Koronární mikrovaskulární dysfunkce pohledem dynamického CZT SPECT se zátěží

Martin Pumprla 4.5.2025

1. Interní klinika kardiologická
   Fakultní Nemocnice Olomouc

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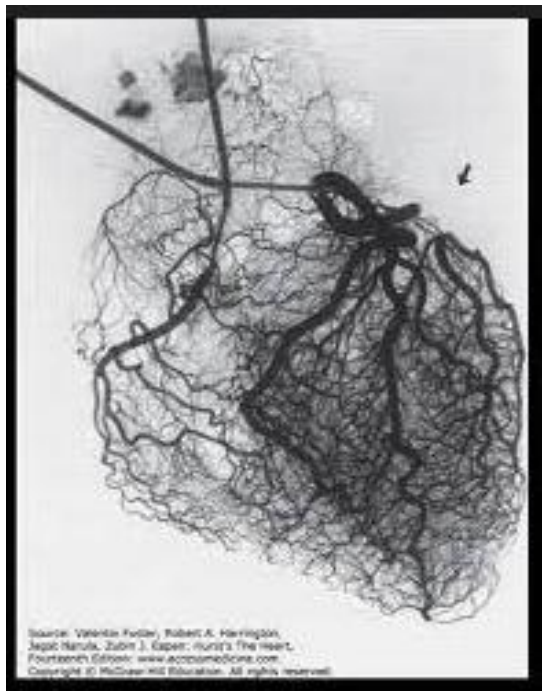

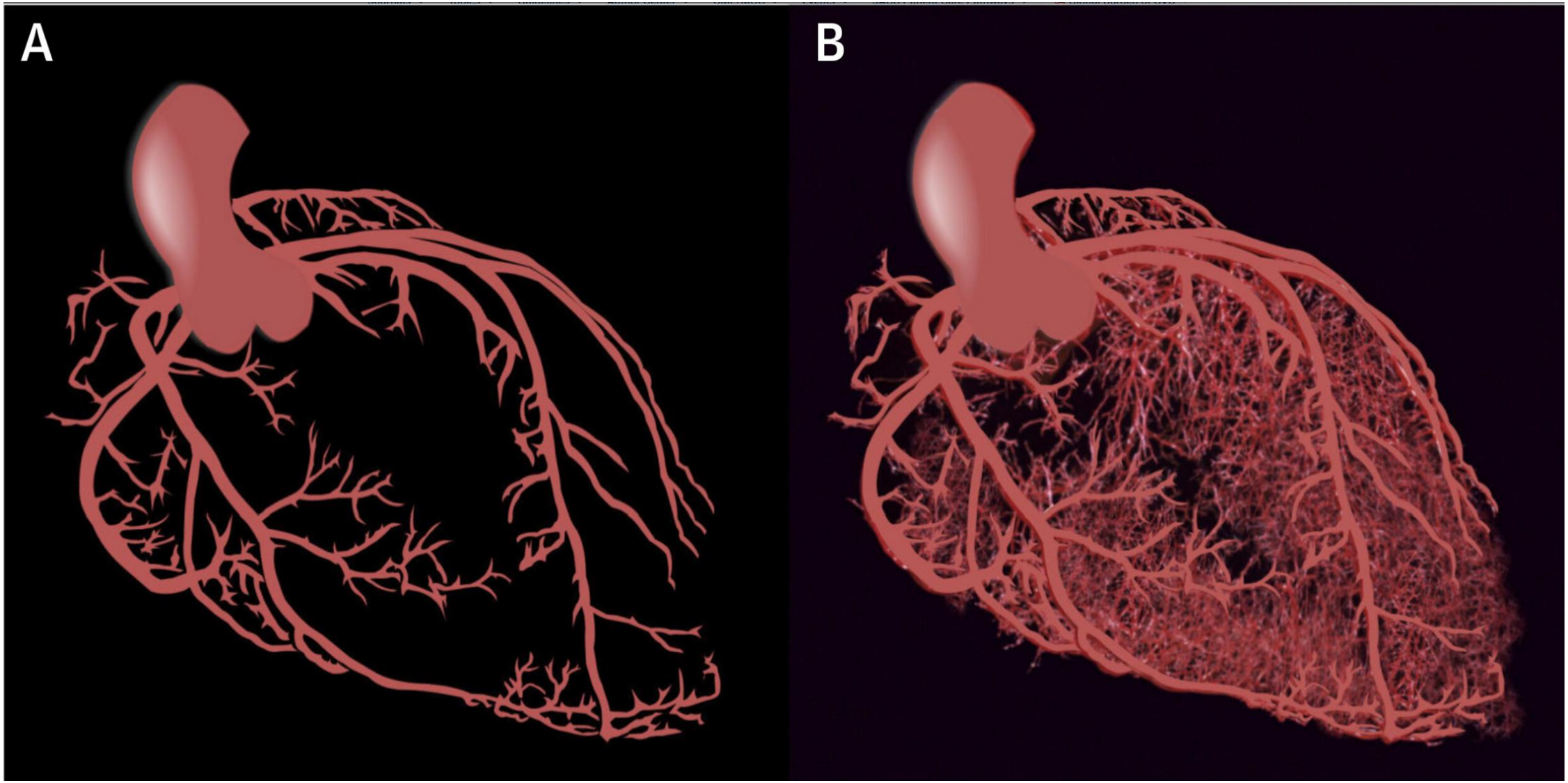
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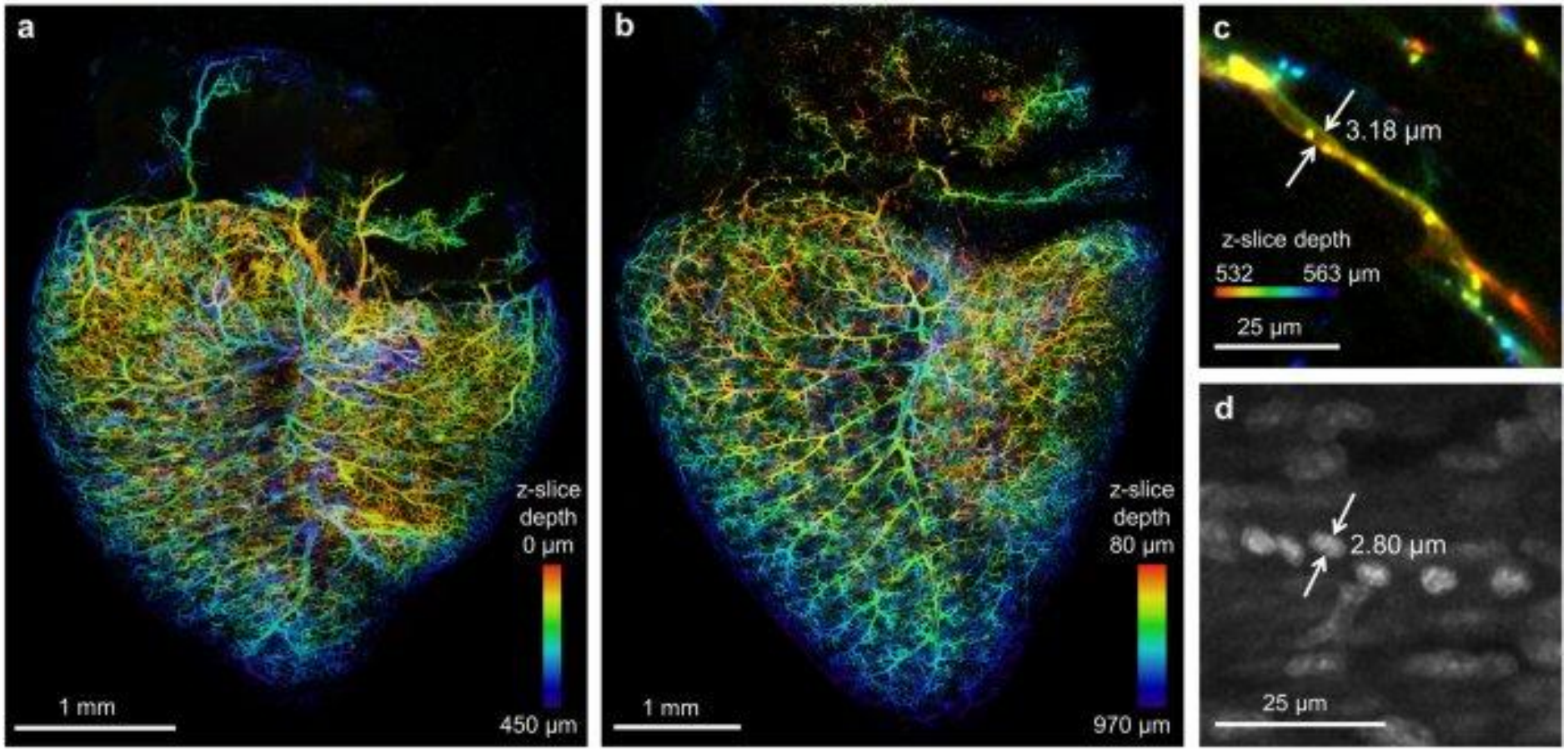
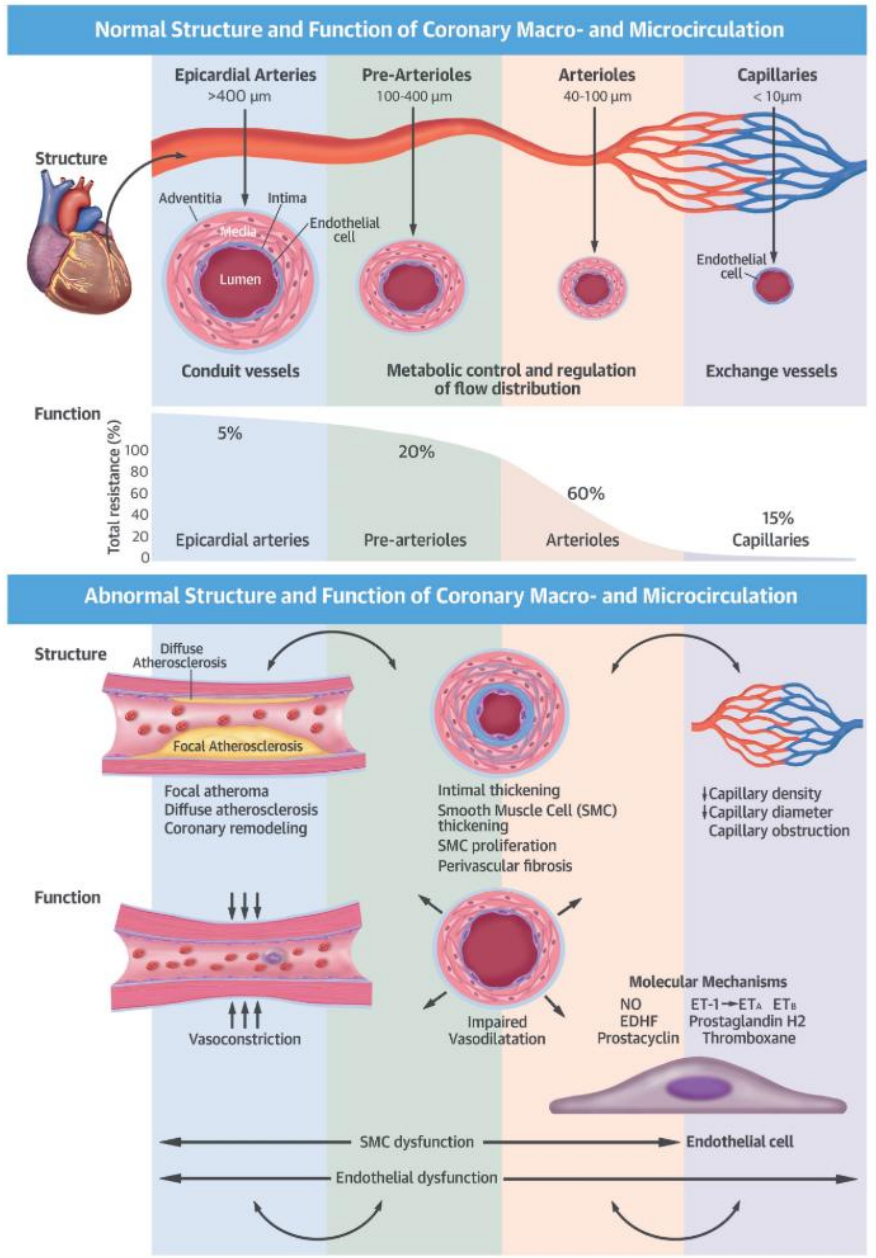
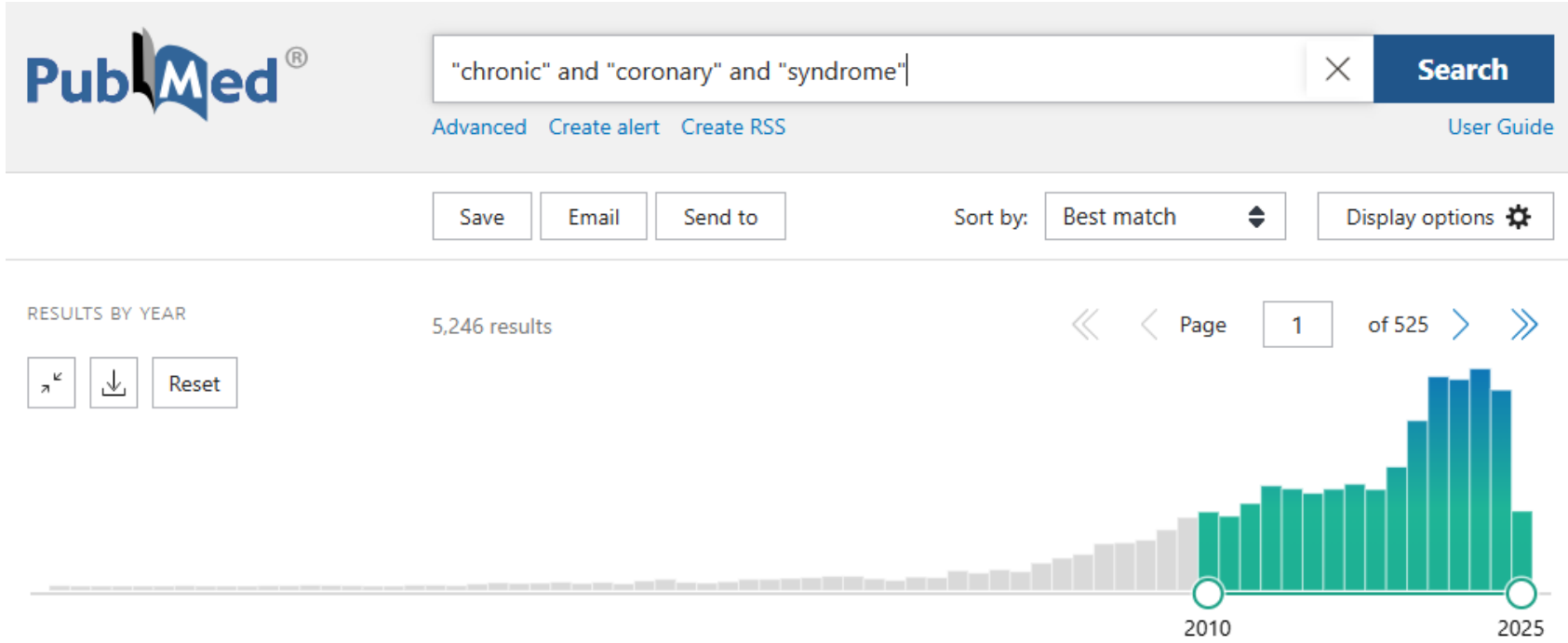
Posterior side of the heart



CENTRAL ILLUSTRATION: Normal and Abnormal Structure and Function of the Coronary Macrocirculation and Microcirculation



Taqueti, V.R. et al. J Am Coll Cardiol. 2018;72(21):2625-41.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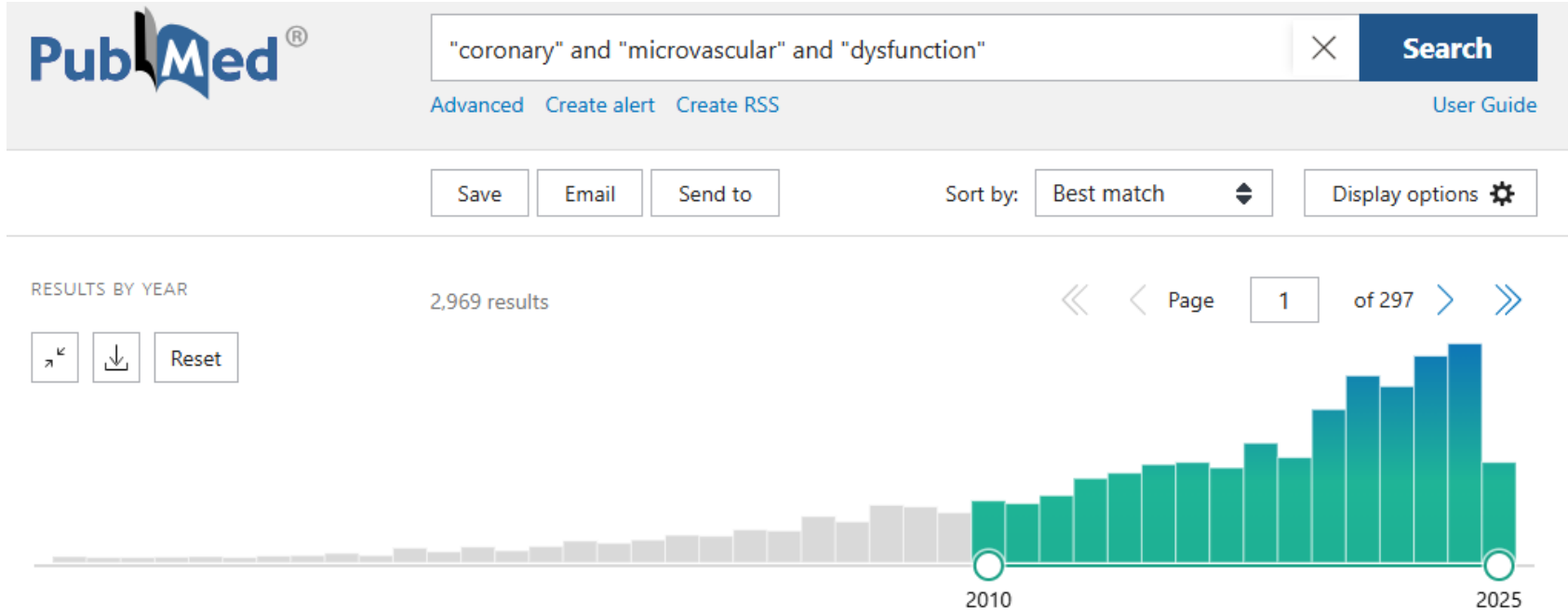
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2019 Guidelines	Class	Level	2024 Guidelines	Class	Level
Diagnosis and management of patients with ANOCA/INOCA					
Guidewire-based CFR and/or microcirculatory resistance measurements should be considered in patients with persistent symptoms, but coronary arteries that are either angiographically normal or have moderate stenoses with preserved iwFR/FFR.	**IIa**	**B**	In persistently symptomatic patients despite medical treatment with suspected ANOCA/INOCA (i.e. anginal symptoms with normal coronary arteries or non-obstructive lesions at non-invasive imaging, or intermediate stenoses with normal iFR/FFR at coronary arteriography) and poor quality of life, intracoronary functional testing is recommended to identify potentially treatable endotypes and to improve symptoms and quality of life, considering patient choices and preferences.	**I**	**B**

In patients with HFpEF with persistent angina or equivalent symptor or CMR perfusion or invasive coronary functional testing should b dysfunction.[883–885,887–889]
In selected patients with HFrEF undergoing high-risk PCI for comple experienced centres.[905–907]
Managing heart failure in CCS patients
It is recommended that CCS patients with HF be enrolled in a multi hospitalization and to improve survival.[526,909–911]
An ACE-I, an MRA, an SGLT2 inhibitor (dapagliflozin or empagliflozin) patients with HFrEF to reduce the risk of HF hospitalization and dea
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended (HFmrEF) or HFpEF to reduce the risk of HF hospitalization or card
An ARB is recommended in symptomatic patients with CCS and HF hospitalization and cardiovascular death.[914]
Sacubitril/valsartan is recommended as a replacement for an ACE-I hospitalization and of cardiovascular and all-cause death.[693]
Diuretics are recommended in CCS patients with HF and signs and/ capacity, and reduce HF hospitalizations.[915]
An ICD is recommended to reduce the risk of sudden death and all-c ischaemic aetiology (unless they have had an MI in the prior 40 days), a provided they are expected to survive substantially longer than 1 ye
An ICD is recommended to reduce the risk of sudden death and all- arrhythmia causing haemodynamic instability, and who are expected reversible causes or unless the ventricular arrhythmia has occurred
CRT is recommended for CCS patients with symptomatic HF, sinus rh an LBBB QRS morphology to improve symptoms and survival and to
CRT rather than right ventricular pacing is recommended for patien indication for ventricular pacing for high-degree AV block in order to

ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, ang coronary artery bypass grafting; CAD, coronary artery disease; CCS, chron resonance; CRT, cardiac resynchronization therapy; FFR, fractional flow rese ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICA, inva LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MI, myoc percutaneous coronary intervention; PET, positron emission tomography; SGLT
[a]Class of recommendation.
[b]Level of evidence.

5.2. Angina/ischaemia with non-obstructive coronary arteries

5.2.1. Definition

A large proportion of patients undergoing coronary angiogra cause of angina do not have obstructive epicardial coronary (ANOCA). In these patients, the prevalence of demonstrable isc (INOCA) varies, depending on the stress test performed, betwe and 30% (*Figure 12*).[926–928] Angina/ischaemia with non-obstruct onary arteries is more frequent among women (approximately 70%) than in men (30% to 50%) referred for ICA.[7,929] The m between blood supply and myocardial oxygen demands leadin gina and ischaemia in ANOCA/INOCA may be caused by CM or epicardial coronary artery spasm.[36] However, these conditi rarely correctly diagnosed, and, therefore, no tailored therapy scribed for these patients. As a consequence, these patients c to experience recurrent angina with poor QoL, leading to re hospitalizations, unnecessary repeat coronary angiography, and cardiovascular outcomes in the short and long term.[36]

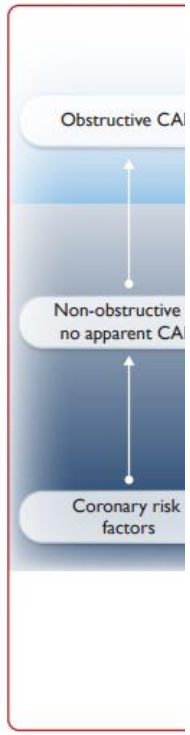


Figure 12 Prevalence of disea ANOCA, angina with non-obst onary arteries. In the ILIAS (Incl referred for invasive coronary a these patients. An impaired CF invasive functional testing in on of acetylcholine and test proto

5.2.2.1. Microvascular angina

Microvascular angina is the clini caused by structural or functio ture (leading to impaired CFR a ance) and/or abnormal vasoco dynamic arteriolar obstructio chanisms may co-exist and cor

The prevalence of MVA non-obstructive CAD who h transthoracic Doppler echoca vasively or by PET with differe had CMD.[935,936] The thresho depending on the technique Doppler); the threshold is a

5.2.2.2. Epicardial vasospas

Vasospastic angina is the clin caused by abnormal vasocon ary arteries leading to a dyn diagnostic criteria for VSA h and epicardial VSA can co-ex nosis.[947] Concomitant endot tients with INOCA with i impaired adenosine-mediate

The Japanese population h spasm than Western popula tiple coronary spasms (≥2 s Japanese (24.3%) and Taiwa higher than those in Caucasi

5.2.3. Clinical present

Angina/ischaemia with non-c with a wide variation in its c may vary over time. Failure t a patient with documented search pathway to elucidate

5.2.4. Short- and long

Symptoms of angina/ischaem are associated with advers Angina/ischaemia with non-c with poor QoL, higher risk verse events, including morta hospital readmissions and re incidence of all-cause death obstructive atherosclerosis v cally normal epicardial vesse by stress echocardiography higher incidence of events co cise electrocardiographic str higher risk of adverse cardio diagnosed by PET or transth higher risk in patients with tion.[300,962] Microvascular an with increased major advers rates over a 5-year follow-up with major adverse events, and syncope.[963] In a group non-invasive testing did not higher risk of long-term card coronary physiological assess the identification of patient s in long-term cardiovascular

5.2.5. Diagnosis

The presence of myocardial obstructive CAD on CCTA picion of ANOCA/INOCA. T sively based on invasive microcirculation, given that the coronary microcirculatic and invasive tests have been vascular function (*Figure 13*).

Figure 13 Diagnostic algori non-obstructive coronary art raphy; CFR, coronary flow re therapy; HMR, hyperaemic m IMR, index of microcirculator emission tomography; SPECT

bradycardia effect of Ach ca Ach is short in contrast to was previously used for th The diagnosis of MVA and V vasospasm is made accordin considered positive for m

Figure 14 Spas electrocardiogram (i) endothelial-de (100–200 μg). Thi by i.c. adenosine ([a]The incremental

of coronary vasos Ach boluses of u ported.[37,970,971] In gorithm was also

At the end of t to i.v. administrat enosine[973] is asse patients with cor can be used[974] b the risk of induci

Different prot shows an exampl that may be adop nosing vasospasm unlicensed, paren an experienced in

5.2.6. Manage non-obstruct

Management sho disciplinary care therapeutic mana tablished ANOC atherosclerosis ar style factors is wa

Figure 15 Treatment of angi with non-obstructive coronary coronary arteries. Treatment treatment according to underl

with ranolazine, an antianginal and ventricular compliance b load.[983] Spinal cord stimulatio fractory after medical therapy

There are currently severa ANOCA/INOCA. The Wom Non-ObstRuctIve CORon NCT03417388) is currently

Recommendation Table 25 — Recommendations for diagnosis and management of patients with angina/ischaemia with non-obstructive coronary arteries (see also Evidence Table 25)

Recommendations	Class[a]	Level[b]
Diagnosis of ANOCA/INOCA endotypes		
In persistently symptomatic patients despite medical treatment with suspected ANOCA/INOCA (i.e. anginal symptoms with normal coronary arteries or non-obstructive lesions at non-invasive imaging, or intermediate stenoses with normal FFR/iFR at coronary arteriography) and poor quality of life, invasive coronary functional testing is recommended to identify potentially treatable endotypes and to improve symptoms and quality of life, considering patient choices and preferences.[36,37,298,930,939,985]	I	B
In persistently symptomatic patients with documented or suspected ANOCA/INOCA, transthoracic Doppler of the LAD, stress echocardiography, CMR, and PET may be considered for the non-invasive assessment of coronary/myocardial flow reserve.[44,231,233–235,300,986,987]	IIb	B
Diagnostic tests for vasospastic angina		
In individuals with suspected vasospastic angina, a resting 12-lead ECG recording during angina is recommended.	I	C
In patients with suspected vasospastic angina and repetitive episodes of rest angina associated with ST-segment changes that resolve with nitrates and/or calcium antagonists, invasive coronary functional testing is recommended to confirm the diagnosis and to determine the severity of underlying atherosclerotic disease.	I	C
In individuals with suspected vasospastic angina and frequent symptoms, ambulatory ST-segment monitoring should be considered to identify ST-segment deviation during angina.[192–194]	IIa	B
Management of ANOCA/INOCA		
In symptomatic patients with ANOCA/INOCA, medical therapy based on coronary functional test results should be considered to improve symptoms and quality of life.[298,977]	IIa	A
For the management of endothelial dysfunction, ACE-I should be considered for symptom control.[988]	IIa	B
For the management of microvascular angina associated with reduced coronary/myocardial blood flow reserve, antianginal medications aiming at preventing demand myocardial ischaemia should be considered for symptom control.[989,990]	IIa	B
For the treatment of isolated vasospastic angina		
Calcium channel blockers are recommended to control symptoms and to prevent ischaemia and potentially fatal complications.[991–996]	I	
Nitrates should be considered to prevent recurrent episodes.[993,997,998]	IIa	
For the treatment of overlapping endotypes		
In patients with evidence of overlapping endotypes, combination therapy with nitrates, calcium channel blockers, and other vasodilators may be considered.[999,1000]	IIb	

ACE-I, angiotensin-converting enzyme inhibitor; ANOCA, angina with coronary arteries; CMR, cardiac magnetic resonance; ECG, electro fractional flow reserve; iFR, instantaneous wave-free ratio; INOCA, non-obstructive coronary arteries; LAD, left anterior descending; PET, tomography.
[a]Class of recommendation.
[b]Level of evidence.

Continued

5.3. Other specific patient groups

5.3.1. Older adults

Between 2015 and 2050, the proportion of the world aged >60 years is set to nearly double to 22%. Ageing patients to a high incidence and prevalence of CAD, and women. Typically, in the context of CVD, older pa fined as those ≥75 years of age;[1] it should be noted, h such age cut-offs are relatively arbitrary, and biological a this threshold in clinical practice. Clinical characteristic adult population are heterogeneous, with frailty, comor tive function, and health-related QoL playing important ing clinical care and as predictors of adverse outco Older patients often present with symptoms other which may delay the diagnosis of CCS.[1004]

Ageing is often accompanied by both comorbidities a consequently leads to potentially excessive polypharma ing treatment decisions, clinicians should take into acc ited external validity of RCTs for older adults.[36] Olde often underrepresented in RCTs as a consequence of teria and under-recruitment,[531,1006,1007] though the shown to have a higher underlying risk for cardio comes.[1008] The treatment of CCS in older adults is co a higher vulnerability to complications for both conser vasive strategies, such as bleeding, renal failure, and ne pairments, all of which require special attention. The compared with bare-metal stents, in combination with ation of DAPT, is associated with significant safety and efits in older adults.[1009] Frailty is of utmost importance decision-making.[1010]

5.3.2. Sex differences in chronic coronary s

Ischaemic heart disease is the leading cause of mortality fo they have been historically underrepresented in R Differences in symptom presentation, in the accuracy of d for obstructive CAD, and other factors that lead to diffe evaluation, or early treatment of women with myocar

ESC GL 2024 pro chronické koronární syndromy zahrnují i diagnostiku **ischemie a anginy u bez obstrukce koronárních tepen.**

Problematice **koronární mikrovaskulární dysfunkce** se věnuje i **AHA GL 2023** Management of Patients With Chronic Coronary Disease

Dvě odlišné formy:

ANGINA with non-obstructive coronary arteries ANOCA

ISCHEMIA with non-obstructive coronary artery INOCA

ANOCA

Charakteristikou ANOCA je absence srdeční ischemie

Pacienti s ANOCA mohou vykazovat anginózní symptomy nebo jejich ekvivalenty, jako je dušnost, avšak dostupné testy (zátěžová ergometrie, echokardiografie, nukleární zátěžové testy) jsou negativní.

INOCA

Naopak INOCA označuje již přítomnost myokardiální ischemie, v terénu neobstrukční CAD.
Pacient může mít pozitivní zátěžovou ergometrii, změny na EKG, či elevovaný troponin.

V **minulosti** byl tento stav označován jako **syndrom X**, avšak vzhledem k pokroku v porozumění patogenezi je dnes preferován termín ischemie bez obstrukce koronárních tepen.

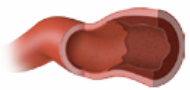
B

Main mechanisms of myocardial ischaemia in chronic coronary syndromes

Epicardial

Structural

Atherosclerosis (focal or diffuse)

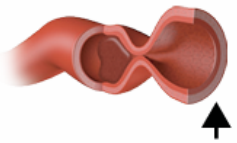


Stabilized intramural haematoma

Myocardial bridge

Coronary aneurysm

Functional



Epicardial vasospasm

Endothelial dysfunction and/or VSMC hyperreactivity

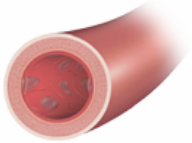
Autonomic dysregulation

Microvascular

Structural

- Inward arteriolar remodelling
- Capillary rarefaction
- Intravascular plugging
- Perivascular fibrosis or infiltration
- Extramural compression (myocardial hypertrophy, increased LVEDP)

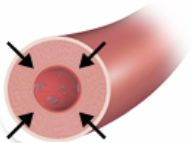
Functional



Impaired vasodilation

Endothelial dysfunction and/or VSMC hyperreactivity

Autonomic dysregulation



Increased vasoconstriction

Vazospazmy

Zvýšená kontraktilita hladkého svalstva při **deficitu NO** při **endoteliální dysfunkci**, či hypersenzitivita na vazokonstrikční stimuly

Rizikové faktory:

Kouření	**Emoční stres**	**Hyperventilace**	**Náhlý chlad**	**Ranní fyzická zátěž**	**Drogy**

Vazokonstrikci sledujeme spíše u mladších pacientů a u žen

Mikrovaskulární remodelace

Strukturální změny, obstrukce, či útlak mikrocirkulace, vedoucí ke snížené rezervě

Rizikové faktory:

Diabetes mellitus	**Kouření**	**Hypertenze**	**Dyslipidémie**	**Ateroskleróza**

Spíše u **starších pacientů**

CMD se vyskytuje i u řady dalších stavů, včetně **revmatologických onemocnění** (systémový lupus erythematodes, revmatoidní artritida), **hypertrofické kardiomyopatie** a **srdeční amyloidózy**

EPIDEMIOLOGIE

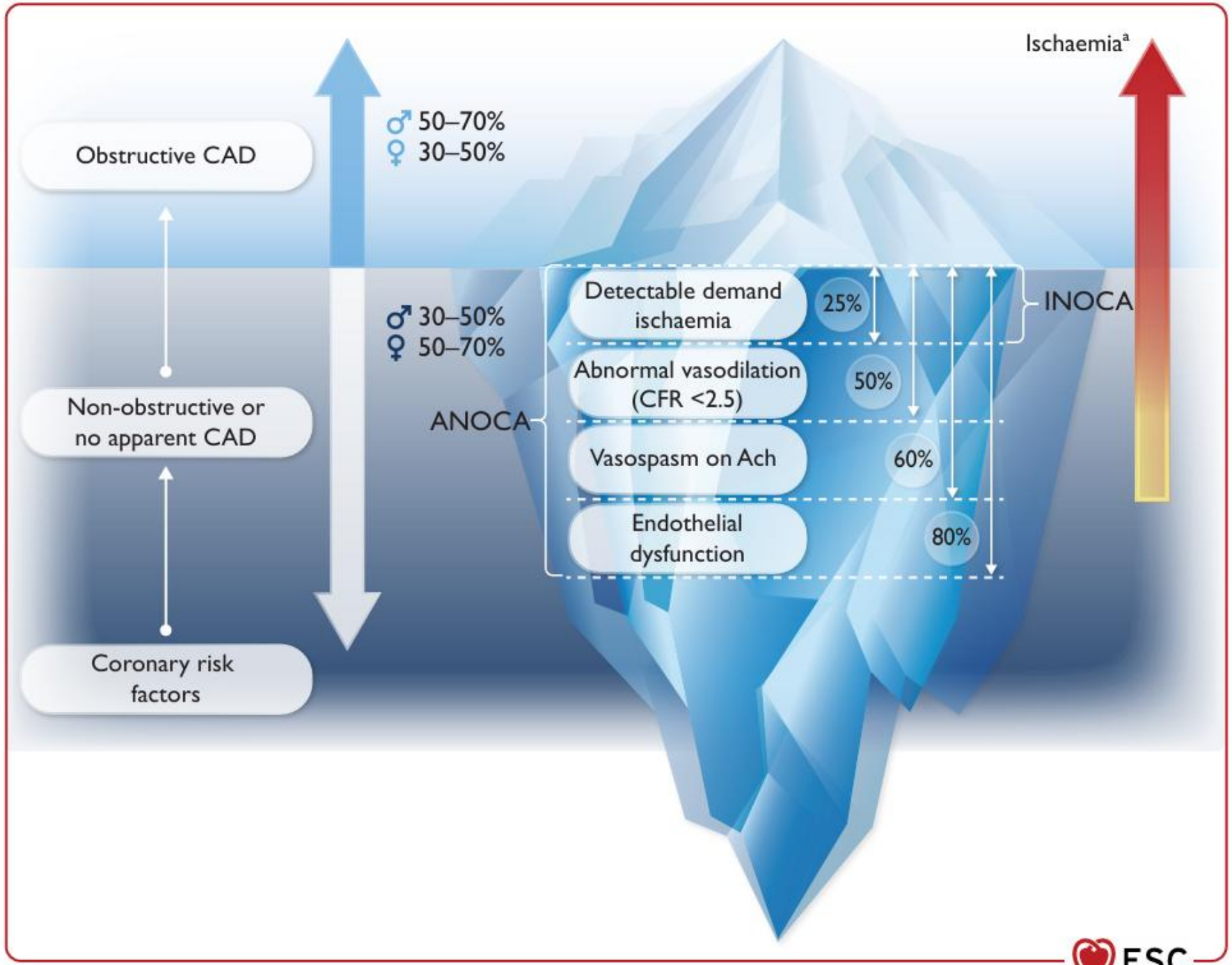
Mikrovaskulární dysfunkce je časté onemocnění.

Metaanalýza 56 studií zahrnujících více než 14 400 pacientů prokázala u pacientů indikovaných ke koronarografii prevalenci CMD až 41% (95 % CI 36–47 %).

U většiny pacientů s ANOCA/INOCA se symptomy objevují v souvislosti s **fyzickou námahou** a/nebo **emočním stresem** a typicky **ustupuje v klidu**.

Symptomy **mohou limitovat každodenní aktivity**. Během epizody mohou být přítomny tachykardie, akcelerace hypertenze či vegetativní doprovod.

Prediktorem výskytu **diastolické dysfunkce** a **srdečního selhání se zachovalou ejekční frakcí (HFpEF)**. Může se manifestovat i jako **infarkt myokardu bez obstrukce koronárních tepen (MINOCA).**


Ischaemia[a]
Obstructive CAD
♂ 50–70%
♀ 30–50%
Non-obstructive or no apparent CAD
♂ 30–50%
♀ 50–70%
Coronary risk factors
ANOCA
Detectable demand ischaemia
25%
Abnormal vasodilation (CFR <2.5)
50%
Vasospasm on Ach
60%
Endothelial dysfunction
80%
INOCA

DIAGNOSTIKA

- Diagnóza **mikrovaskulární anginy** je stanovena na základě kritérií mezinárodní pracovní skupiny **COVADIS**, která zahrnují
  I. přítomnost anginózních symptomů
  II. objektivní průkaz ischemie
  III. koronarograficky verifikovanou absenci obstrukční CAD
  IV. důkaz koronární mikrovaskulární dysfunkce

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International standardization of diagnostic criteria for microvascular angina☆

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ABSTRACT

Standardization of diagnostic criteria for ischemic symptoms due to coronary microvascular dysfunction (CMD) is needed for further investigation of patients presenting with anginal chest pain consistent with "microvascular angina" (MVA). At the annual *Coronary Vasomotion Disorders International Study Group* (COVADIS) Summits held in August 2014 and 2015, the following criteria were agreed upon for the investigative diagnosis of microvascular angina: (1) presence of symptoms suggestive of myocardial ischemia; (2) objective documentation of myocardial ischemia, as assessed by currently available techniques; (3) absence of obstructive CAD (<50% coronary diameter reduction and/or fractional flow reserve (FFR) >0.80) (4) confirmation of a reduced coronary blood flow reserve and/or inducible microvascular spasm. These standardized criteria provide an investigative structure for mechanistic, diagnostic, prognostic and clinical trial studies aimed at developing an evidence base needed for guidelines in this growing patient population. Standardized criteria will facilitate microvascular angina registries and recruitment of suitable patients into clinical trials. Mechanistic research will also benefit from the implementation of standardized diagnostic criteria for MVA.

1. Introduction

Myocardial ischemia that develops in the absence of hemodynamically significant coronary artery stenoses continues to puzzle physicians worldwide and a large proportion of patients with this condition are discharged from specialty medical attention with a diagnosis of "non-cardiac chest pain". A recent U.S. study in over 400,000 individuals undergoing diagnostic coronary angiography for suspected obstructive epicardial coronary disease showed that 59% had either normal coronary arteriograms or non-obstructive (<50% stenosis) coronary artery disease (CAD) [1]. Of importance, the arterial coronary tree comprises not only the epicardial arteries, but also smaller arteries and arterioles (<500 μm). The latter feed the capillaries and represent an important part of the coronary microcirculation, namely the main site of regulation of myocardial blood flow. The term coronary microvascular dysfunction (CMD) was proposed to cover a large number of clinical scenarios characterized by evidence of a reduced Coronary Flow Reserve (CFR) in the absence of obstructive epicardial disease [2]. Several studies have demonstrated coronary microvascular dysfunction (CMD) in a large proportion of patients with non-obstructive CAD (~30–50%) even after exclusion of epicardial spasm using provocative testing with acetylcholine [3,4]. COVADIS, the *Coronary Vasomotion Disorders International Study Group*, was established to develop standardized criteria for coronary vasomotor disorders thereby facilitating the clinical diagnosis of affected patients and promoting international collaborative research endeavors to improve our understanding of these elusive disorders. This paper focuses on the standardization of criteria for microvascular angina (MVA) attributable to CMD, in patients presenting with angina pectoris or ischemic-like symptoms

Abbreviations: CAD, coronary artery disease; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance imaging; COVADIS, Coronary Vasomotion Disorders International Study Group; CTA, computed tomography angiography; FFR, fractional flow reserve; MVA, microvascular angina; PET, positron emission tomography.

☆ The manuscript has been handled by the Guest editor Prof. Peter Schwartz.

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[2] JCK and NBM contributed equally to the manuscript.

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0167-5273/

DIAGNOSTIKA invazivní

U pacientů bez obstrukční CAD s recidivujícími symptomy je vhodné podrobné vyšetření zaměřené na hodnocení **koronární průtokové rezervy (CFR)**, která je klíčovým parametrem **remodelace mikrocirkulace**.

CFR představuje **relativní poměr** mezi **maximálním koronárním průtokem**, který indukujeme adenosinem, **a klidovým koronárním průtokem**.

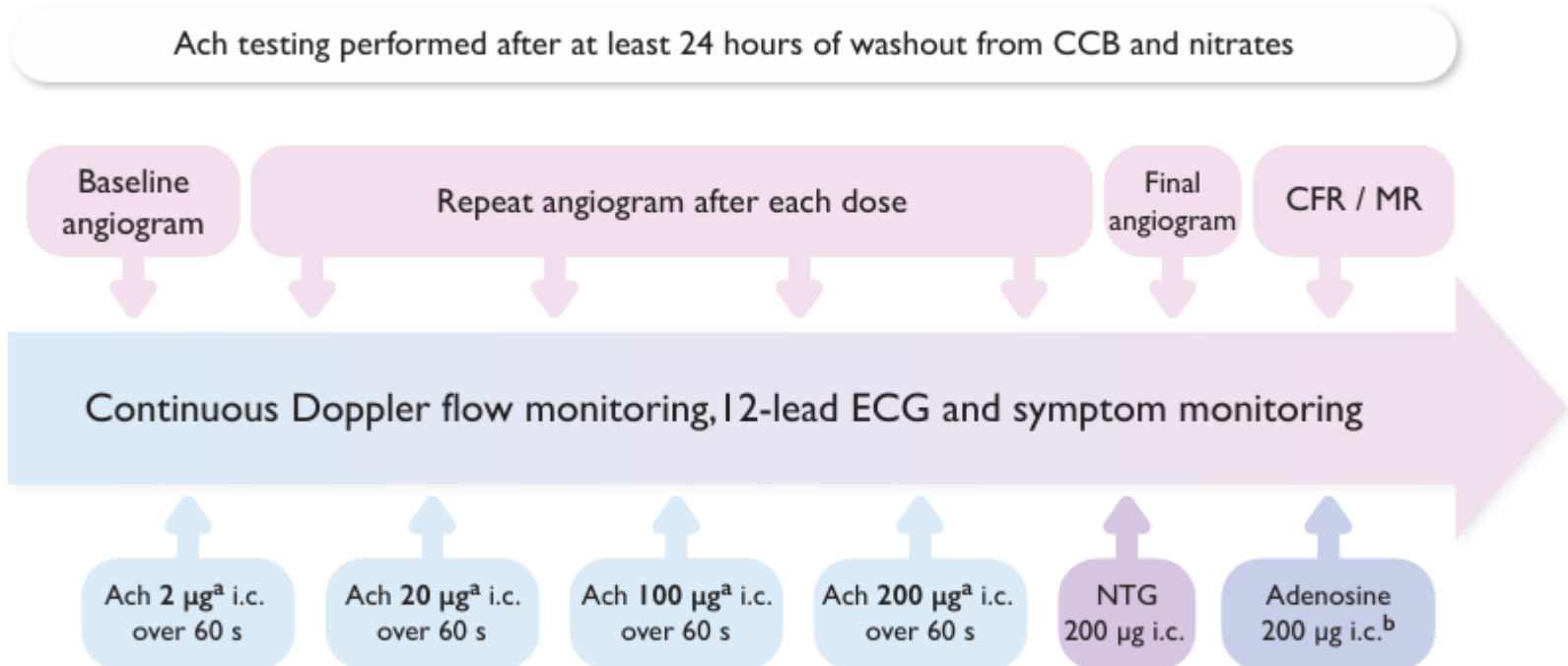
Normální hodnoty CFR se pohybují v rozmezí **2,5–5**, přičemž hodnoty **≤2,5** při absenci obstrukční CAD svědčí pro CMD. Je to **míra restrikce vazodilatace mikrocirkulace.**

Druhým parametrem **index mikrovaskulární rezistence** (IMR [U]).

K vyloučení mikrovaskulárních vazospazmů využíváme invazivní test aplikací acetylcholinem.

Test je považován za pozitivní pro vazospastickou anginu, pokud dojde k rozvoji příznaků doprovázených ischemickými změnami na EKG a angiograficky prokazatelnou ≥90% redukcí lumina koronární tepny. Pokud je redukce lumina <90 %, a jsou přítomné příznaky a ischemické změny na EKG, stanovuje se diagnóza mikrovaskulárního vazospazmu.

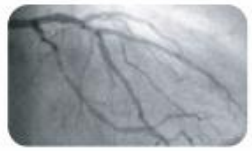
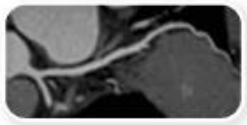
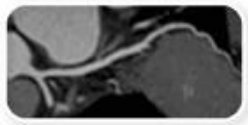
Ach- and adenosine-based vasoreactivity protocol



DIAGNOSTIKA neinvazivní

Neinvazivní hodnocení myokardiální průtokové rezervy (MFR):		
srdeční magnetickou rezonancí (CMR)	pozitronovou emisní tomografií (PET)	**dynamickým CZT SPECT se zátěží**

Přestože vyšetření CMD pomocí PET opakovaně platilo za zlatý standard, dle recentních studií má srovnatelné výsledky **dynamický CZT SPECT**, který pro svou **dostupnost a menší náročnost** může PET vyšetření v budoucnu ve využitelnosti předčít.

Risk factor-weighted clinical likelihood of obstructive CAD	Appropriate first-line test for suspected CCS
Very high >85%	Invasive coronary angiography 
High >50–85%	Functional imaging  PET/SPECT CMR Stress ECHO
Moderate >15–50%	CCTA  OR Functional imaging  PET/SPECT CMR Stress ECHO
Low >5–15%	Adjust the clinical likelihood  OR CCTA 
Very low ≤5%	Defer further testing

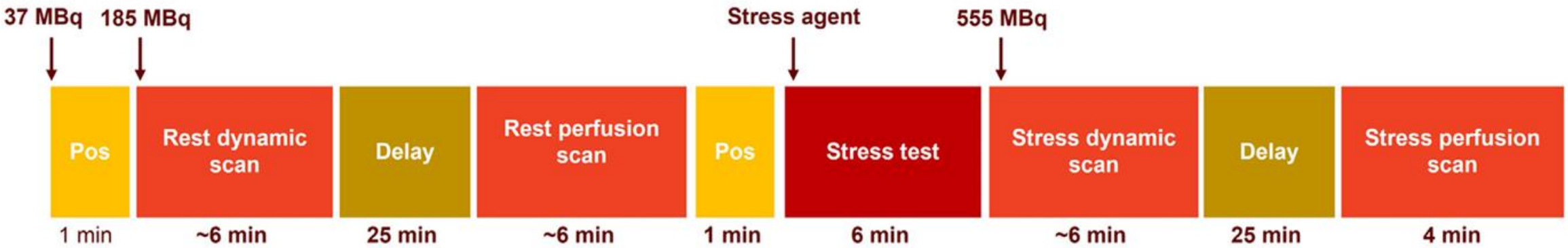
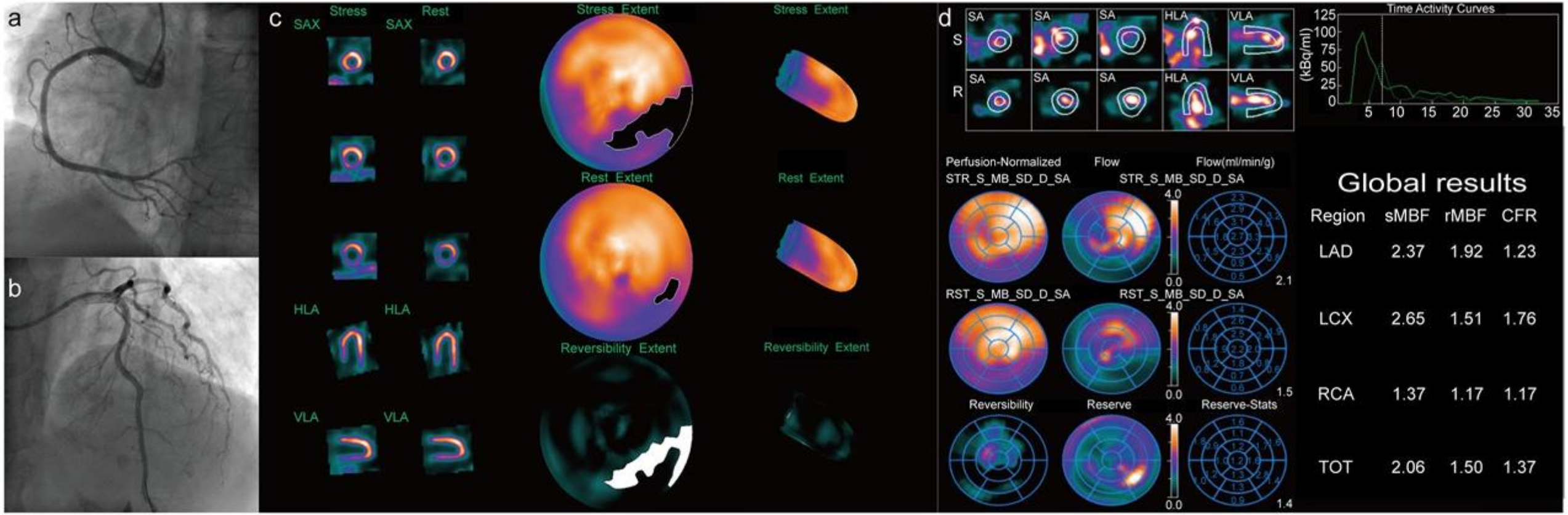


Fig. 1. Diagram shows one-day low-dose rest/stress protocol for cadmium-zinc-telluride single-photon emission computed tomography. A dose of 37 MBq of 99mTc-sestamibi is administered for a 60-s pre-scanning acquisition, to check patient position. Then, the remaining dose is injected and a list mode dynamic acquisition of six minutes starts. Standard rest perfusion scanning is also performed after dynamic rest scanning. Then pharmacological stress agent is administered, along with stress dose, and stress dynamic scan is performed, followed by a standard stress perfusion scanning.


a
b
c
SAX
Stress
SAX
Rest
HLA
HLA
VLA
VLA
Stress Extent
Rest Extent
Reversibility Extent
Stress Extent
Rest Extent
Reversibility Extent
d
S
R
SA
SA
SA
HLA
VLA
SA
SA
SA
HLA
VLA
Time Activity Curves
(kBq/ml)
125
100
75
50
25
0
5
10
15
20
25
30
35
Perfusion-Normalized
STR_S_MB_SD_D_SA
Flow
STR_S_MB_SD_D_SA
Flow(ml/min/g)
4.0
0.0
2.1
RST_S_MB_SD_D_SA
RST_S_MB_SD_D_SA
4.0
0.0
1.5
Reversibility
Reserve
Reserve-Stats
4.0
0.0
1.4
Global results
Region sMBF rMBF CFR
LAD 2.37 1.92 1.23
LCX 2.65 1.51 1.76
RCA 1.37 1.17 1.17
TOT 2.06 1.50 1.37

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https://doi.org/10.1007/s00259-023-06125-3

ORIGINAL ARTICLE

The prognostic value of CZT SPECT myocardial blood flow (MBF) quantification in patients with ischemia and no obstructive coronary artery disease (INOCA): a pilot study

Han Zhang[1,2] · Federico Caobelli[3] · Wenliang Che[4] · Yan Huang[1,2] · Yu Zhang[1,2] · Xin Fan[1,2] · Xueping Hu[1,2] · Chong Xu[4] · Mengyu Fei[5] · Jiajia Zhang[1,2] · Zhongwei Lv[1,2] · Kuangyu Shi[3,6] · Fei Yu[1,2]

Received: 7 November 2022 / Accepted: 22 January 2023 / Published online: 14 Februa

Abstract

Background Despite the demonstrated adverse outcome, it is difficult t
no obstructive coronary artery disease (INOCA). We aimed to explor
patients.

Methods The study population consisted of a retrospective cohort o
SPECT imaging and invasive coronary angiography (ICA). Dynami
using net retention model. Major adverse cardiovascular events (MA
myocardial infarction, nonfatal stroke, heart failure, late coronary rev

Results During a median follow-up of 15 months (interquartile rang
stress myocardial blood flow (sMBF) ($p < 0.001$) and coronary flow r
the MACE group. Optimal thresholds of sMBF<3.16 and CFR<2.52 w
sMBF (HR: 15.08; 95% CI 2.95–77.07; $p = 0.001$) and CFR (HR: 6.
prognostic factors for MACEs. Only sMBF<3.16 (HR: 11.20; 95% C
when sMBF and CFR were integrated considered. Compared with CI
nation and reclassification ability (C-index improvement = 0.06, $p =$
integrated discrimination improvement (IDI) = 0.10).

Conclusion The preliminary results demonstrated that quantitative ar
INOCA patients, which may allow the stratification for early preventi

Keywords INOCA · CZT SPECT · Myocardial blood flow (MBF) · C

This article is part of the Topical Collection on Cardiology.

Han Zhang and Federico Caobelli contributed equally to this work.

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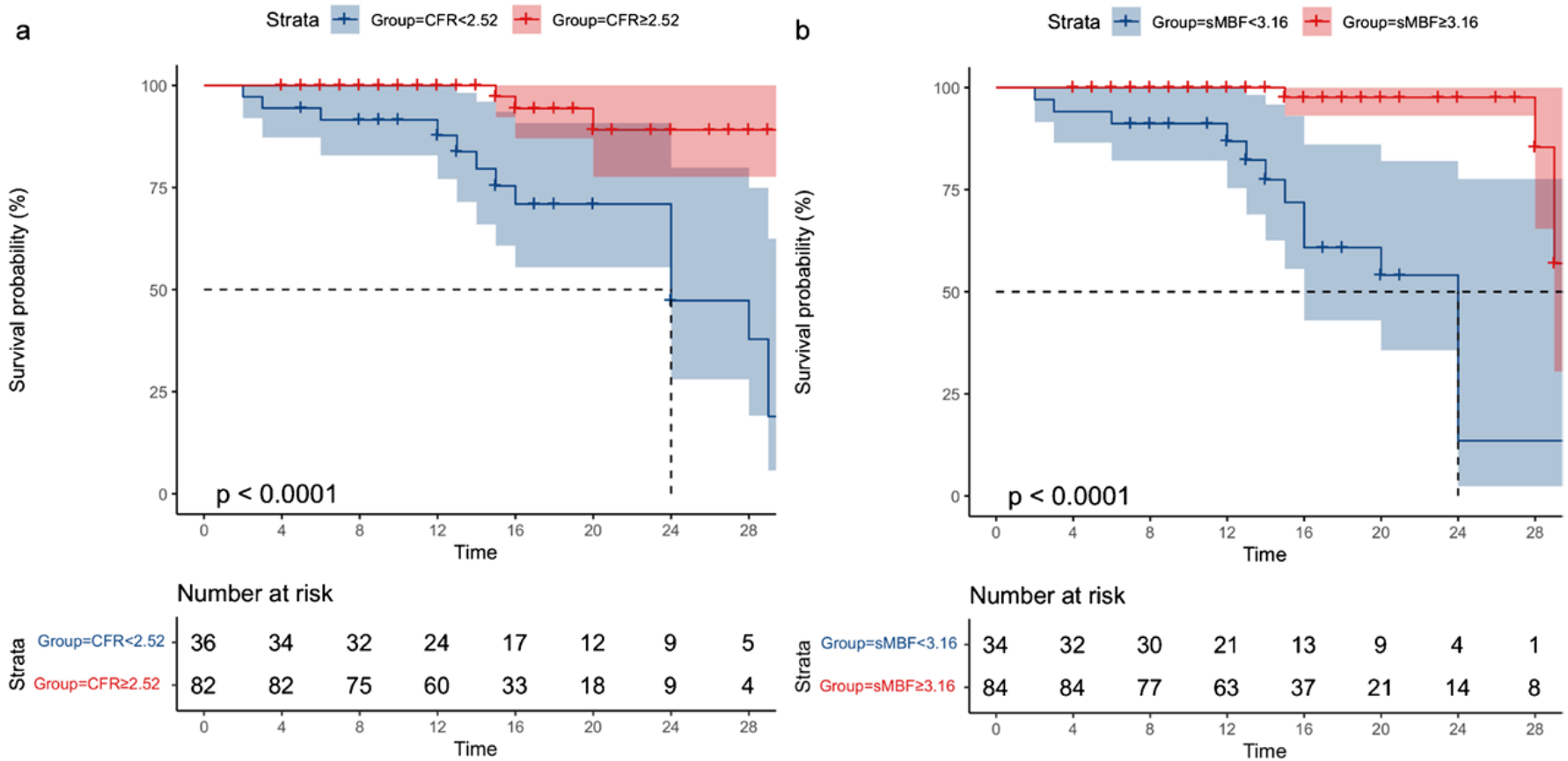
Fig. 4 ROC curves of **a** CFR and **b** sMBF for predicting MACEs in INOCA patients



PROGNÓZA

1

CMD je chronické onemocnění. Je možné symptomy zmírnit prostřednictvím režimových opatření a farmakoterapie, úplné vymizení obtíží je vzácné.

2

CMD **nepředstavuje benigní stav**, je spojena se **zvýšeným rizikem rozvoje CCS a závažných kardiovaskulárních příhod (MACE) s nepříznivou prognózou.**

3

Snížená CFR byla ve studiích nezávisle spojena s vyšší incidencí **diastolické dysfunkce** s hospitalizací pro **srdeční selhání se zachovanou ejekční frakcí (HFpEF)**.

LÉČBA

S cílem zmírnění anginózních symptomů, zlepšení tolerance fyzické zátěže a redukci KV rizika

Úprava životního stylu, pravidelná fyzická aktivita, redukci hmotnosti, zanechání kouření, zvládání stresu.

Léčba KV rizikových faktorů (**hypertenze, dyslipidémie, diabetes, kouření**) dle aktuálních doporučení.

LÉČBA

Farmakoterapie **mikrovaskulární remodelace**: **Beta-blokátory, inhibitory angiotenzin-konvertujícího enzymu (ACEi) a statiny jako léčbu první volby.**

Vazospastické formy **CaB, případně kombinace s nitráty a statiny jako léky první volby.**

U pacientů se symptomatickými **myokardiálními můstky** refrakterními na farmakoterapii lze zvážit chirurgickou revaskularizaci.

Mezi nové terapeutické přístupy patří intervence s cílem **redukce koronárního sinu (CSR).**

Coronary sinus reducer for the treatment of refractory angina (ORBITA-COSMIC): a randomised, placebo-controlled trial

Michael J Foley, Christopher A Rajkumar, Fiyyaz Ahmed-Jushuf, Florentina A Simader, Shayna Chotai, Rachel H Pathimagaraj, Muhammad Mohsin, Ahmed Salih, Danqi Wang, Prithvi Dixit, John R Davies, Tom R Keeble, Claudia Cosgrove, James C Spratt, Peter D O'Kane, Ranil De Silva, Jonathan M Hill, Sukhjinder S Nijjer, Sayan Sen, Ricardo Petraco, Ghada W Mikhail, Ramzi Khamis , Tushar Kotecha, Frank E Harrell, Peter Kellman, Darrel P Francis, James P Howard, Graham D Cole, Matthew J Shun-Shin, Rasha K Al-Lamee

Summary

Background The coronary sinus reducer (CSR) is proposed to reduce angina in patients with stable coronary artery disease by improving myocardial perfusion. We aimed to measure its efficacy, compared with placebo, on myocardial ischaemia reduction and symptom improvement.

Methods ORBITA-COSMIC was a double-blind, randomised, placebo-controlled trial conducted at six UK hospitals. Patients aged 18 years or older with angina, stable coronary artery disease, ischaemia, and no further options for treatment were eligible. All patients completed a quantitative adenosine-stress perfusion cardiac magnetic resonance scan, symptom and quality-of-life questionnaires, and a treadmill exercise test before entering a 2-week symptom assessment phase, in which patients reported their angina symptoms using a smartphone application (ORBITA-app). Patients were randomly assigned (1:1) to receive either CSR or placebo. Both participants and investigators were masked to study assignment. After the CSR implantation or placebo procedure, patients entered a 6-month blinded follow-up phase in which they reported their daily symptoms in the ORBITA-app. At 6 months, all assessments were repeated. The primary outcome was myocardial blood flow in segments designated ischaemic at enrolment during the adenosine-stress perfusion cardiac magnetic resonance scan. The primary symptom outcome was the number of daily angina episodes. Analysis was done by intention-to-treat and followed Bayesian methodology. The study is registered with ClinicalTrials.gov, NCT04892537, and completed.

Findings Between May 26, 2021, and June 28, 2023, 61 patients were enrolled, of whom 51 (44 [86%] male; seven [14%] female) were randomly assigned to either the CSR group (n=25) or the placebo group (n=26). Of these, 50 patients were included in the intention-to-treat analysis (24 in the CSR group and 26 in the placebo group). 454 (57%) of 800 imaged cardiac segments were ischaemic at enrolment, with a median stress myocardial blood flow of 1·08 mL/min per g (IQR 0·77–1·41). Myocardial blood flow in ischaemic segments did not improve with CSR compared with placebo (difference 0·06 mL/min per g [95% CrI –0·09 to 0·20]; Pr(Benefit)=78·8%). The number of daily angina episodes was reduced with CSR compared with placebo (OR 1·40 [95% CrI 1·08 to 1·83]; Pr(Benefit)=99·4%). There were two CSR embolisation events in the CSR group, and no acute coronary syndrome events or deaths in either group.

Interpretation ORBITA-COSMIC found no evidence that the CSR improved transmural myocardial perfusion, but the CSR did improve angina compared with placebo. These findings provide evidence for the use of CSR as a further antianginal option for patients with stable coronary artery disease.

Funding Medical Research Council, Imperial College Healthcare Charity, National Institute for Health and Care Research Imperial Biomedical Research Centre, St Mary's Coronary Flow Trust, British Heart Foundation.

Introduction

The coronary sinus reducer (CSR) is an hourglass-shaped stainless-steel mesh that is percutaneously implanted in the coronary sinus to reduce angina.[1] It is the only antianginal therapy that acts on the cardiac venous circulation, and it is hypothesised to work by redistributing myocardial perfusion from more perfused to less perfused areas. This theory is based on a study in dogs with myocardial infarction treated with coronary sinus occlusion and on single-arm studies of CSR in humans.[2,3] However, no randomised trials to date have verified this proposed mechanism of action.

CSR is currently used for patients with angina and no further options for antianginal medication, percutaneous coronary intervention, or coronary artery bypass grafting. This practice is based on evidence of efficacy in this group

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See Comment page 1514

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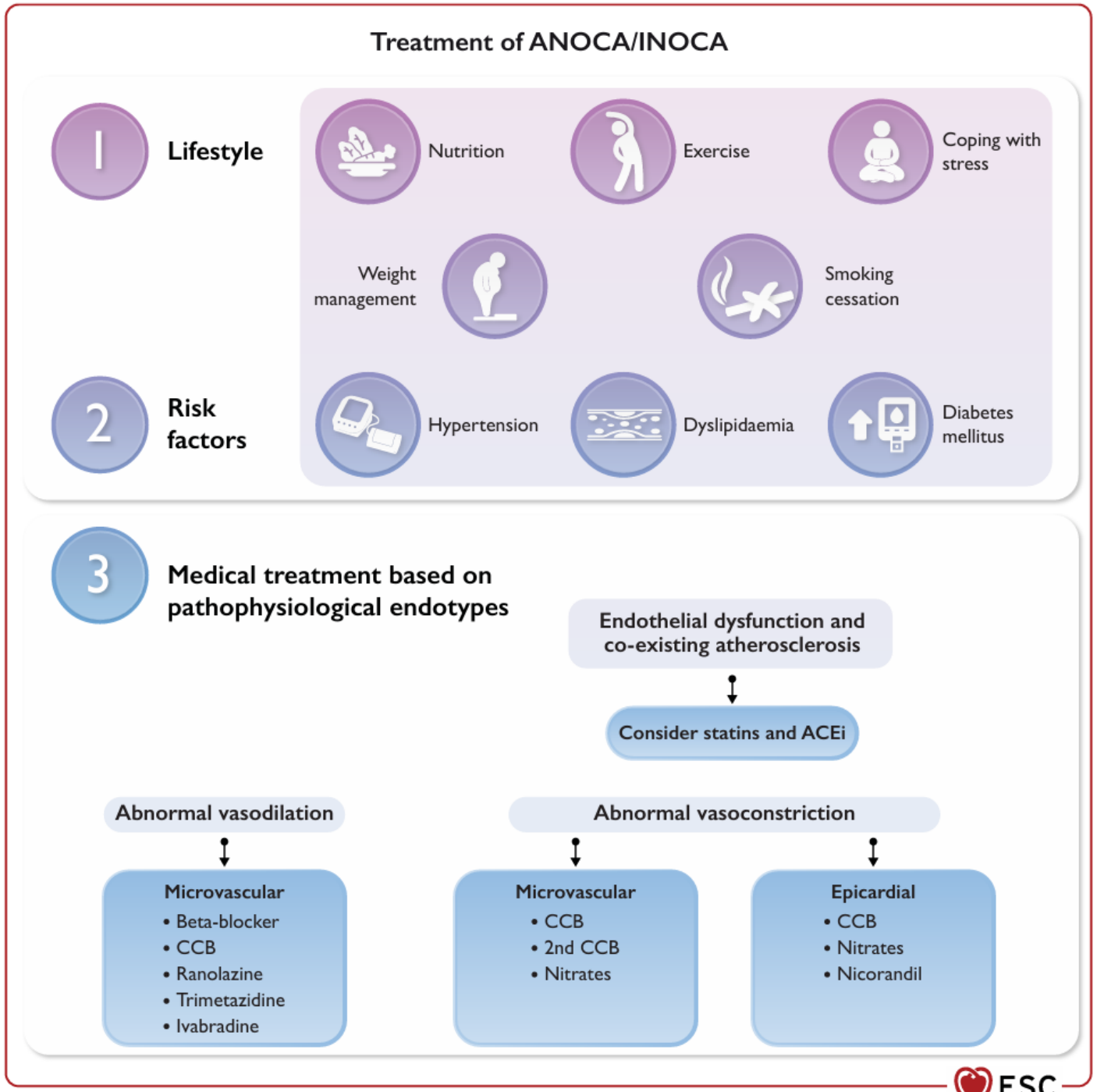
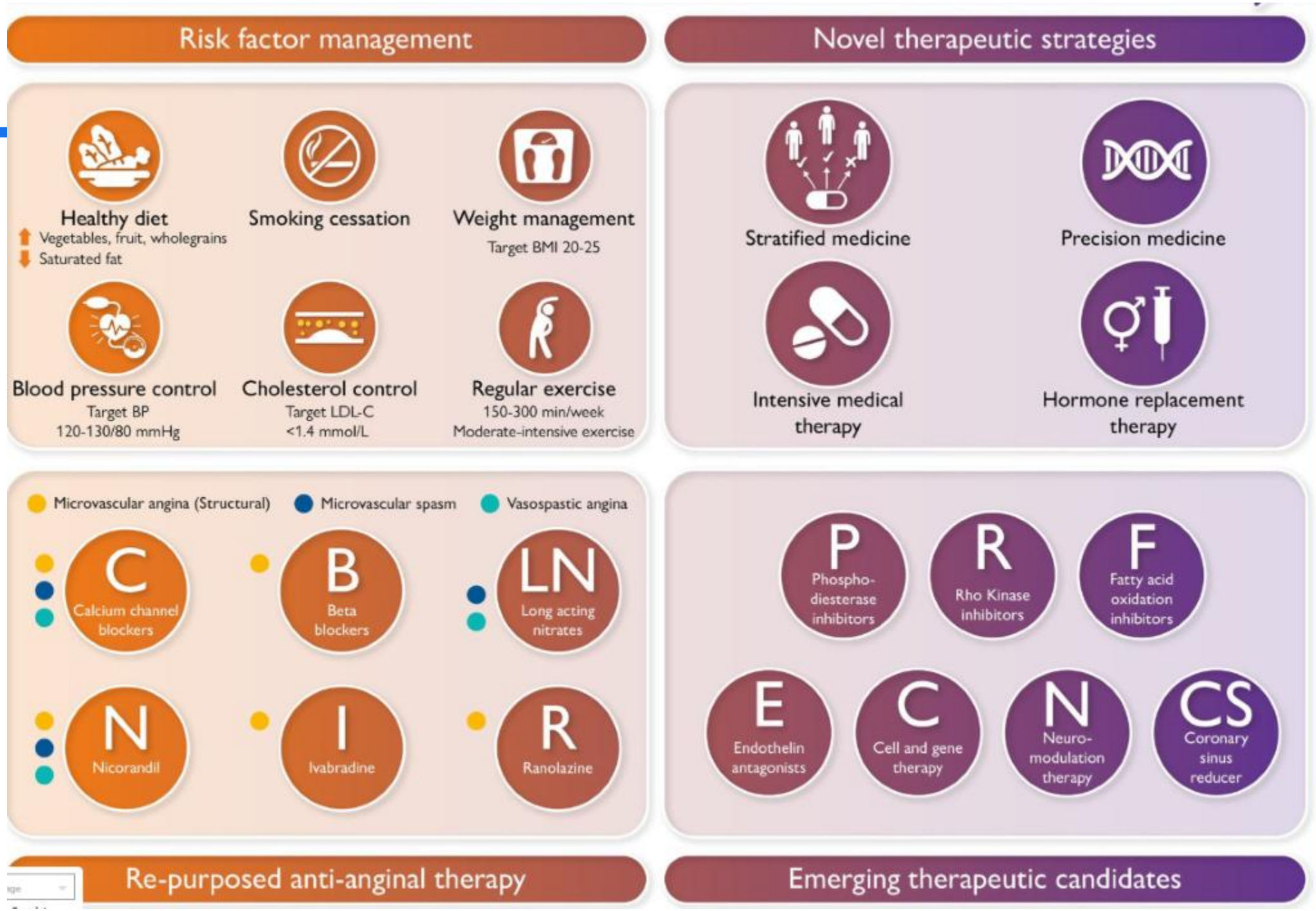

Treatment of ANOCA/INOCA
1
Lifestyle
Nutrition
Exercise
Coping with stress
Weight management
Smoking cessation
2
Risk factors
Hypertension
Dyslipidaemia
Diabetes mellitus
3
Medical treatment based on pathophysiological endotypes
Endothelial dysfunction and co-existing atherosclerosis
Consider statins and ACEi
Abnormal vasodilation
Abnormal vasoconstriction
Microvascular
• Beta-blocker
• CCB
• Ranolazine
• Trimetazidine
• Ivabradine
Microvascular
• CCB
• 2nd CCB
• Nitrates
Epicardial
• CCB
• Nitrates
• Nicorandil
ESC


Risk factor management
Healthy diet
Vegetables, fruit, wholegrains
Saturated fat
Smoking cessation
Weight management
Target BMI 20-25
Blood pressure control
Target BP
120-130/80 mmHg
Cholesterol control
Target LDL-C
<1.4 mmol/L
Regular exercise
150-300 min/week
Moderate-intensive exercise
Novel therapeutic strategies
Stratified medicine
Precision medicine
Intensive medical therapy
Hormone replacement therapy
Microvascular angina (Structural)
Microvascular spasm
Vasospastic angina
C
Calcium channel blockers
B
Beta blockers
LN
Long acting nitrates
N
Nicorandil
I
Ivabradine
R
Ranolazine
P
Phospho-diesterase inhibitors
R
Rho Kinase inhibitors
F
Fatty acid oxidation inhibitors
E
Endothelin antagonists
C
Cell and gene therapy
N
Neuro-modulation therapy
CS
Coronary sinus reducer
Re-purposed anti-anginal therapy
Emerging therapeutic candidates

Recommendations	Class	Level
In symptomatic patients with ANOCA/INOCA, medical therapy based on coronary functional test results should be considered to improve symptoms and quality of life.	IIa	A
For the management of **endothelial dysfunction**, ACE-I should be considered for symptom control.	IIa	B
For the management of **microvascular angina** associated with reduced coronary/myocardial blood flow reserve, beta-blockers should be considered for symptom control.	IIa	B
For the treatment of isolated **vasospastic angina**: • calcium channel blockers are recommended to control symptoms and to prevent ischaemia and potentially fatal complications.	I	A
• nitrates should be considered to prevent recurrent episodes.	IIa	B
In patients with evidence of **overlapping endotypes**, combination therapy with nitrates, calcium channel blockers, and other vasodilators may be considered.	IIb	B

CorMicA Trial

- Studie CorMicA (Coronary Microvascular Angina) hodnotila symptomatické pacienty bez obstrukční CAD s pozitivním invazivním testem na koronární reaktivitu.
- Do intervenční skupiny bylo zařazeno 76 pacientů (74 % žen) a 75 pacientů tvořilo kontrolní zaslepenou skupinu.
- Intervenční skupina byla **léčena antiischemickou farmakoterapií** zahrnující **beta-blokátory** a **ACEi**, doplněnou o léčbu **statiny** a režimová opatření, včetně **odvykání kouření**.
- Tento terapeutický přístup vedl k **signifikantnímu zlepšení anginózních obtíží** a kvality života během **6 měsíců (P=0,001)**, čímž potvrzuje význam cílené léčby u pacientů s CMD.

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Stratified Medical Therapy Using Invasive Coronary Function Testing in Angina

The CorMicA Trial

Thomas J. Ford, MBChB (Hons),[a,b,c] Bethany Stanley, MSc,[d] Richard Good, MD,[a] Paul Rocchiccioli, PhD,[a,b] Margaret McEntegart, PhD,[a,b] Stuart Watkins, MD,[a] Hany Eteiba, MD,[a] Aadil Shaukat, MBChB,[a] Mitchell Lindsay, MD,[a] Keith Robertson, PhD,[a] Stuart Hood, MD,[a] Ross McGeoch, MD,[e] Robert McDade, BSc,[a] Eric Yii,[b] Novalia Sidik, MBChB,[b] Peter McCartney, MBChB,[b] David Corcoran, MBChB,[b] Damien Collison, MB BCh,[a,b] Christopher Rush, MBChB,[b] Alex McConnachie, PhD,[d] Rhian M. Touyz, PhD,[b] Keith G. Oldroyd, MD (Hons),[a,b] Colin Berry, PhD[a,b]

ABSTRACT

BACKGROUND Patients with angina symptoms and/or signs of ischemia but no obstructive coronary artery disease (INOCA) pose a diagnostic and therapeutic challenge.

OBJECTIVES The purpose of this study was to test whether an interventional diagnostic procedure (IDP) linked to stratified medicine improves health status in patients with INOCA.

METHODS The authors conducted a randomized, controlled, blinded clinical trial of stratified medical therapy versus standard care in patients with angina. Patients with angina undergoing invasive coronary angiography (standard care) were recruited. Patients without obstructive CAD were immediately randomized 1:1 to the intervention group (stratified medical therapy) or the control group (standard care, IDP sham procedure). The IDP consisted of guidewire-based assessment of coronary flow reserve, index of microcirculatory resistance, fractional flow reserve, followed by vaso-reactivity testing with acetylcholine. The primary endpoint was the mean difference in angina severity at 6 months (assessed by the Seattle Angina Questionnaire summary score).

RESULTS A total of 391 patients were enrolled between November 25, 2016, and November 12, 2017. Coronary angiography revealed obstructive disease in 206 (53.7%). One hundred fifty-one (39%) patients without angiographically obstructive CAD were randomized (n = 76 intervention group; n = 75 blinded control group). The intervention resulted in a mean improvement of 11.7 U in the Seattle Angina Questionnaire summary score at 6 months (95% confidence interval [CI]: 5.0 to 18.4; p = 0.001). In addition, the intervention led to improvements in the mean quality-of-life score (EQ-5D index 0.10 U; 95% CI: 0.01 to 0.18; p = 0.024) and visual analogue score (14.5 U; 95% CI: 7.8 to 21.3; p < 0.001). There were no differences in major adverse cardiac events at the 6-month follow-up (2.6% controls vs. 2.6% intervention; p = 1.00).

CONCLUSIONS Coronary angiography often fails to identify patients with vasospastic and/or microvascular angina. Stratified medical therapy, including an IDP with linked medical therapy, is routinely feasible and improves angina in patients with no obstructive CAD. (CORonary MICrovascular Angina [CorMicA]; NCT03193294) (J Am Coll Cardiol 2018;72:2841–55) © 2018 by the American College of Cardiology Foundation.

ZÁVĚR

Zvýšeným rizikem rozvoje **srdečního selhání**, **chronického koronárního syndromu**, rozvojem **invalidity** a vyšší **incidencí MACE**, včetně vyšší **morbidity a mortality**.

Rekurentní symptomy, snížení QoL, časté hospitalizace a **opakovaná vyšetření, často zbytečně.**

Zvýšeným rizikem rozvoje **srdečního selhání**, **chronického koronárního syndromu**, rozvojem **invalidity** a vyšší **incidencí MACE**, včetně vyšší **morbidity a mortality**.

Negativní psychologické a sociální dopady.

Nedostatečná diagnostika a léčba zároveň **zvyšují náklady na zdravotní péči** a vedou k **častějším invazivním vyšetřením**.

Take home message

- **Koronární mikrovaskulární dysfunkce je častá a podceňovaná** – vyskytuje se až u 40 % pacientů s anginózními obtížemi a normálním výsledkem na koronarografii.
- **Klinicky významný „neviditelný“ problém** – CMD se neprojeví na běžné angiografii, ale zvyšuje **riziko MACE, KV morbiditu a mortalitu, riziko diastolické dysfunkce a HFpEF**
- **Snížené MBF a CFR = horší prognóza** – tyto parametry pomáhají identifikovat pacienty s vyšším rizikem a potřebu časné intervence.
- **Dynamický CZT SPECT je dostupná a prognosticky cenná metoda** – umožňuje kvantifikaci MBF a CFR i bez invazivního zákroku.
- **Cílená léčba má smysl** – výsledky studie CorMicA ukazují, že individualizovaná terapie zlepšuje symptomy i kvalitu života.

Děkuji za pozornost