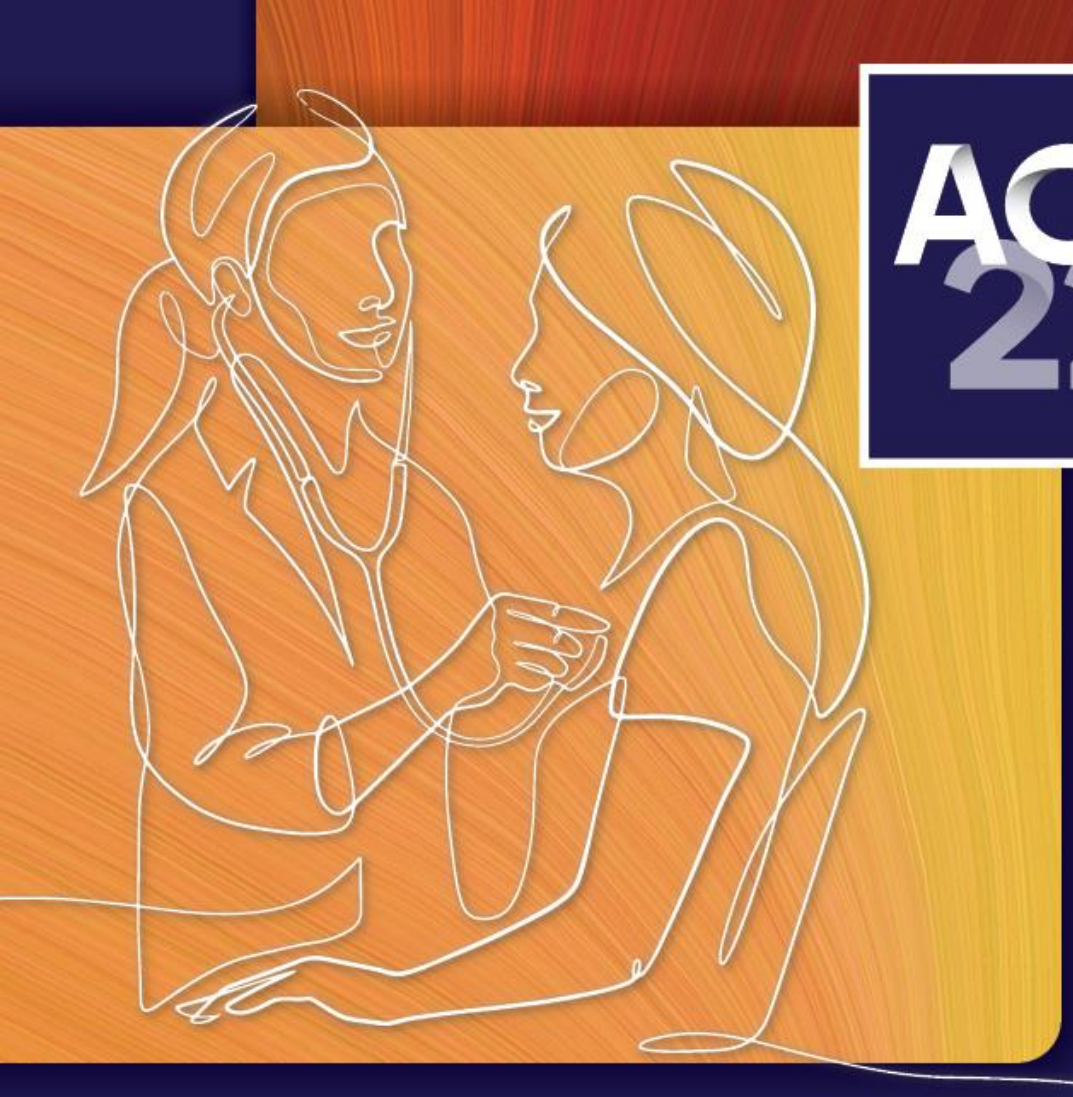

ACC 22

TRANSFORMING CARDIOVASCULAR CARE FOR YOU. FOR YOUR TEAM. FOR YOUR PATIENTS.

AMERICAN COLLEGE of CARDIOLOGY

EDIT-CMD trial

Efficacy of Diltiazem to Improve Coronary Vasomotor Dysfunction in Patients with Angina and Non Obstructive Coronary Arteries

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Disclosure statement of financial interest

I, Tijn Jansen, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

The EDIT-CMD trial was sponsored by research grants from Abbott

Background

- Up to 40% of patients undergoing coronary angiography for stable angina do not have obstructive coronary artery disease (ANOCA)[1]
- In 60-90% coronary vasomotor dysfunction (CVDys) is the underlying pathophysiology[2]
- CVDys consists of two major endotypes[3]
  - Coronary artery spasm
  - Coronary microvascular dysfunction (CMD)
- Both endotypes can be assessed by coronary function testing (CFT)
- ANOCA patients have a worse prognosis, and adequate therapy is paramount[4]

1 Johnston, EHJ 2011 2 Suda, JACC 2019 3 EAPCI expert consensus, EHJ 2020 4 Jespersen, EHJ 2012

Background

- Guidelines recommend the use of calcium channel blockers (CCBs) to reduce symptoms in Coronary vasomotor dysfunction[1]
- Diltiazem is one of the most frequently prescribed medications in these patients[2,3]
- However, these recommendations are based on dated, small, non-randomized trials[1]
- The effect of diltiazem has never been evaluated in ANOCA patients in a blinded placebo controlled randomized trial

1 Knuuti, EHJ 2020 2 EAPCI consensus document, EHJ 2020 3 CorMicA trial, Ford, JACC 2018

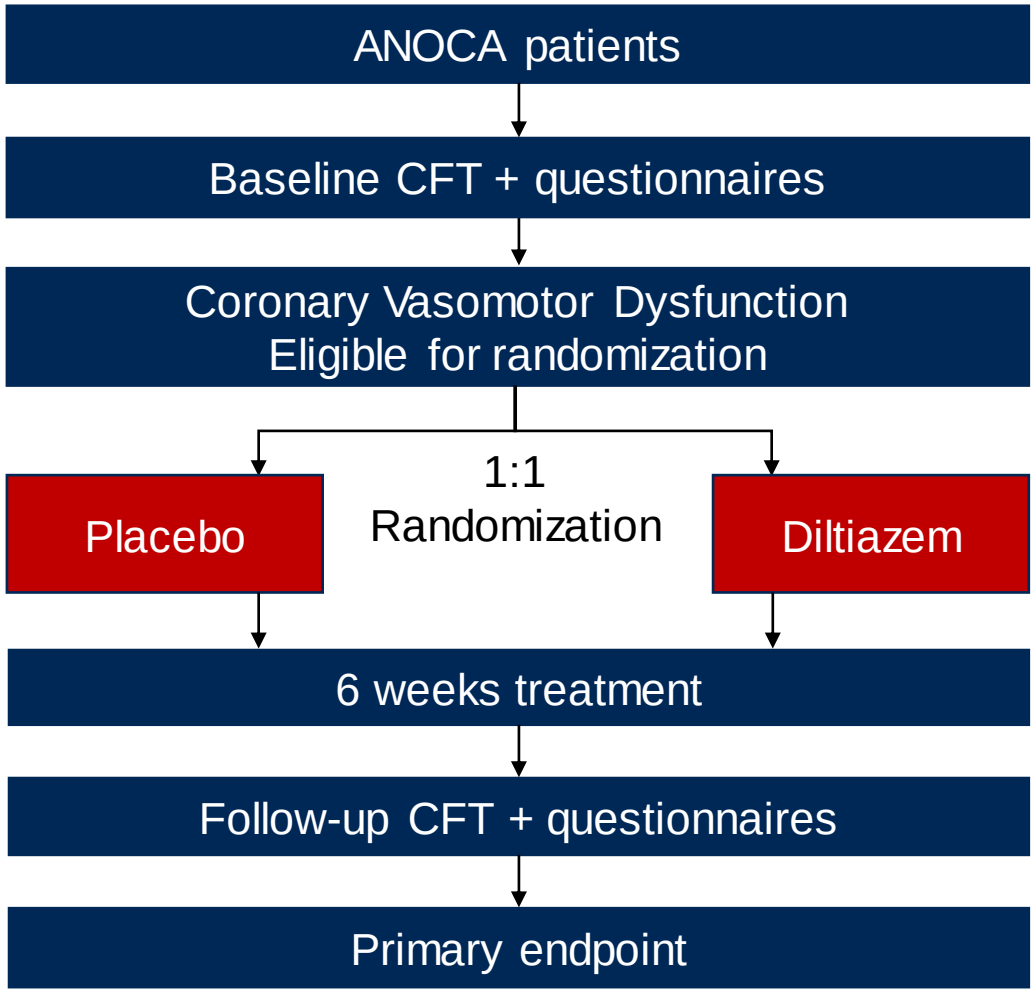
Objective

- EDIT-CMD: randomized, double blind, placebo-controlled trial

- **Primary objective:**
  - To determine treatment success of diltiazem on coronary vasomotor dysfunction as assessed by repeated coronary function testing

- **Secondary objective:**
  - To assess the effect of diltiazem on symptoms and quality of life

Trial design



Trial organization

Principle Investigators

Suzette Elias-Smale, Niels van Royen, Annemiek de Vos, Pieter Smits.

Data Safety Monitoring Board

Freek Verheugt (chair), Eric Boersma (statistician), Nico Pijls (clinical expert)

Trial statistician

Steven Teerenstra

Study coordinator

Regina Konst, Tijn Jansen

Radboudumc university medical center

MAASSTAD ZIEKENHUIS een santeon ziekenhuis

catharina een santeon ziekenhuis

Key in- and exclusion criteria

Inclusion criteria

- ✓ Age >18 years
- ✓ Chronic angina (≥ 2x/week)
- ✓ No obstructive CAD (< 5 years)
  - CAG: < 50% stenosis, or intermediate stenoses (50 - 70%) with FFR > 0.80 or iFR > 0.89
  - CCTA: finding of non-obstructive coronary arteries

Exclusion criteria

- X Use of CCB < 2 weeks
- X Contra-indication to coronary function testing:
  - Contraindication for adenosine, acetylcholine
  - Ongoing dipyridamole treatment.
- X Contra-indication for treatment with CCB
- X Other cause of angina deemed highly likely by the treating physician.
- X LVEF< 50%; PCI < 3 months; history of CABG; Surgically uncorrected significant congenital or valvular heart disease, cardiomyopathy or myocarditis; eGFR < 30; significant hepatic impairment; Pregnancy; life expectancy < 1 year.
- X Symptomatic hypotension or systolic BP < 100 mmHg at screening visit on 2 consecutive measurements.

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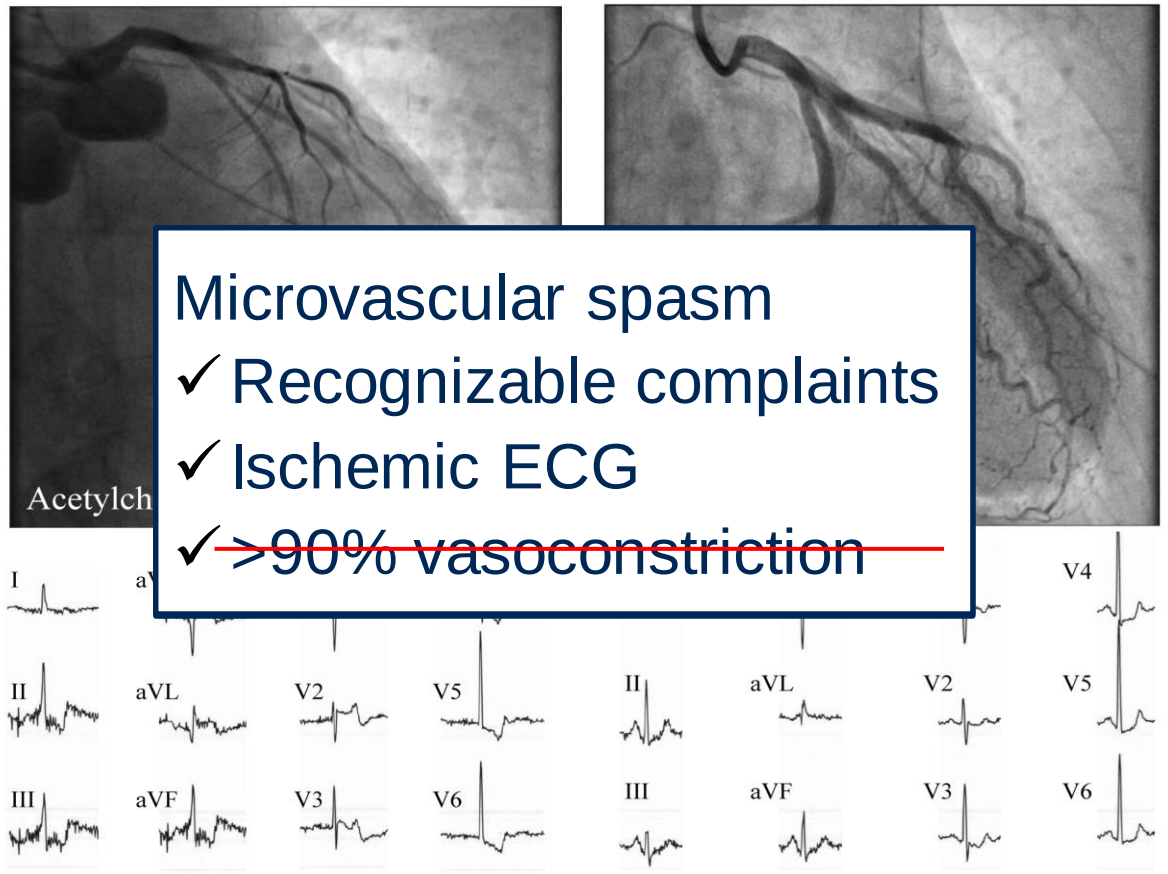
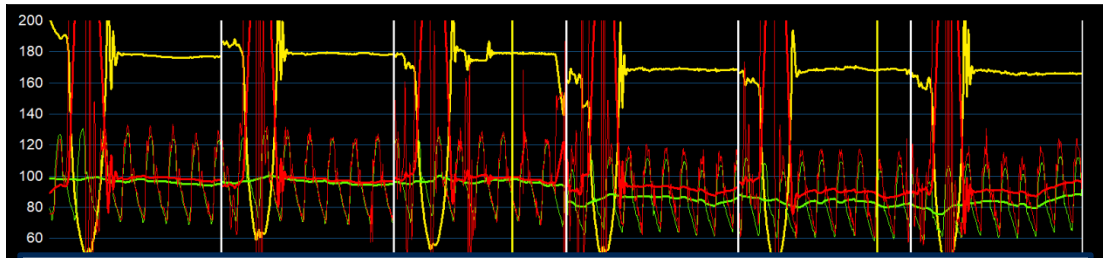
Methods – Coronary function testing

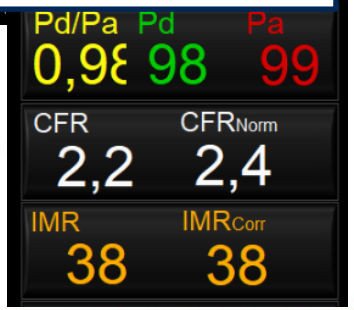
- Endotype
  - Coronary artery spasm
- Method
  - Acetylcholine (ACH) spasm provocation
- Assessment
  - Epicardial spasm
  - Microvascular spasm
  - No spasm



Methods – Coronary function testing

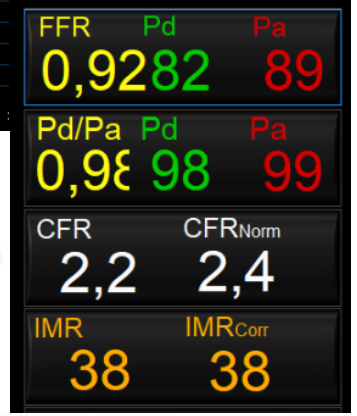


Coronary Microvascular Dysfunction
- CFR < 2.0
and/or
- IMR ≥ 25



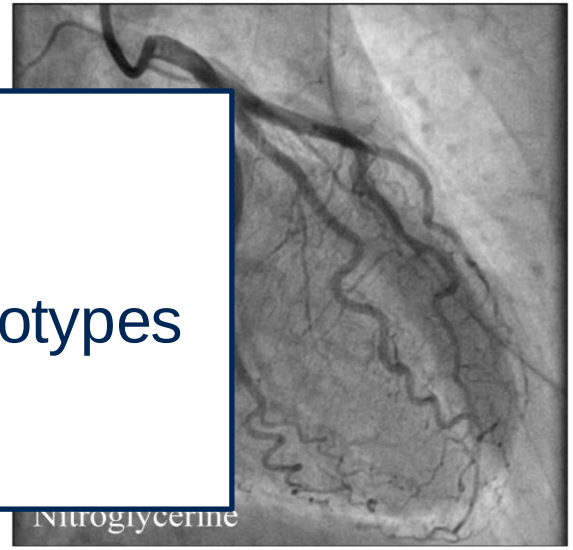
- Endotype
  - Coronary microvascular dysfunction (CMD)
- Method
  - Bolus thermodilution method with adenosine (ADE)
- Assessment
  - Coronary flow reserve (CFR)
  - Index of microvascular resistance (IMR)

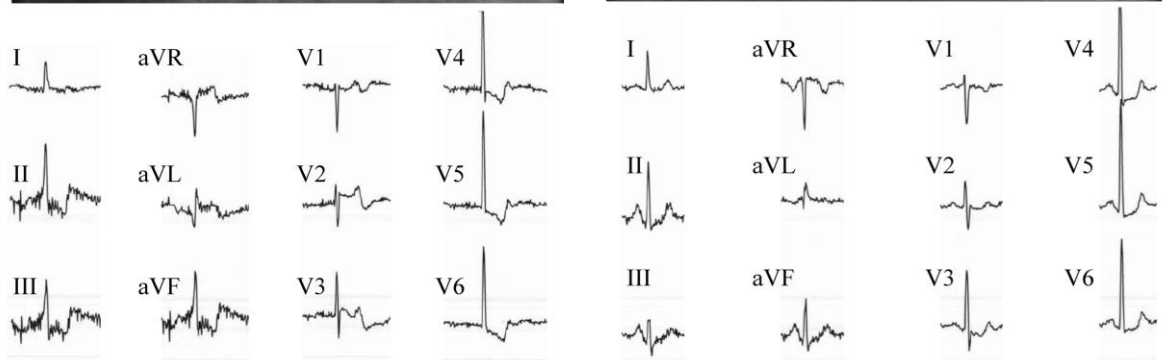
Methods – Primary endpoint



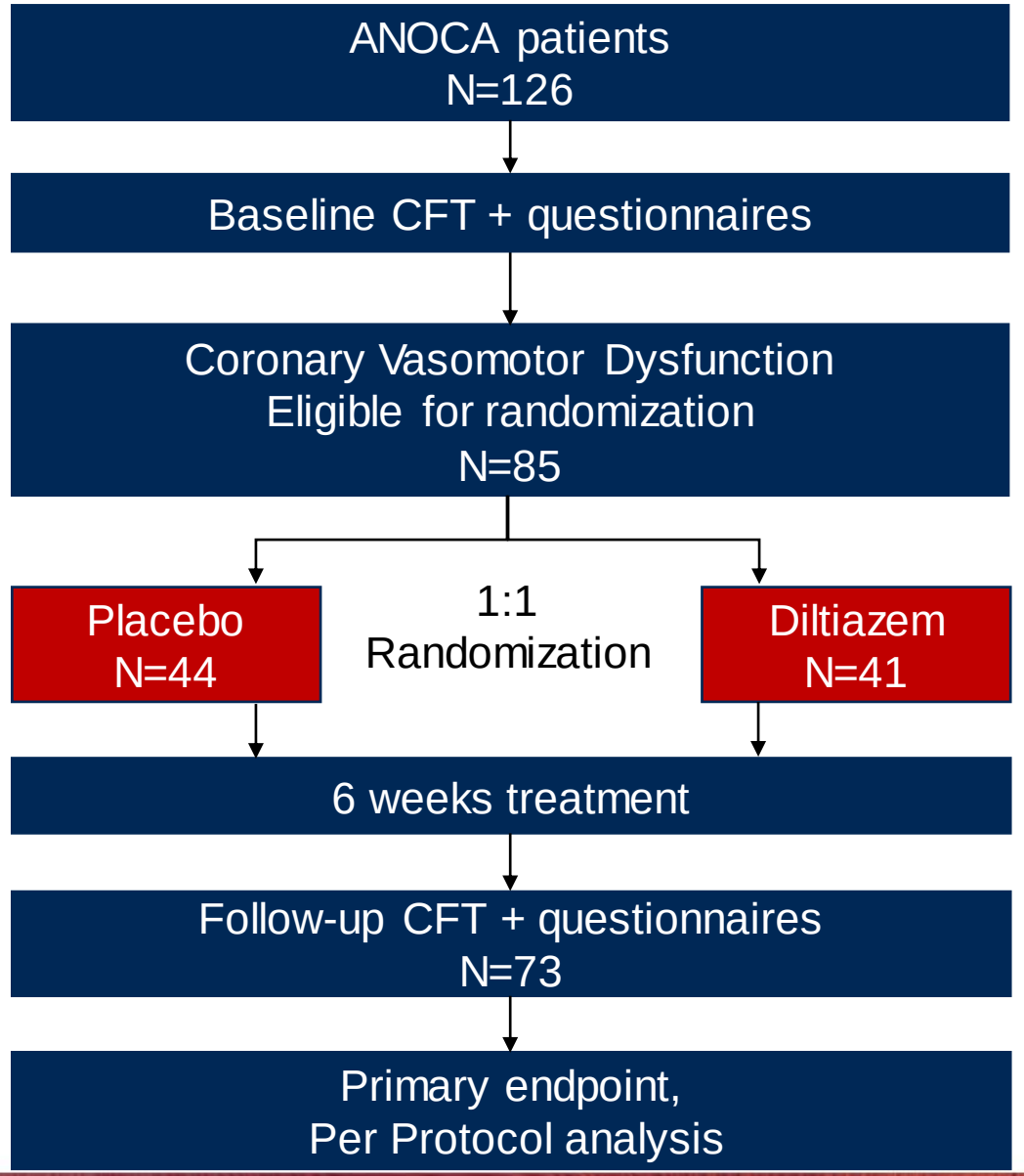
Successful treatment:

- Normalization of one of the abnormal endotypes
- No normal endotype becoming abnormal





Trial flow diagram



Results - Baseline

	Placebo N = 44	Diltiazem N = 41
Age (years)	58 ± 9	58 ± 9
Male gender	36%	31%
History of MI	18%	15%
History of PCI	23%	22%
Hypertension	52%	54%
Dyslipidemia	41%	46%
Diabetes	9%	10%
Current/former smoker	54%	41%
Premature CAD in first-degree relative	52%	51%
Migraine	16%	12%

	Placebo N = 44	Diltiazem N = 41
Angina characteristics		
Angina CCS III/IV	52%	44%
Angina at rest	89%	85%
Angina occurs during exercise	77%	76%
Medication		
Aspirin	46%	54%
Beta-blocker	30%	32%
Statin	34%	54%
ACEi/ARB	39%	44%
Nitrates	23%	27%
Nicorandil	11%	22%

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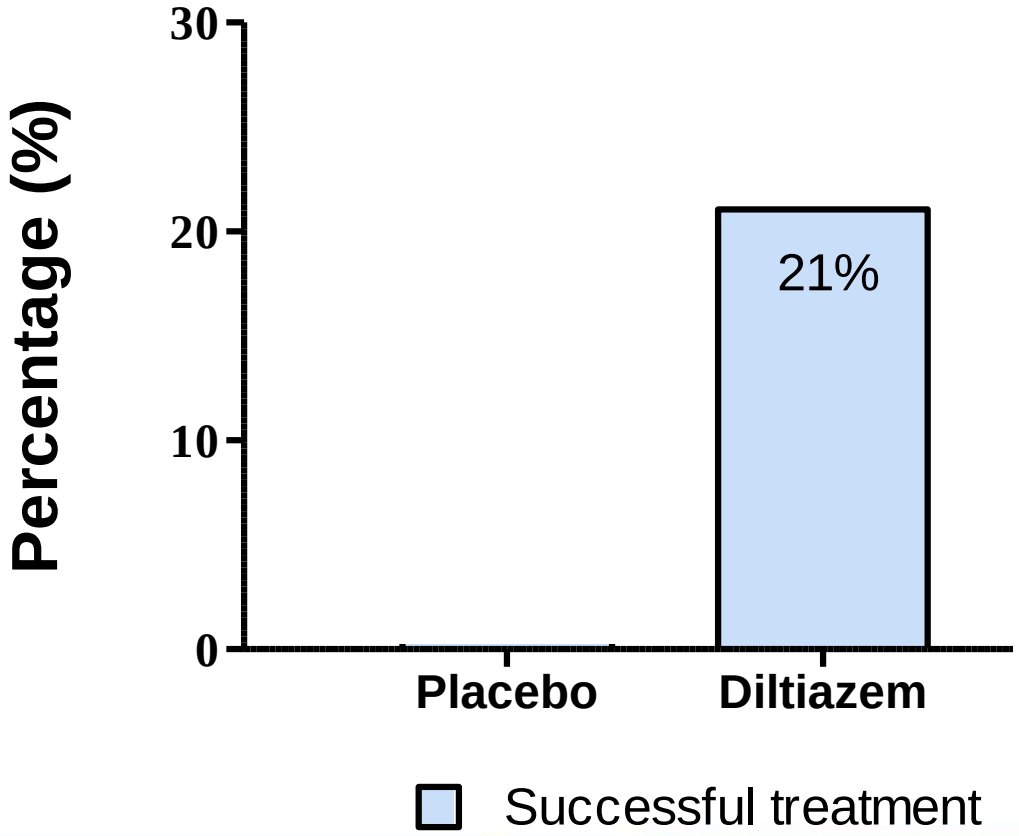
Results – Baseline CFT

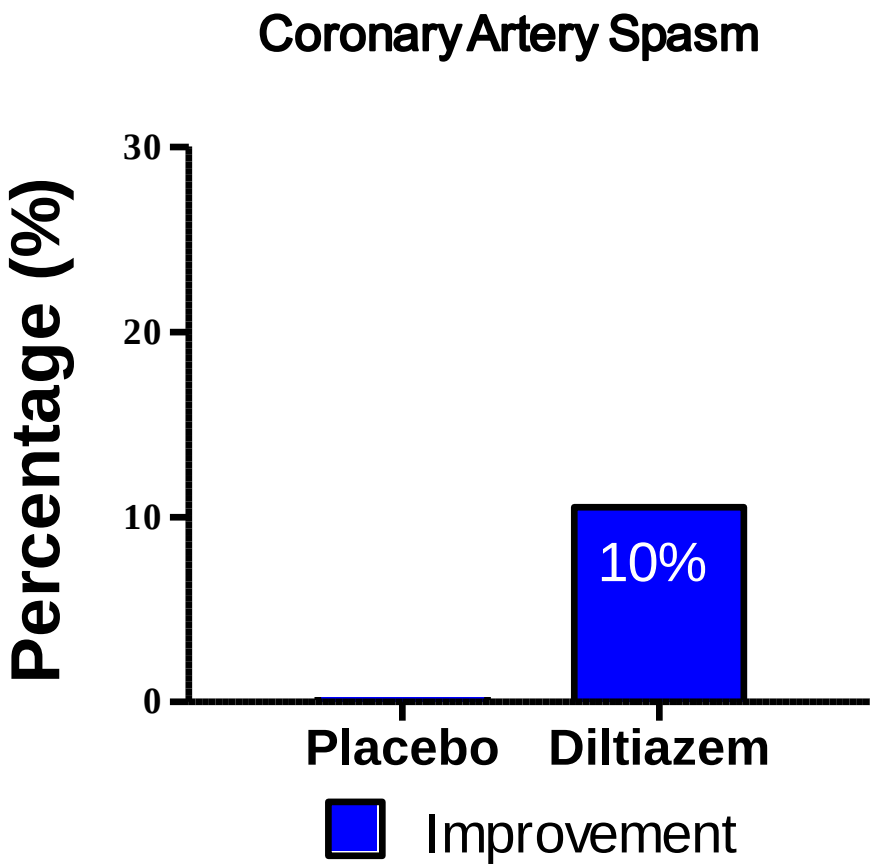
	Placebo N = 44	Diltiazem N = 41
First ACH test		
Epicardial spasm	24 (55%)	19 (48%)
Microvascular spasm	11 (25%)	10 (25%)
No spasm	9 (20%)	11 (27%)
First ADE test		
Microvascular dysfunction	32 (73%)	22 (54%)
Normal function	12 (27%)	19 (46%)

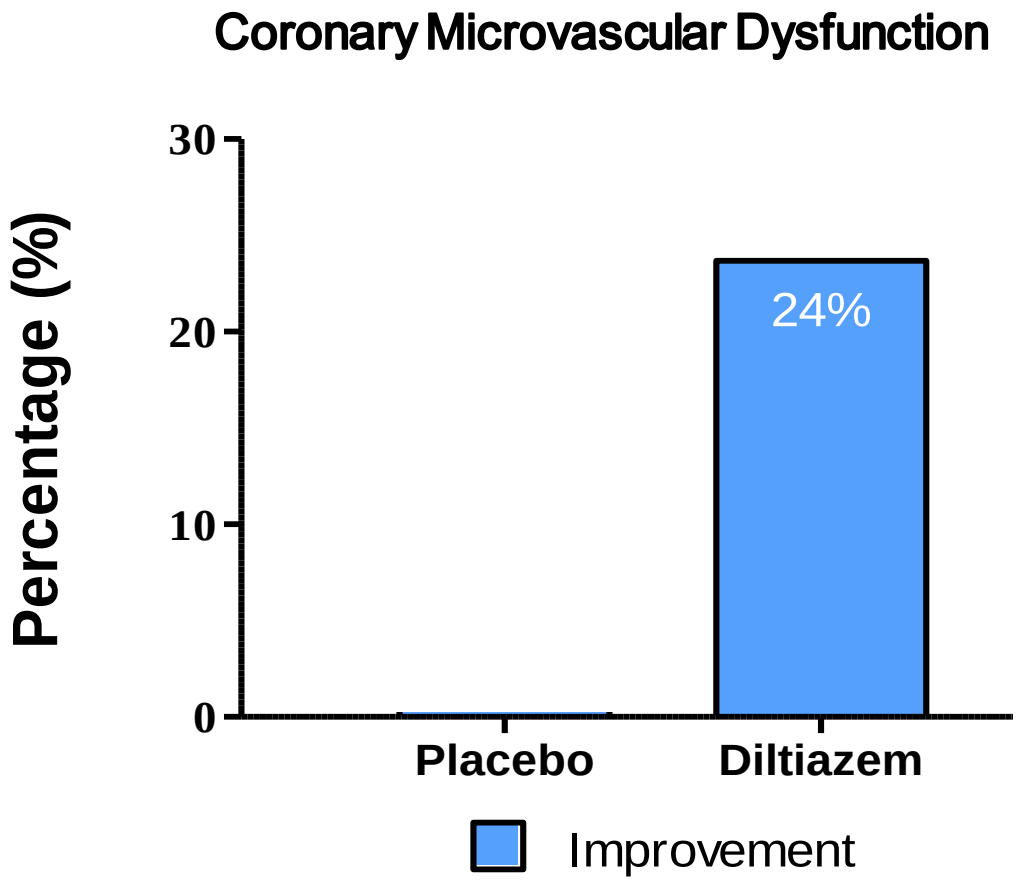
Results – Primary outcome



No difference in treatment success on coronary vasomotor dysfunction

Results – Primary outcome





Results – Secondary outcomes

	Placebo (n = 35)		Diltiazem (n = 38)		Intervention Effect	
	Baseline	Follow-up	Baseline	Follow-up	Difference in Change	P-value
Physiological measurements						
CFR	3.1 ± 1.5	4.1 ± 2.7	3.7 ± 1.6	3.2 ± 1.2	1.35	**0.012**
IMR	27.2 ± 11.7	27.5 ± 19.1	25.3 ± 12.7	23.5 ± 13.6	3.5	0.43
Tmn (rest)	1.04 ± 0.47	1.21 ± 0.54	1.00 ± 0.38	0.95 ± 0.40	0.23	**0.05**
Tmn (hyperemia)	0.36 ± 0.18	0.37 ± 0.25	0.31 ± 0.18	0.32 ± 0.19	0.006	0.92

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CFR increases in placebo and decreases in diltiazem

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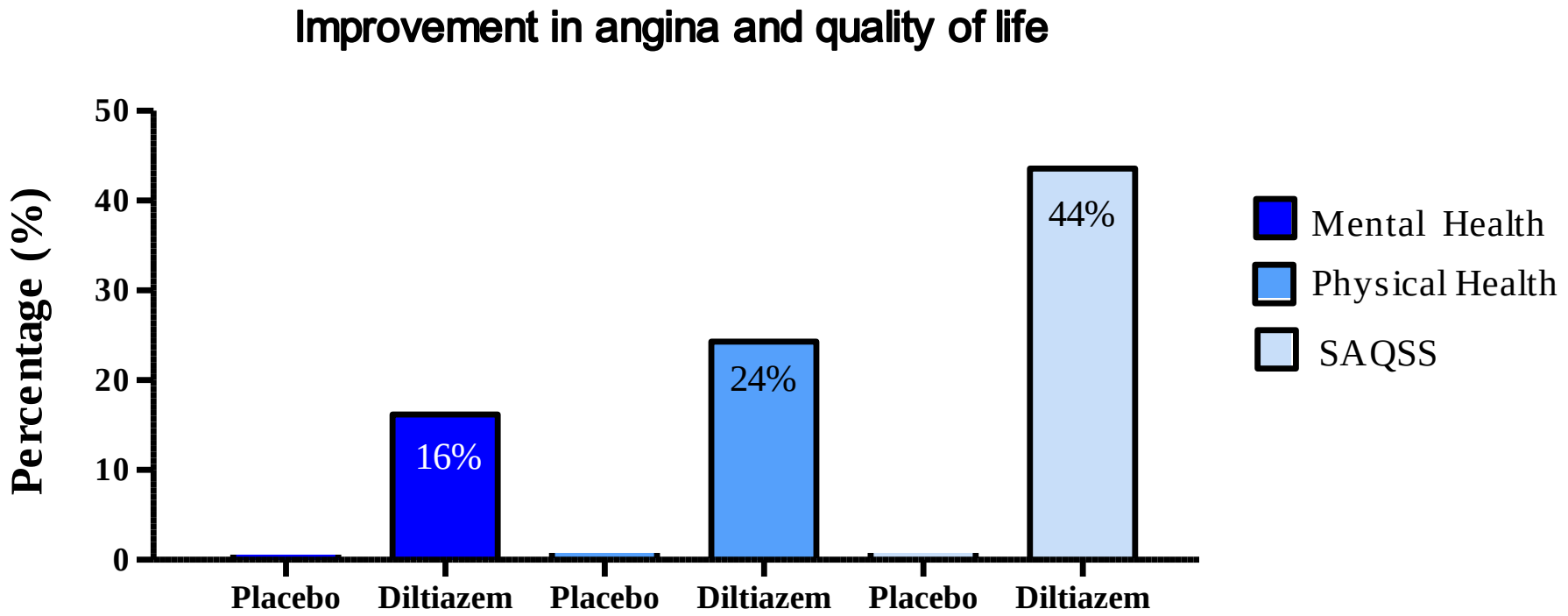
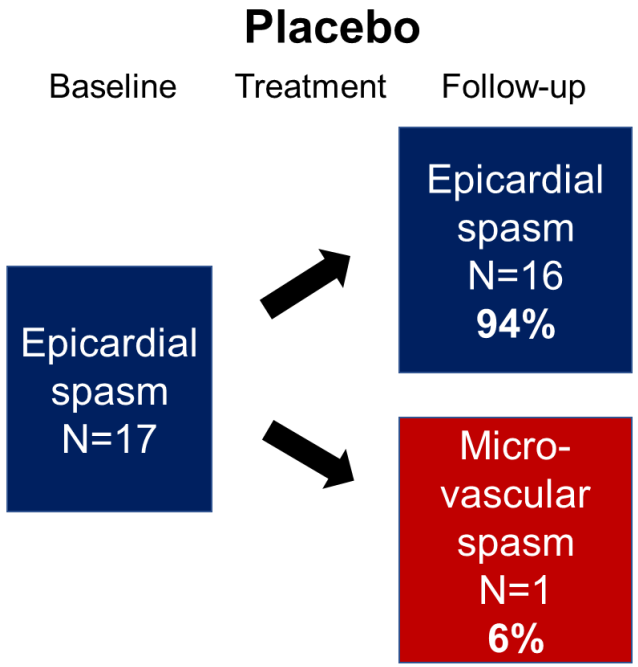
No differences in change in IMR between placebo and diltiazem

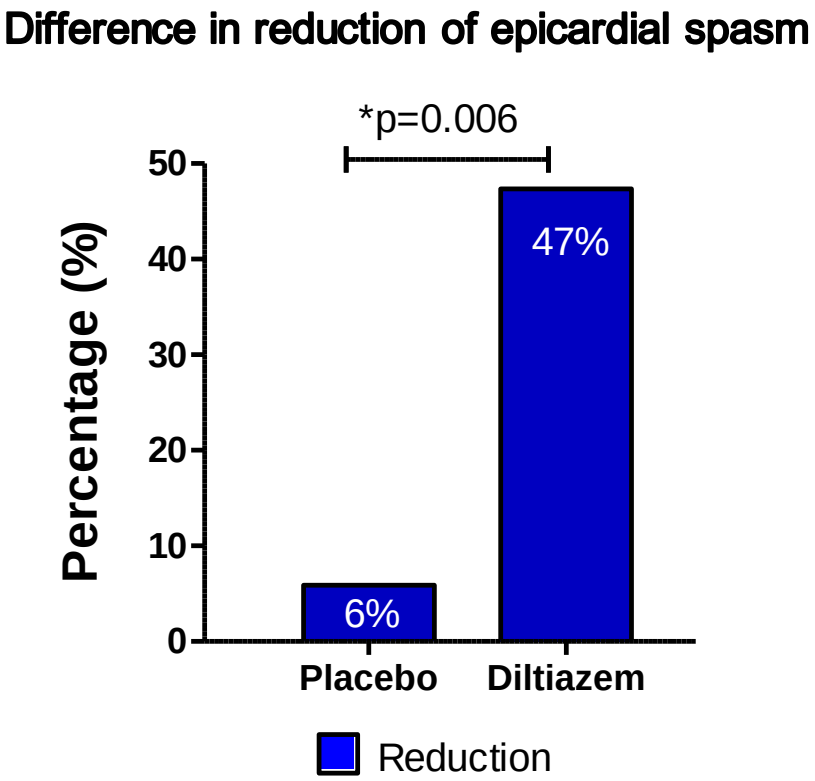
Results – Secondary outcomes



No difference in symptom improvement between placebo and diltiazem

Results – Secondary outcomes





Diltiazem seems to reduce epicardial spasm

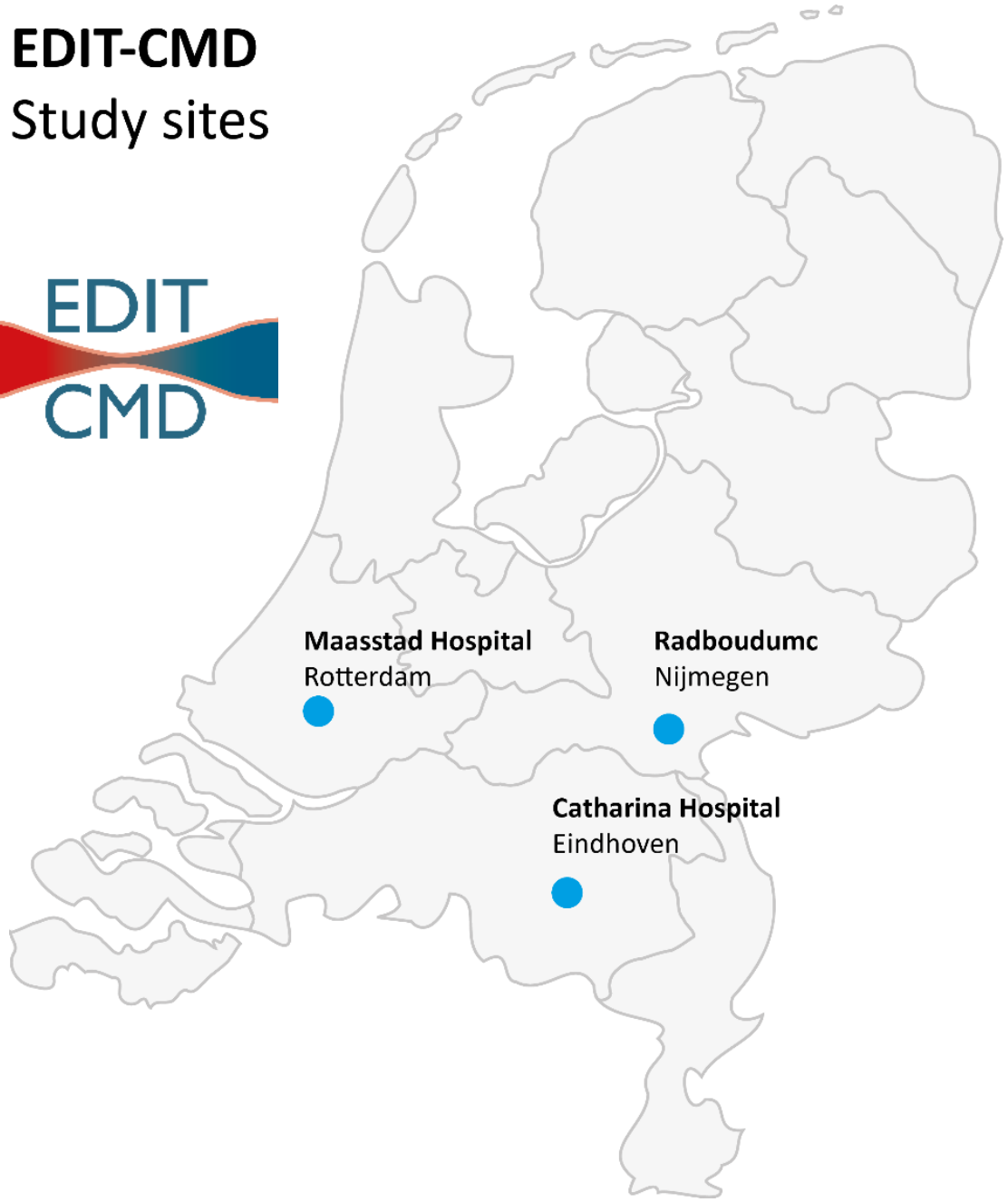
Conclusions

- 6 weeks of treatment with diltiazem was not effective in improving coronary vasomotor dysfunction, symptoms or quality of life as compared to placebo
- Diltiazem seems to reduce epicardial spasm as compared to placebo
- Large trials on the effect of medical therapy on the individual endotypes are warranted
- This study using repeated CFT provides a platform for future research

Publication

- The manuscript of the EDIT-CMD trial is accepted for simultaneous publication in JACC Cardiovascular Imaging

EDIT-CMD
Study sites



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