoo SY, Song SG, Lee J, et al. Efficacy of cilostazol on uncontrolled coronary vasospastic angina: a pilot study. *Cardiovascular Therapeutics*. 2013;31(3):179-185. doi:10.1111/j.1755-5922.2012.00312.x.
23. Shin E, Lee J, Yoo SY, et al. A randomised, multicentre, double blind, placebo controlled trial to evaluate the efficacy and safety of cilostazol in patients with vasospastic angina. *Heart*. 2014;100(19):1531-1536. doi:10.1136/heartjnl-2014-305986.
24. Neglia D, Fommei E, Varela-Carver A, et al. Perindopril and indapamide reverse coronary microvascular remodelling and improve flow in arterial hypertension. *Journal of Hypertension*. 2011;29(2):364-372. doi:10.1097/hjh.0b013e328340a08e.
25. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. *The New England Journal of Medicine*. 2010;362(10):886-895. doi:10.1056/nejmoa0907272.
26. Banerjee D, Sabe SA, Xing H, et al. Canagliflozin improves coronary microvascular vasodilation and increases absolute blood flow to the myocardium independent of angiogenesis. *The Journal of Thoracic and Cardiovascular Surgery*. 2023;166(6):e535-e550. doi:10.1016/j.jtcvs.2023.08.017.
27. Case BC, Merdler I, Medranda GA, et al. Understanding Patient Characteristics and Coronary Microvasculature: Early Insights from the Coronary Microvascular Disease Registry. *The American Journal of Cardiology*. 2023;205:97-103. doi:10.1016/j.amjcard.2023.07.159.
28. Schindler TH, Dilsizian V. Coronary microvascular dysfunction. *JACC: Cardiovascular Imaging*. 2020;13(1):140-155. doi:10.1016/j.jcmg.2018.11.036.
29. Kuruvilla S, Kramer CM. Coronary microvascular dysfunction in women: an overview of diagnostic strategies. *Expert Review of Cardiovascular Therapy*. 2013;11(11):1515-1525. doi:10.1586/14779072.2013.833854.
30. Pepine CJ, Anderson RD, Sharaf BL, et al. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia. *Journal of the American College of Cardiology*. 2010;55(25):2825-2832. doi:10.1016/j.jacc.2010.01.054.

31. Rutledge T, Reis SE, Olson MB, et al. Depression symptom severity and reported treatment history in the prediction of cardiac risk in women with suspected myocardial ischemia. *Archives of General Psychiatry*. 2006;63(8):874. doi:10.1001/archpsyc.63.8.874.
32. Pries AR, Reglin B. Coronary microcirculatory pathophysiology: can we afford it to remain a black box? *European Heart Journal*. February 2016;ehv760. doi:10.1093/eurheartj/ehv760.
33. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2003;23(2):168-175. doi:10.1161/01.atv.0000051384.43104.fc.
34. Sara JD, Toya T, Ahmad A, et al. Mental stress and its effects on vascular health. *Mayo Clinic Proceedings*. 2022;97(5):951-990. doi:10.1016/j.mayocp.2022.02.004.
35. Williams JK, Kaplan JR, Manuck SB. Effects of psychosocial stress on endothelium-mediated dilation of atherosclerotic arteries in cynomolgus monkeys. *Journal of Clinical Investigation*. 1993;92(4):1819-1823. doi:10.1172/jci116772.