Hart- en vaatziekten bij vrouwen: ‘je gaat het pas zien als je het doorhebt!’

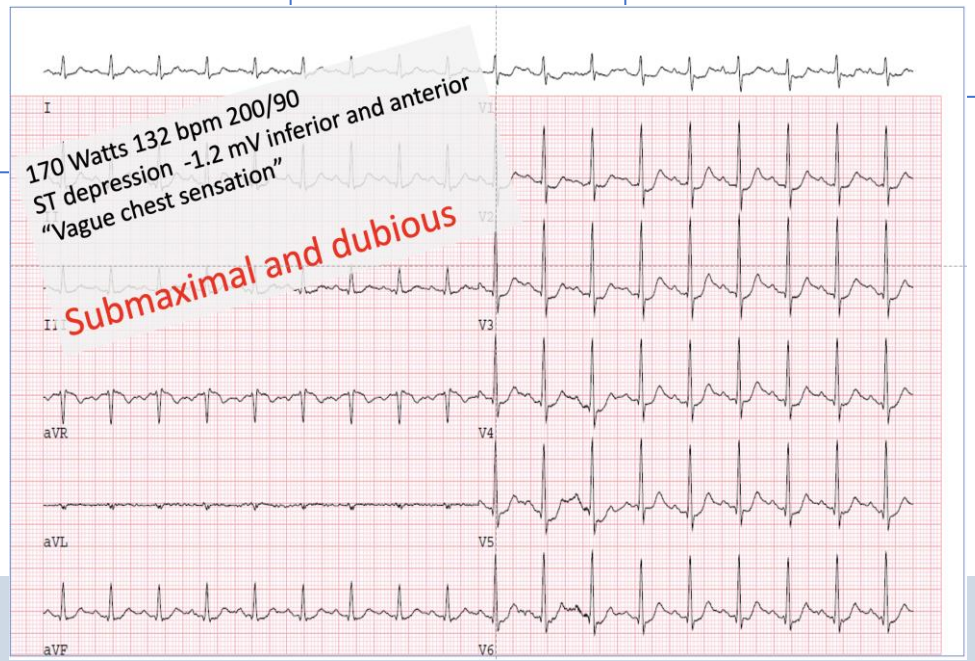
Dr. Yolande Appelman
Interventiecardioloog
Amsterdam UMC

Sex and gender in research
Why does it matter

Angina and coronary angiography
Setting the stage

54-yr sportive woman:
- Since at least two years,
- Episodes of chest pain,
- Not necessarily exercise-induced
- Constrictive
- Vague irradiations to the troat and both arms
- Duration: 10-20 minutes
- Not daily, but frequently

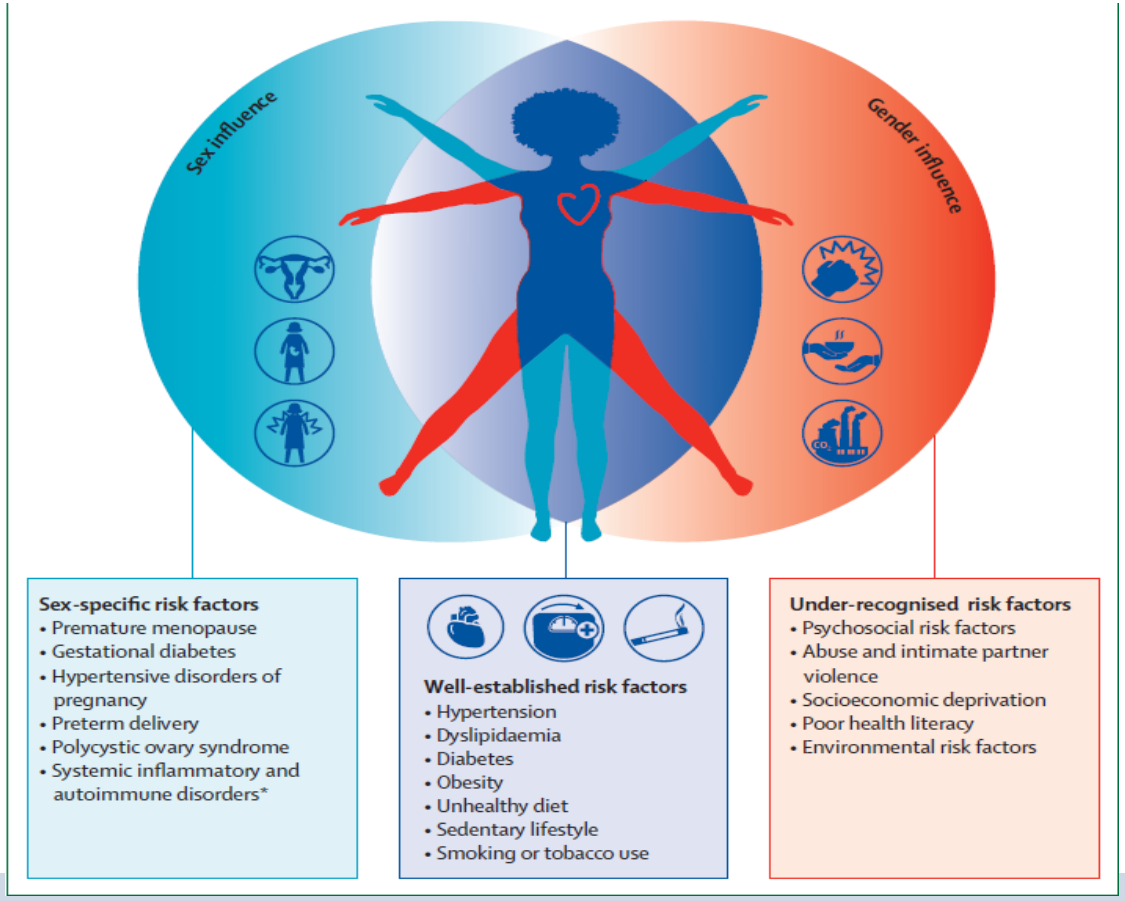
Risk Factors:
- HT +
- Former moderate smoker
- Hyperlipidemia +
- Diabetes -
- Family history –

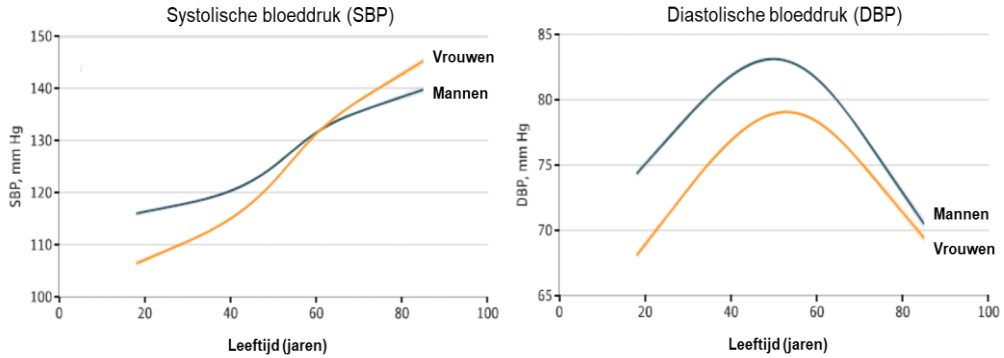


This is the third time she has been admitted to the Emergency Room

The *Lancet* women and cardiovascular disease Commission: reducing the global burden by 2030

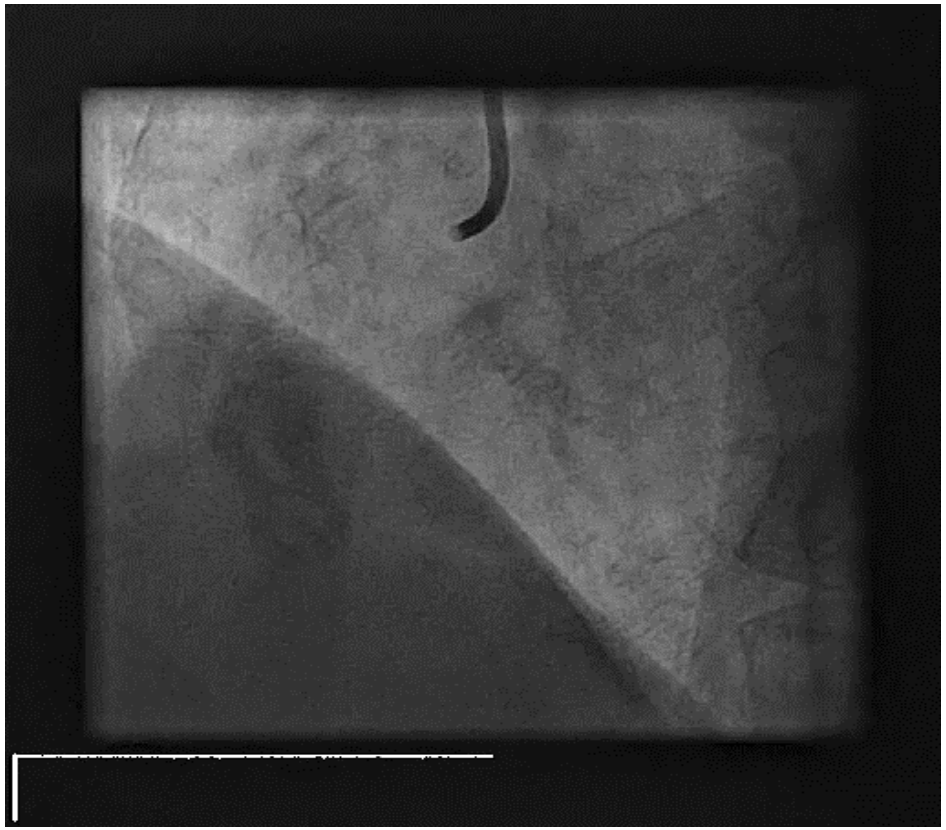
Birgit Vogel, Monica Acevedo, Yolande Appelman, C Noel Bairey Merz, Alaide Chieffo, Gemma A Figtree, Mayra Guerrero, Vijay Kunadian, Carolyn S P Lam, Angela H E M Maas, Anastasia S Mihailidou, Agnieszka Olszanecka, Jeanne E Poole, Clara Saldarriaga, Jacqueline Saw, Liesl Zühlke, Roxana Mehran





Vogel et al; Lancet 2021 Women and CV Disease Commission

Angina and coronary angiography
No obstructions



Angina and no coronary obstruction
How often do we see it?

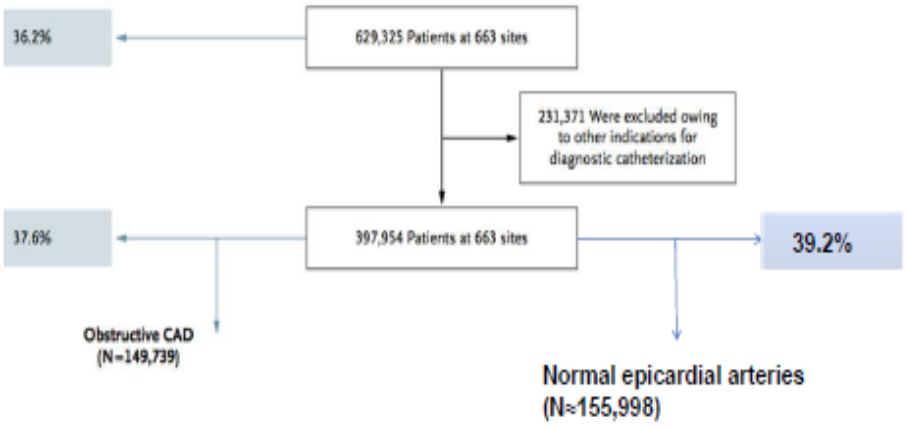
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Low Diagnostic Yield of Elective Coronary Angiography

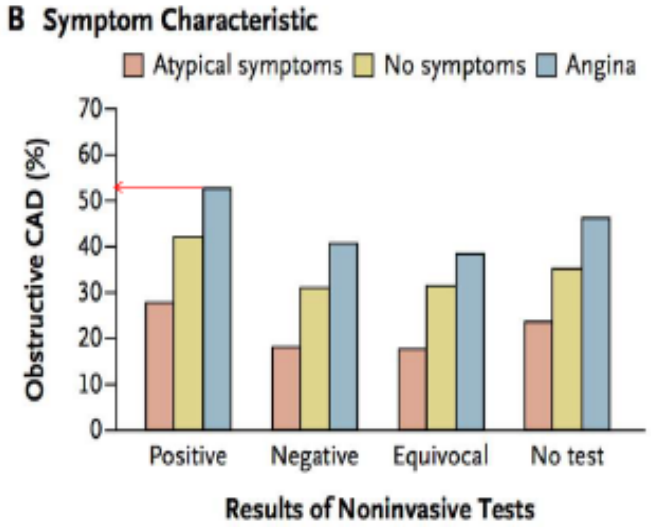
Manesh R. Patel, M.D., Eric D. Peterson, M.D., M.P.H., David Dai, M.S., J. Matthew Brennan, M.D., Rita F. Redberg, M.D., H. Vernon Anderson, M.D., Ralph G. Brindis, M.D., and Pamela S. Douglas, M.D.

CAG for suspected obstructive CAD



Patel et al, 2010, NEJM

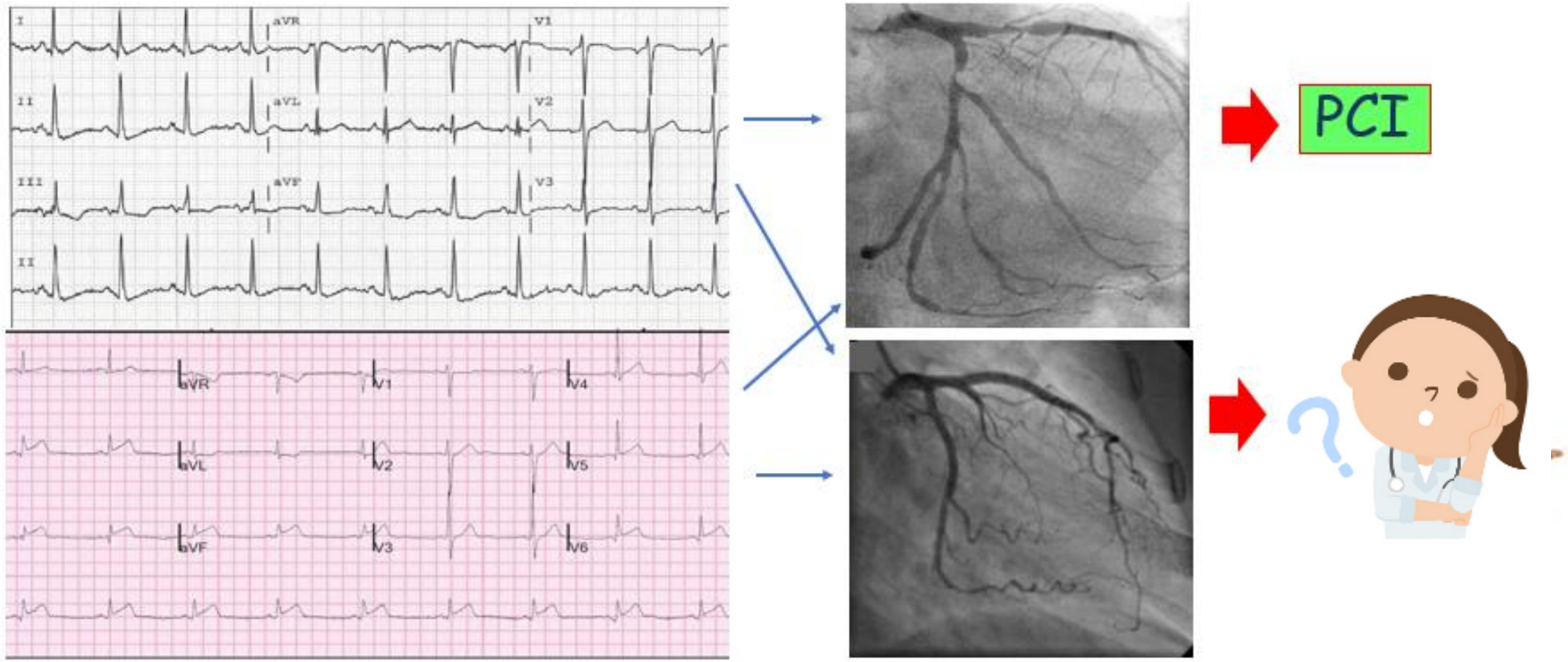
Positive non-invasive test + typical angina



Patel et al, 2010, N

Angina and no coronary obstruction

How often do we see it?



Angina and no coronary obstruction
How often do we see it?

About half of all patients with angina do *not* have obstructive coronary arteries (ANOCA) but have signs and symptoms ischaemia: ***INOCA***

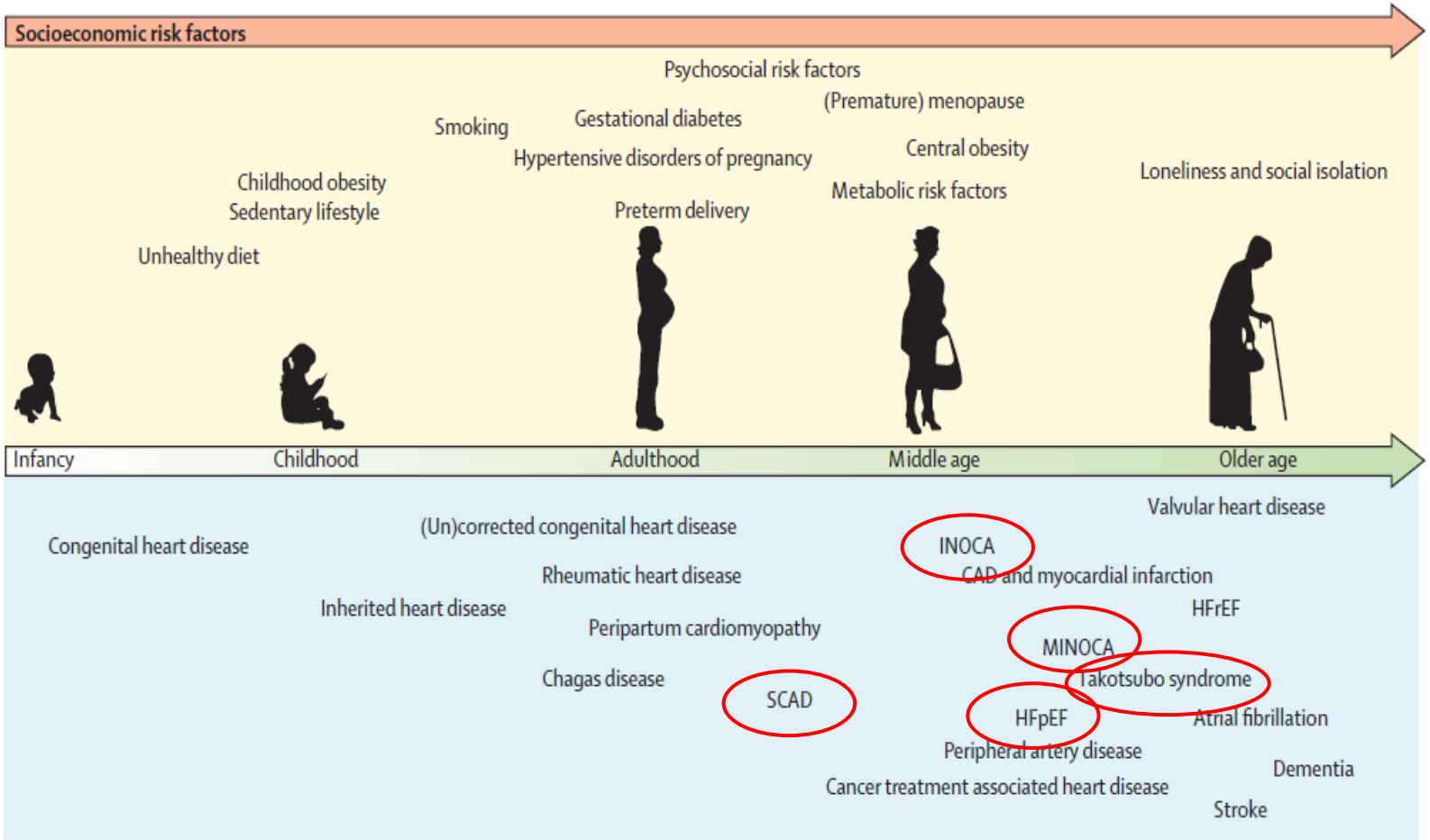
Higher prevalence of ANOCA amongst women[1,2]

RELEVANCE? Patients are often wrongfully reassured, while chest pain symptoms lead to[4,5]:

- Higher mortality 1.5x
- Anxiety & limited physical activity
- Reduced quality of life
- Higher repeated hospitalization 40%
- Higher rate of repeated angiography 30%
  Higher healthcare cost

Kunadian et al. 2020 EHJ 2021 EuroInterv; NVVC Leidraad juni 2020,

Lifecycle of a woman
Age, riskfactors and CV disease

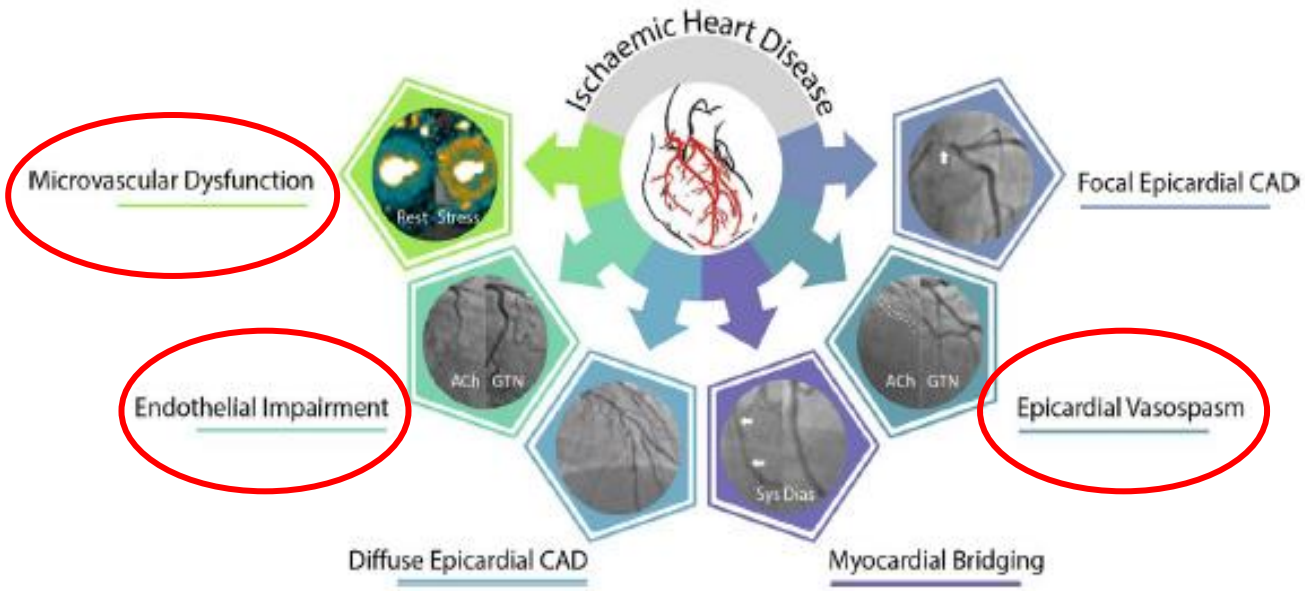


Vogel et al; Lancet 2021 Women and CV Disease Commission

Angina and no coronary obstruction
Mechanisms of ischemia

Angina = ischemia: mismatch between oxygen demand and supply

Coronary vasomotor dysfunction



Ford et al; 2017

Angina and no coronary obstruction
Concensus document

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

Vijay Kunadian (UK, Document Chair)[1*], Alaide Chieffo (Italy, Document Co-Chair)[2], Paolo G. Camici (Italy)[3], Colin Berry (UK)[4], Javier Escaned (Spain)[5], Angela H. E. M. Maas (Netherlands)[6], Eva Prescott (Denmark)[7], Nicole Karam (France)[8], Yolande Appelman (Netherlands)[9], Chiara Fraccaro (Italy)[10], Gill Louise Buchanan (UK)[11], Stephane Manzo-Silberman (France)[12], Rasha Al-Lamee (UK)[13], Evelyn Regar (Germany)[14], Alexandra Lansky (USA, UK)[15,16], J. Dawn Abbott (USA)[17], Lina Badimon (Spain)[18], Dirk J. Duncker (Netherlands)[19], Roxana Mehran (USA)[20], Davide Capodanno (Italy)[21], Andreas Baumbach (UK, USA)[22,23]

NVVC Leidraad

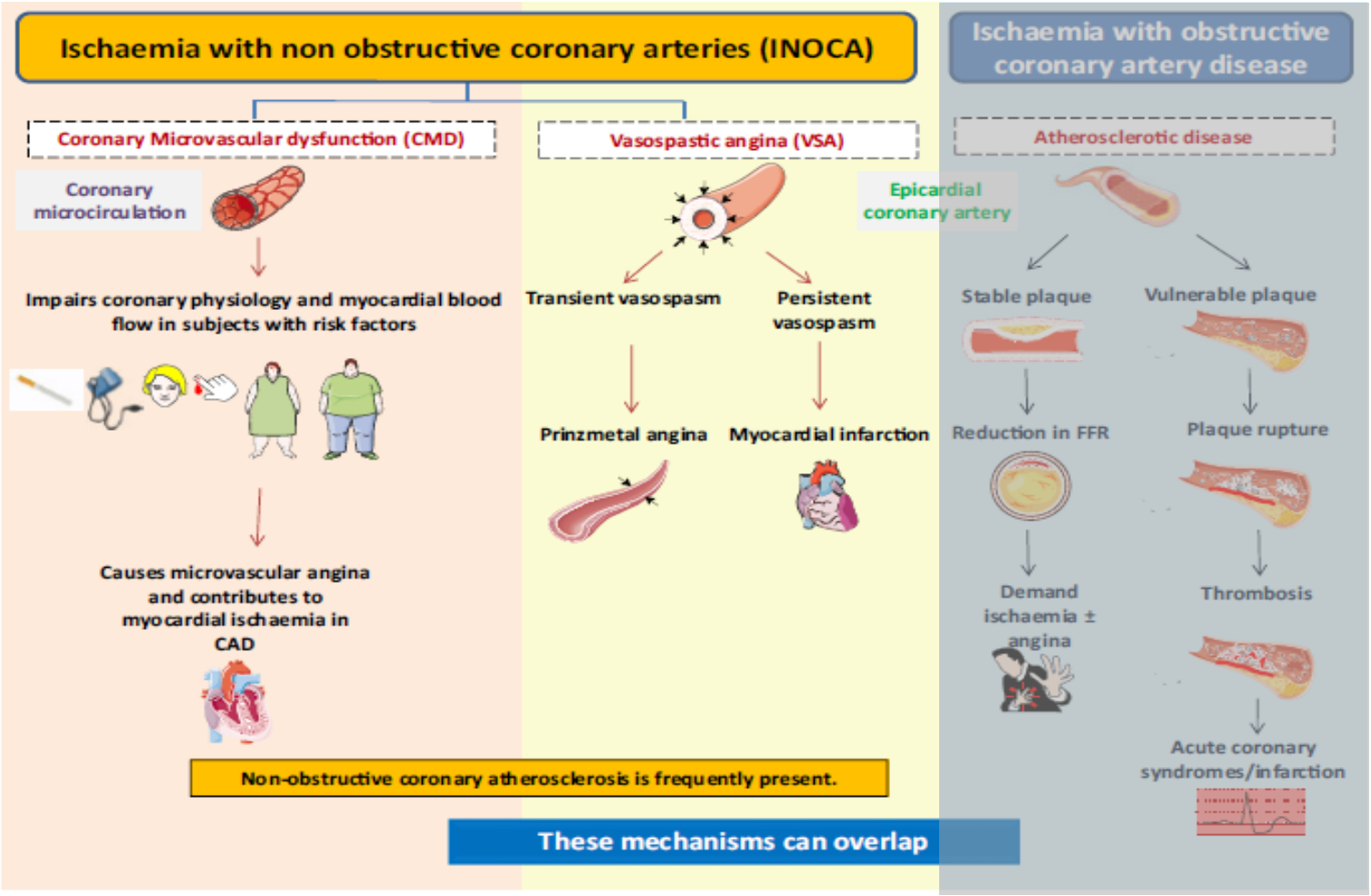
"Pijn op de borst zonder obstructief coronairlijden"

(INOCA: ischemia no obstructive coronary artery disease)

EAPCI expert consensus paper on INOCA EHJ & EuroIntervention 2020
ESC guidelines CCS 2019

Angina and no coronary obstruction
Concensus document

60-80% due to coronary microvascular dysfunction and/or vasospasm

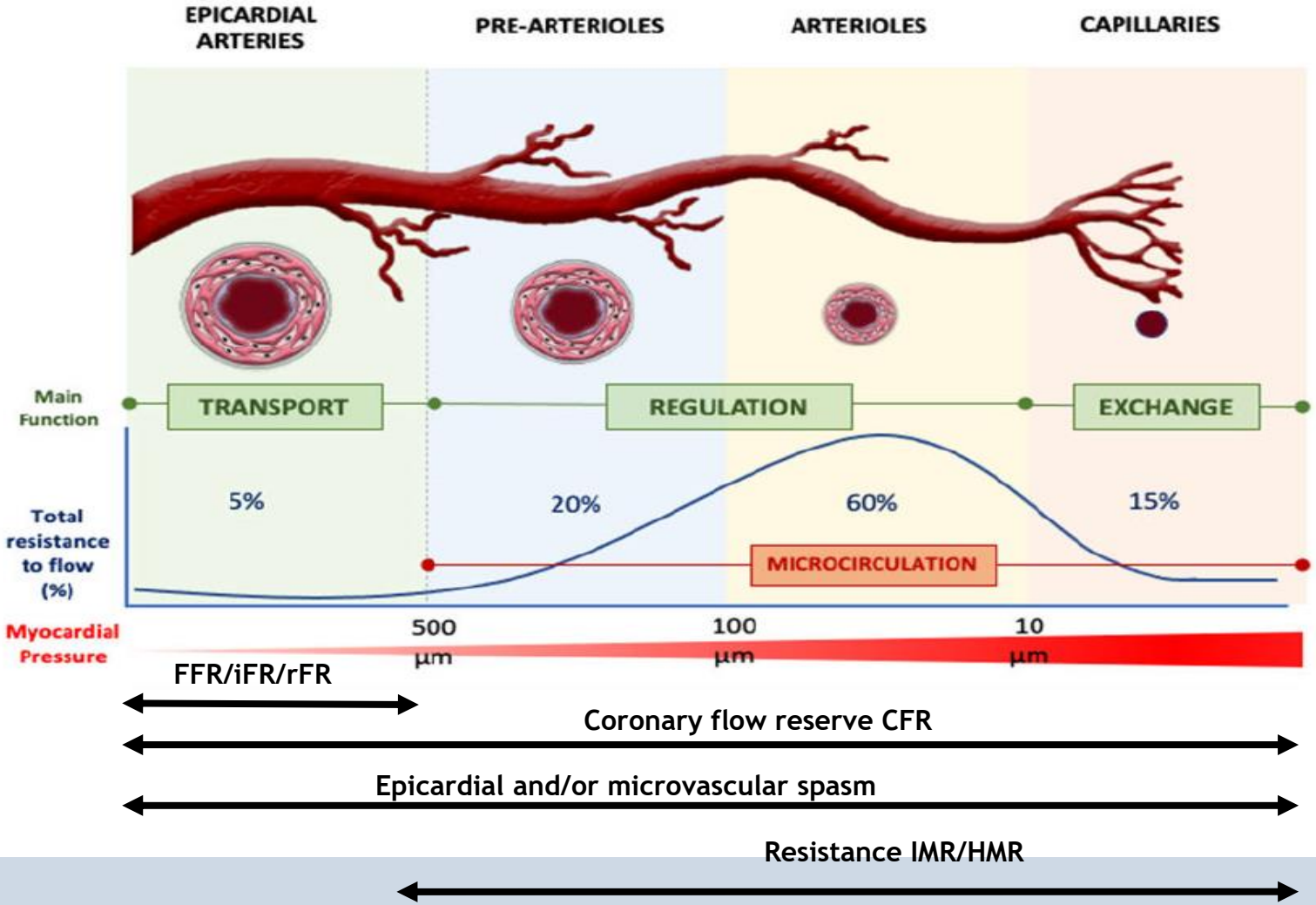


EAPCI expert consensus paper on INOCA EHJ & EuroIntervention 2020
ESC guidelines CCS 2019

Pathophysiology
Bloodsupply

Macrocirculation: conductance function

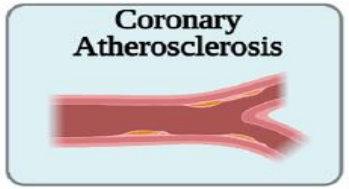
Microcirculation: Regulation & distribution of flow matching needs



Del Buono MG 2021 JACC

Pathophysiology
Endotypes

Structural abnormalities



Obstructive coronary artery disease

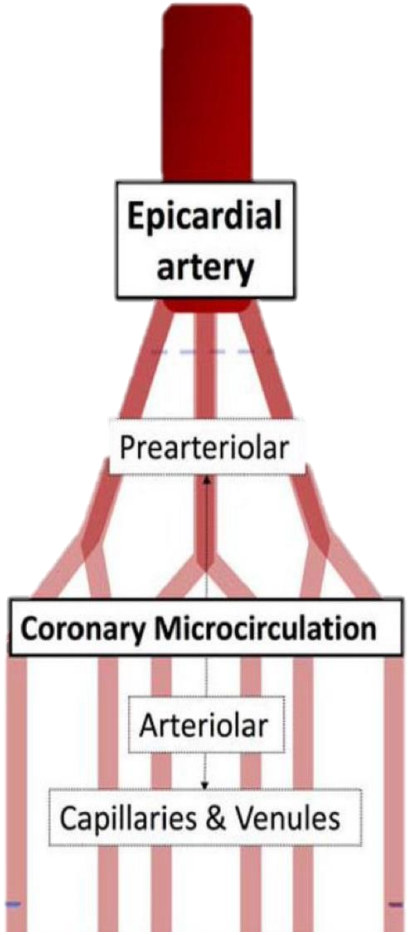
- iFR/FFR-guided revascularization

Structural Mechanisms

- Perivascular inflammation
- Arteriolar remodeling and fibrosis
- Capillary rarefaction
- Capillary obliteration
- Microthrombi
- Hemostatic factors

Structural coronary microvascular disease

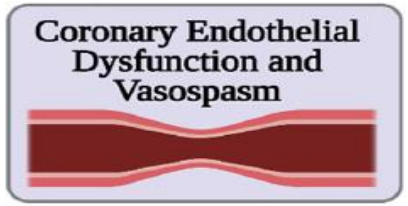
- Coronary Flow Reserve (CFR) ↓
- Microvascular resistance (HMR/IMR) ↑



Functional abnormalities

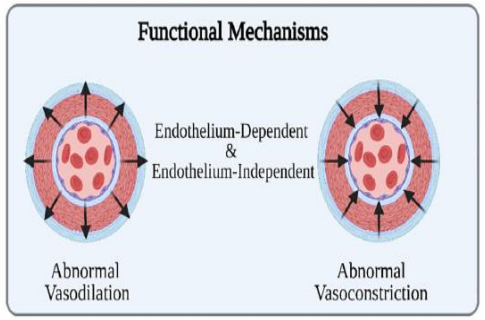
Vasospastic Angina Endothelial dysfunction

- Acetylcholine spasm provocation test
- Graded acetylcholine infusion



Functional coronary microvascular disease

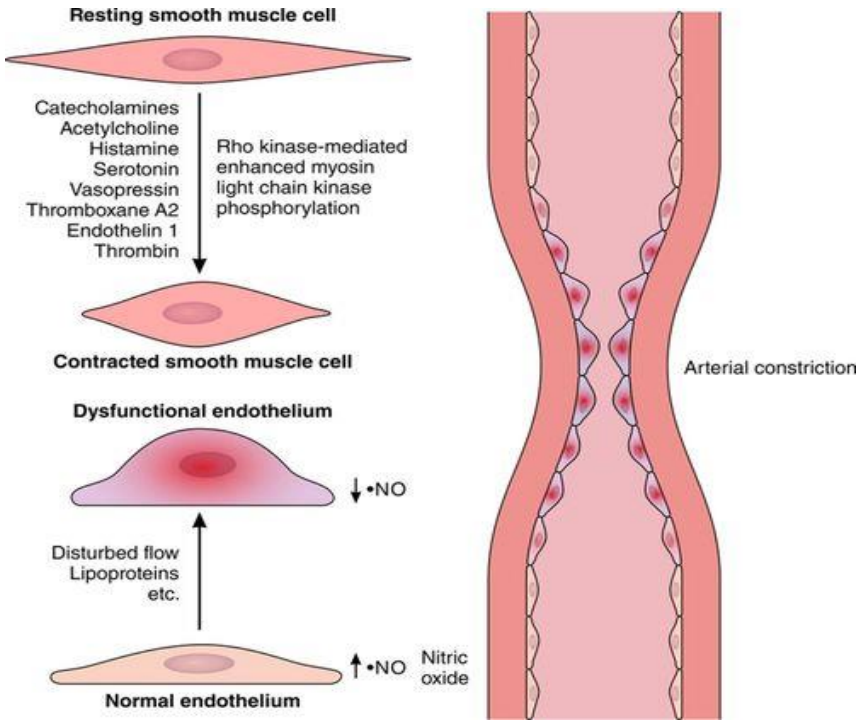
- Graded acetylcholine infusion
- Acetylcholine spasm provocation test
- Coronary Flow Reserve (CFR) ↓
- Microvascular resistance (HMR/IMR) ↑



Metha P 2022 Int J Cardiol

Pathophysiology
Coronary vasospasm

Acetylcholine
Autonomic nervous system neurotransmitter



Spasm: endothelial dysfunction & vascular smooth muscle cell hyperreactivity

ICFT protocol AUMC

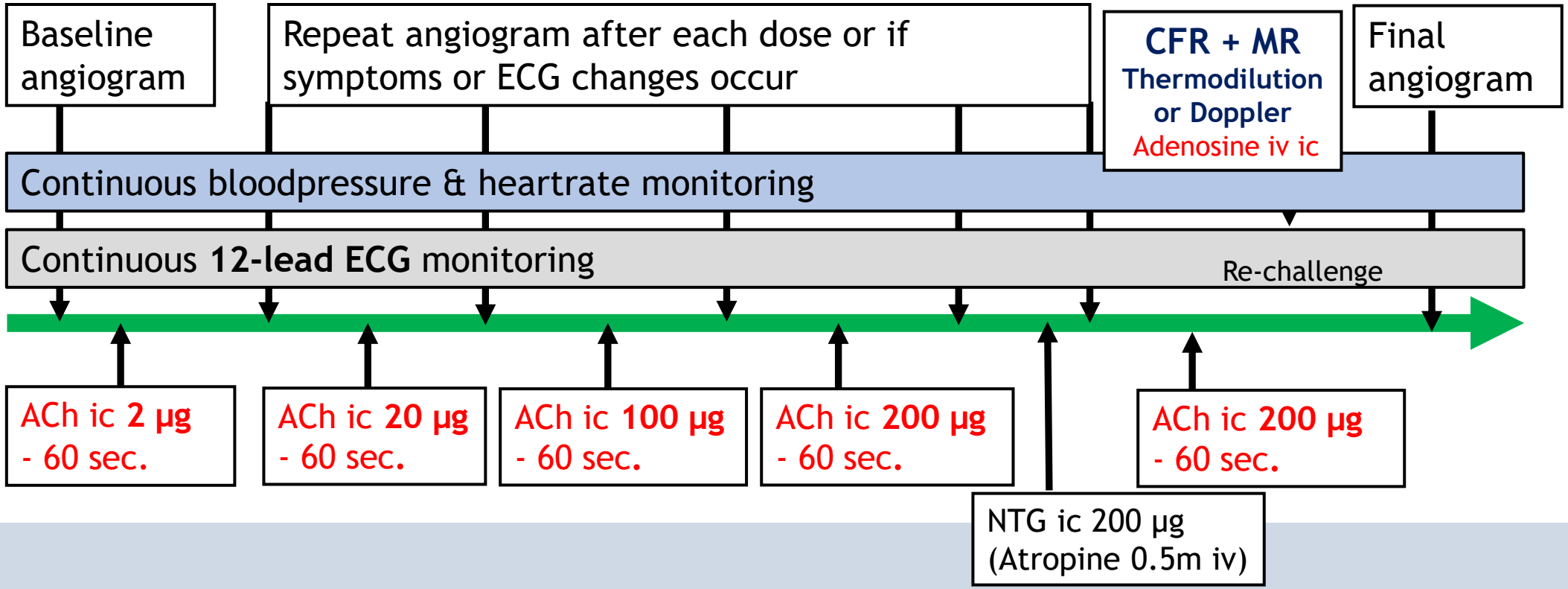
How to distinguish the endotypes

Acetylcholine reactivity test

- *Epicardial spasm*
- *Microvascular spasm*

Adenosine

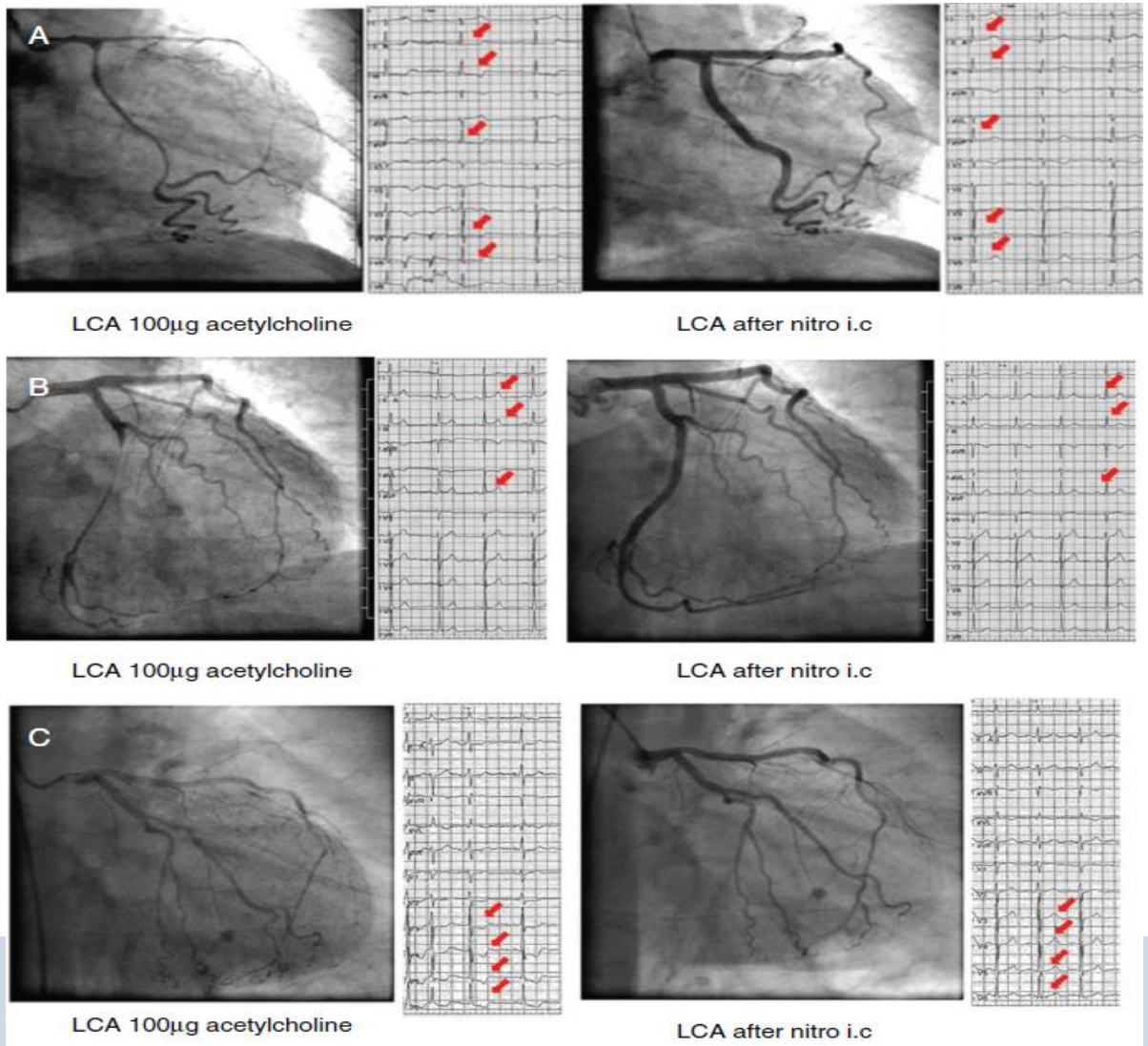
- *Microvascular dysfunction*
  - *Coronary flow reserve*
  - *Microvascular resistance*



Acetylcholine testing
Example epicardial spasm

Epicardial spasm:

- >90% epicardial vasoconstriction
- Angina
- Ischemic ECG changes

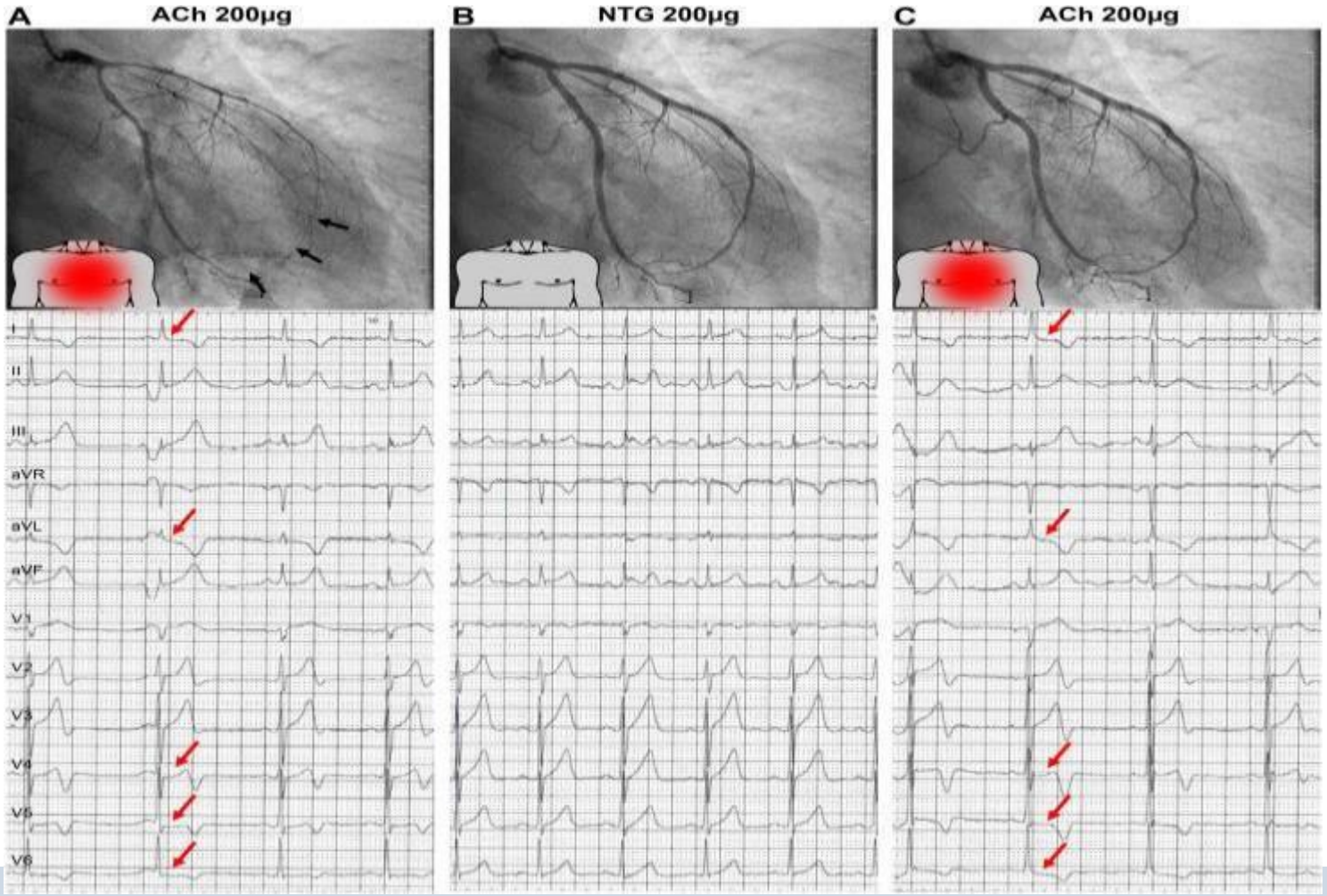


Seitz 2020 REC CardioClinics

Acetylcholine testing
Example epicardial spasm & microvascular spasm

Epicardial spasm:

- >90% epicardial vasoconstriction
- Angina
- Ischemic ECG changes



Microvascular spasm:

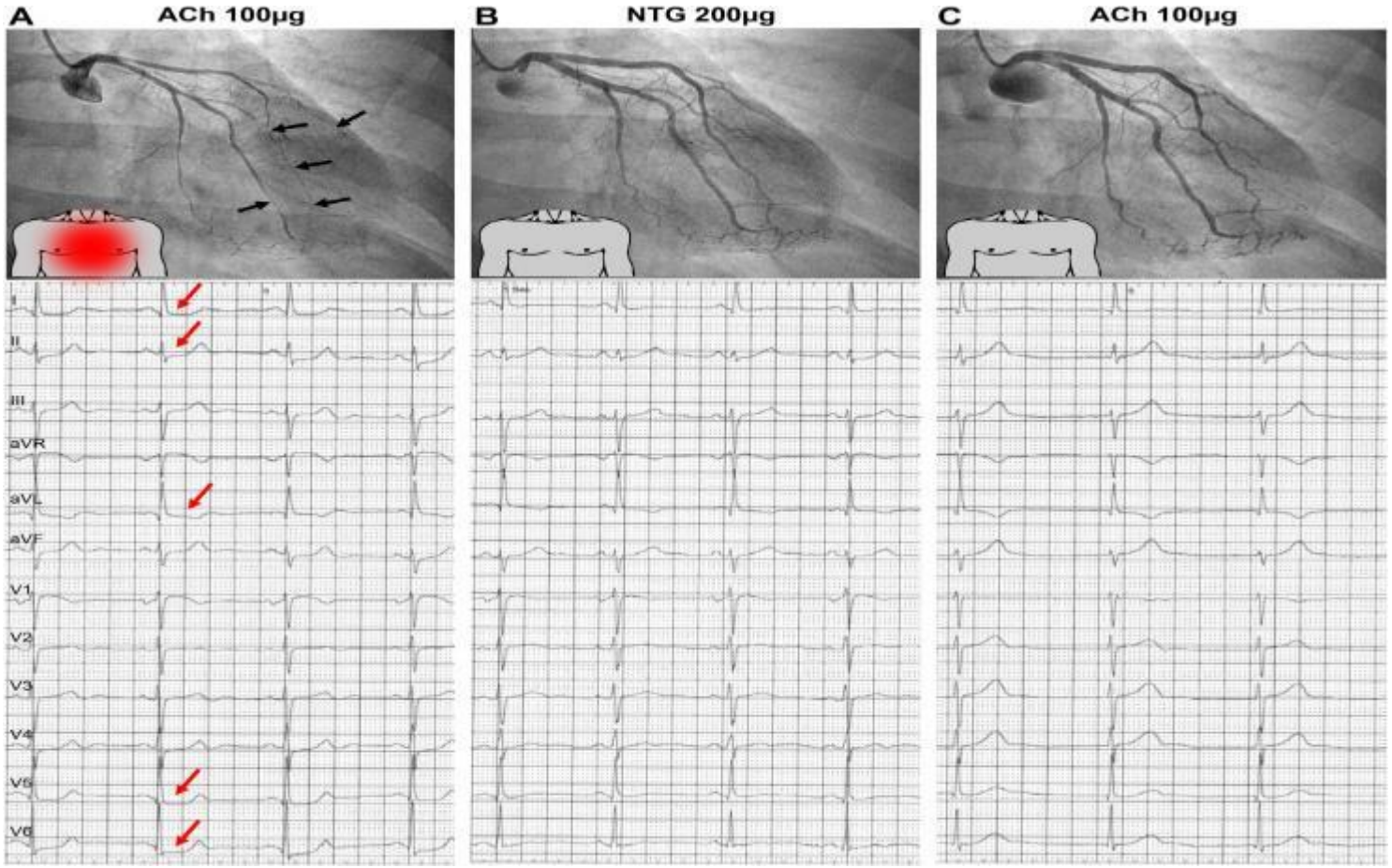
- <90% or no epicardial vasoconstriction
- Angina
- Ischemic ECG changes

Seitz 2022 JACC CV interv

Acetylcholine testing
Example epicardial spasm & nitrate responder

Epicardial spasm:

- >90% epicardial vasoconstriction
- Angina
- Ischemic ECG changes



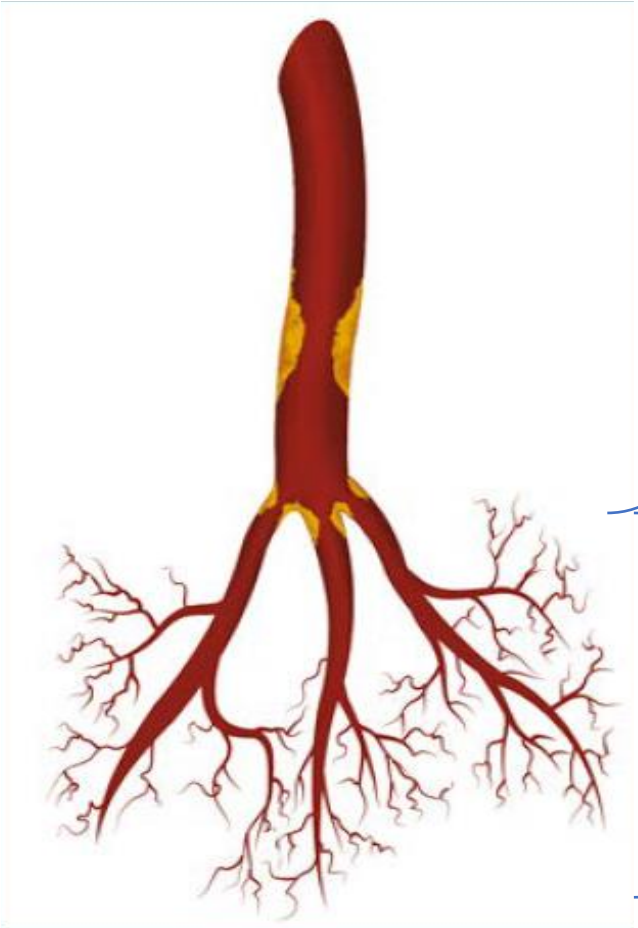
Seitz 2022 JACC CV interv

Coronary flow reserve
Definition

Overall Coronary Flow

$$\frac{\text{hyperemic flow}}{\text{baseline flow}}$$

CFR > 2.0



Epicardial Disease

FFR
rFR; iFR
Other NHPRs

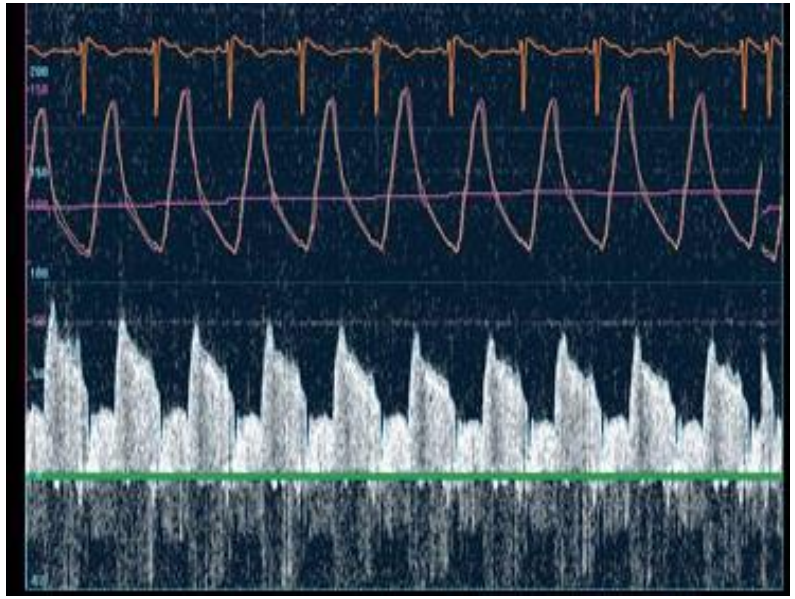
Microvascular Resistance

HMR = Pd hyperemia / hyperemic flow
IMR = Pd x Hyperemic T_{mn}

HMR > 2.5
IMR > 25

Coronary flow reserve
Definition

Doppler wire or Combowire Philips, USA



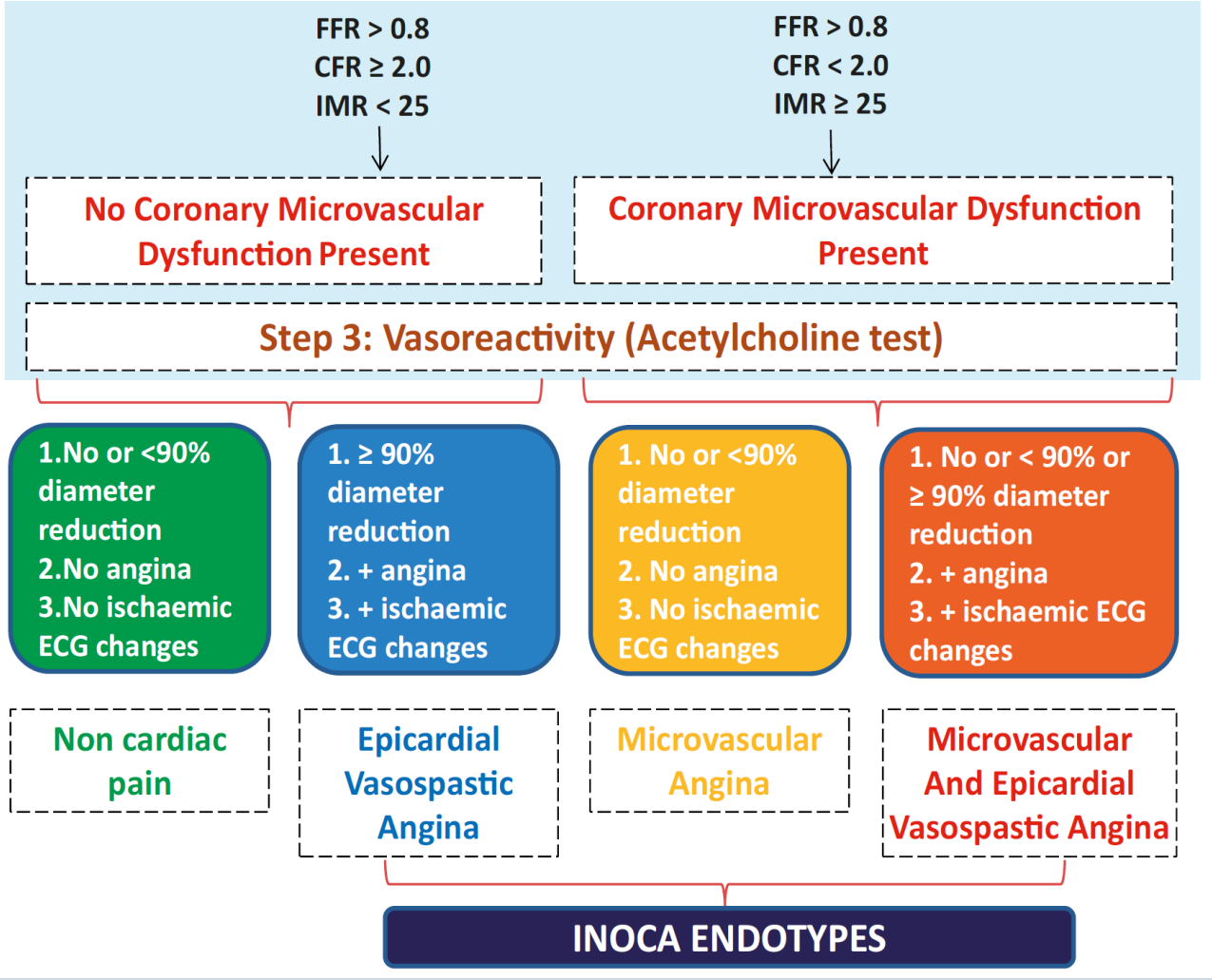
Adenosine ic

Pressure-temperature guidewire Abbot Vascular, USA

Adenosine iv

van de Hoef et al., Nat Rev Cardiol 2013

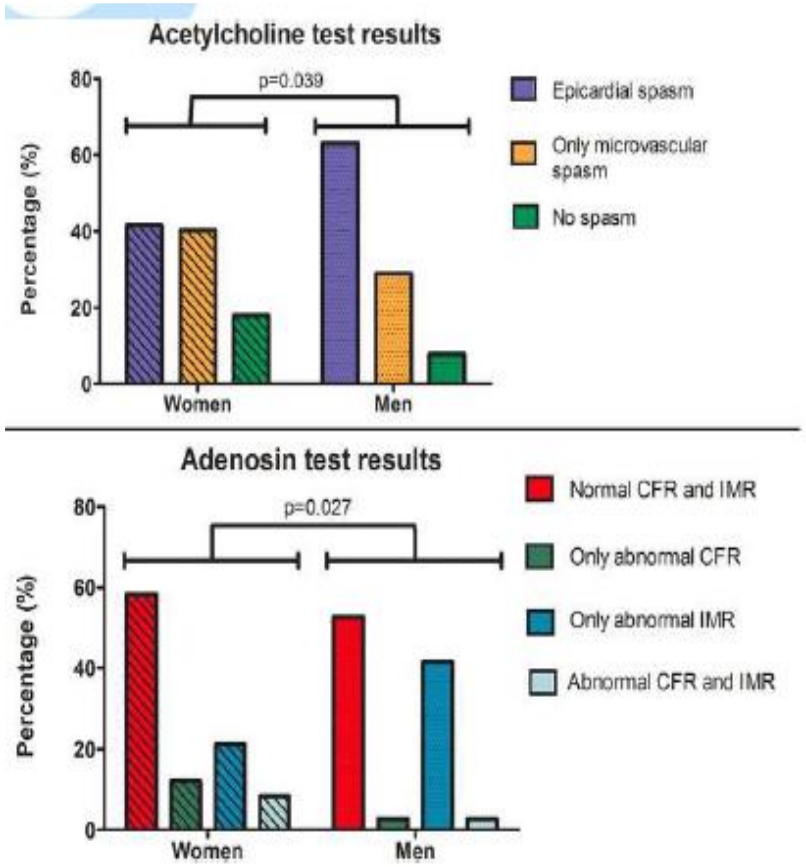
Adenosine and Acetylcholine testing
Diagnostic criteria



EAPCI expert consensus paper on INOCA EHJ & EuroIntervention 2020
ESC guidelines CCS 2019

Why is ICFT important

Improve understanding of pathophysiology



- Sex-differences in vasomotor dysfunction

Women: higher prevalence of microvascular spasm

Men: higher prevalence of epicardial spasm

Women & Men low prevalence of CMD

Jansen 2021 Front CV Med

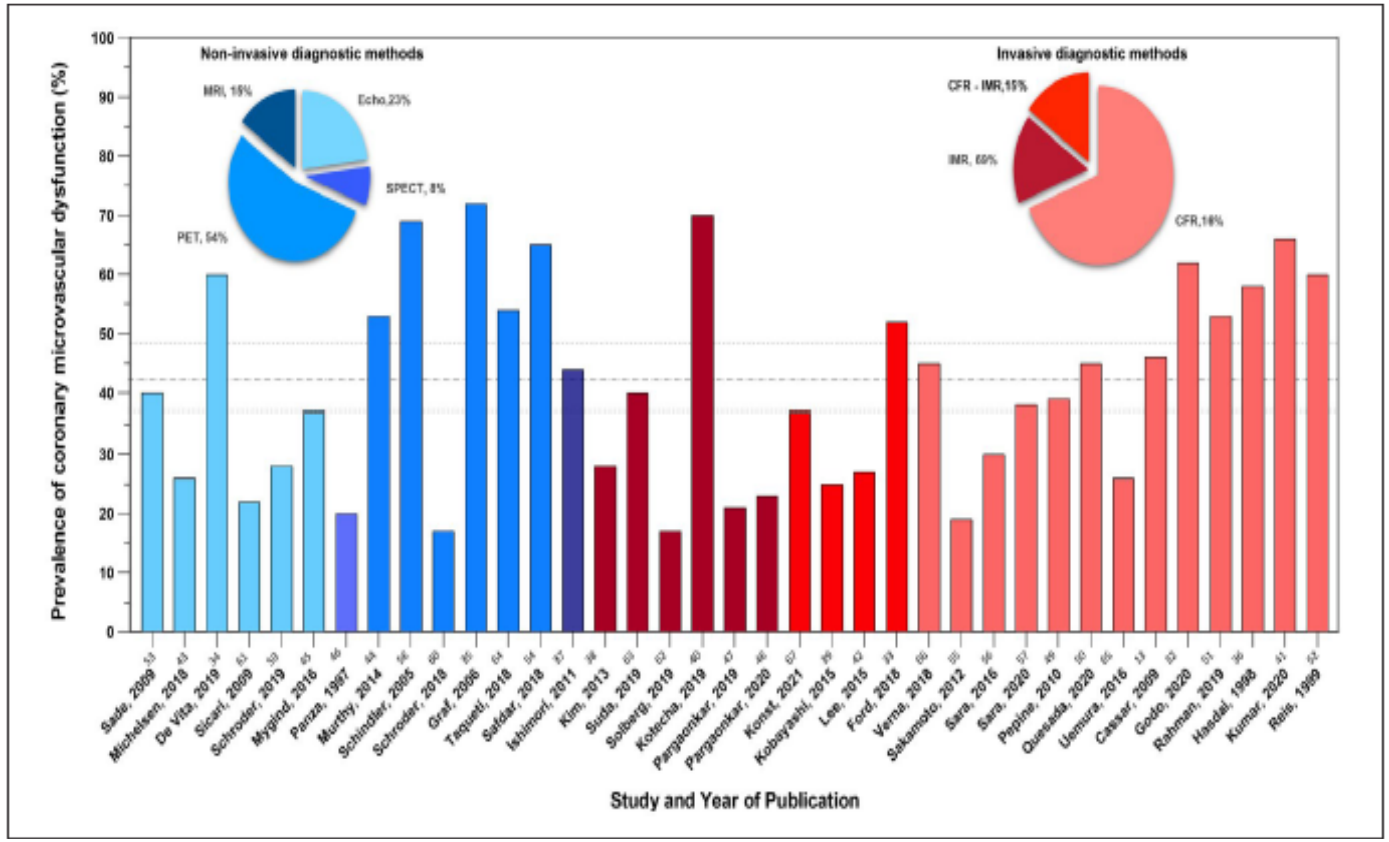
CMD

Prevalence

> 14.000 patients
no-obstructive CAD
65% women 35% men

Prevalence CMD

CFR ↓20-40%
IMR ↑25-60%
CFR↓+ IMR↑ 25-55%



Mileva N. 2022 JAHA Systematic Review-Meta analysis

ICFT
Why is it important

Patient perspective

- Diagnosis
- Tailored treatment

Research (and ultimately patient) perspective

- To improve
  - Understanding of pathophysiology
  - Diagnosis
  - Treatment
  - QoL

Coronary vasomotor dysfunction
Not benign

847 patients with angina + unobstructed coronary arteries → Intracoronary acetylcholine spasm provocation testing → Long-term follow-up: 7.2 (6.5-7.9) years

MAIN RESULTS

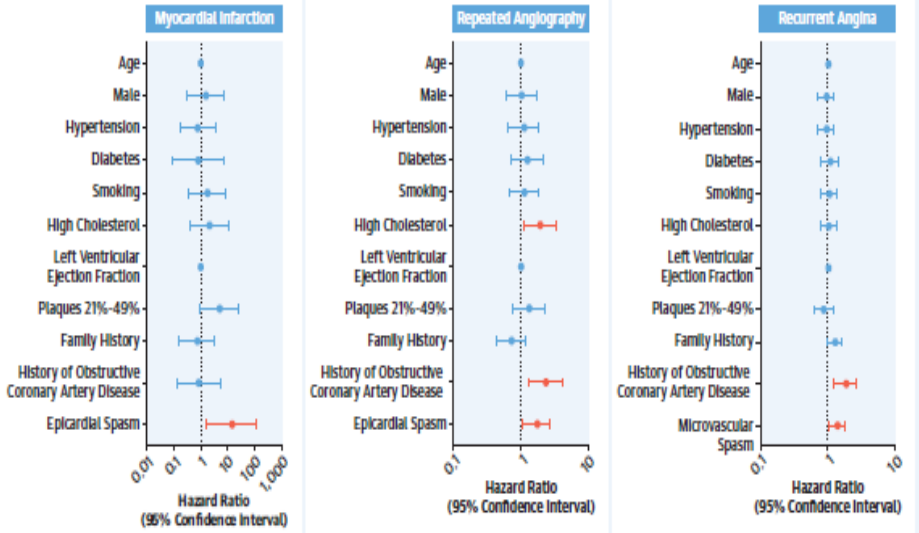
Mortality

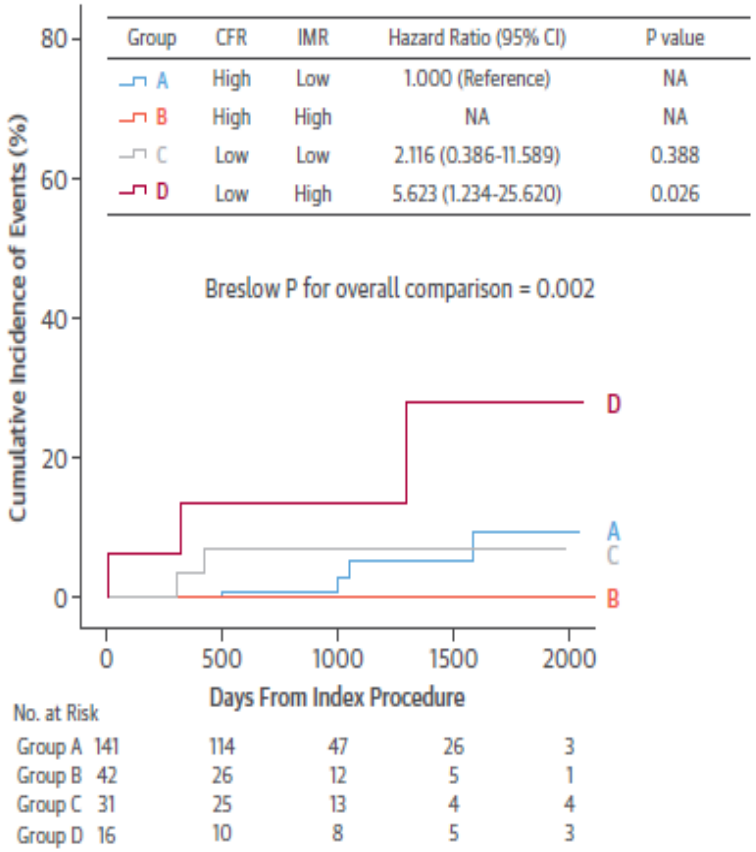
All-Cause Mortality 7.5% in 7 years (≈1.0% per year)

Cardiac Mortality 0.9% in 7 years (≈0.1% per year)

Low Mortality independent of coronary spasm

Predictors of Morbidity



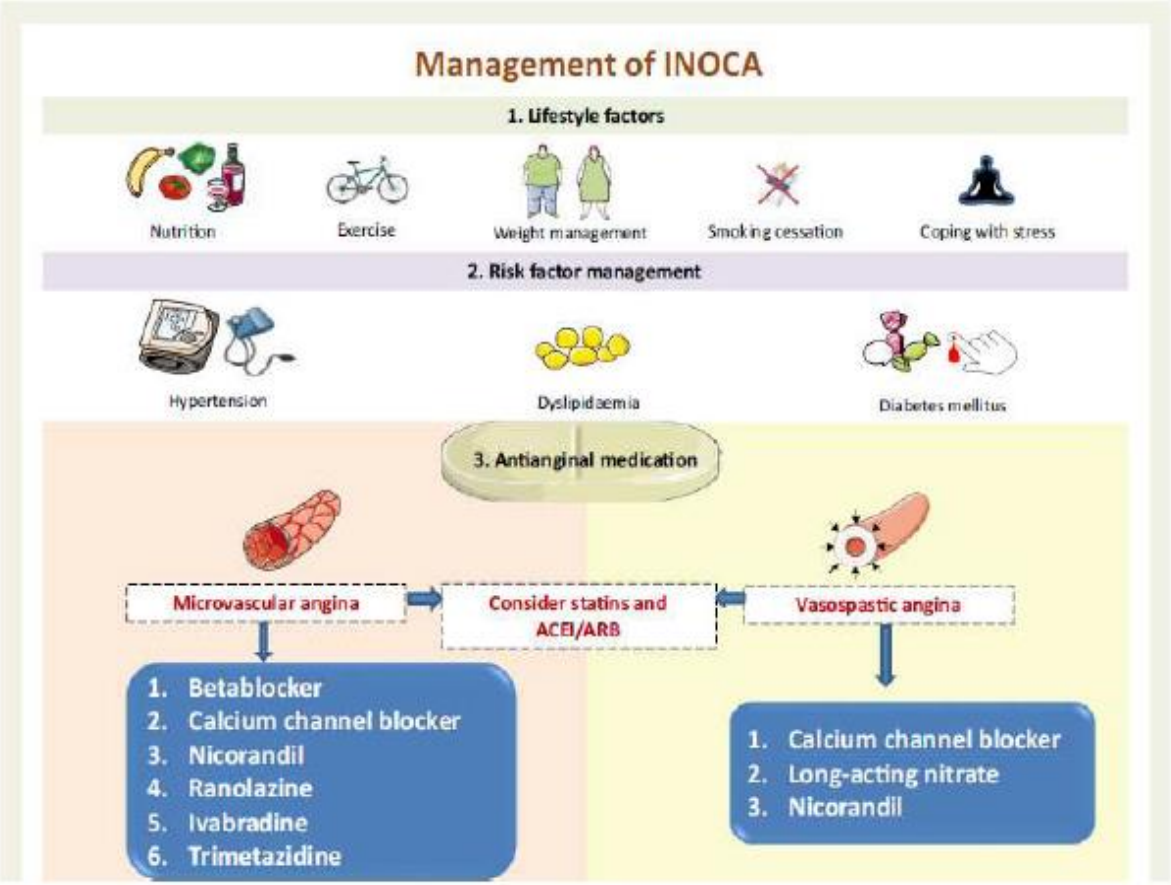


Group	CFR	IMR	Hazard Ratio (95% CI)	P value
A	High	Low	1.000 (Reference)	NA
B	High	High	NA	NA
C	Low	Low	2.116 (0.386-11.589)	0.388
D	Low	High	5.623 (1.234-25.620)	0.026

Seitz 2020 JACC Interv

Lee 2016 JACC

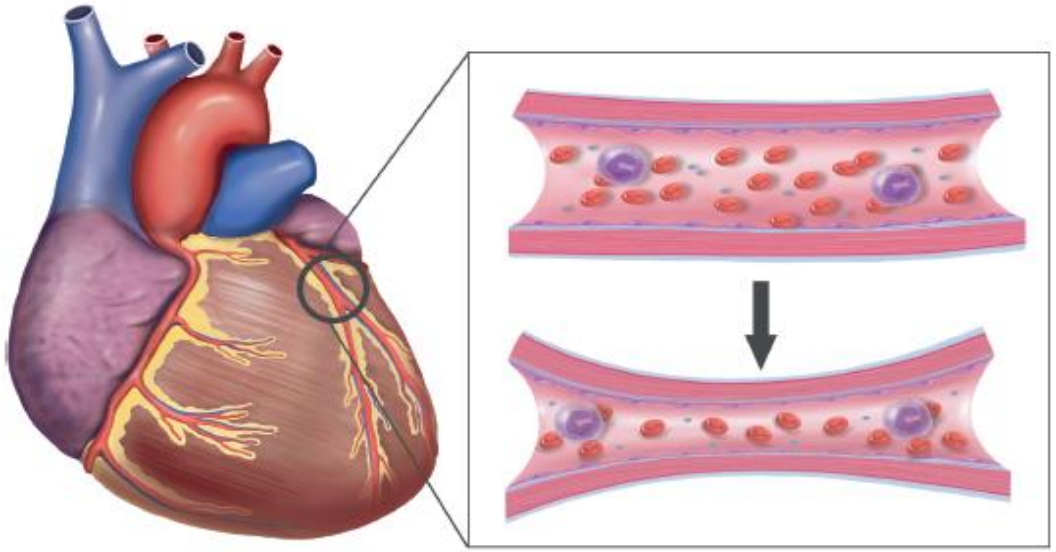
Why is ICFT important
To tailor treatment



EAPCI expert consensus paper on INOCA EHJ & EuroIntervention 2020
ESC guidelines CCS 2019

Why is ICFT important

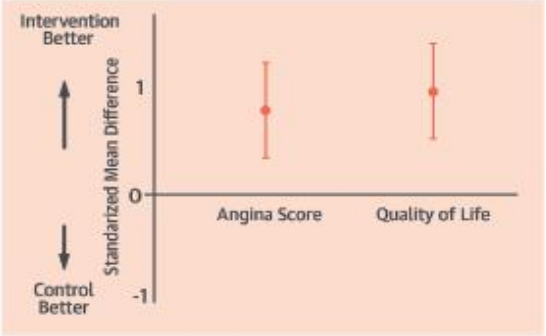
Diagnosis enables tailored treatment and improves QoL



Stratified Medicine in Patients with INOCA:

- Microvascular Angina
- Vasopastic Angina
- Non-Cardiac Chest Pain

→ **Improved Angina and Quality of Life**



Ford 2018 JACC CorMicA-trial

Take home messages

- Angina in patients with no obstructive coronary artery disease (ANOCA) can be related to ischemia: INOCA and MINOCA

- ANOCA higher prevalence in women!

- Important underlying pathofysiologic mechanisms related to vasomotor dysfunction:
  - Coronary spasm (epi en microvascular)
  - Coronary microvascular dysfunction (CMD)
  - Endothelial dysfunction

- Invasive coronary function testing (ICFT) is the only way to unravel the underlying pathophysiologic mechanisms and <u>should be considered</u> in pts with persistent symptoms but no coronary obstruction

- More research is needed to narrow the knowledge gap

Registry

IMPRESS CONSORTIUM

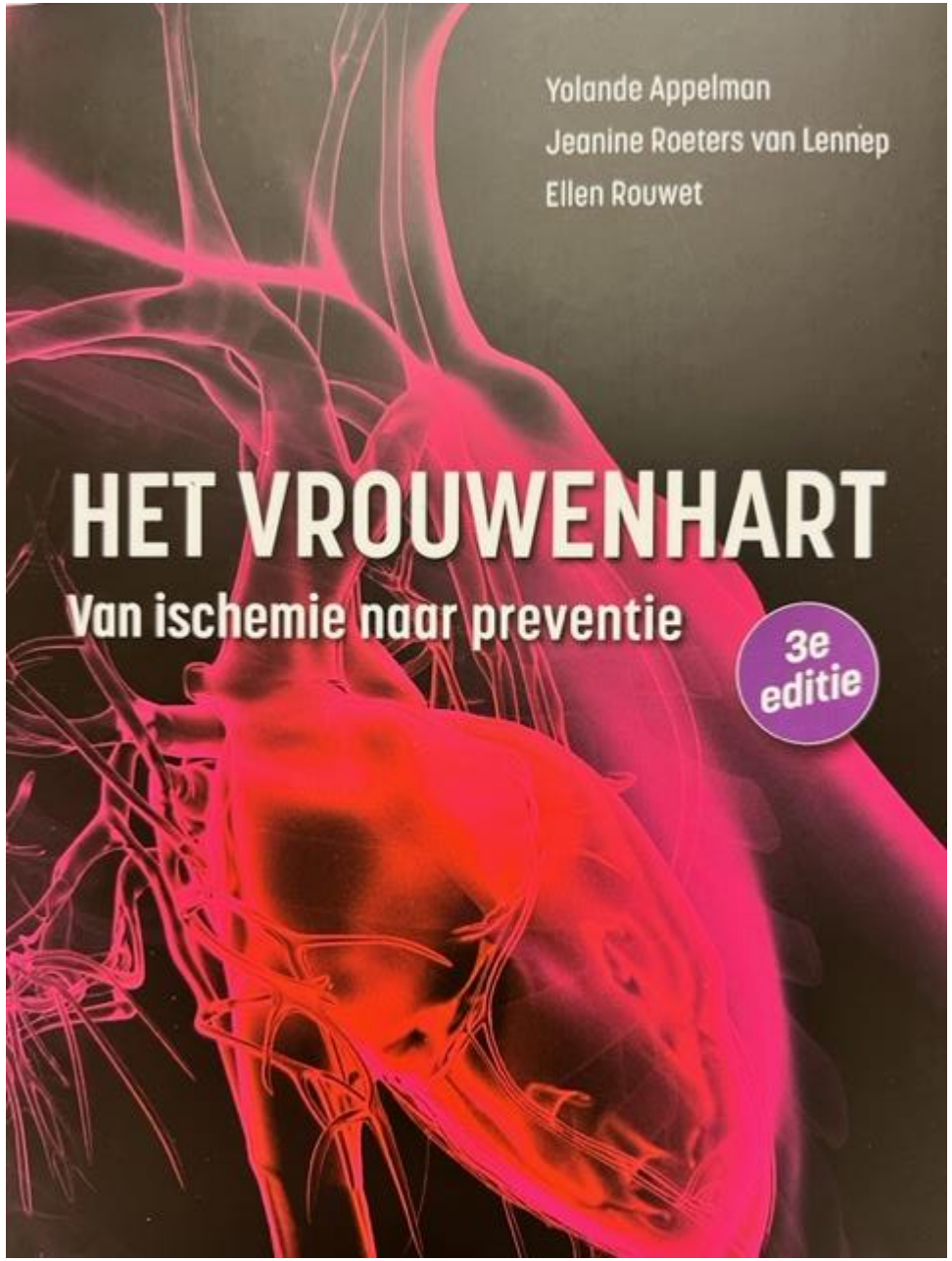
Questionnaires (among others)

- Type of symptoms
- Medication use
- Quality of Life
- Female specific risk factors

Research questions

- Investigate the prevalence of the different endotypes of ANOCA?
- Investigate the clinical characteristics of ANOCA patients?
- Provide procedural data on ICFT
- Investigate the follow-up of ANOCA patients

Courtesy of C. Crooijmans RadboudUMC


Yolande Appelman
Jeanine Roeters van Lennep
Ellen Rouwet
HET VROUWENHART
Van ischemie naar preventie
3e editie