

# WELKOM

## Refereeravond Cardiologie

Maandag 5 februari 2024

18:30 – 21:00

**AMGEN**<sup>®</sup>  
Cardiovascular

 **Boehringer  
Ingelheim**

 **MSD**

 **NOVARTIS**

 **zuyderland**

# Refereeravond Cardiologie 5 februari 2024

18:30 uur: **Welkom en Inleiding op het thema**

*Patty Winkler, Interventiecardioloog Zuyderland MC*

18:45 uur: **Inoca, mechanismen en behandelopties**

*Uyen Nguyen, AIOS Cardiologie*

19:15 uur: **Minoca, welk stramien te volgen?**

*Nils Rollersbroich, AIOS Cardiologie*

19:45 uur: **Pauze**

20:15 uur: **“Novel treatments INOCA**

*Patty Winkler, Interventiecardioloog Zuyderland MC*

20:45 uur: **Vragen en Afsluiting**

# Refereeravond Cardiologie

## INOCA/ANOCA mechanismen en behandelopties

Uyen Chau Nguyen  
AIOS cardiologie

05 februari 2024



**zuyderland**

# Mechanismen ischemie



# Achtergrond

## Angina pectoris

- Symptoom ischemische hartziekte
- Wereldwijd 112 miljoen patiënten
- Coronairangiogram: 70 % geen obstructief coronairlijden

## Coronaire vaatdysfunctie

- Coronaire microvasculaire dysfunctie
- Epicardiale vasospasmen
- 70% vrouw, 43% man

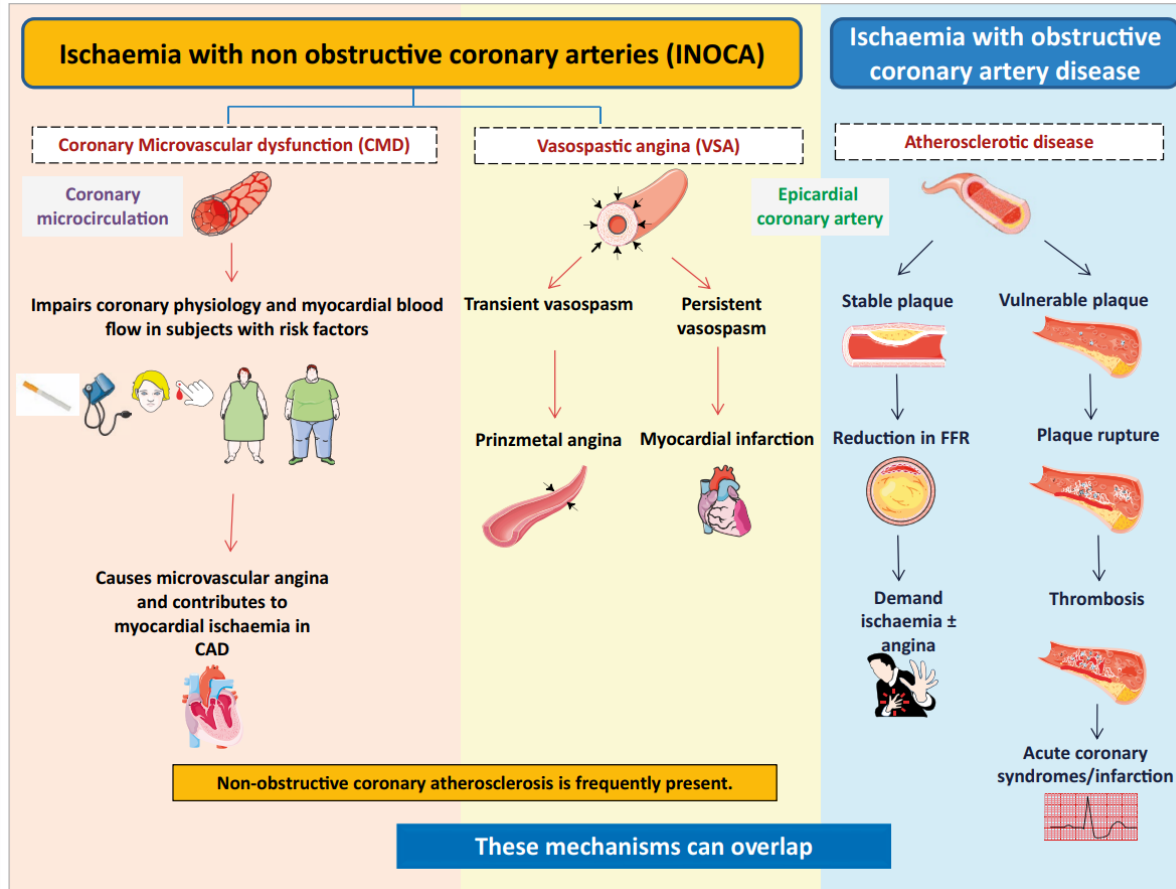
# INOCA/ANOCA

**“Angina of ischemia with no obstructive coronary disease”**

## **Oorzaak**

- Mismatch bloed voorziening en zuurstofbehoefte
- Typisch bij niet-obstructief coronairlijden
- Coronaire microvasculaire dysfunctie/ epicardiale spasmen of mengbeeld

# Mechanismen overlap



# Impact INOCA/ANOCA

## Verhoogd risico

- Myocardinfarct, herseninfarct, hartfalen en cardiovasculair overlijden

## Chronische klachten

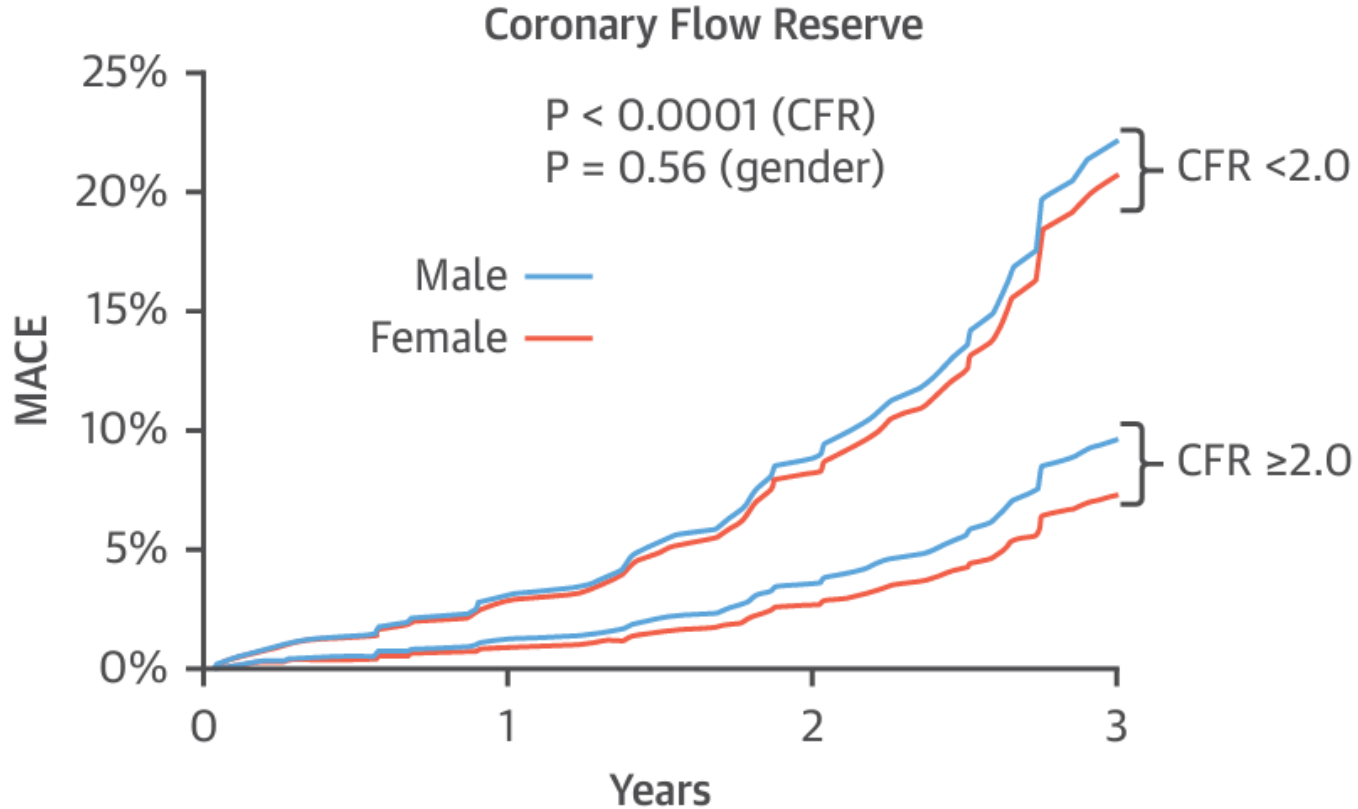
- Herhaaldelijke diagnostiek en EHH bezoek

## Slechtere kwaliteit van leven

- Verminderde arbeidsparticipatie



# CMD geassocieerd met belangrijke cardiovasculaire events



# CorMiCA trial

## “Stratified Medical Therapy Using Invasive Coronary Function Testing in Angina”

391 patienten zonder obstructief coronairlijden

Dubbelblind RCT 1:1

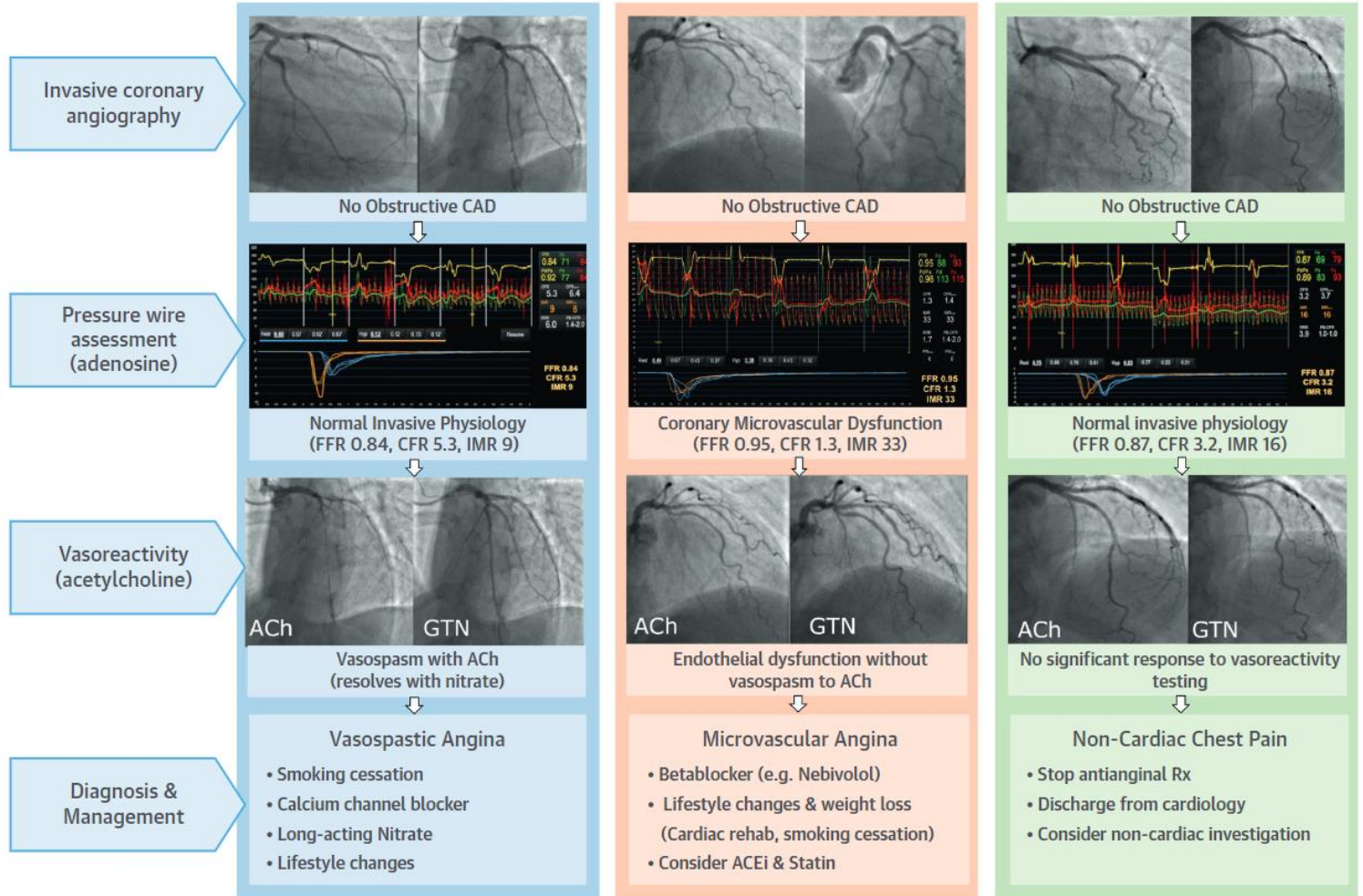
**Interventie:** gerichte behandeling na aantonen coronaire vaatsdysfunctie

**Controle:** standaard zorg (sham invasieve diagnostiek)

**FIGURE 1** Stratified Medical Therapy Guided by an IDP in Patients With Angina but No Obstructive CAD

**Stratified Medicine in Patients with INOCA:**

- Microvascular Angina
- Vasospastic Angina
- Non-Cardiac Chest Pain

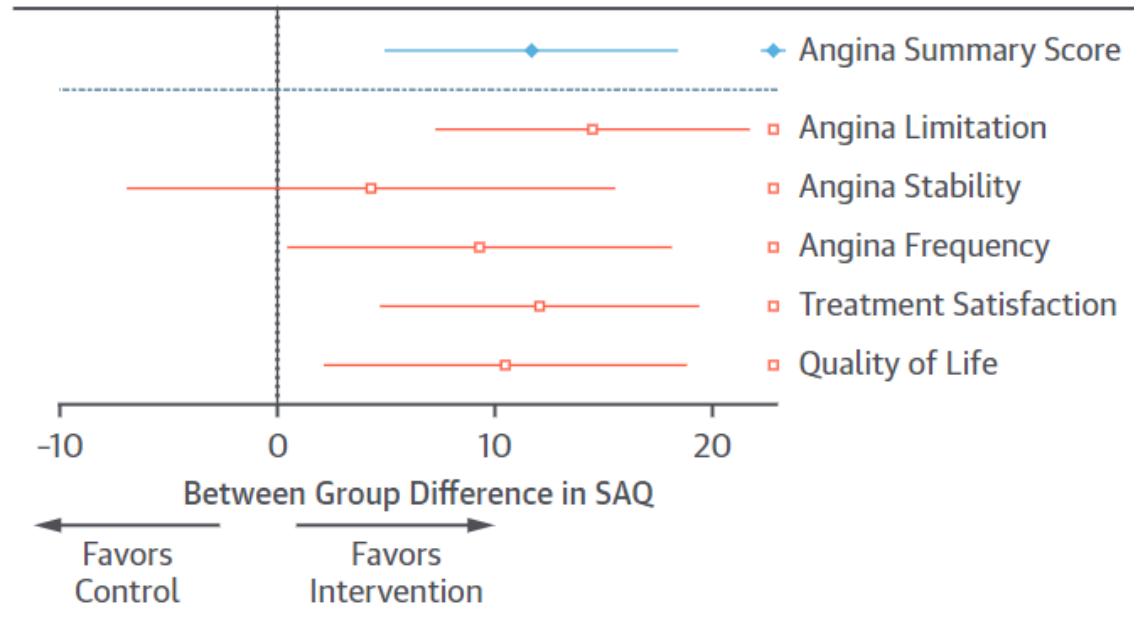


Ford et al. JACC 2018.

# CorMiCA trial

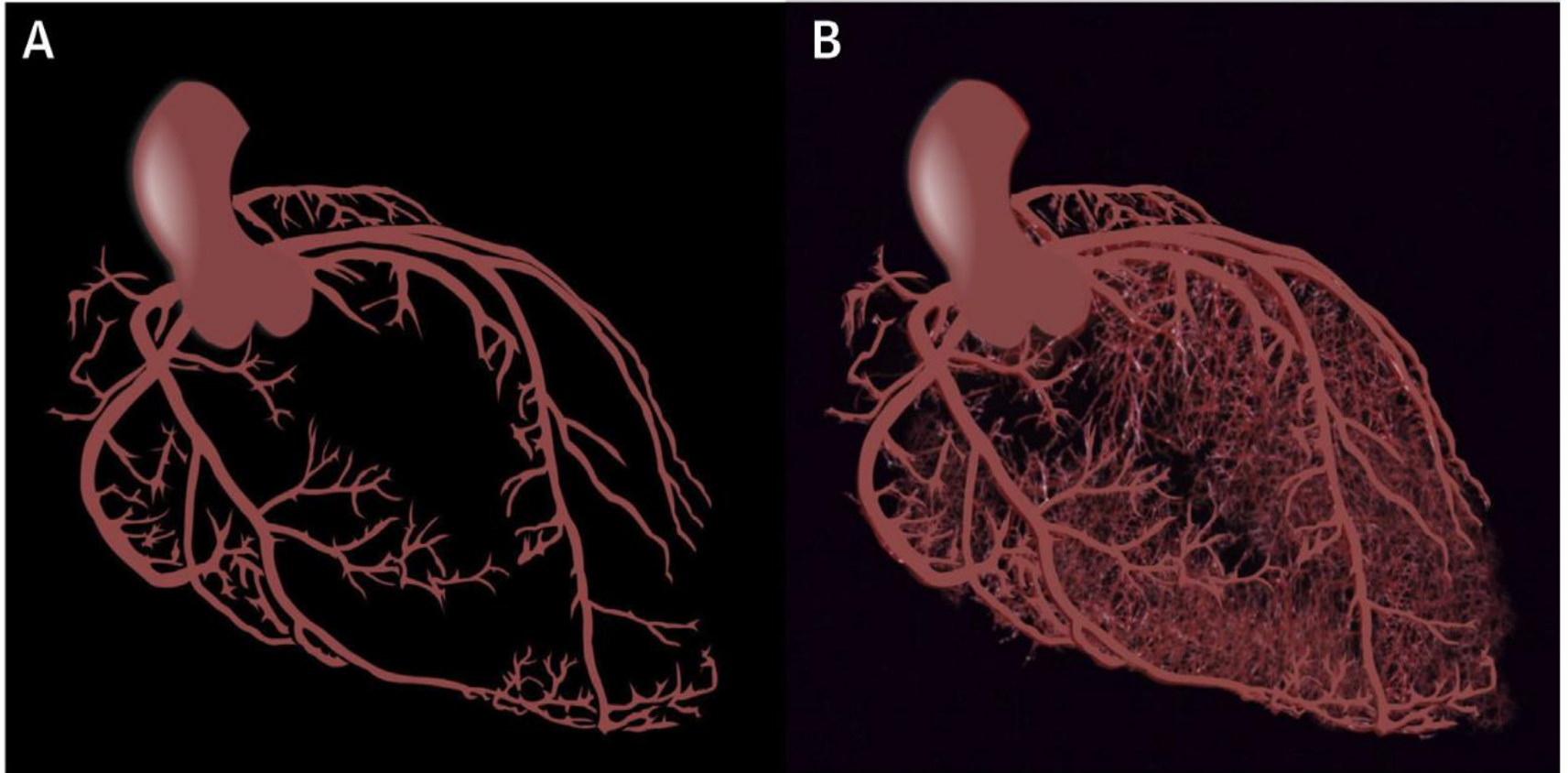
## Gerichte diagnostiek en behandeling

- 1) Vermindering AP klachten
- 2) Verbeteren kwaliteit van leven
- 3) Geen verschil MACE

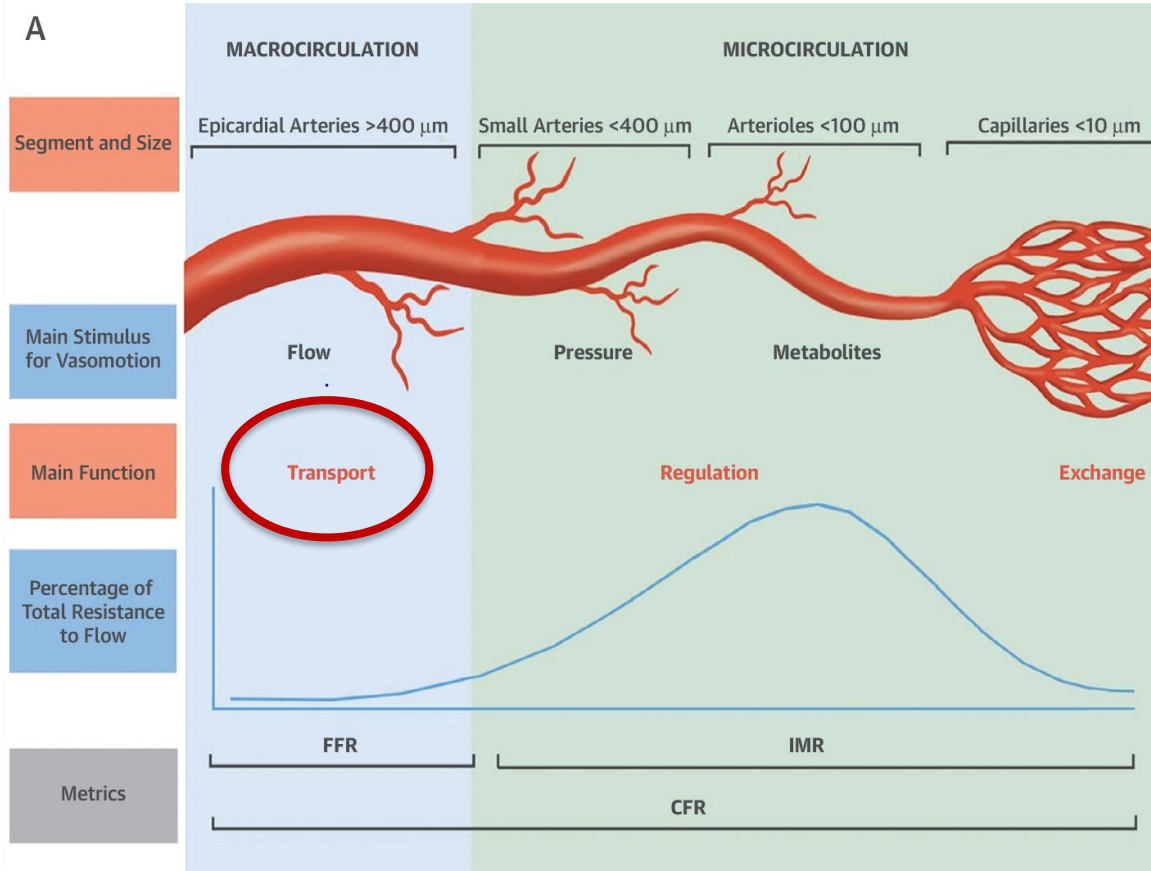


Vervolg CorMiCA trial 2

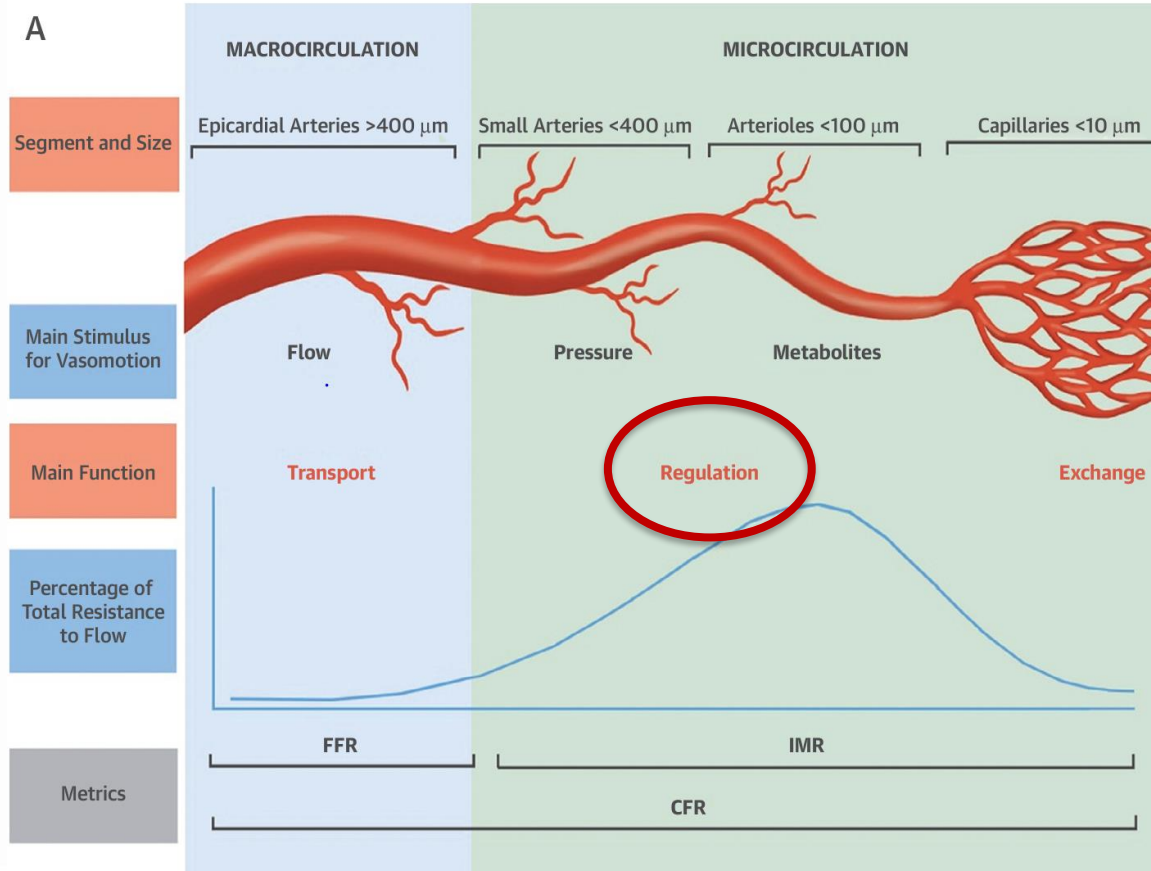
# Macrocirculatie <10% totale circulatie



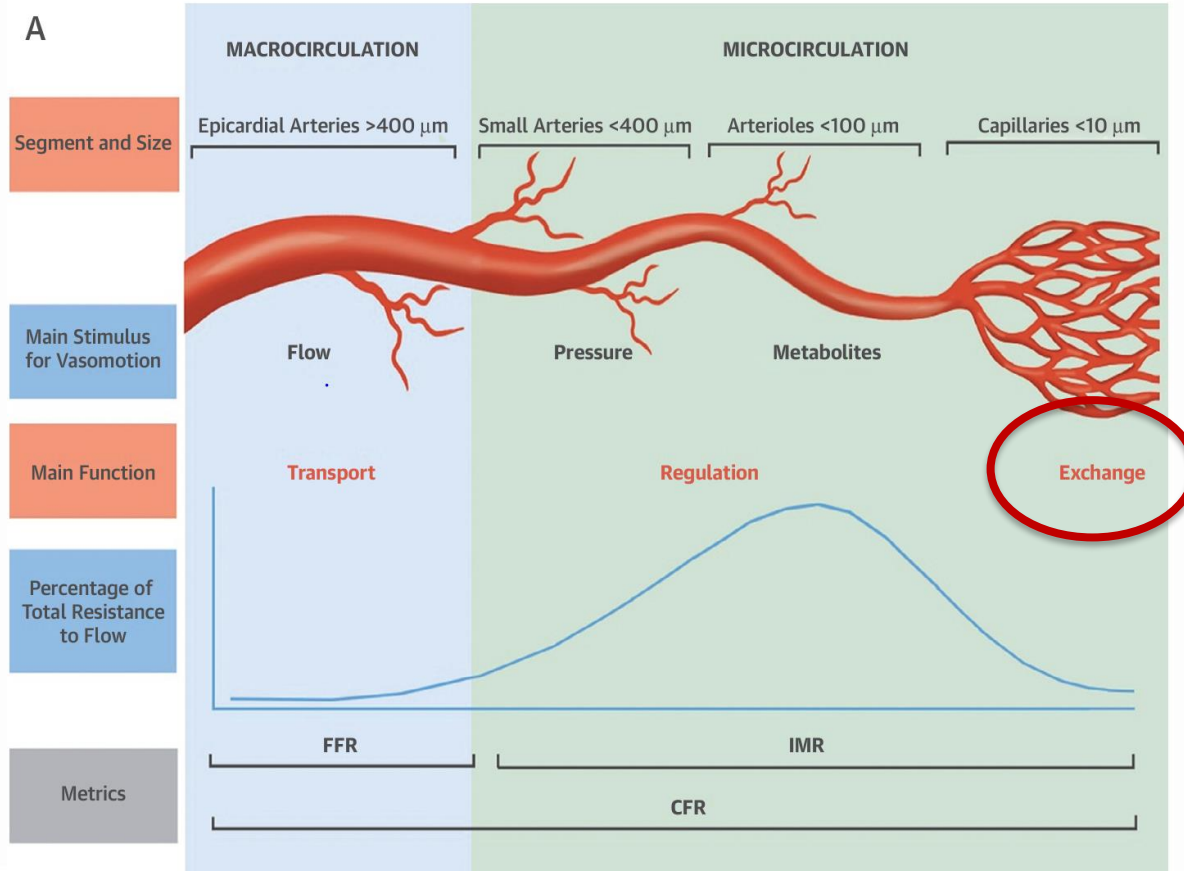
# Coronaire pathofysiologie



# Coronaire pathofysiologie



# Coronaire pathofysiologie





# Coronaire pathofysiologie

## Functioneel

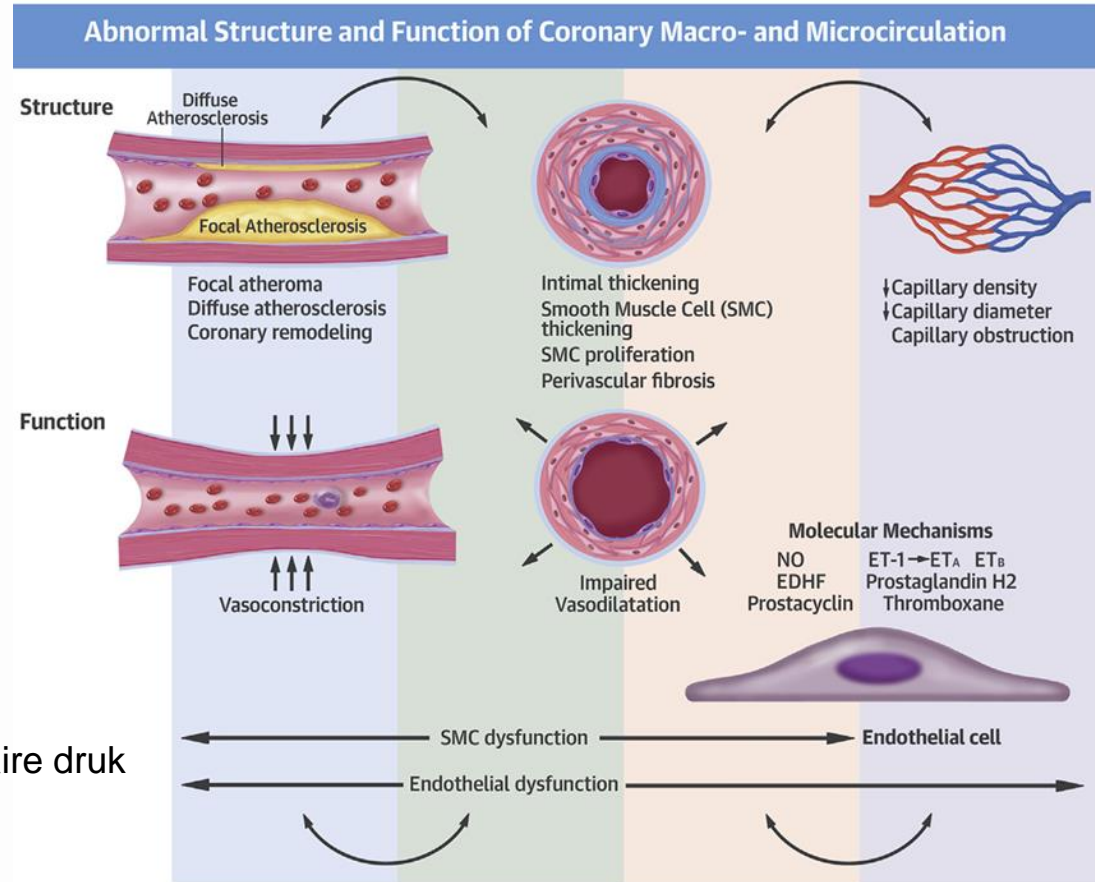
- Microvasculair spasme
- Abnormale vasodilatatie
- Endotheel disfunctie
- Dysfunctie gladde spiercellen

## Structureel

- Remodelling arteriolen
- Intravasculaire verstopping
- Perivasculaire fibrose
- Afname aantal capillairen

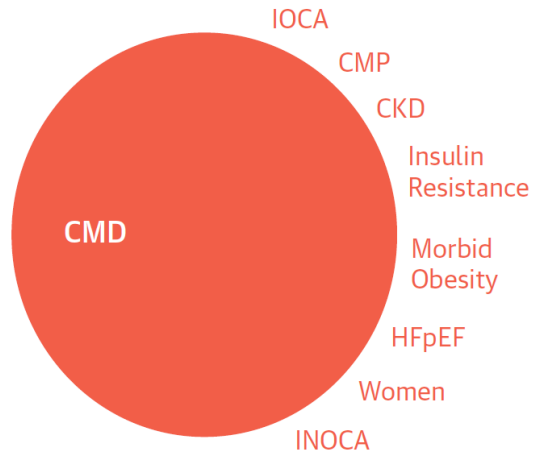
## Myocardiaal

- LVH
- Verminderde diastolische tijd
- Amyloidose
- Toegenomen intramyocardiale of -cavitaire druk
- Oedeem



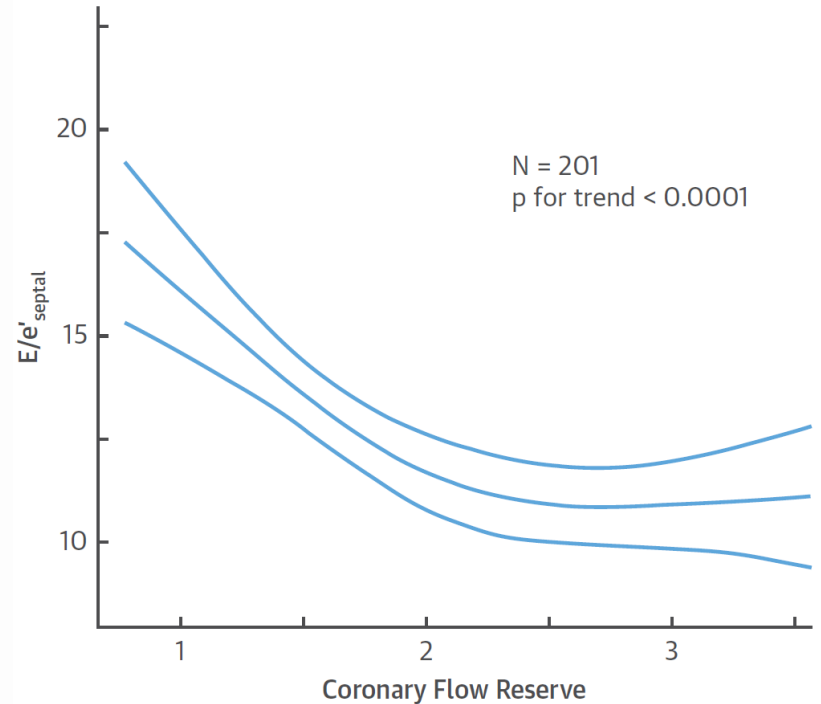
# Multifactoriële pathofysiologie

## A Patient Subgroups



## B Potential Therapies

- Coronary Revascularization
- Cardiac Transplantation
- Device Therapy
- Nepilysin Inhibitor
- Statin
- PCSK-9 Inhibitor
- SGLT-2 Inhibitor
- GLP-1 Agonist
- Gastric Bypass
- Anti-Inflammatory Therapy



# Symptomen

## **Microvasculaire angina → inspanningsgerelateerd**

- Angina houdt aan na inspanning
- Uitgelokt door hartkloppingen en stress
- Intensiteit wisselt dag tot dag
- Aanzienlijke belemmering dagelijks leven

## **Vasospasme → in rust**

- Voornamelijk nacht of vroege ochtend

**Geen onderscheid coronaire vaatdysfunctie en obstructief coronairlijden.**

# Risicofactoren

## Coronaire microvasculaire dysfunctie

- Klassiek
  - hypertensie, DM, roken, hypercholesterolemie, obesitas) beperkt.
- Niet-klassiek
  - Reumatische ziekten
  - Inflammatoire darmziekten.
  - Vrouw specifiek: migraine, pre-eclampsia, HELLP, zwangerschapshypertensie en – diabetes, spontane abortus, menopauze.

## Epicardiale vasospasmen

- Geen klassieke risicofactoren behoudens roken.
- Triggers: hyperventilatie, stress, cocaine, niet-selectieve betablokker.
- Andere vasospastische aandoeningen: migraine en Raynaud.

# Diagnostische criteria vasospasme

**Table I Coronary Artery Vasospastic Disorders**  
**Summit diagnostic criteria for vasospastic angina<sup>a</sup>**

Vasospastic angina diagnostic criteria elements

- (1) *Nitrate-responsive angina*—during spontaneous episode, with at least one of the following:
  - (a) Rest angina—especially between night and early morning
  - (b) Marked diurnal variation in exercise tolerance—reduced in morning
  - (c) Hyperventilation can precipitate an episode
  - (d) Calcium channel blockers (but not  $\beta$ -blockers) suppress episodes
- (2) *Transient ischaemic ECG changes*—during spontaneous episode, including any of the following in at least two contiguous leads:
  - (a) ST segment elevation  $\geq 0.1$  mV
  - (b) ST segment depression  $\geq 0.1$  mV
  - (c) New negative U waves
- (3) *Coronary artery spasm*—defined as transient total or subtotal coronary artery occlusion ( $> 90\%$  constriction) with angina and ischaemic ECG changes either spontaneously or in response to a provocative stimulus (typically acetylcholine, ergot, or hyperventilation)

# Diagnostiek vasospasme

## Recommendations for investigations in patients with suspected vasospastic angina

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
An ECG is recommended during angina if possible.	I	C
Invasive angiography or coronary CTA is recommended in patients with characteristic episodic resting angina and ST-segment changes, which resolve with nitrates and/or calcium antagonists, to determine the extent of underlying coronary disease.	I	C
Ambulatory ST-segment monitoring should be considered to identify ST-segment deviation in the absence of increased heart rate.	IIa	C
An intracoronary provocation test should be considered to identify coronary spasm in patients with normal findings or non-obstructive lesions on coronary arteriography and a clinical picture of coronary spasm, to diagnose the site and mode of spasm. <sup>412,414,438–440</sup>	IIa	B

“is recommended (consensus)”

“should be considered”

“may be considered”

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# Diagnostische criteria microvasculaire angina

**Table 2**

Clinical criteria for suspecting microvascular angina (MVA)\*.

1. Symptoms of myocardial ischemia
  - a. Effort and/or rest angina
  - b. Angina equivalents (i.e. shortness of breath)
2. Absence of obstructive CAD (<50% diameter reduction or FFR > 0.80) by
  - a. Coronary CIA
  - b. Invasive coronary angiography
3. Objective evidence of myocardial ischemia
  - a. Ischemic ECG changes during an episode of chest pain
  - b. Stress-induced chest pain and/or ischemic ECG changes in the presence or absence of transient/reversible abnormal myocardial perfusion and/or wall motion abnormality
4. Evidence of impaired coronary microvascular function
  - a. Impaired coronary flow reserve (cut-off values depending on methodology use between  $\leq 2.0$  and  $\leq 2.5$ )
  - b. Coronary microvascular spasm, defined as reproduction of symptoms, ischemic ECG shifts but no epicardial spasm during acetylcholine testing.
  - c. Abnormal coronary microvascular resistance indices (e.g. IMR > 25)
  - d. Coronary slow flow phenomenon, defined as TIMI frame count >25.

**Definitive**

**Suspected**

# Diagnostiek microvasculaire angina

## Investigations in patients with suspected coronary microvascular angina

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
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. <sup>412,413</sup>	<b>IIa</b>	<b>B</b>
Intracoronary acetylcholine with ECG monitoring may be considered during angiography, if coronary arteries are either angiographically normal or have moderate stenoses with preserved iwFR/FFR, to assess microvascular vasospasm. <sup>412,438–440</sup>	<b>IIb</b>	<b>B</b>
Transthoracic Doppler of the LAD, CMR, and PET may be considered for non-invasive assessment of CFR. <sup>430–432,441</sup>	<b>IIb</b>	<b>B</b>

“should be considered”

“may be considered”

© ESC 2019



# Non-invasieve diagnostiek

**TABLE 1** Strengths and Limitations of Select Diagnostic Techniques for the Evaluation of CMD

	Accuracy	Reproducibility	Diagnostic Threshold	Prognostic Validation	Availability	Cost
Noninvasive*						
PET	++++	++++	CFR <2	++++	++	\$\$\$
CMR	+++	+++	MPRI <2	++	++	\$\$\$
Doppler echocardiography	++	+++	CFVR <2	+++	++++	\$
Invasive*						
CFR	++++	++++	<2.3	+++	++++	\$\$\$\$
IMR	++++	+++	>25 U	++	++	\$\$\$\$

## PET-CT

- Meest betrouwbaar
- Tracers: water, ammonia, rubidium
- Zelfde CFR afkapwaarde als invasief
- Beperkt beschikbaar

# Non-invasieve diagnostiek

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Invasive*						
CFR	++++	++++	<2.3	+++	++++	\$\$\$\$
IMR	++++	+++	>25 U	++	++	\$\$\$\$

## CMR

- Myocardiale perfusie index (MPRI)
- Voornamelijk onderzoeksverband
- MPRI <1.4 vergelijkbaar met invasieve IMR >25
- Beperkt beschikbaar

# Non-invasieve diagnostiek

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Invasive*						
CFR	++++	++++	<2.3	+++	++++	\$\$\$\$
IMR	++++	+++	>25 U	++	++	\$\$\$\$

## Echocardiografie

- CFR in LAD bepaald in rust en tijdens adenosine.
- Beschikbare techniek en goedkoop.
- Beperkte toepassing: expertise en echovenster.

**Non-invasieve diagnostiek  
beperkte rol**

# Invasieve coronaire functietest: wanneer zinvol?

## Voor de patient

- Acceptatie van ziekte.
- Cardiale diagnose arbeids(on)geschiktheidstraject.

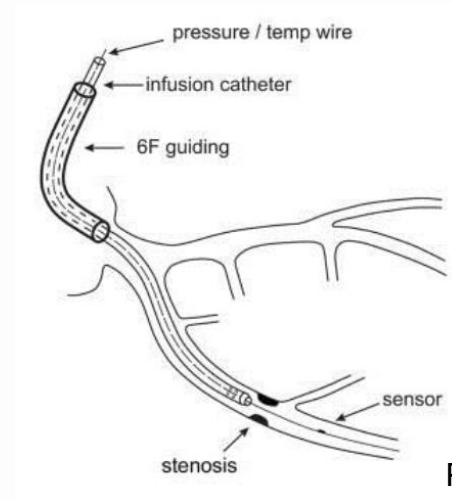
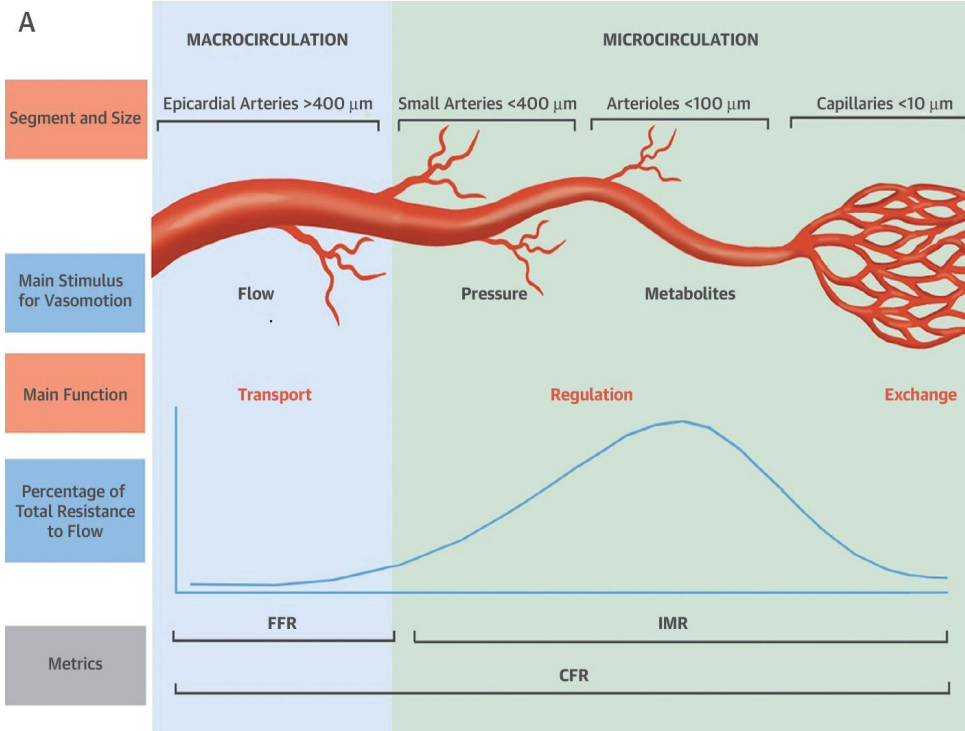
## Voor de cardioloog

- Niet aanslaan van medicamenteuze behandeling.
- Coronaire vaatdysfunctie met zekerheid uitsluiten.

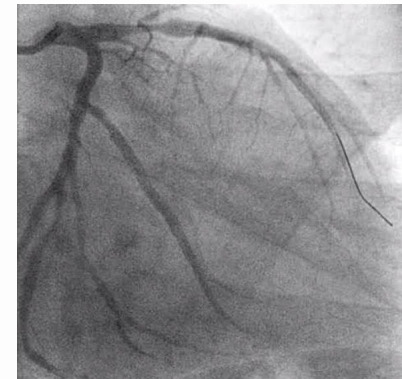
## Meerderheid patienten

- WD coronaire vaatdysfunctie starten met medicatie en lifestyle adviezen.

# Wat te meten?

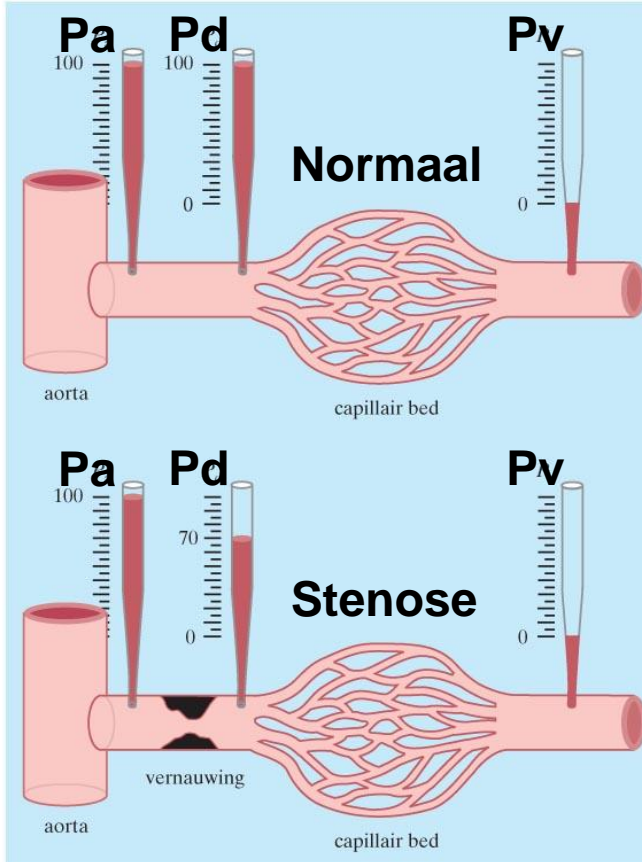


Patty Winkler.



Mathew et al. JACC cardiovascular imaging. 2020.

# Fractionele flowreserve (FFR)



**Ratio distale coronaire druk en normale druk (aorta)**

Hemodynamische vernauwing  $< 0.80$ .

Druk = Flow \* Weerstand

Flow = Druk / Weerstand

- Normale flow =  $(P_a - P_v) / \text{weerstand}$
- Stenose flow =  $(P_d - P_v) / \text{weerstand}$

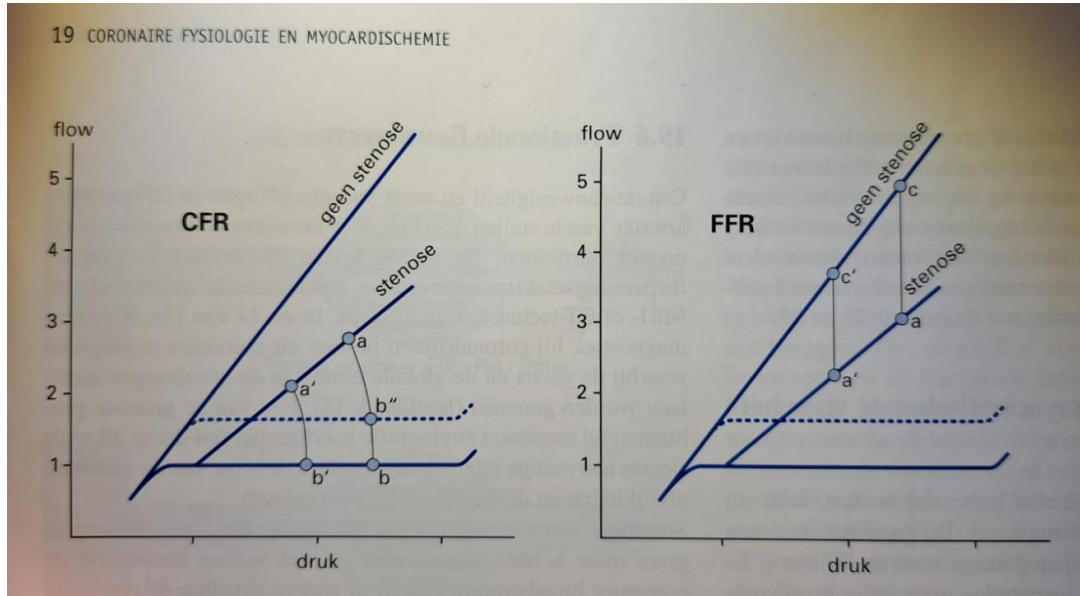
Fractionele flow reserve

- Stenose flow / normale flow =
- $(P_d - P_v) / (P_a - P_v) =$
- $P_d - P_a$

# Coronaire flow reserve (CFR)

## Coronaire flow reserve (CFR)

- Mate waarin de coronaire bloedstroom kan toenemen
- Coronaire microvasculaire dysfunctie  $< 2.0$
- $CFR = \text{Hyperemische flow} / \text{rust flow}$



# Microvasculaire weerstand

## Index van microvasculaire weerstand (IMR)

- Thermodilutie
- Distale coronaire druk \* mean transit time tijdens hyperemie
- Coronaire microvasculaire dysfunctie >25 U

## Hyperemische microvasculaire weerstand (HMR)

- Doppler
- Intracoraire druk / hyperemische flow snelheid
- Coronaire microvasculaire dysfunctie >1.9 mmHg/cm/s



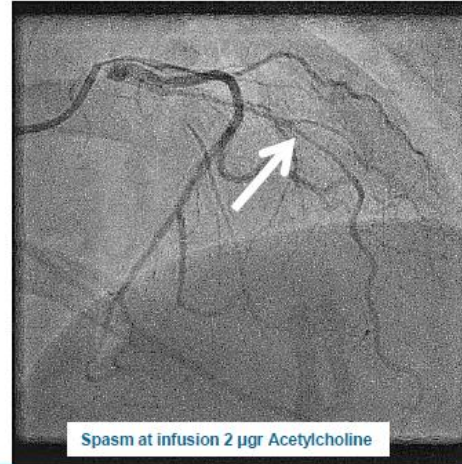
# Intra-coronaire acetylcholine test

## Mechanisme:

- Neurotransmitter parasympathisch zenuwstelsel
- Muscarinerge receptoren
  - Endotheel → NO → vasodilatatie
  - Gladde spiercellen → vasoconstrictie
  - Netto effect: vasodilatatie of vasoconstrictie

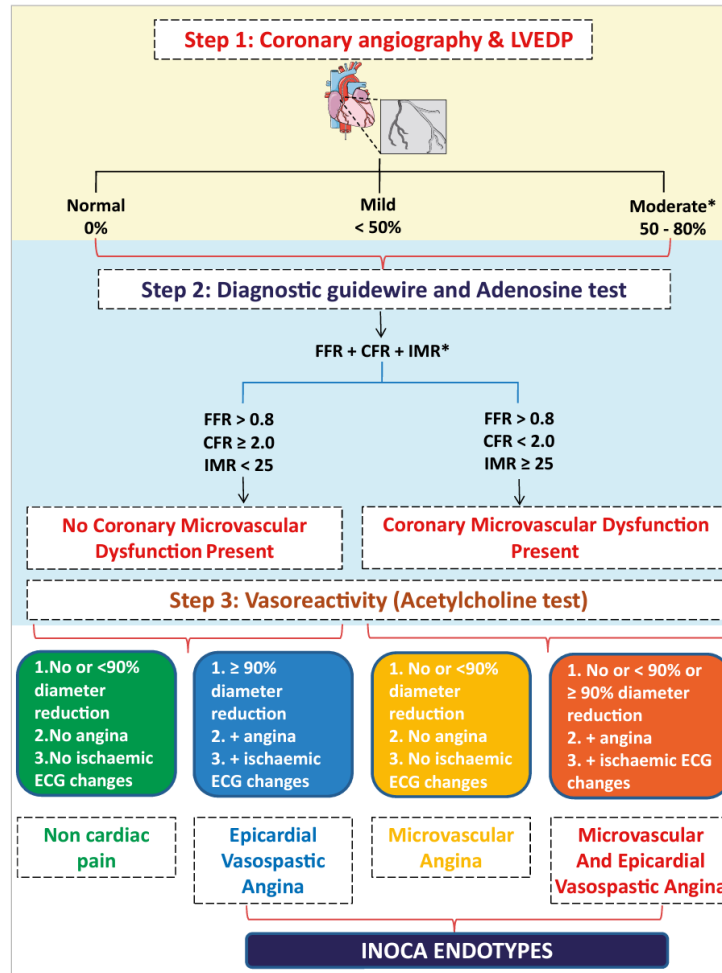
## Diagnose epicardiale spasme:

- Herkenbare klachten
- Ischemische ECG veranderingen
- >90% coronaire lumen reductie.
  - bij <90% lumen reductie → microvasculaire spasmen



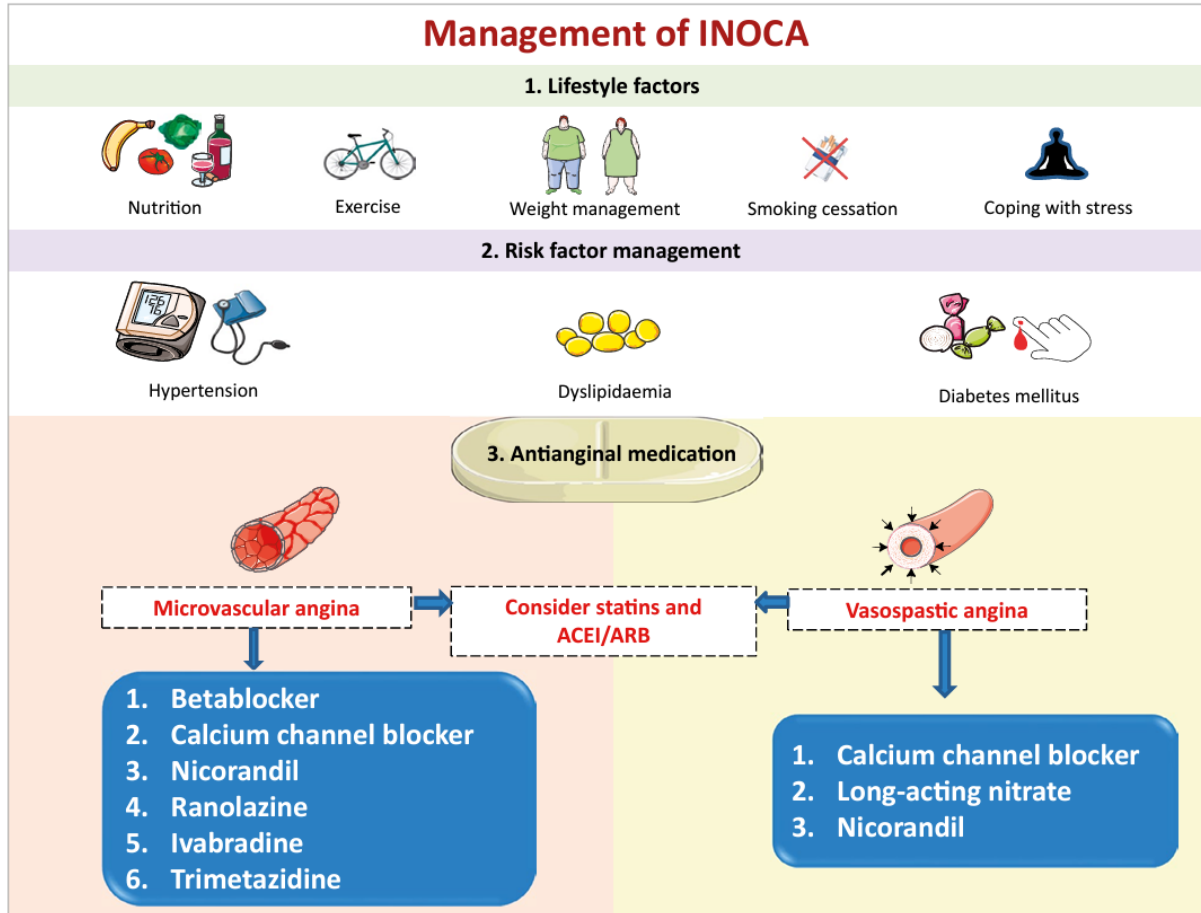
Patty Winkler.

# Invasive work-up



Kunadian et al. 2021.  
Coronary interventions.

# Behandeling



Kunadian et al. 2021.  
Coronary interventions.

# Take home messages INOCA/ANOCA

- 1) Ischemie/angina zonder obstructief coronairlijden
- 2) Non-invasieve diagnostiek beperkt
- 3) Bij mannen en vrouwen
- 4) Slechte prognose
- 5) Ondergediagnosticeerd



**"Listening to patient symptoms is the melody of healing"**

*Dr. Helen B. Taussig (1898 –1986)*



**Table 1** Classes of recommendations

	Definition	Wording to use	
Classes of recommendations	<b>Class I</b>	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
	<b>Class II</b>	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
	<b>Class IIa</b>	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
	<b>Class IIb</b>	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
	<b>Class III</b>	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

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**Table 2** Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

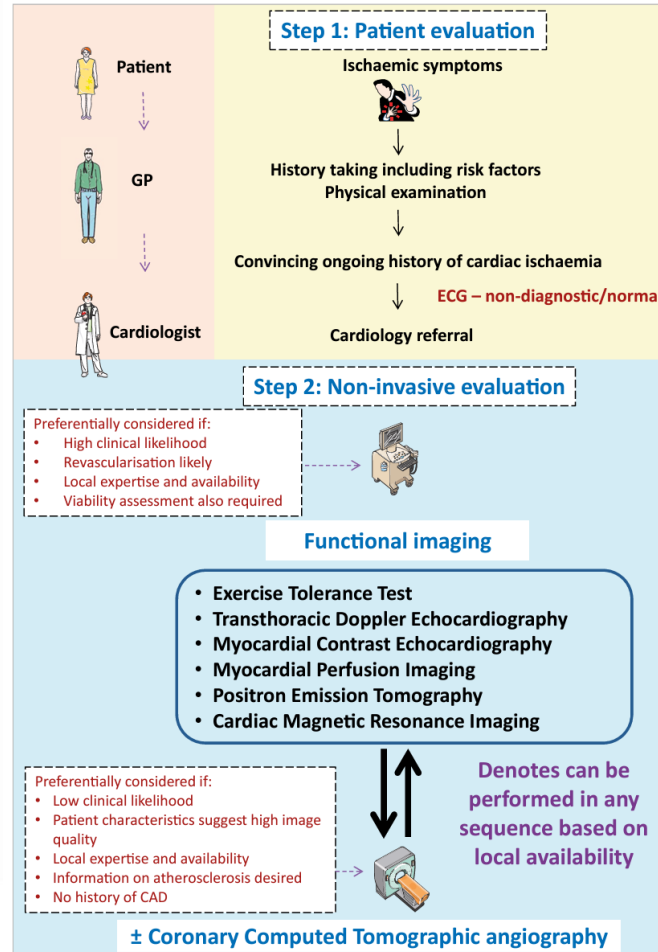
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**TABLE 1 Various Cardiac Imaging Modalities and Their Advantages and Disadvantages**

Modality	Technique	Advantages	Disadvantages
Contrast echocardiography	Constant infusion of echocardiographic contrast microbubbles until the cavity is filled, followed by ultrasound destruction of microbubbles	<ul style="list-style-type: none"> <li>• Bedside procedure</li> <li>• Minimal risk</li> <li>• No radiation</li> <li>• Relatively inexpensive</li> </ul>	<ul style="list-style-type: none"> <li>• Microbubble use not FDA approved for perfusion (no reimbursement)</li> <li>• Operator dependent</li> <li>• Poor images related to obesity or the presence of lung disease</li> <li>• Very few validation studies for MVD</li> </ul>
Transthoracic Doppler echocardiography	Pulsed-wave Doppler performed on the proximal left anterior descending artery	<ul style="list-style-type: none"> <li>• Bedside procedure</li> <li>• Minimal risk</li> <li>• No radiation</li> <li>• Relatively inexpensive</li> <li>• Correlated well with intracoronary Doppler wire</li> </ul>	<ul style="list-style-type: none"> <li>• Operator dependent</li> <li>• Difficult imaging because of obesity or the presence of lung disease</li> <li>• Poor correlation with PET</li> <li>• Very limited data with use in nonobstructive CAD</li> </ul>
CT	Dynamic first-pass vasodilator stress and then rest perfusion imaging	<ul style="list-style-type: none"> <li>• Anatomic coronary data and perfusion data with the same study</li> </ul>	<ul style="list-style-type: none"> <li>• Perfusion quantification only allowed in high-radiation dynamic perfusion imaging</li> <li>• Radiation exposure</li> <li>• Risk for contrast-induced nephropathy and contrast allergic reactions</li> <li>• Limited in renal failure</li> <li>• Limited validation in nonobstructive CAD</li> <li>• Limited availability</li> <li>• Iodinated contrast can cause vasodilation leading to overestimation of MBF</li> </ul>
PET	Dynamic first-pass vasodilator stress and then rest perfusion images	<ul style="list-style-type: none"> <li>• Most validated modality for MBF quantification in nonobstructive CAD</li> <li>• Extensive prognostic data</li> <li>• Segmented MBF</li> <li>• Relatively low radiation exposure because of radiotracers with short half-lives</li> <li>• Not affected by renal dysfunction</li> <li>• Good reproducibility and accuracy</li> <li>• CT can allow for some anatomic assessment of coronary arteries</li> </ul>	<ul style="list-style-type: none"> <li>• Radiation exposure</li> <li>• Expensive</li> <li>• Technology is not widely available</li> </ul>
SPECT	Dynamic first-pass vasodilator stress and then rest perfusion images	<ul style="list-style-type: none"> <li>• More widely available than PET and CMR</li> </ul>	<ul style="list-style-type: none"> <li>• Requires new-generation cameras</li> <li>• Minimal validation in nonobstructive CAD</li> <li>• Radiation exposure is high</li> </ul>
CMR	Dynamic first-pass vasodilator stress and then rest perfusion images	<ul style="list-style-type: none"> <li>• No radiation exposure</li> <li>• Excellent spatial resolution</li> <li>• Allows tissue characterization with the same study</li> <li>• Validated against invasive measurements and PET</li> </ul>	<ul style="list-style-type: none"> <li>• Expensive</li> <li>• Technology is not widely available</li> <li>• Very minimal prognostic data</li> <li>• Difficult for patients because of frequent breath holds and length of time of the examination</li> <li>• Limited in renal failure</li> </ul>

CAD = coronary artery disease; CMR = cardiac magnetic resonance; CT = computed tomography; FDA = U.S. Food and Drug Administration; MBF = myocardial blood flow; MVD = microvascular dysfunction; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

# Non-invasieve diagnostiek



Afwezigheid ischemie sluit het niet uit



# Refereeravond Cardiologie

## MINOCA

Nils Rollersbroich  
AIOS cardiologie

05.02.2024



**zuyderland**

# MINOCA

## Myocardial Infarction and Non-Obstructive Coronary Arteries

### Definitie:

- 1) Acut myocardinfarct
- 2) Niet-obstructief coronairlijden (stenose visueel  $< 50\%$  of  $\text{FFR} > 0.80$ )
- 3) Geen alternatieve verklaring

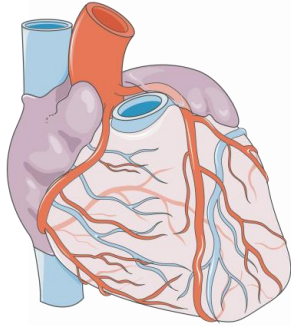
# MINOCA

## Epidemiologie

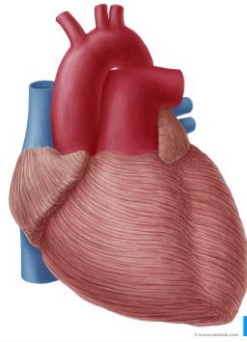
- Bij 6-14% van patienten met myocardinfarct sprake van MINOCA
- 1/3 STEMI vs. 2/3 non-STEMI
- Jongere patienten, mannen vs. vrouwen (1:5)
- Ca. 75% wordt ontslagen zonder definitieve diagnose
- Ca. 20% heeft recidiverende POB, ca. 14% wordt binnen 1 jaar heropgenomen

# MINOCA

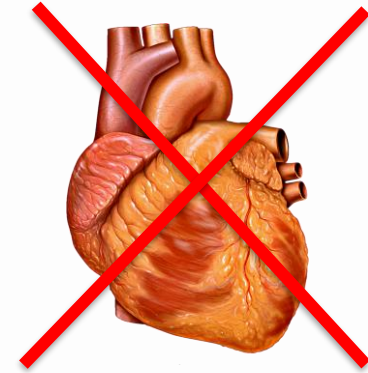
Onderverdeling in:



**1. coronair**



**2. myocardiaal**



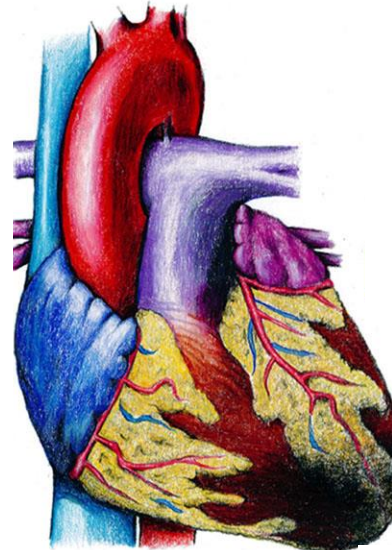
**3. niet-cardiaal**

→ voorlopige dynamische werkdiagnose

# (echte) MINOCA

Onderverdeling in:

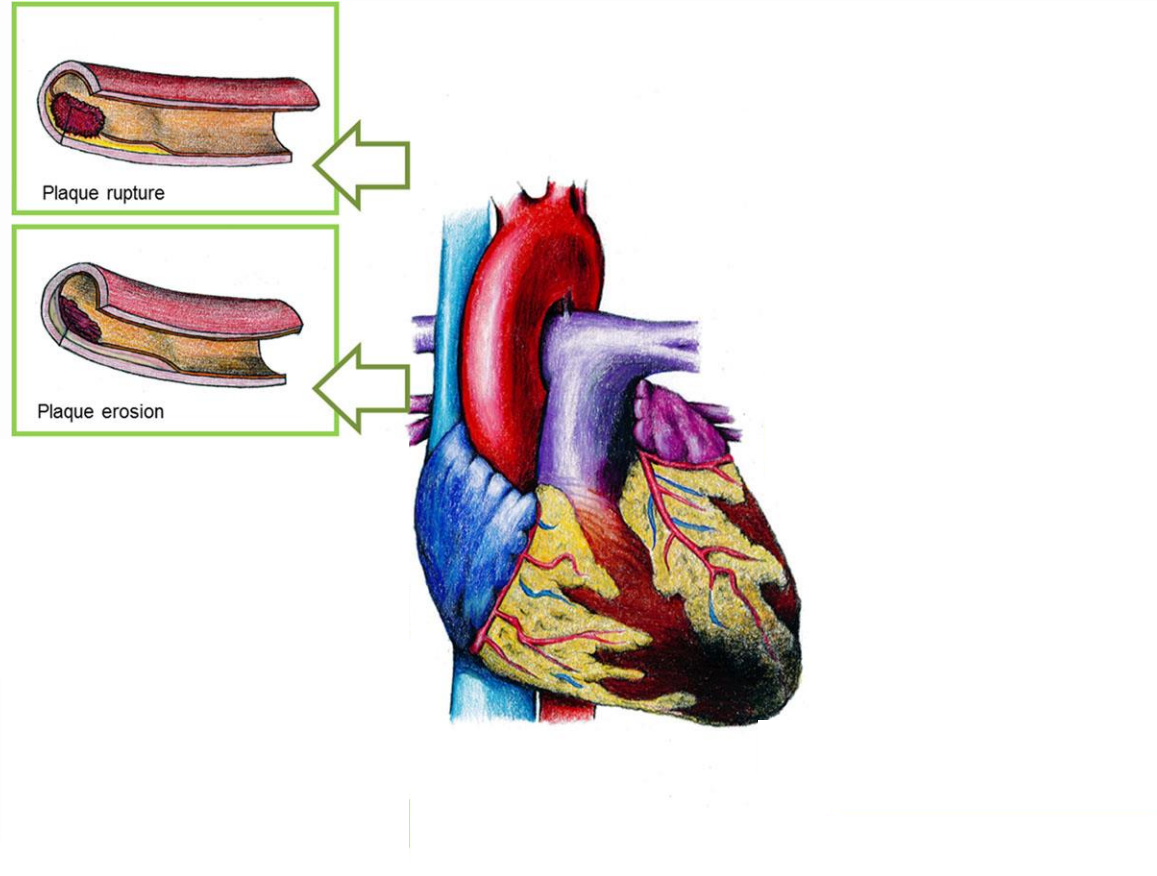
## 1. Coronair



# (echte) MINOCA

Onderverdeling in:

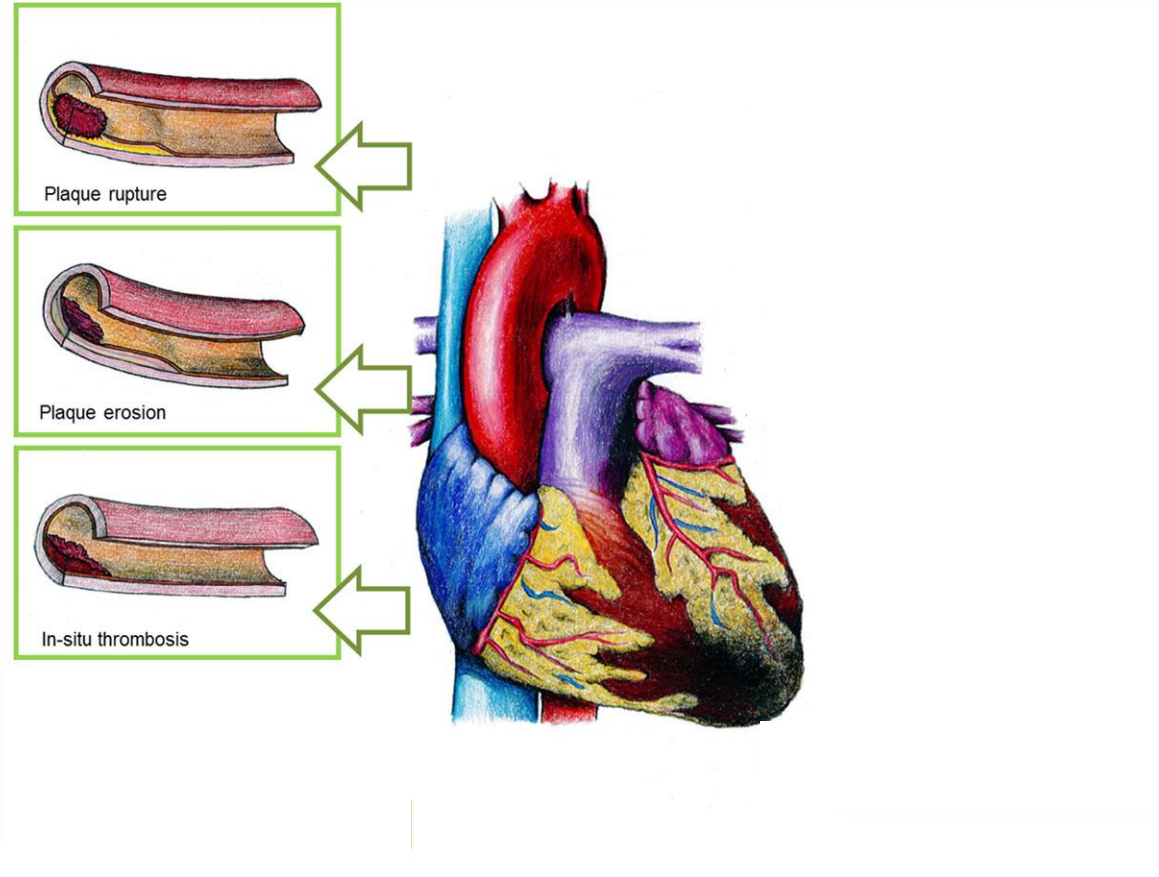
## 1. Coronair



# (echte) MINOCA

Onderverdeling in:

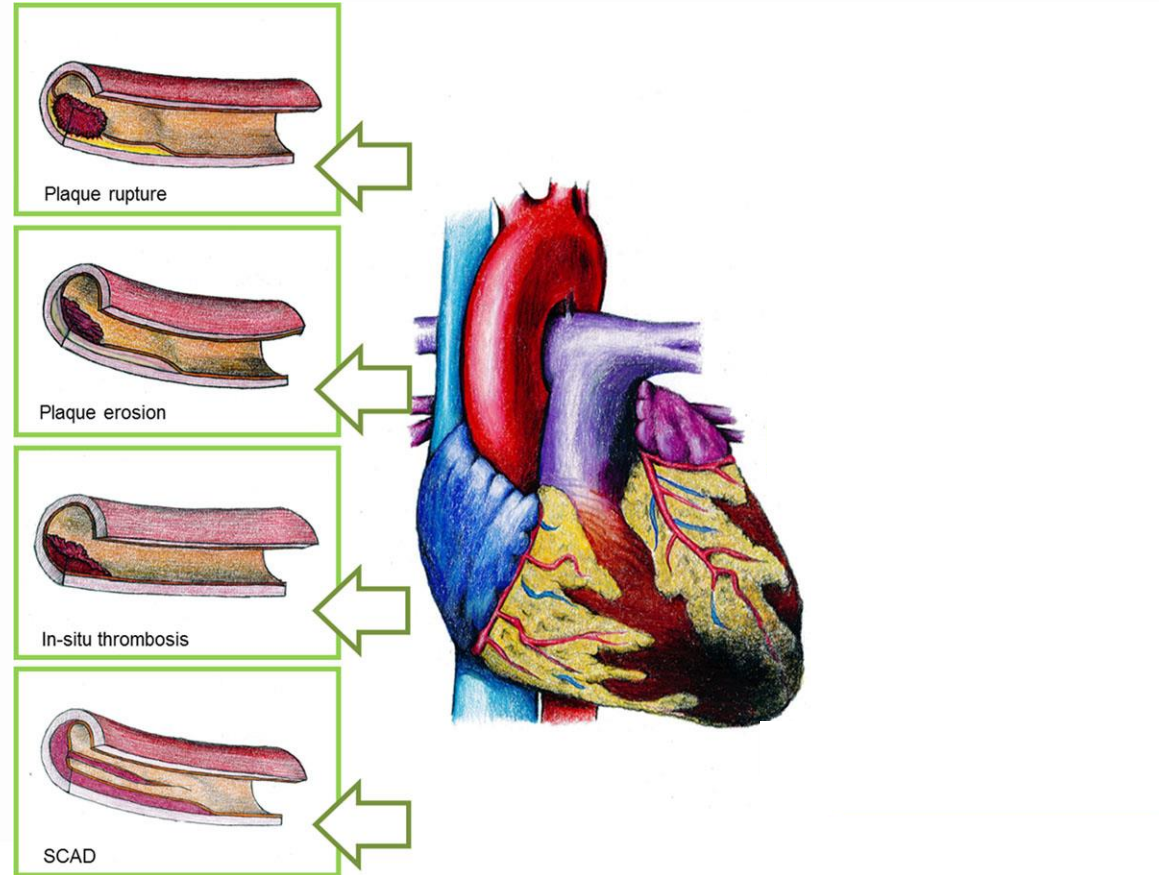
## 1. Coronair



# (echte) MINOCA

Onderverdeling in:

## 1. Coronair

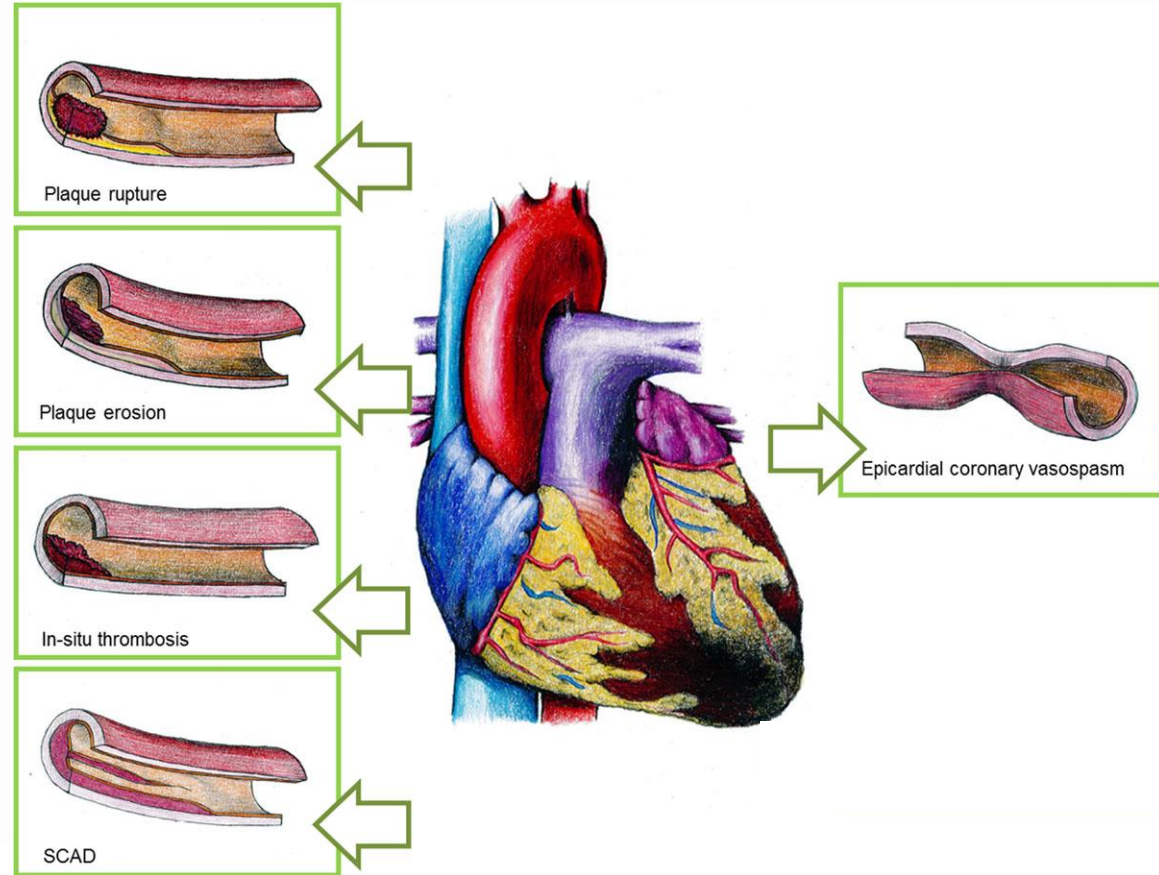




# (echte) MINOCA

Onderverdeling in:

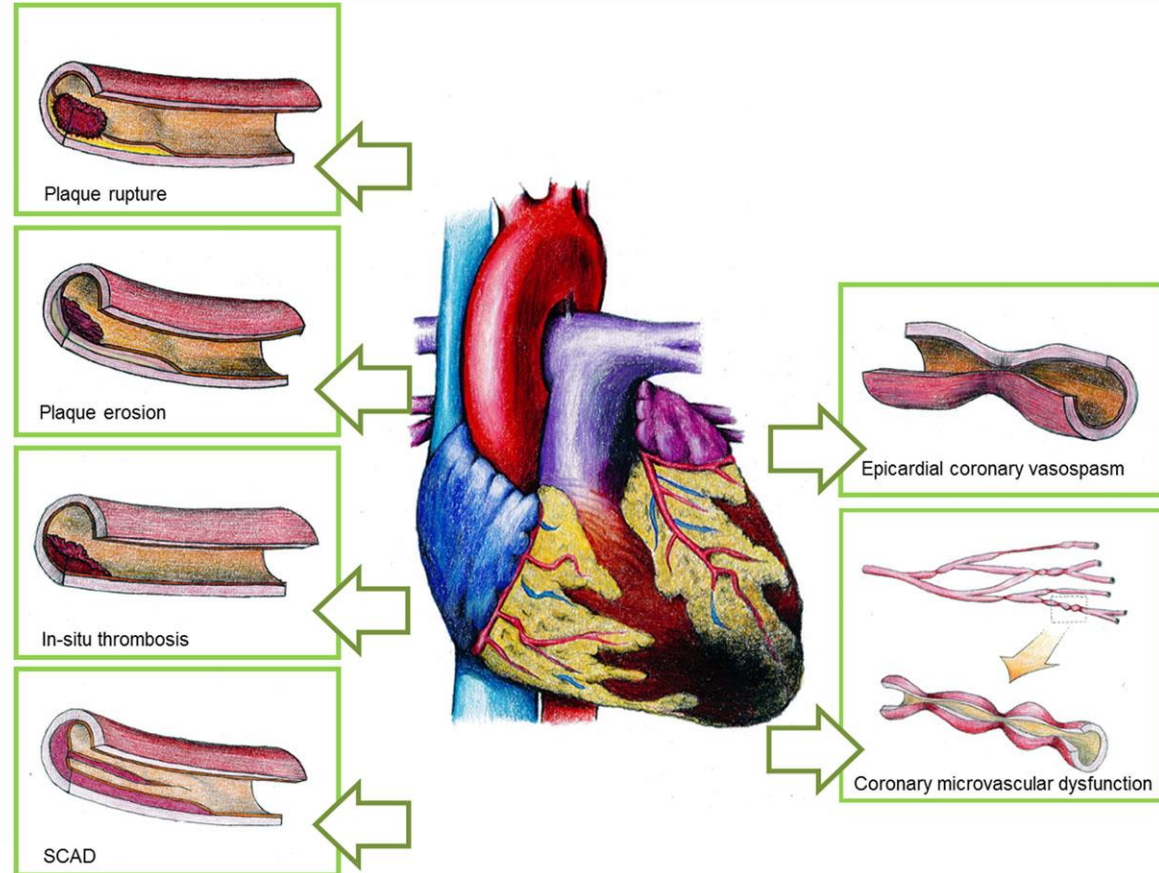
## 1. Coronair



# (echte) MINOCA

Onderverdeling in:

## 1. Coronair



# (non-)MINOCA

Onderverdeling in:

## 2. Myocardiaal

- Myocarditis
- Takotsubo
- hCMP, dCMP
- Andere cardiomyopathieën (tachy CMP, cardiotoxine, chemotherapie)
- Cor contusie

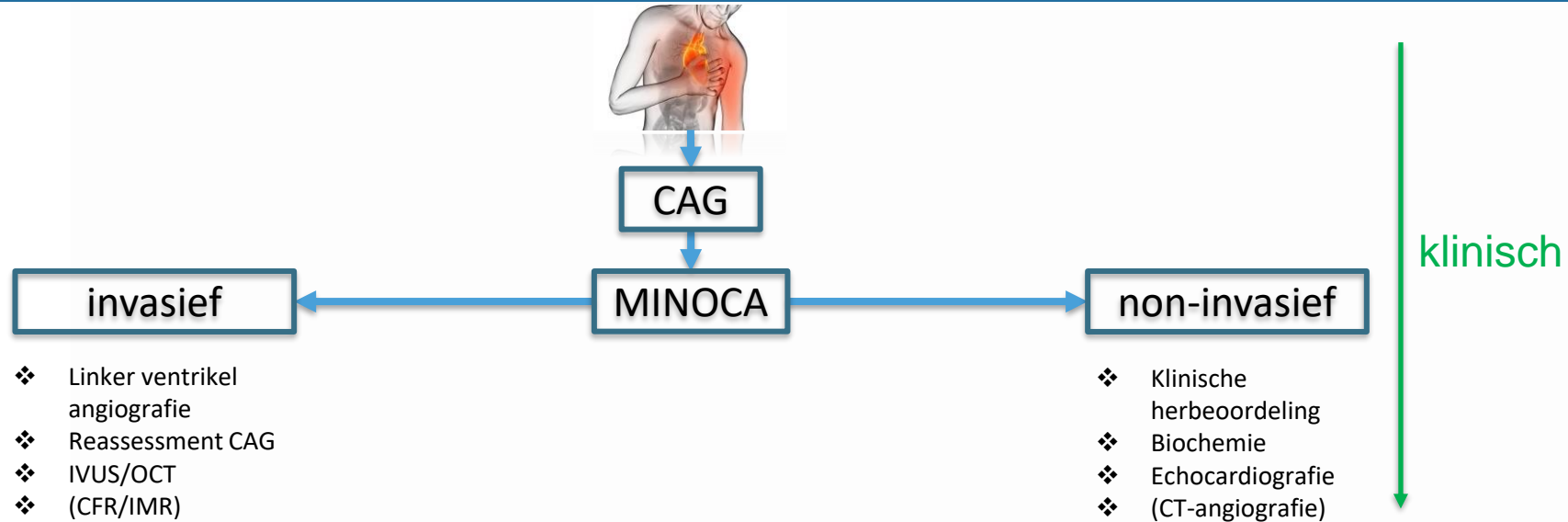
# (non-)MINOCA

Onderverdeling in:

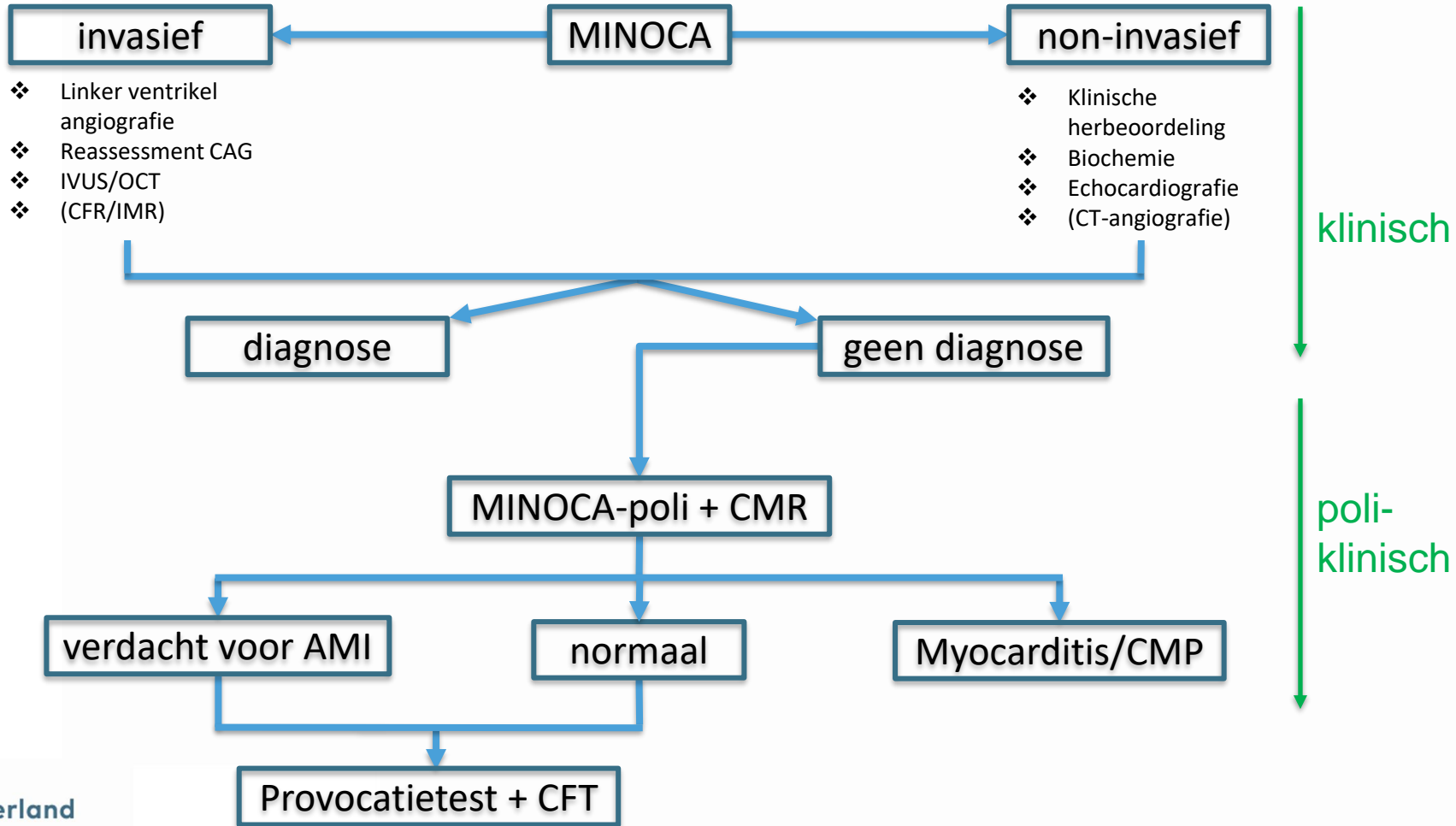
## 3. Niet-cardiaal

- CVA
- LE
- Sepsis
- ARDS
- Anemie
- Hyperthyreoidie
- ...

# Work-up van MINOCA

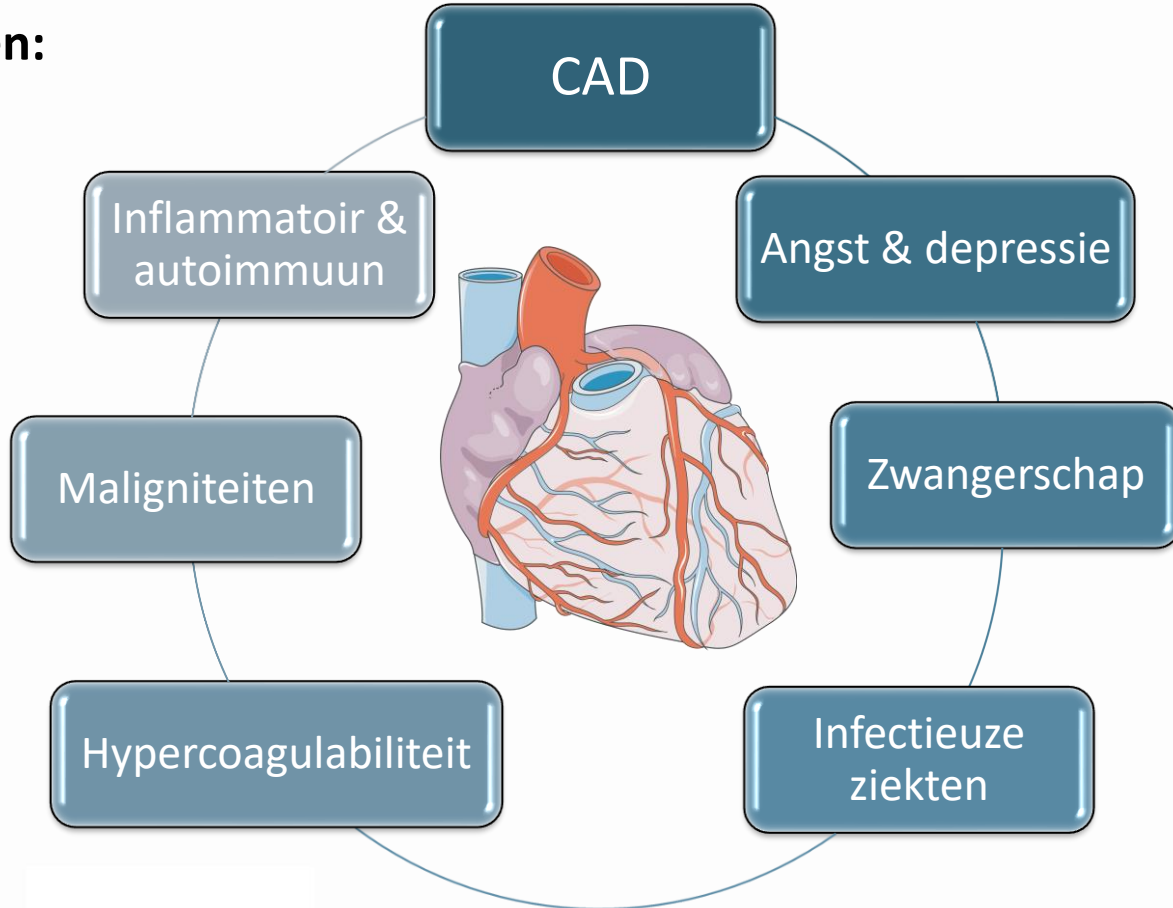


# Work-up van MINOCA



# MINOCA

## Risicofactoren:



# Management of (M)INOCA

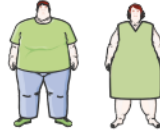
## 1. Lifestyle factors



Nutrition



Exercise



Weight management



Smoking cessation



Coping with stress



# Management of (M)INOCA

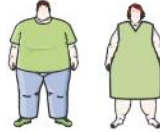
## 1. Lifestyle factors



Nutrition



Exercise



Weight management



Smoking cessation



Coping with stress

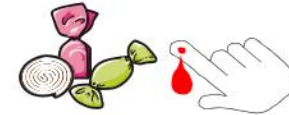
## 2. Risk factor management



Hypertension



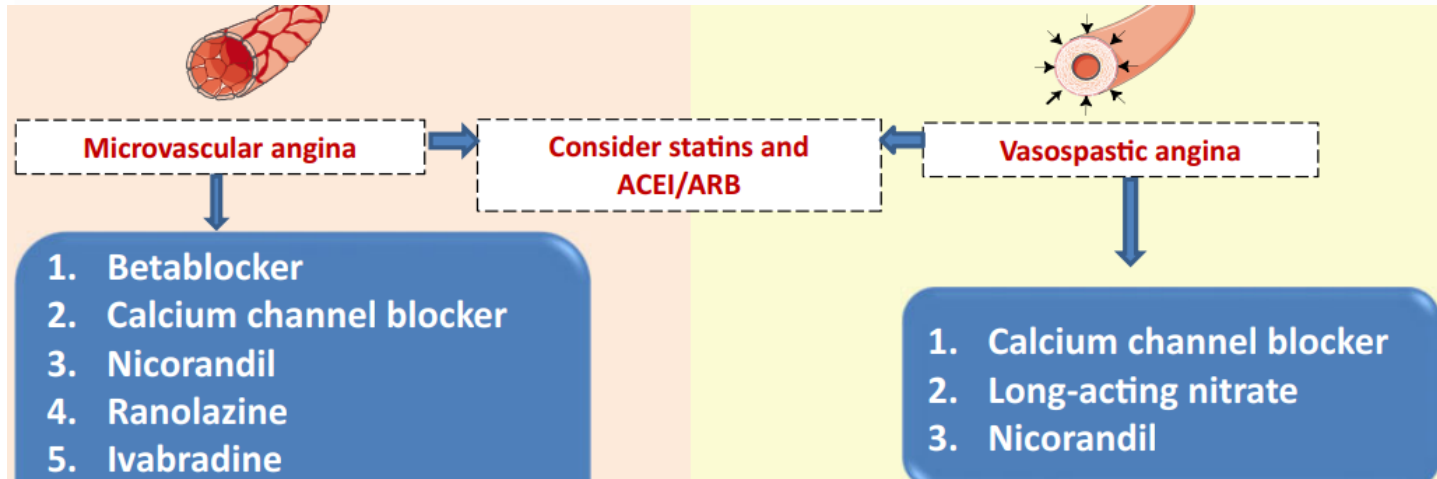
Dyslipidaemia



Diabetes mellitus

# Management of (M)INOCA

## 3. (Antianginal) medication



## **EDIT trial**

Efficacy of Diltiazem to Improve Coronary Vasomotor Dysfunction in ANOCA

- Eerste gerandomiseerd, placebogecontroleerde studie
- 85 patienten met CMD (CFR < 2.0, IMR > 25)
- Diltiazem (tot 360 mg /dag) vs placebo gedurende 6 weken

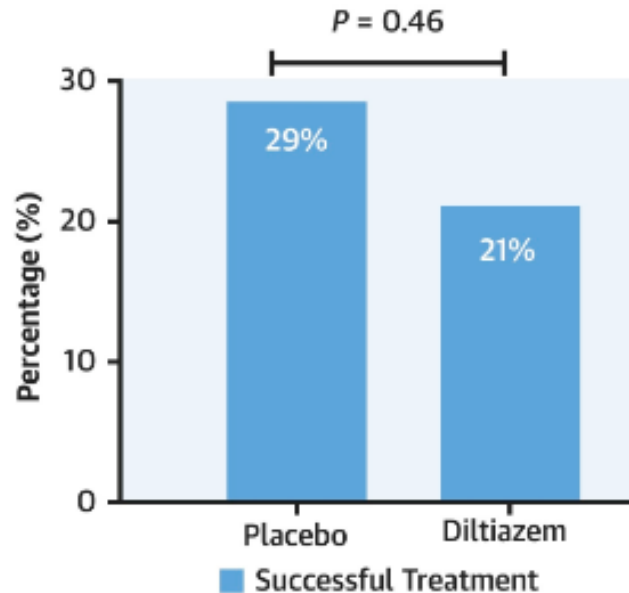
# MINOCA:

## EDIT trial

Efficacy of Diltiazem to Improve Coronary Vasomotor Dysfunction in ANOCA

Primary Endpoint  
No Additional Effect of Diltiazem in Treatment Success

→ Geen normalisatie van CFR en/of IMR.



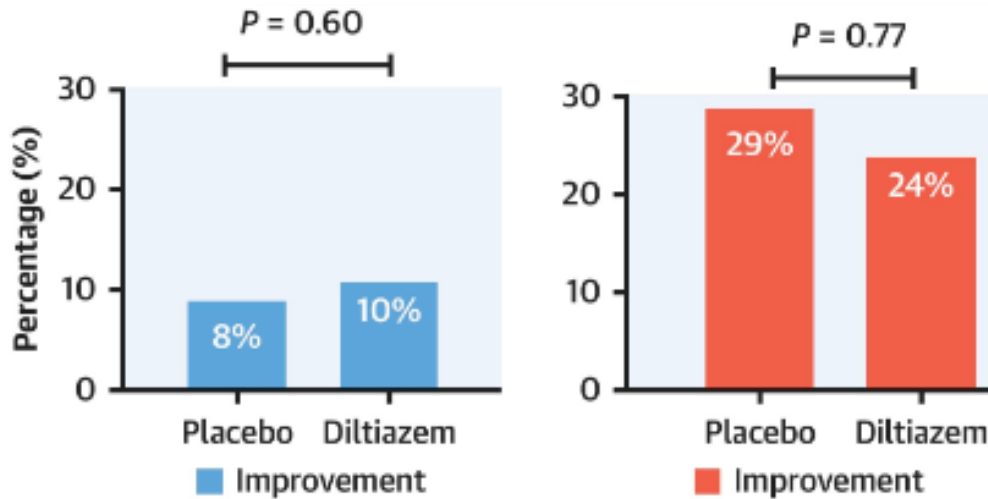
# MINOCA:

## EDIT trial

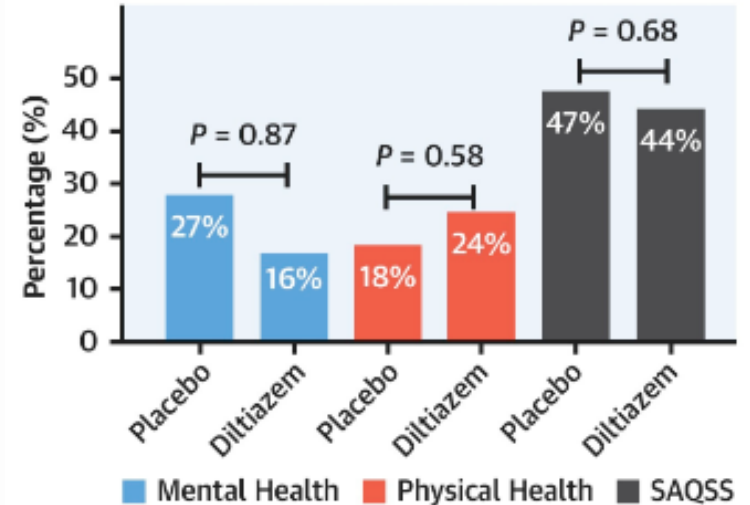
Efficacy of Diltiazem to Improve Coronary Vasomotor Dysfunction in ANOCA

Secundaire eindpunten:

No Improvement in Coronary Function Test Results



No Effect in Improvement in Angina and Quality of Life



# Management of (M)INOCA

## 3. (Antianginal) medication

Plaqueruptuur/-erosie = DAPT  
Myocarditis = Ascal

# Management of (M)INOCA

## SCAD

- ❖ Conservatief
- ❖ Ascal
- ❖ P2Y12-remmer
- ❖ Betablokker
- ❖ Statine?
- ❖ Antiangineuze med.
- ❖ Verwijzing vasc. INT

# Take-home message

## ❖ MINOCA

- ❖ ~ 10% van ACS
- ❖ Impact
- ❖ Dynamische werkdiagnose -> zoek naar de etiologie
- ❖ OCT/CMR/CFT -> 'must'!
- ❖ Gepersonaliseerde behandeling (lifestyle, anti-angineuze med., antistolling)





# Refereeravond Cardiologie

## Novel treatments

**Patty Winkler**  
**Interventiocardiooloog**

05.02.2024



**zuyderland**

# INHOUD

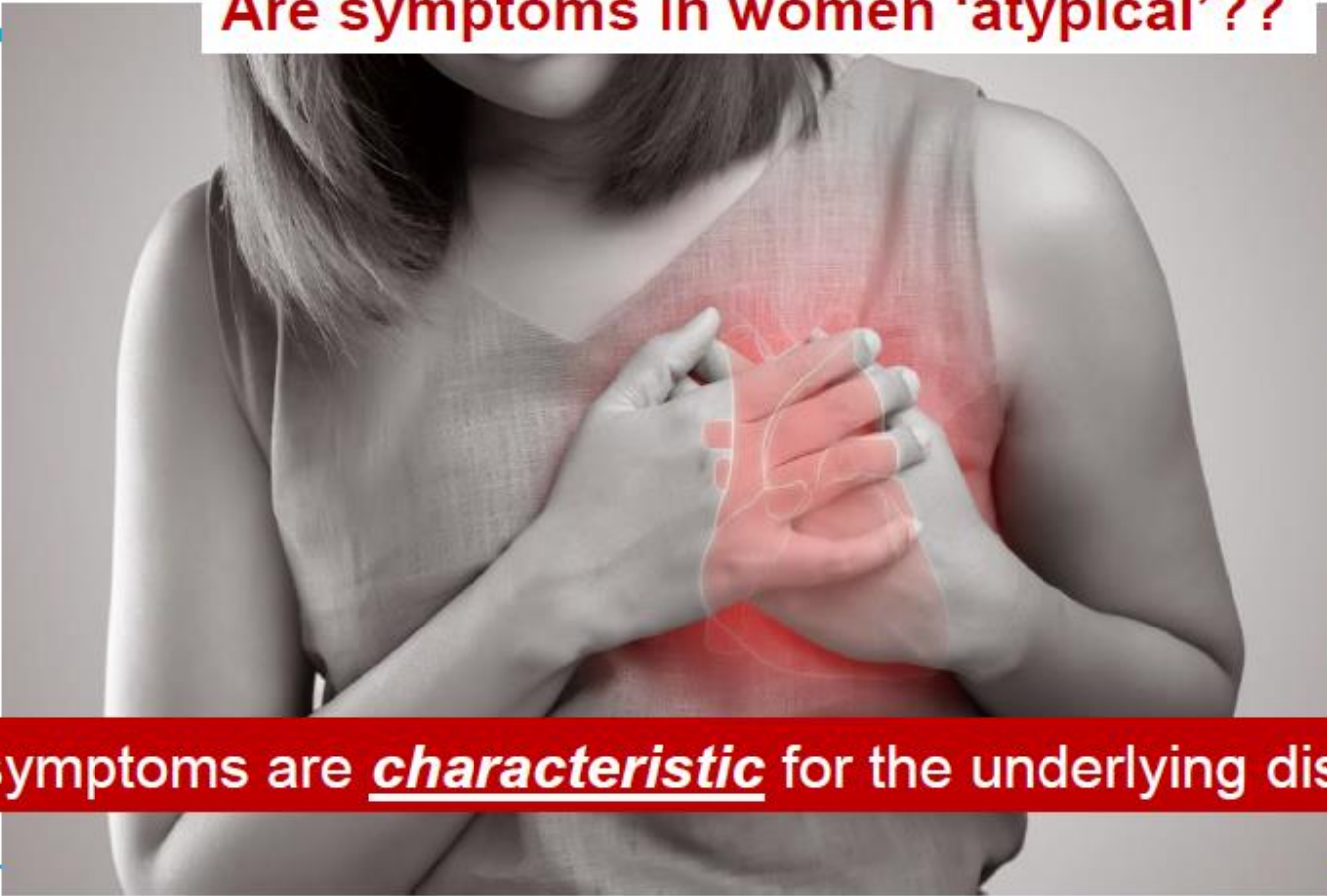


- INOCA
- THERMODILUTIE
- CASUSSEN
- NOVEL TREATMENTS
- STUDIES
- TAKE HOME MESSAGES

# AP bij INOCA

- Meest voorkomende manifestatie van ischemie en coronairlijden
- Atypisch
  - » Niet sternaal (keel/kaak/schouderbladen,epigastrio)
  - » Dyspnoe als equivalent AP
  - » Niet bij inspanning
  - » Rust, stress, soms uren
- Beperkend
  - » QoL
  - » Prognose
  - » MACCE, CV rehospitalisatie

Are symptoms in women 'atypical'??



No, symptoms are characteristic for the underlying disease

# Verskil in coronaire biologie

♀

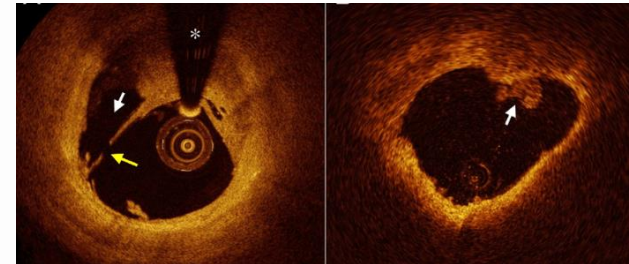
- smallere epicardialen
- basis en hyperemische coronaire flow hoger
- meer shear stress op endotheel
  - diffuus en non obstructieve plaques
  - minder (gecalcificeerde) plaque
  - minder necrose plaque kern
  - ACS: meer plaque erosie tov plaque ruptuur bij ♂



diffuse atherosclerosis

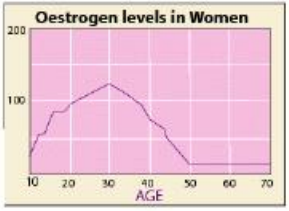
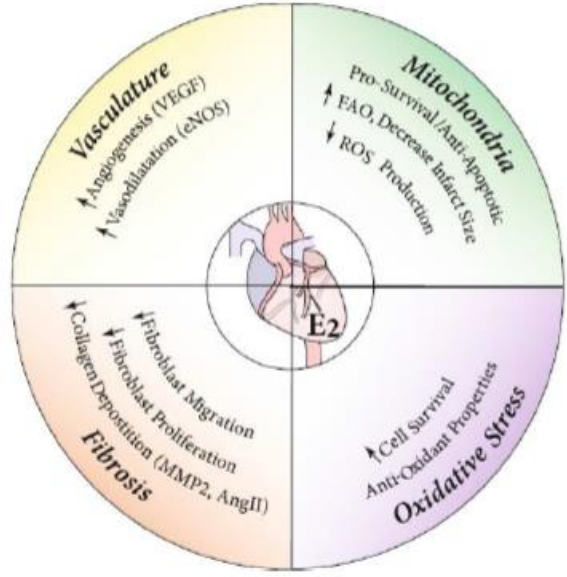


focal stenosis





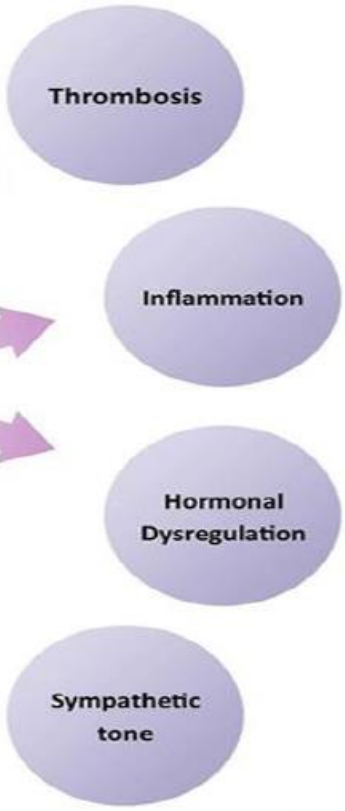
**Beneficial vascular effects  
of estrogens:**

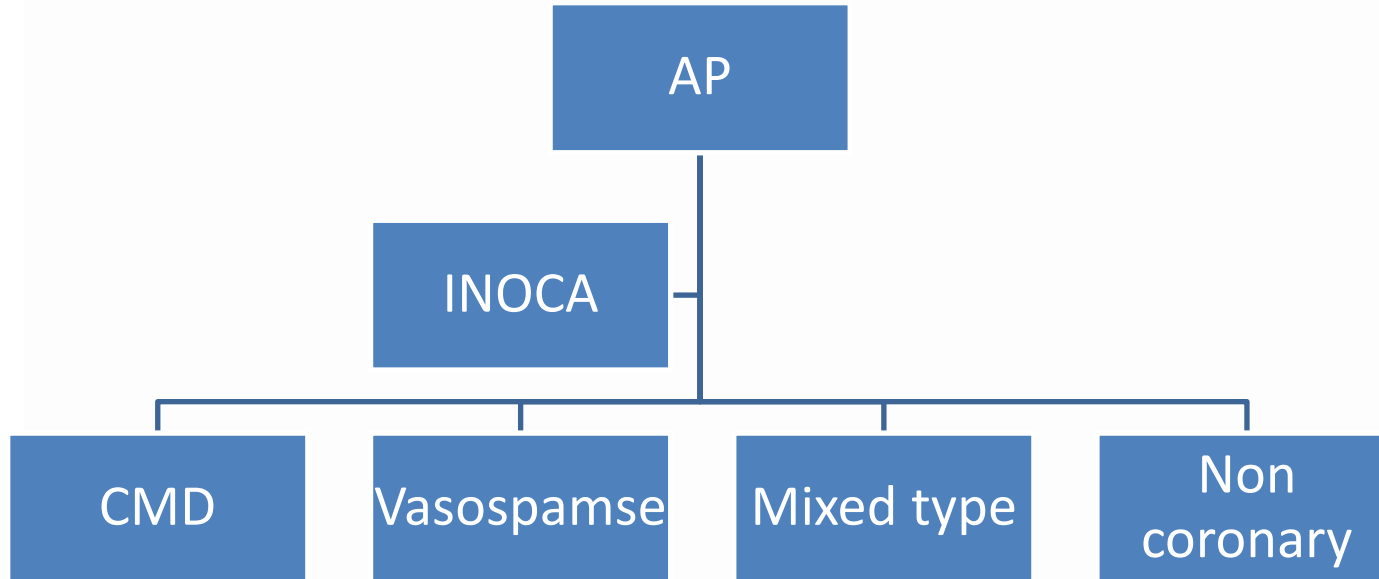


**Menopause**



**Risk factors**  
↑↑







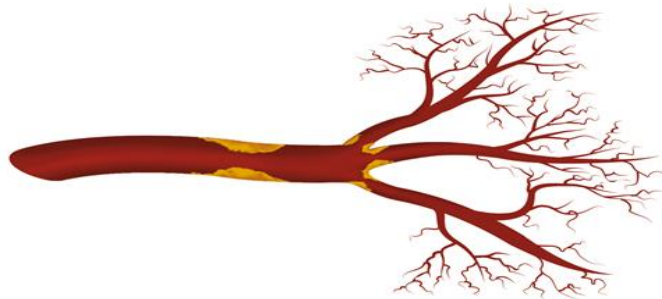
# Coronary Microvascular Dysfunction classification

<b>CMVD</b>	<b>Definition</b>
Type 1	Primary, i.e. in the absence of structural heart disease
Type 2	In the presence of cardiomyopathies (incl. LVH, HCM, DCM, amyloidosis)
Type 3	In the presence of obstructive CAD (incl. ACS)
Type 4	After coronary interventions
Type 5	After cardiac transplantation

# Complete coronaire hartfysiologie

## Epicardial disease

- FFR
- RFR



## Microvascular disease

- IMR
- CFR
- Absolute Flow/Resistance

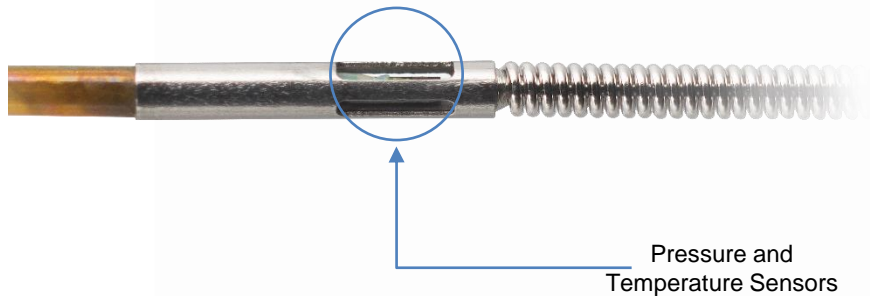


# Defenities

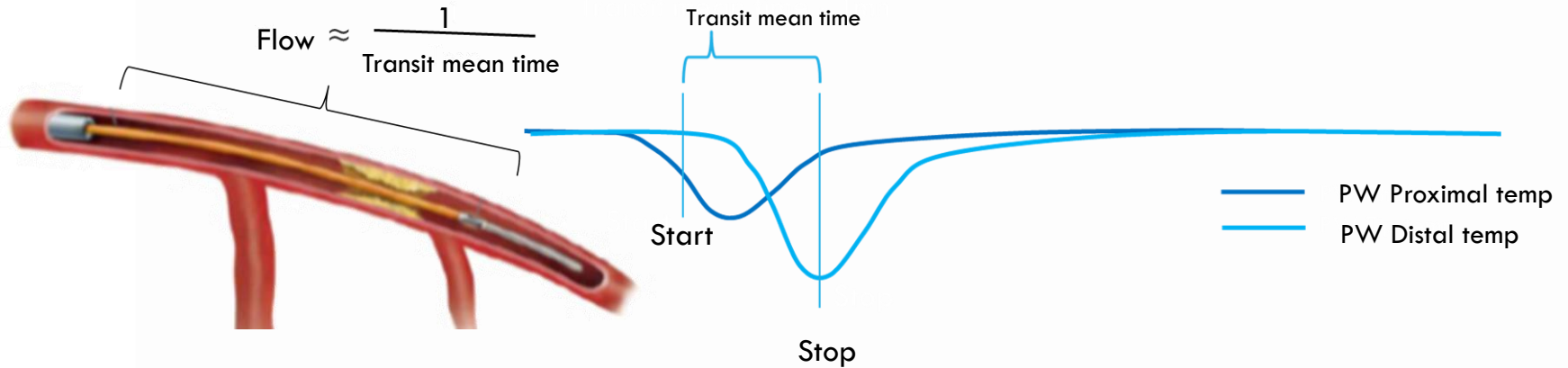
- CFR = vasodilatatie vermogen van coronaire vasculatuur
- IMR = coronaire vasculaire weerstand in microcirculatie
- Abs Q/R = absolute coronaire flow/weerstand

# Measuring Flow

- The PressureWire™ X Guidewire bevat 3 sensors:
  - 1 pressure sensor : FFR, RFR
  - 2 temperature sensors: flow measurement dmV thermodilutie methode



# CFR - BOLUS THERMO-DILUTIE



**CFR – Coronary Flow Reserve**

$$\text{CFR} = \frac{\text{Hyp flow}}{\text{Resting flow}} = \frac{1/\text{Tmn}_{\text{hyp}}}{1/\text{Tmn}_{\text{rest}}}$$

# CFR

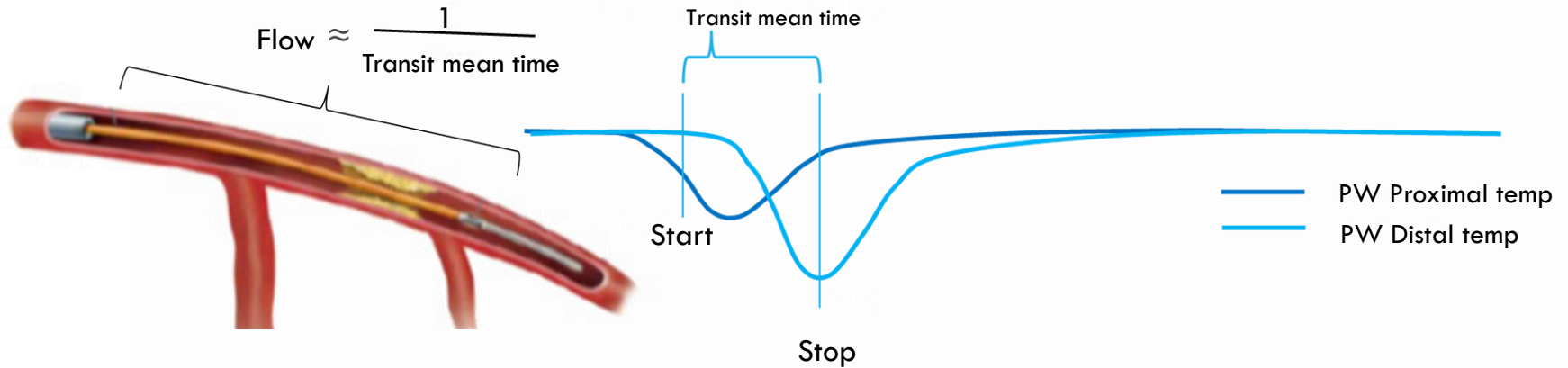
- CFR indicates the maximum increase in coronary artery flow above the normal resting volume:

$$\text{CFR} = \frac{T_{mn} \text{ at rest}}{T_{mn} \text{ at hyperemia}}$$

Normal CFR:  $\geq 2.5$

FFR	Pd	Pa
0,72	72	100
Pd/Pa	Pd	Pa
0,85	82	96
CFR	CFR <sub>Norm</sub>	
3,6	4,9	
IMR	IMR <sub>Corr</sub>	
18	16	

# IMR - BOLUS THERMO-DILUTIE



$$\begin{aligned} \text{IMR} &= \Delta \text{ druk} / \text{flow} \\ &= (\text{Pd} - \text{Pv}) / (1 / \text{Tmn}) \\ &= \text{Pd} \times \text{Tmn} \text{ (met max hyperemie)} \end{aligned}$$

# IMR

- IMR indicates the level of microcirculatory resistance in the target artery territory:

$$\text{IMR} = \text{distal pressure (Pd) at hyperemia} \times T_{mn}$$

Normal IMR: < 25

FFR	Pd	Pa
0,72	72	100
Pd/Pa	Pd	Pa
0,85	82	96
CFR	CFR <sub>Norm</sub>	
3,6	4,9	
IMR	IMR <sub>Corr</sub>	
18	16	

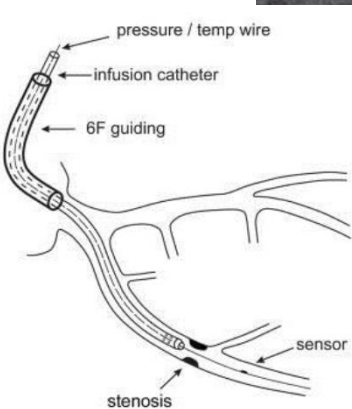
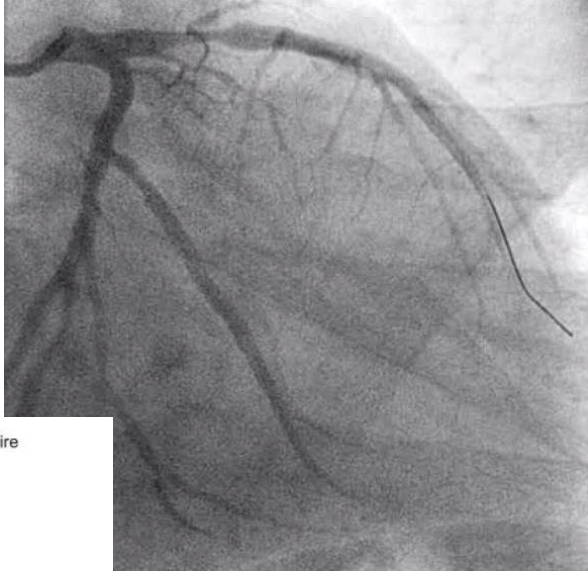


# CFR/IMR - thermodilutie

- PressureWire X, Coroventis Coroflow
- Bolus saline injection
- Hypermie met Adenosine iv

☐ CFR =  $Tmn\_Rest/Tmn\_Hyp$  → Afwijkend < 2,0

☐ IMR =  $Pd \times TmnHyp$  → Afwijkend > 25

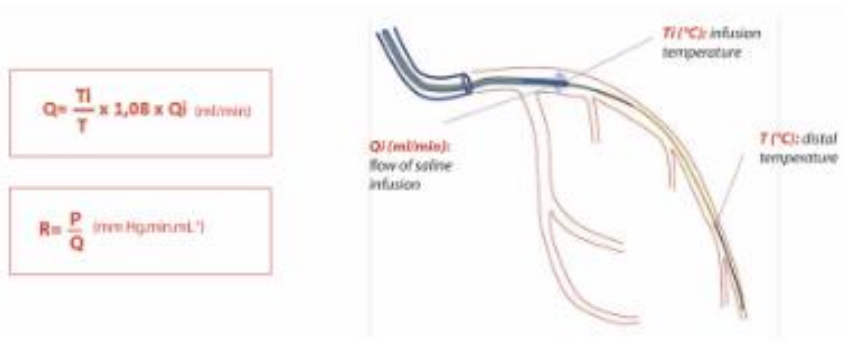


# Absolute Flow and Resistance - TOEKOMST

- Pressure X wire, Coroventis Coroflow
- Rayflow catheter over guidewire for continuous saline injection (no adenosin)

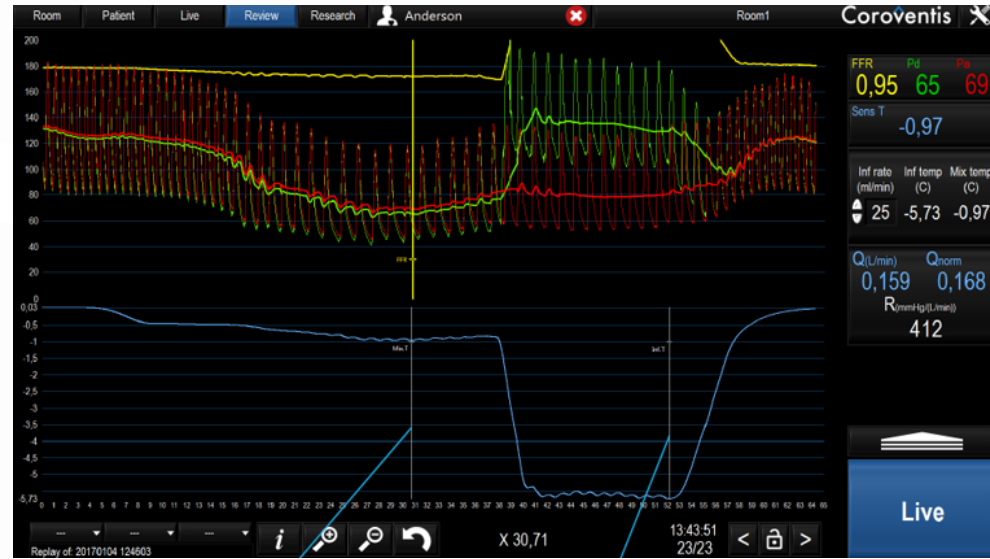
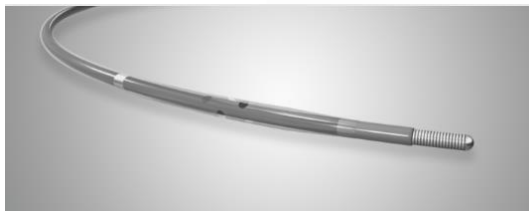
☐ Abs  $Q_{cor} = Q_b = Q_i \times (T_i/T) \times 0.8 \rightarrow$  Afwijkend < 200 mL/min LAD

☐ Abs  $R = P_d / Q_{cor} \rightarrow$  Afwijkend > 500 WU LAD



$$Q = \frac{T_i}{T} \times 1,08 \times Q_i \text{ (ml/min)}$$

$$R = \frac{P}{Q} \text{ (mmHg/min/L)}$$



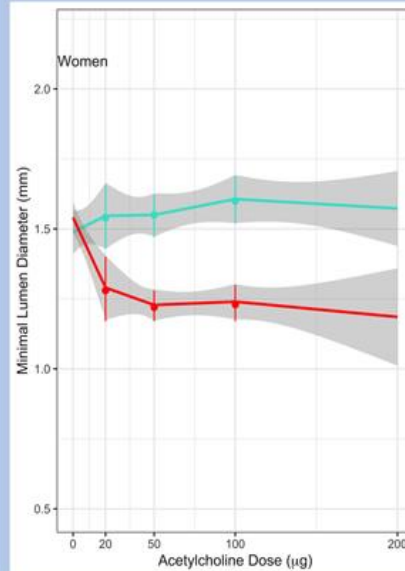
# Ach bij Vasospasme

Relationship of Intracoronary Acetylcholine and Vessel Diameter in Angina and Non-obstructive CAD

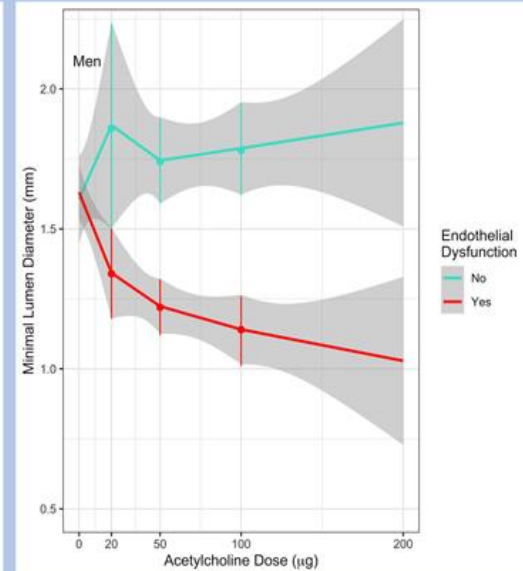
Intracoronary acetylcholine (IC Ach) provocation testing is the gold standard test for assessing coronary endothelial function



Women and men respond differently to IC Ach. Men demonstrate an Ach-MLD dose-response relationship at all doses, while women have minimal change in MLD at higher Ach doses



Women



Men

# CASUS 1 & 2

# Casus 1 , Dhr P, 57 jaar

RvK: Op poli ivm atypische pijn op de borst

> Sec opinion, onbegrepen/vertrouwen weg vv verwijzing via HA naar Zuyderland

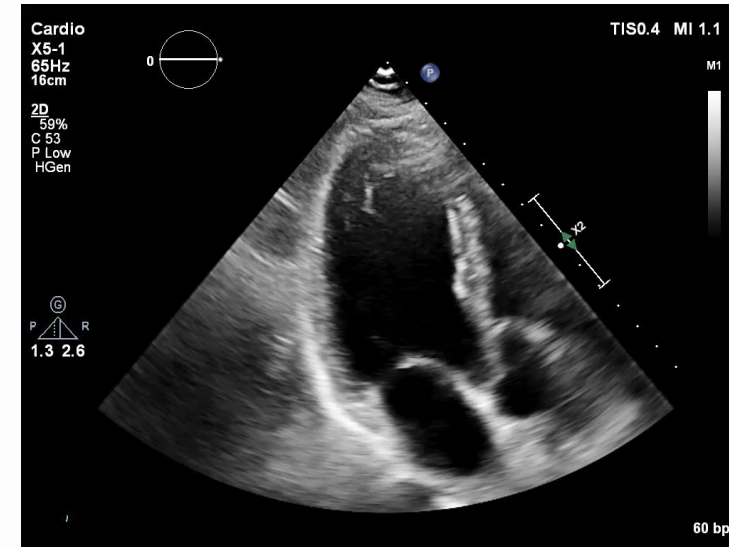
- **VG:**

- HT, OSAS
- 2011 DDDR pacemaker voor SSS met RV lead repositie
- 2011 slaapstoornissen en angsten
- 2013 POB : CT coronairen ca score 1, fam HVZ+
- 2014 Pafib

- **Med:** Carbasalaat 100 mg, atorva 40 mg, ivabradine 2dd 5 mg, telmisartan 40 mg, quetiapine 1dd 6,25 mg  
nitro sl zn

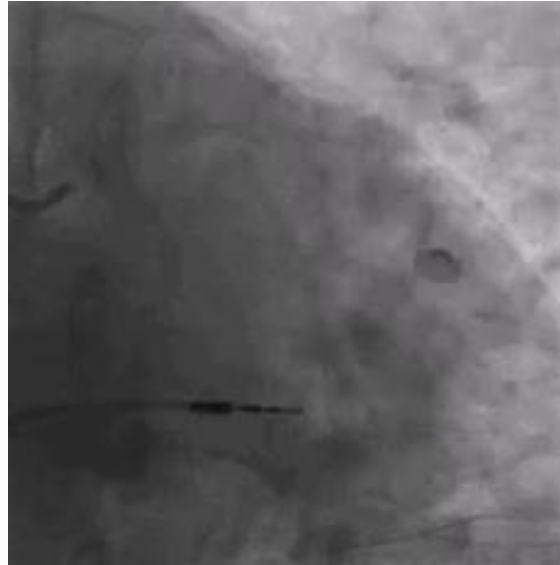
# Casus 1, Dhr P, 57 jaar

- **A/** veel zorgen fam fors belast HVZ, al jaren POB, nooit iets gevonden, sinds 1 mnd progressief, bij stress en vaak bij inspanning, POB soms uren aanhouden.  
Roken-, HT+, HC- wilde zelf statine, DM-
- **LO/** BP 115/72 mmhg, BMI 28, palpatie gb
- **AO/**
  - ECG gb
  - Lab: hb 9.7, LDL 1.0, hba1c 34, GFR > 90
  - TTE: EF 50-55%, IL iets hypokinesie?, kleppen/drukken gb
  - Ergo: goede inspanning 190 watt, geen duidelijke ischemie
- **C/** atypische POB DD atypische angina pectoris
- **B/** MCR op proef start.....en wat nu ??????

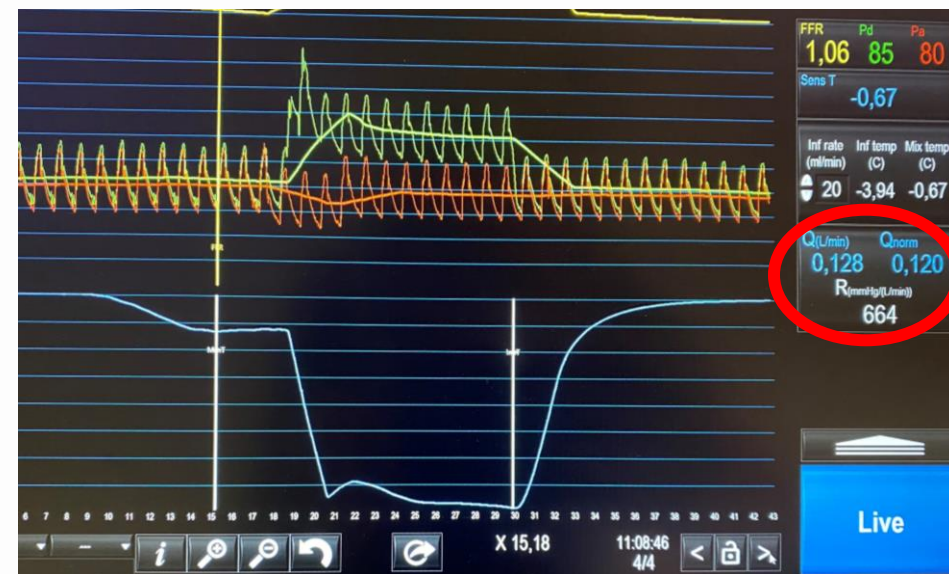


# Casus 1, Dhr P, 57 jaar

CAG met eventueel CMD metingen > geen belangrijke epicardiale stenosen



# Casus 1, Dhr P, 57 jaar



LAD niet afwijkend, RCA CFR/IMR/Abs R afwijkend : CMD +



# Casus 1, Dhr P, 57 jaar

- CAG: geen epicardiaal belangrijke stenosen
- In RCA afwijkende IMR en Abs Q&R dus.....diagnose CMD +
- **B/** MCR gestopt ivm hoofdpijn, telmisartan stop ivm hypotensie  
Start ikorel 2dd 5 mg

# Casus 1, Dhr P, 57 jaar

- **Leefstijl** eerder al op orde, nog stress minderen
- **Beloop med**
  - Ikorel 2dd 5 mg → minder AP, wel hoofdpijn
  - Palpataties ook wv start bisoprolol 2,5 mg → minder palpataties, nog stress > AP
  - Nifedipine 2dd 10 mg ret → obstipatie en flushes, gestopt
  - Start minitran pleister en ophoging naar 5 mg/24 uur → AP praktisch weg !

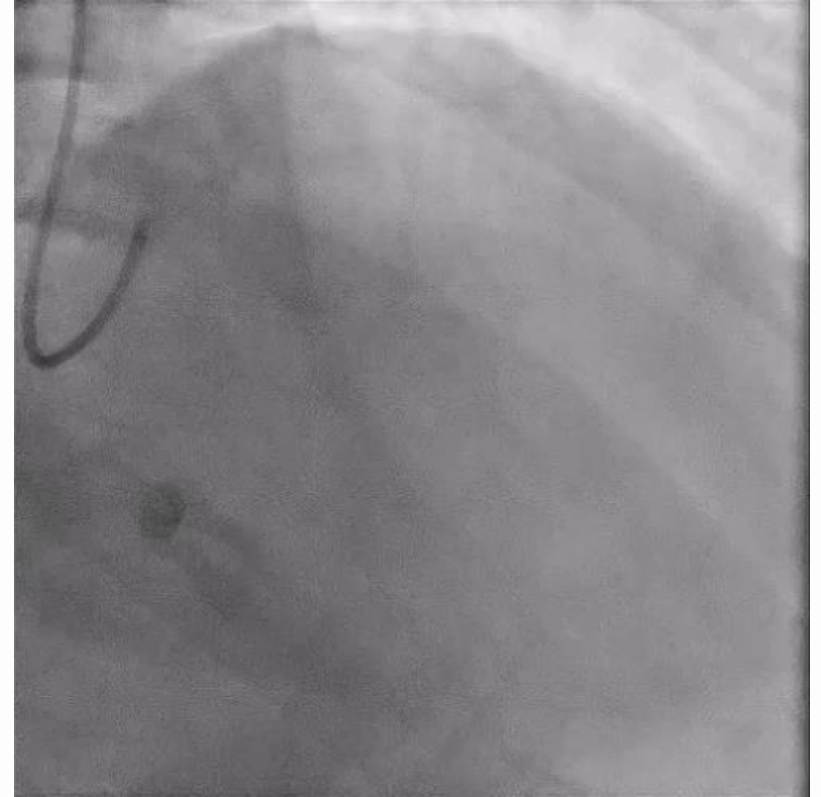
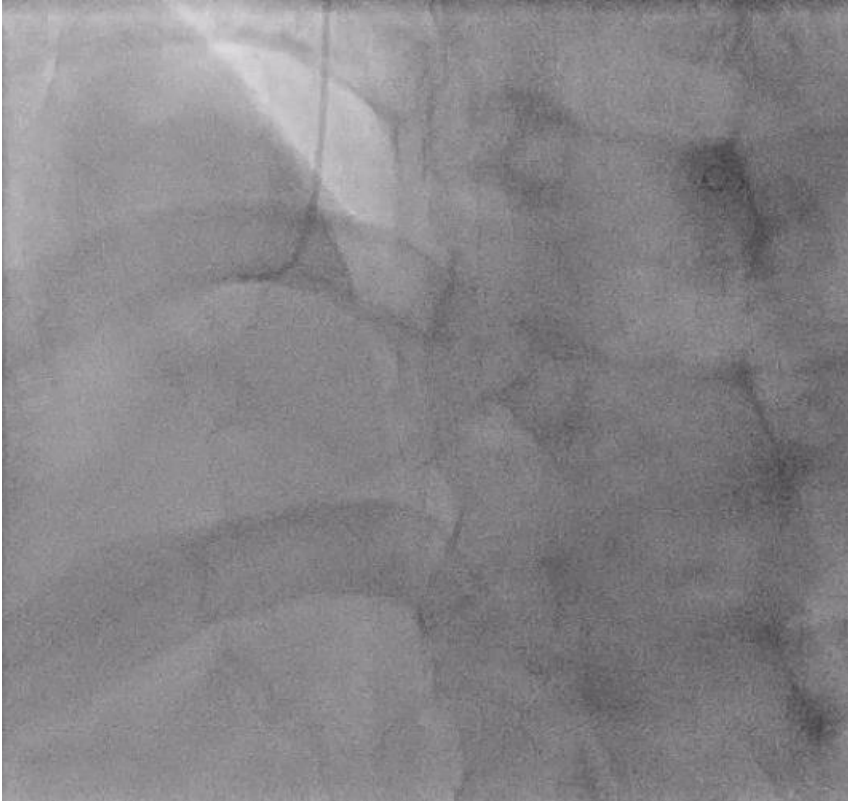
# Casus 2 , Mevr I, 71 jaar

- Opname ivm weer NSTEMI
- **VG:**
  - HT
  - HC
  - 2016 NSTEMI, CAG wo, MRI cor gb, LVEF goed
  - 2018 PAV, PTCA
- **Med:** Ascal 80 mg, rosu 20 mg, ezetrol 10 mg, perindopril 2 mg, thyrox 25 mcg, nitro sl
- **A/** al Jaren stabiele AP, nu herkenbaar, na nitro niet weg

# Casus 2 , Mevr I, 71 jaar

- **AO/**
  - ECG: SR 72/min,, neg T in I en AVL, anterior neg T
  - Lab: LDL 3.0 LipA 26 hba1c 53 gfr 74 trop 623 CK max 316 hb 7.9 CRP 1
  - TTE: EF 43%, anteroseptaal en apicaal hypokinesie tot akinesie, geringe Mi, RVSP 25 mmhg
    - tov 09.2022 achteruitgang

# Casus 2 , Mevr I, 71 jaar



# Casus 2 , Mevr I, 71 jaar



# Casus 2 , Mevr I, 71 jaar

## C/ recidief NSTEMI

- ECG en TTE LAD mogelijk probleem
- CAG: LAD atherosclerose, geen significant epicardiaal lijden
- OCT: atherosclerose, geen instabiele plaque/plaqueruptuur/erosie/trombus
- CFR/IMR niet afwijkend
  
- WD MINOCA > Plan: spasmetesten, med beleid

# Casus 2 , Mevr I, 71 jaar

- Spasmetesten
  - Max 100 mcg Acetylcholine ic
  - Epicardiaal spasme LAD +++

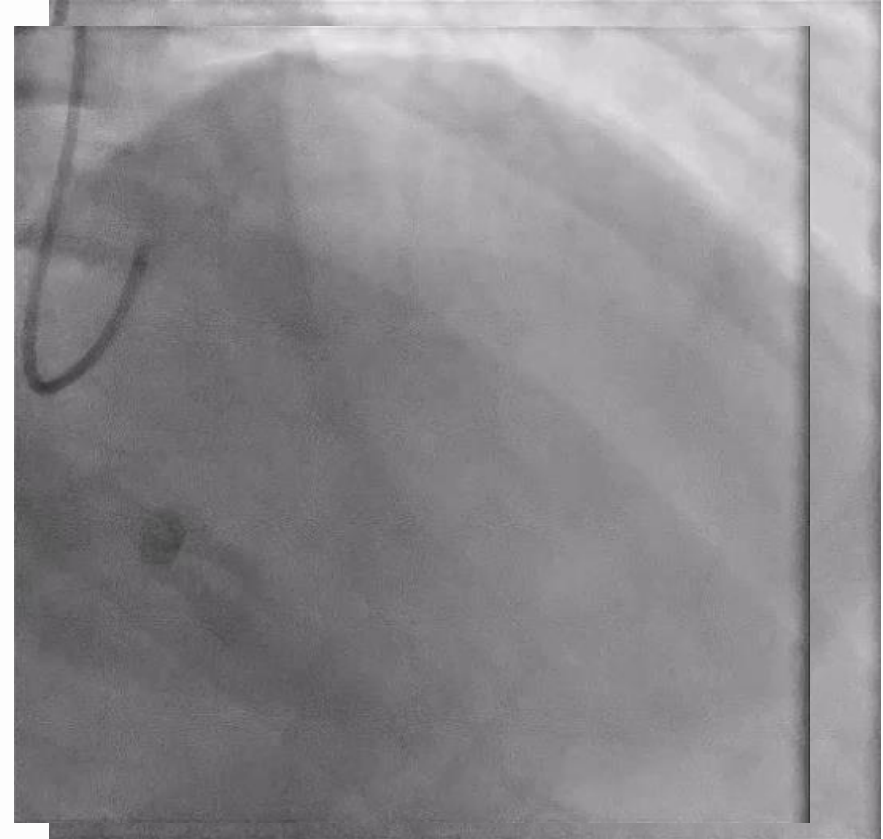




# Casus 2 , Mevr I, 71 jaar

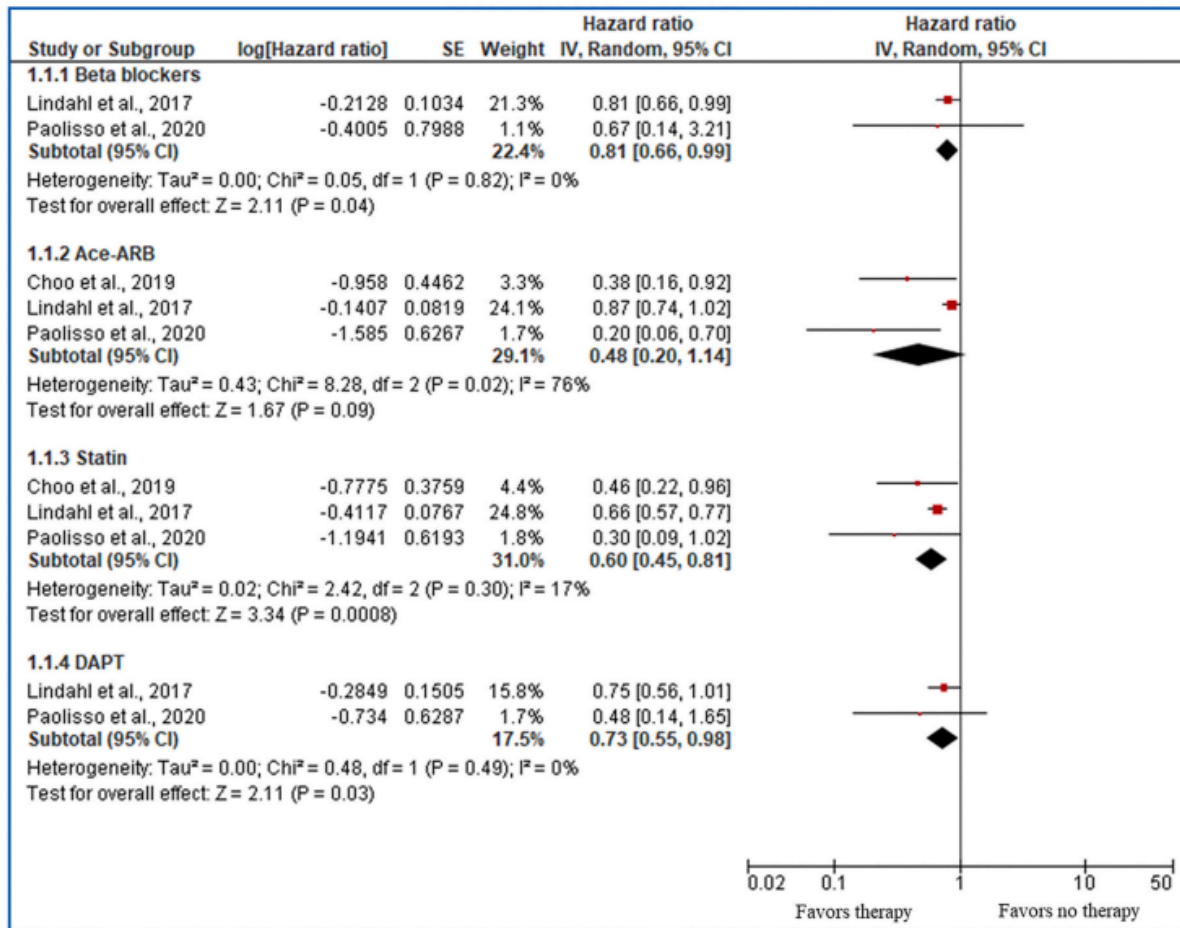
- Spasmetesten
  - Max 100 mcg Acetylcholine ic
  - Epicardiaal spasme LAD +++

B/ nifedipine en ikorel > AP ccs 1-2



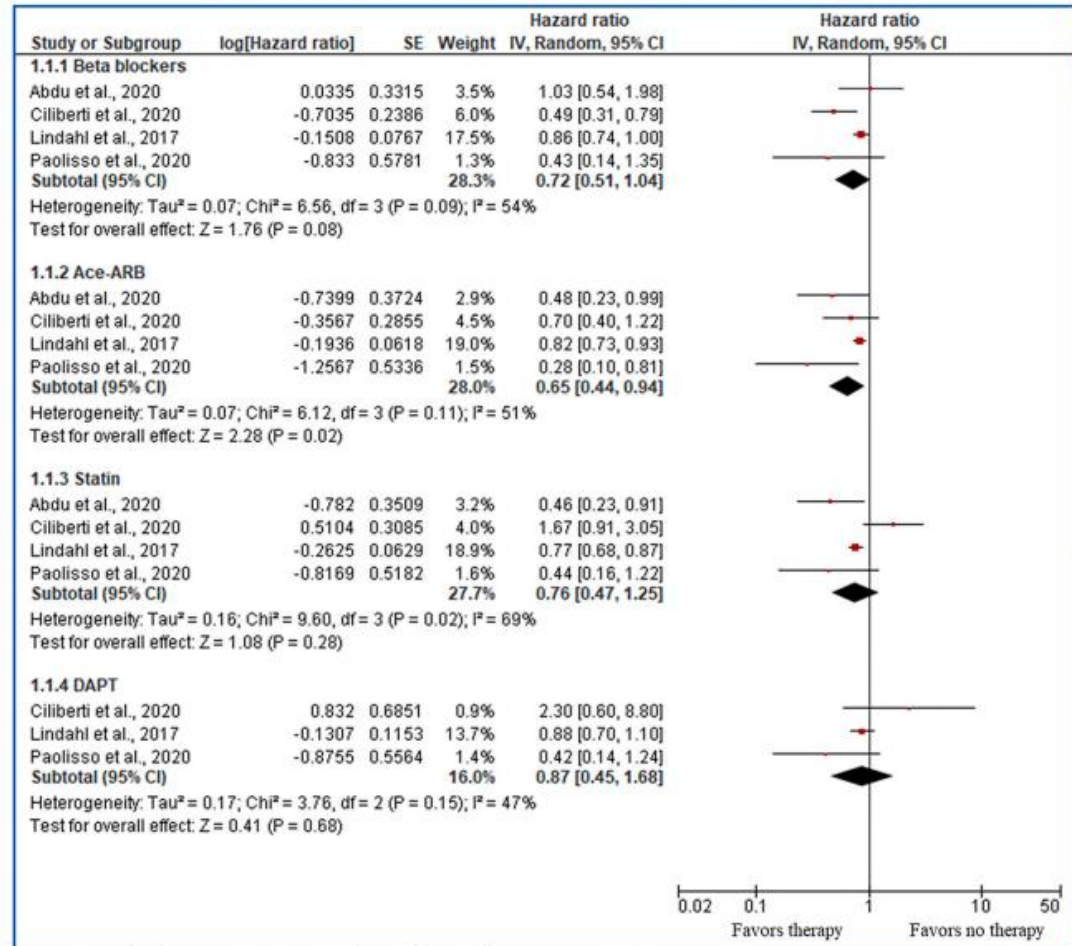
# MINOCA

## ALL-CAUSE DEATH

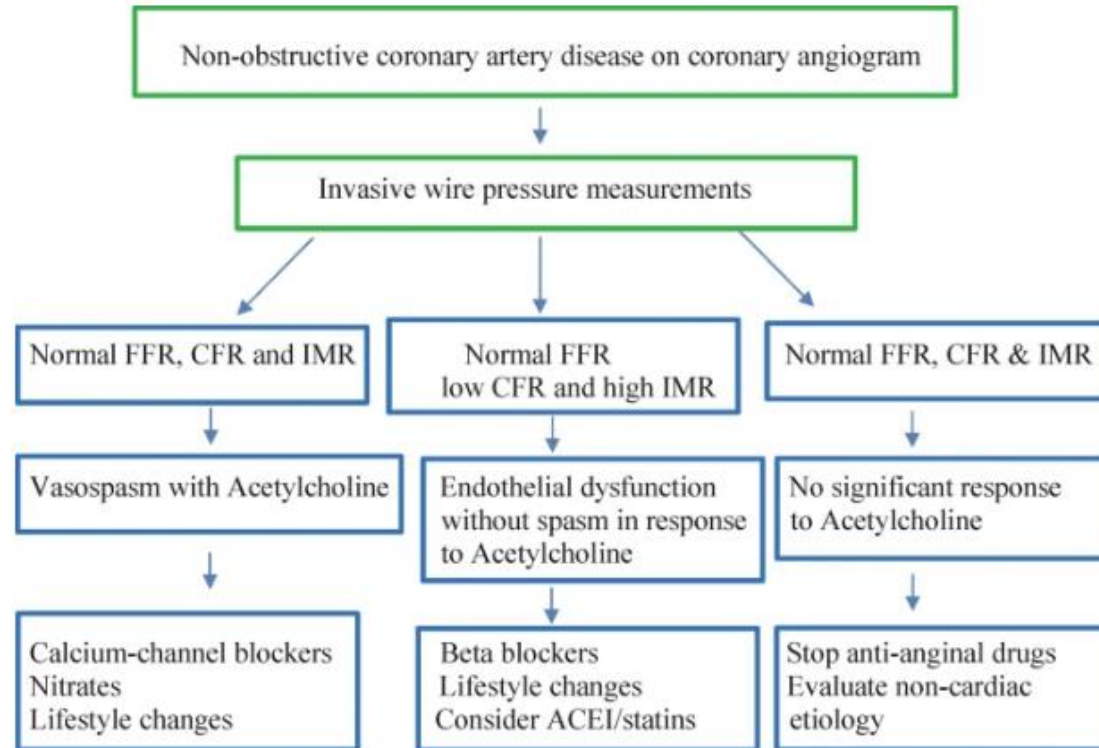


# MINOCA

## MAJOR ADVERSE CARDIOVASCULAR EVENTS

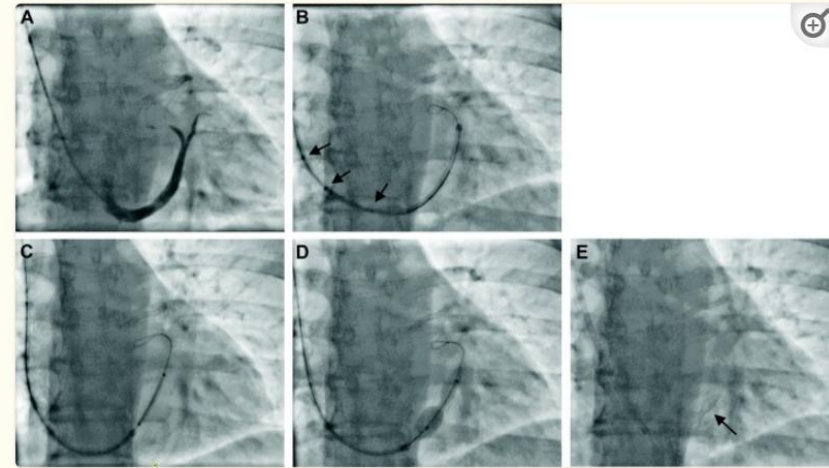
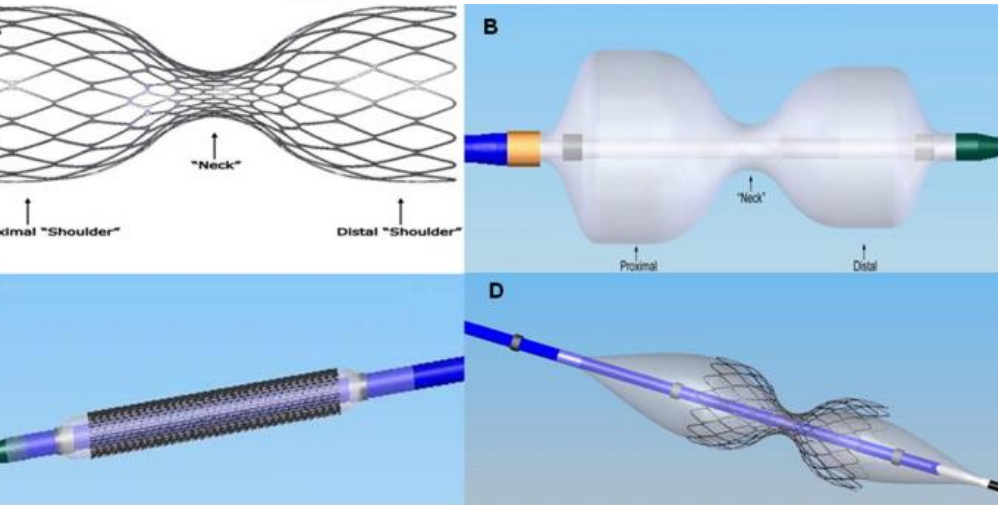


# INOCA



# NOVEL TREATMENTS

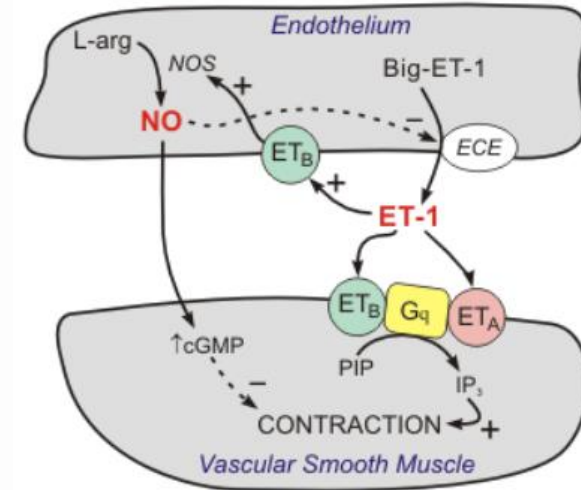
# REDUCER



- CS narrowing surgical in 1955, success CABG/PCI > decreased interest
- = Ballon expandable stainless steel device, in CS implant
- Action: raise venous backpressure > dilation subendocardial vessels, recruits capillaries > reduces microvascular resistance > redistributes blood to ischaemic myocardium > improvements in myocardial ischaemia
- Class 2B indication in refractory angina

# Endotheline receptor antagonist (ERA)

- Bosentan: EDIT 2 trial, RCT, vasospasme, vs placebo
- Zibotentan: PRIZE trial, RCT, vasospasme, vs placebo
- ERA
  - affiniteit voor de receptoren endotheline A en B
  - Vermindering pulmonale & systemische vaatweerstand > toename HMV (niet hartfrequ)
- Indicaties nu: PHT, ulcera bij systemische sclerose



# Eigen studies

- CMD - AP registry
- CMD - HFpEF registry
- POSITIVE SHOCK (CMD)
- VIAGRA bij spamse

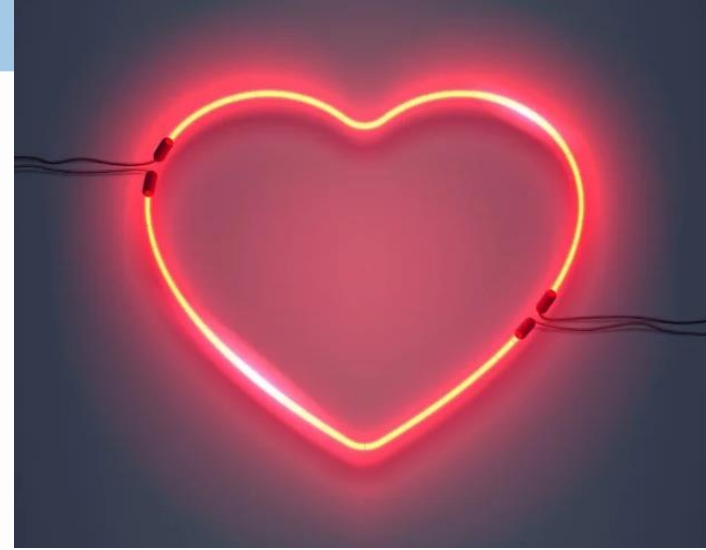


# Aankomende studies

- iCorMica: beleid obv direct CMD metingen na CAG vs CAG alleen
- CorCTCA trial : na CT > CAG+CMD+spasme> beleid nav endotypes vs control
- WARRIOR: vrouwen, IMT vs usual care
- MINOCA-BAT: bblokker en ACE-I, 2:2 design
- StratMed-MINOCA: MRA in CMD
- PROMISE: precision medicine approach

# TAKE HOME MESSAGES

- (M)INOCA is níet benigne
- Meten is weten
- Geen epicardiaal lijden denk aan:
  - (M)INOCA
- Precision medicine approach > etiologie zoektocht



# Uitrijkaart parkeerplaats

Bij het arriveren op het parkeerterrein heeft u een parkeerkaart uit de automaat bij de slagboom ontvangen.



-Heeft u minder dan 3 uur geparkeerd? Dan kunt u gewoon uitrijden met de parkeerkaart die u heeft ontvangen bij aankomst.

Heeft u langer dan 3 uur geparkeerd? Dan gelieve bij de receptie de uitrijkaart laten scannen zodat u zonder oponthoud de parkeerplaats kunt verlaten.

*Dank aan onze sponsors voor het  
mede mogelijk maken van deze  
refereeravond:*



De volgende refereeravond zal plaatsvinden op:  
3 Juni 2024