



Identifier l'INOCA

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DÉCLARATION DE LIENS D'INTÉRÊT AVEC LA PRÉSENTATION

Intervenant : Stéphane MANZO-SILBERMAN, Paris

Je n'ai pas de lien d'intérêt lié à la présentation à déclarer

Background

- Last decades focus on obstructive coronary artery disease
- Non obstructive coronary artery disease (NOCAD)
 - **21-46% in stable angina¹⁻³**
 - 11-16% in NSTEMI
 - 1-14% in MINOCA
- **60% due to coronary microvascular dysfunction**
- Underestimated problem



Patients are often wrongfully reassured, while chest pain symptoms lead to^{4,5}:

- Higher mortality
- Anxiety
- Limited physical activity
- Reduced quality of life
- Higher rate of repeated procedures and medical assessment
- Higher healthcare cost

1) Jespersen, L., et al., EHJ, 2012

2) Patel, M.R., et al., NEJM, 2010

3) Sedlak, T.L., et al., Am Heart J, 2013

4) Johnson, B.D., et al., Circulation, 2004

5) Olson, M.B., et al., EHJ, 2003

Quizz: Diagnostiquer les INOCA

1. Impossible, ca n'existe pas!
2. En pratique aucun intérêt: il n'y a pas de traitement
3. C'est faisable en pratique courante invasive
4. C'est faisable en pratique courante non invasive


INOCA


Epicardial spasm


Microvascular dysfunction 

MINOCA


Epicardial spasm

Microvascular dysfunction 

Spontaneous coronary artery dissection (SCAD) 

Takotsubo 

Pulmonary embolism

Systemic disease 

Myocarditis



Higher prevalence in women

MINOCA = myocardial infarction with NOCAD

Courtesy of Yolande Appelman

Coronary obstruction

- ▶ Coronary evaluation
 - ▶ Coronary angiogram
 - ▶ CTscan
- ▶ Classification:
 - ▶ 0-20%: normal
 - ▶ 20-50%: non obstructive : NOCAD
 - ▶ 50-70% + inducible Ischemia or $FFR \leq 0.8$: Obstructive ischemia
 - ▶ ≥ 70 : obstructive CAD

1) Andersson HB., et al., EHJ, 2018

2) Dehmer GJ., et al., JACC, 2012

3) Douglas PS., et al., JACC, 2011

4) Patel MR, et al., J Nucl Cardiol, 2017

5) Kohl P., et al., Eur J Cardiothorac Surg, 2014

Author, Publication Year	Study Population	Test Performed	End Point	Results—Annual Events Rate* (%)	
No Obstructive CAD—Anatomical Testing				Normal Coronary Arteries	Nonobstructive CAD
Gulati, 2009 ³⁵	Chest pain or noninvasive positive tests for ischemia	Coronary angiography	All-cause death, nonfatal MI, nonfatal stroke, hospitalization for heart failure	1.5	3.1
Ovrehus, 2011 ³⁶	Stable angina	Coronary computed tomography angiography	Death and MI	0	0.6
			Cardiac death, MI, revascularization	0	1
Jespersen, 2012 ¹⁵	Chest pain	Coronary angiography	Cardiovascular mortality, hospitalization for MI, heart failure, or stroke	1.8	2.8
Petretta, 2012 ³⁷	Anginal symptoms and 15%–85% pretest likelihood of CAD	Coronary computed tomography angiography	Cardiac death, nonfatal MI, unstable angina, revascularization	0	3.4
Maddox, 2014 ⁴	Chest pain or noninvasive positive tests for ischemia	Coronary angiography	All-cause death, MI	1.48	2.41
Nielsen, 2017 ⁴¹	Chest pain	Coronary computed tomography angiography	Revascularization MI, and all-cause death	0.4	0.9
Kenkre, 2017 ⁴⁰	Chest pain or noninvasive positive tests for ischemia	Coronary angiography	All-cause death	1	1.7
			Cardiac death	0.6	1.1
No Obstructive CAD—Functional Testing				Normal Test	Abnormal Test
Johnson, 2004 ¹⁰	Chest pain or noninvasive positive tests for ischemia	Magnetic resonance spectroscopy	All-cause death, MI, heart failure, stroke, other vascular events, and hospitalization for unstable angina	4.4	14
Schindler, 2005 ³⁸	Chest pain	Positron emission tomography	Cardiovascular death, acute coronary syndrome, MI, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, ischemic stroke, or peripheral revascularization	0.9	5–7
Doyle, 2010 ³⁹	Chest pain or noninvasive positive tests for ischemia	Cardiac magnetic resonance imaging	All-cause death, nonfatal MI, or hospitalization for worsening anginal symptoms	4	12
Murthy, 2014 ²⁶	Chest pain	Positron emission tomography	Cardiac death, nonfatal MI, late revascularization, and hospitalization for heart failure	2.7	6.7

Definition of CMD

	Microvascular Dysfunction	Macrovascular Dysfunction
Non-Endothelial Dependent	CFR in response to adenosine ≤ 2.5	Change in coronary artery diameter in response to nitroglycerin $< 20\%$
Endothelial Dependent	Change in CBF in response to acetylcholine $< 50\%$	Change in coronary artery diameter in response to acetylcholine $< 0\%$
Coronary Spasm	Chest Pain + EKG changes Change in coronary artery diameter in response to acetylcholine $< 90\%$	

Figure 4. Proposed diagnostic criteria of coronary dysfunction using reactivity testing. CBF, coronary blood flow; CFR, coronary flow reserve; EKG, electrocardiography.

- ▶ *Definite:* patients presenting with angina pectoris or ischemic-like symptoms in the absence of flow-limiting CAD with both objective evidence of myocardial ischemia and CMD.
- ▶ *Suspected:* patients presenting with angina pectoris or ischemic-like symptoms in the absence of flow-limiting CAD with objective evidence of myocardial ischemia or evidence of impaired CMD alone.

Disorder of coronary artery function

CMD	↑ Microvascular resistance (IMR ≥ 25)	The IMR represents a quantitative metric of microvascular function independent of resting haemodynamics
	↓ Coronary vasorelaxation (CFR < 2.0)	IMR = distal coronary pressure * transit time (average time for 3 saline bolus runs at hyperaemia) CFR by thermodilution. A CFR < 2.0 reflects the failure to increase coronary flow above two times the resting flow in response to a hyperaemic stimulus
	Microvascular spasm	Reproduction of usual angina during intracoronary infusion of ACh with ischaemic ST-segment changes but no significant epicardial coronary constriction ($< 90\%$ reduction in epicardial coronary diameter). Represents inappropriate susceptibility to microvascular constriction
VSA	Epicardial spasm	Epicardial coronary artery spasm is defined as <ul style="list-style-type: none">• $\geq 90\%$ reduction in coronary diameter following intracoronary administration of ACh (100 μg)• Reproduction of usual symptoms• ST segment deviation on the ECG
Non-cardiac (control)	Nil	Exclusion of diffuse or obstructive epicardial coronary disease (FFR > 0.8) Normal invasive metrics of coronary artery function: <ul style="list-style-type: none">• CFR ≥ 2.0• IMR < 25• Negative provocation testing (ACh)

Functional testing

- ▶ Invasive testing
 - ▶ Coronary Blood Flow and epicardial artery diameter
 - ▶ Endothelium-dependent probes: Acetylcholin, bradykinin...
 - ▶ Exercise, mental-stress, cold pressor test
 - ▶ Coronary Flow reserve
 - ▶ Endothelium-independent probes: adenosin, nitroglycerin
 - ▶ Doppler flow wire
 - ▶ Thermodilution wire
 - ▶ IMR
 - ▶ Acetylcholine test for coronary microvascular spasm
 - ▶ Coronary slow flow phenomenon (TIMI frame count)
 - ▶ Safe: no death, <1% procedure related adverse experiences
 - ▶ *IVUS/ OCT ----→ MINOCA*

1) Lee BK., et al., Circ, 2015

2) Ong P., et al., Circ, 2014

3) Wei J., et al., JACC Cardiovasc Interv 2012

Functional testing

- ▶ **Non-Invasive testing**
 - ▶ PET Positron emission tomography:
 - ▶ Reproducible evaluation of CBF
 - ▶ Evaluation Myocardial perfusion, LV function
 - ▶ CFR
 - ▶ Transthoracic Echo Doppler
 - ▶ Coronary flow velocity (CFV) of the LAD rest = dipyridamole
 - ▶ 20% INOCA : reduced CFV reserve < 2.0
 - ▶ Low CFV reserve : greater symptoms and limitations
 - ▶ cMRI
 - ▶ Subendocardial perfusion: Myocardial perfusion reserve index
 - ▶ Adenosin stress : 63% abnormal
 - ▶ Native T1 mapping and perfusion reserve index

1) Taqueti VRet al., Circ, 2015

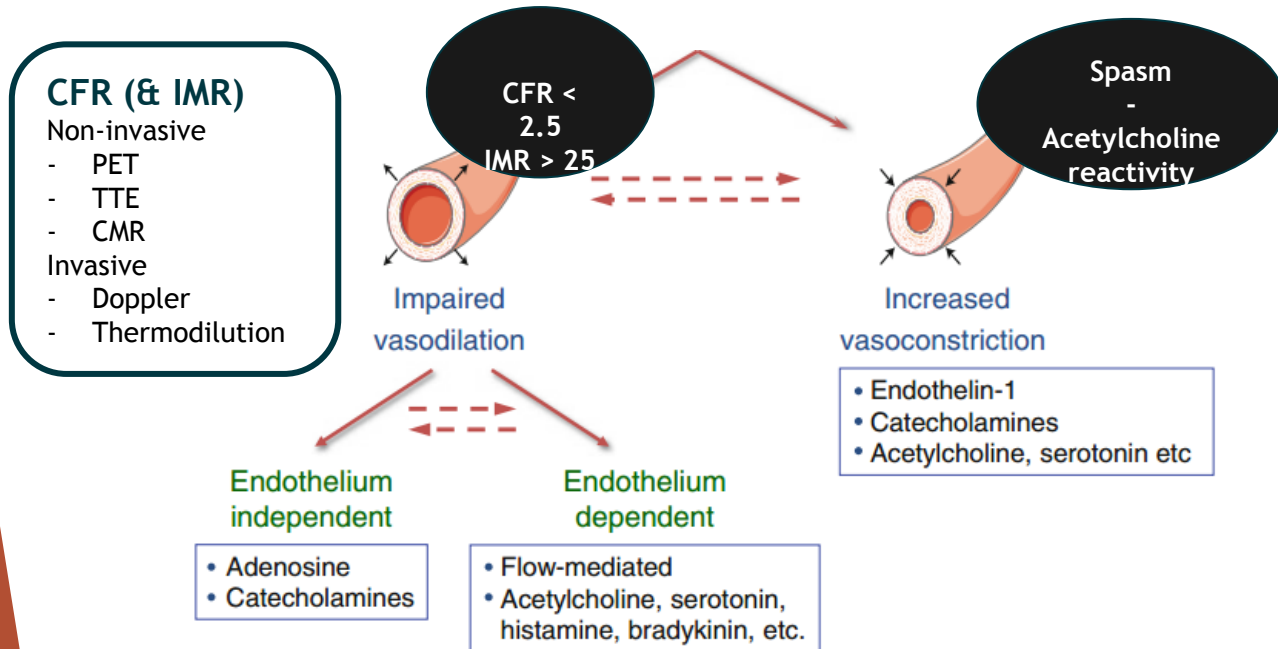
2) Mygind ND., et al., JAHA 2016

3) Lanza GA, et al., JACC , 2008

4) Thomson LE., et al., Circ Cardiovasc Imaging, 2015

5) Shaw JL., Int J Cardiol., 2018

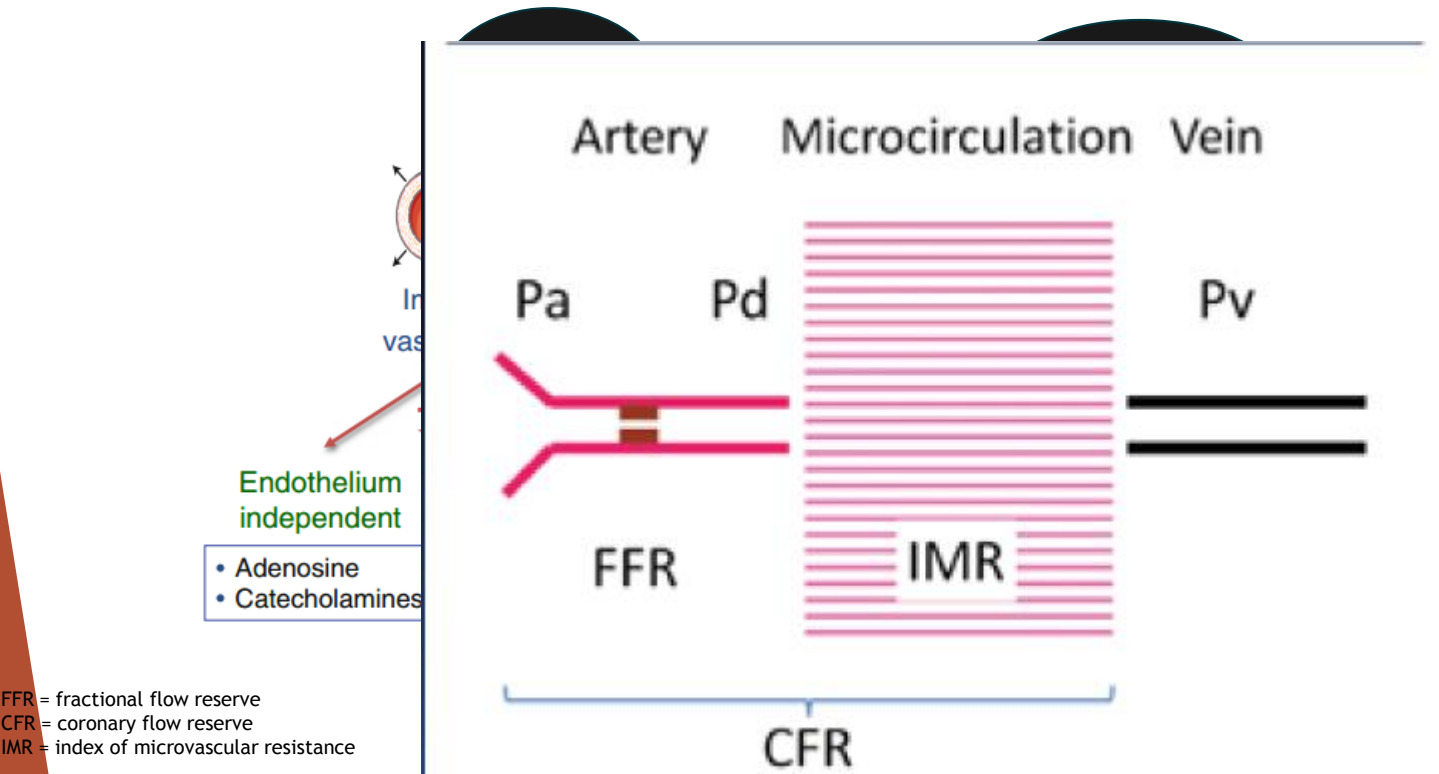
Coronary microvascular dysfunction



- CFR (& IMR)**
- Non-invasive
 - PET
 - TTE
 - CMR
 - Invasive
 - Doppler
 - Thermodilution

FFR = fractional flow reserve
 CFR = coronary flow reserve
 IMR = index of microvascular resistance

Coronary microvascular dysfunction



How to diagnose CMD

Non-invasive tests

- ▶ PET
- ▶ CMR
- ▶ SPECT
- ▶ TTDE
- ▶ MCE

We're not there yet:

- No accurate golden standard
- No recommendations in current guidelines
- Unknown impact of age and sex

microvascular spasm
(TIMI frame count)

PET = Positron Emission Tomography
CMR = Cardiac Magnetic Resonance
SPECT = Single-Photon Emission Computed Tomography

TTDE = Trans Thoracic Doppler Echocardiography
MCE = Myocardial Contrast Echocardiography

CFR = Coronary flow reserve
IMR = Index of microvascular resistance
HMR = Hyperemic index of microvascular resistance

Prevalence of CMD

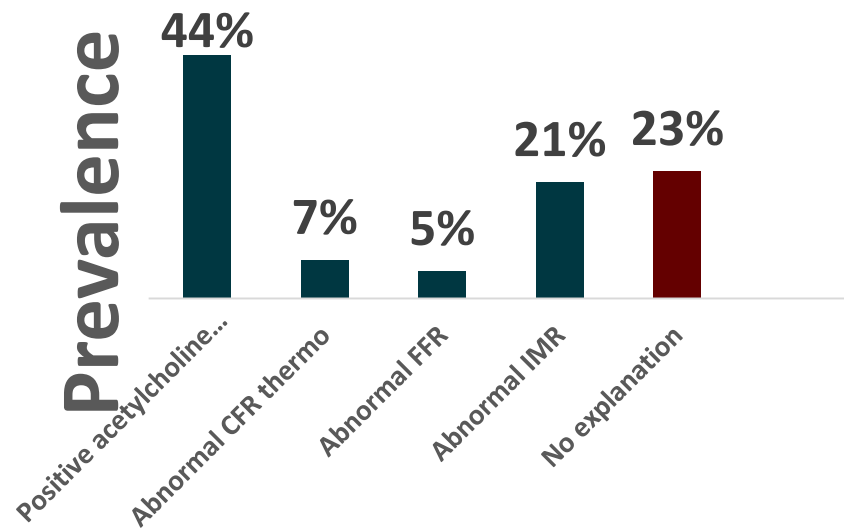
- ▶ Variable between 22-64%¹
- ▶ Due to heterogeneity in
 - ▶ Definition
 - ▶ Inclusion criteria
 - ▶ Cut-off values
 - ▶ Imaging modalities

Table 1. Prevalence of CMD in Observational Studies With Various Testing Modalities

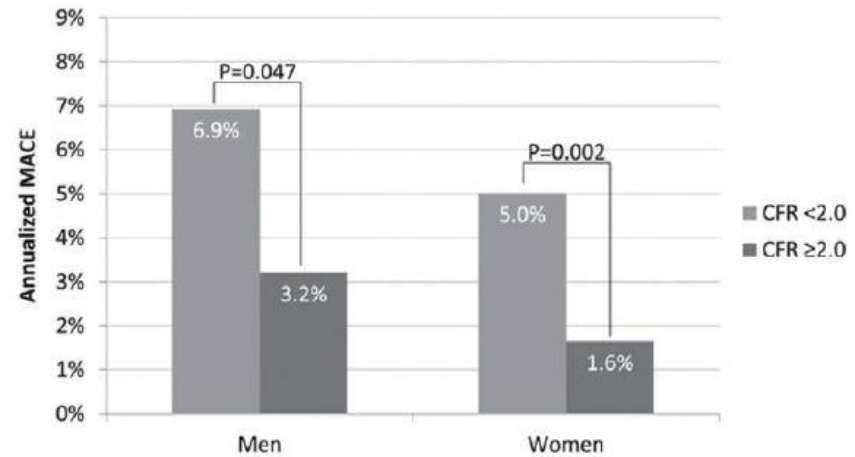
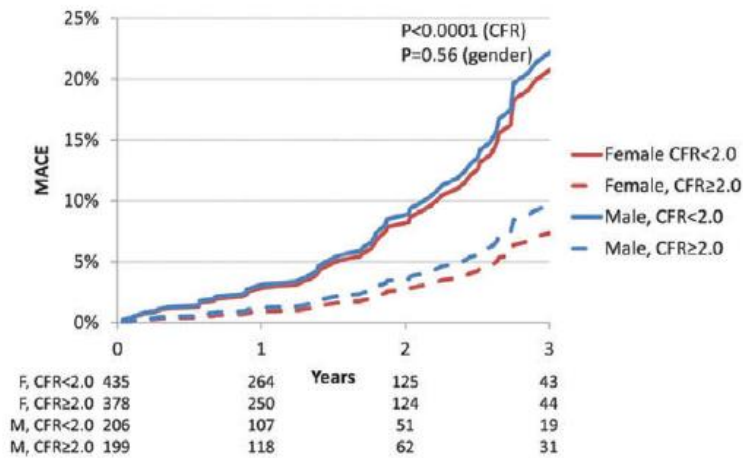
Author	Year	Test	Sample size	Prevalence of CMD (%)	Male (%)	Female (%)
Hasdai et al ¹⁷	1998	Coronary reactivity test	203	59	–	–
Reis et al ¹⁹	2001	Coronary reactivity test	159	47	–	47
Sade et al ¹⁸	2009	TTDE (CFR <2.0)	68	40	–	40
Sicari et al ¹⁸	2009	TTDE (CFR <2.0)	394	22	25	19
Cassar et al ¹²⁷	2009	Coronary reactivity test	367	63	61	65
Wei et al ¹	2012	Coronary reactivity test	293	49	–	49
Murthy et al ³	2014	PET (CFR <2.0)	1,218	53	51	54
Sara et al ²⁰	2015	Coronary reactivity test	1,439	64	60	66
Mygind et al ²⁷	2016	TTDE (CFR <2.0)	919	26	–	26

CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; PET, positron emission tomography; TTDE, transthoracic Doppler echocardiography.

Invasive evaluation of NOCAD in 139 patients



Impact of CMD



Risk factors and CMD

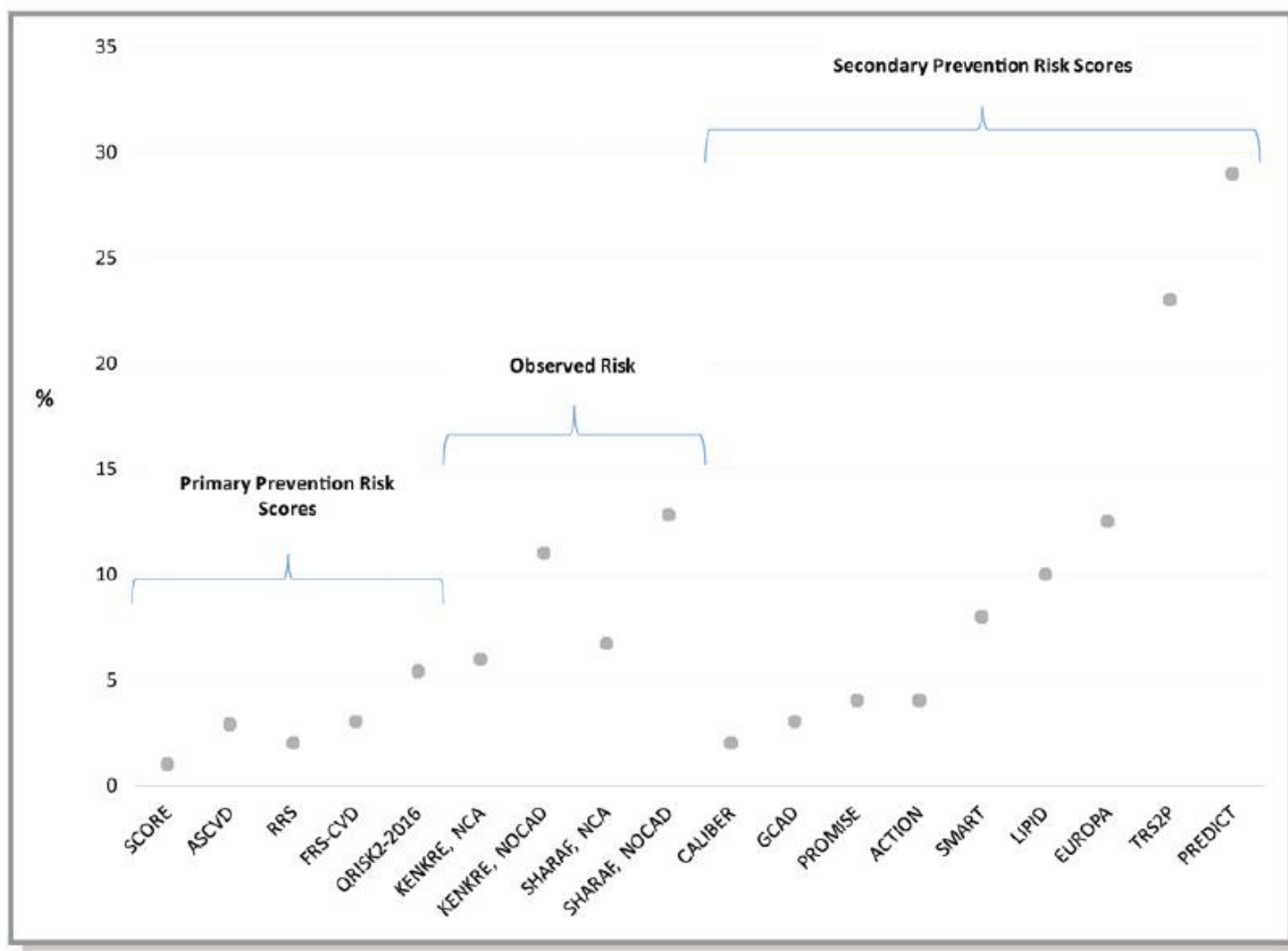
- ▶ Similar to the traditional risk factors of obstructive CAD
- ▶ Smoking
- ▶ Diabetes
- ▶ Aging
- ▶ Hypertension
- ▶ High LDL
- ▶ Systemic inflammation

We're not there yet:

- No accurate figures from trials
- Unknown impact of age and sex
- Unknown impact of depression and stress
- Unknown impact of female specific risk factors
- Unknown impact of hormonal changes

1) Brainin, P., et al, Inter J of Cardiol, 2018 systematic review and meta-analysis on prognosis

Risk evaluation



Limits

	CVD Primary Prevention Guidelines	Stable CAD Guidelines		Secondary CVD Prevention Guidelines	Knowledge Gaps
Detection	N/A	Likelihood of CAD score	Limited to the presence of obstructive CAD	Limited to established coronary or other atherosclerotic vascular disease	Evidence regarding the utility, benefits, and risks of invasive and noninvasive detection strategies in INOCA patients is needed to develop evidence-based detection guidelines
		Stress testing	Limited to the presence of obstructive CAD		
		CCTA	Limited to anatomical coronary plaque/stenosis and obstructive CAD flow		
		Coronary angiography	Limited to anatomical stenosis and obstructive CAD flow; no evidence-based guidelines for less than obstructive CAD		
Risk assessment	Limited to asymptomatic patients	Limited to stable known or suspected obstructive CAD		Risks scores limited to prior MI and established CAD	Risk scores developed in INOCA populations to develop evidence-based risk assessment guidelines are needed
Treatment	Limited to asymptomatic patients	Echoes treatment recommendations for specific subgroups of patients from UA/NSTEMI guidelines. Emphasis on the lack of dedicated treatment trials for INOCA		Limited to established coronary or other atherosclerotic vascular disease	MACE trials to inform evidence-based guidelines for treatment strategies are needed

CAD indicates coronary artery disease; CCTA, computed coronary tomography angiography; CVD, cardiovascular disease; INOCA, ischemia and no obstructive coronary artery disease; MACE, major adverse cardiovascular events; MI, myocardial infarction; N/A, not applicable; NSTEMI, non-ST-segment-elevation myocardial infarction; UA, unstable angina.

Microvascular disease, what little we know



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