#FullPhysiology

*In Daily Practice*

# REDUCE-CMD

**micRovascular and EpicarDial invasive evalUation in patients with reduCed ejEction fraction CardioMyopathy**

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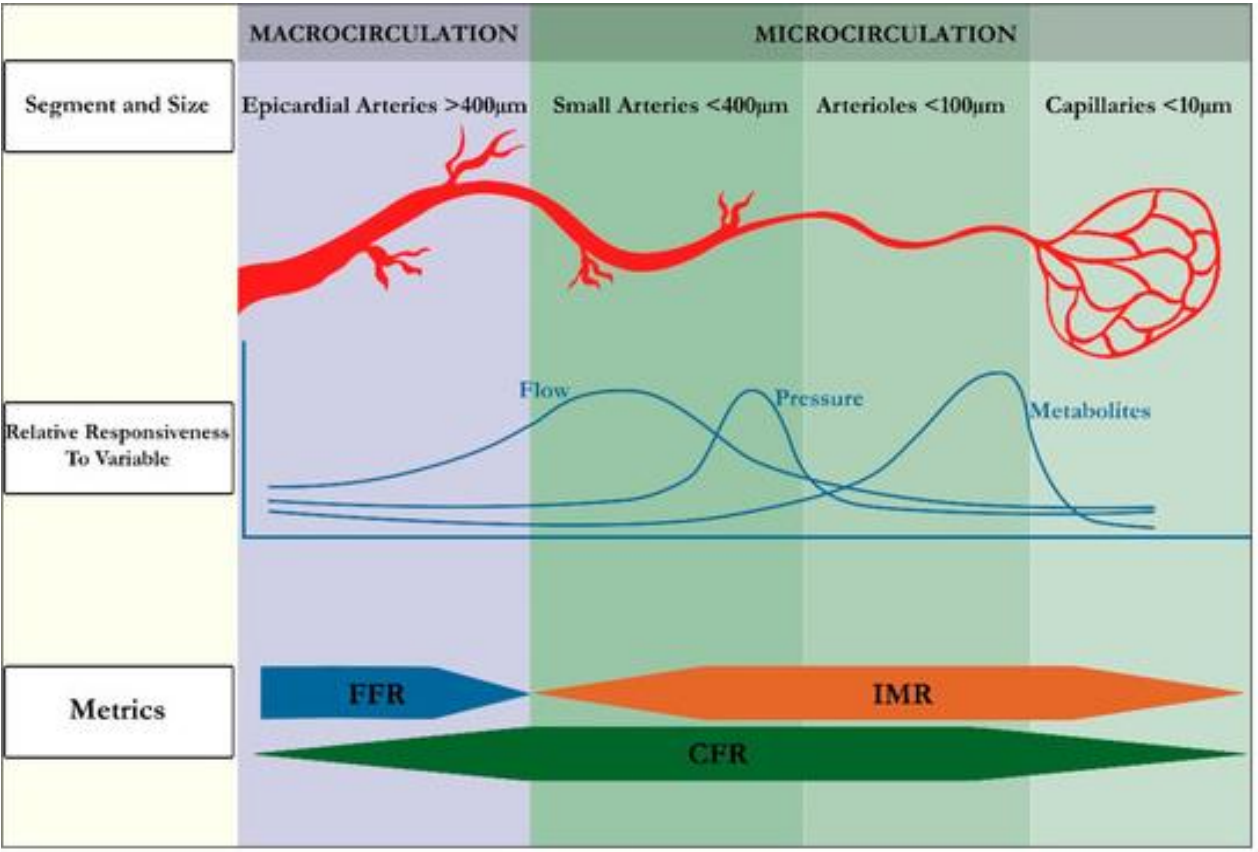
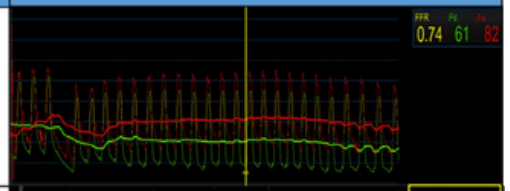
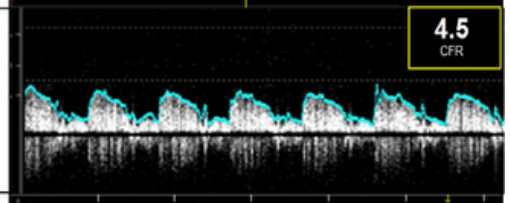
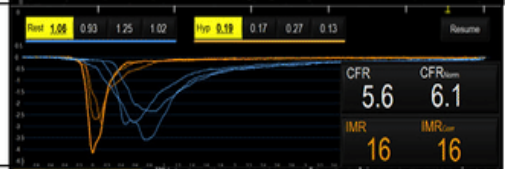
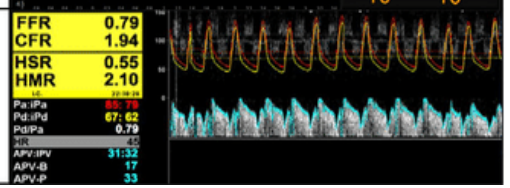
# Background - Coronary physiology evaluation




| | Formula | Cutoff Value | Implications | Example |
|---|---|---|---|---|
| FFR | FFR = Pd/Pa | ≤0.80 | Functionally significant coronary stenosis |  |
| CFR | $APV_h/APV_b$ *Doppler<br>$Tmn_b/Tmn_h$ *Thermodilution | <2 | Unspecific macrovascular and microvascular inability to increase flow |  |
| IMR | IMR = Pd x $Tmn_h$ *Thermodilution | >25 | Specific microvascular dysfunction |  |
| HMR | HMR = $Pd/APV_h$ *Doppler | >2 | Specific microvascular dysfunction |  |

JRD Clarke et al. J. Clin. Med. 2020, 9(1), 86; https://doi.org/10.3390/jcm9010086

F Diez-Delhoyo. Trends Cardiovasc Med. 2020 Aug;30(6):346-352.

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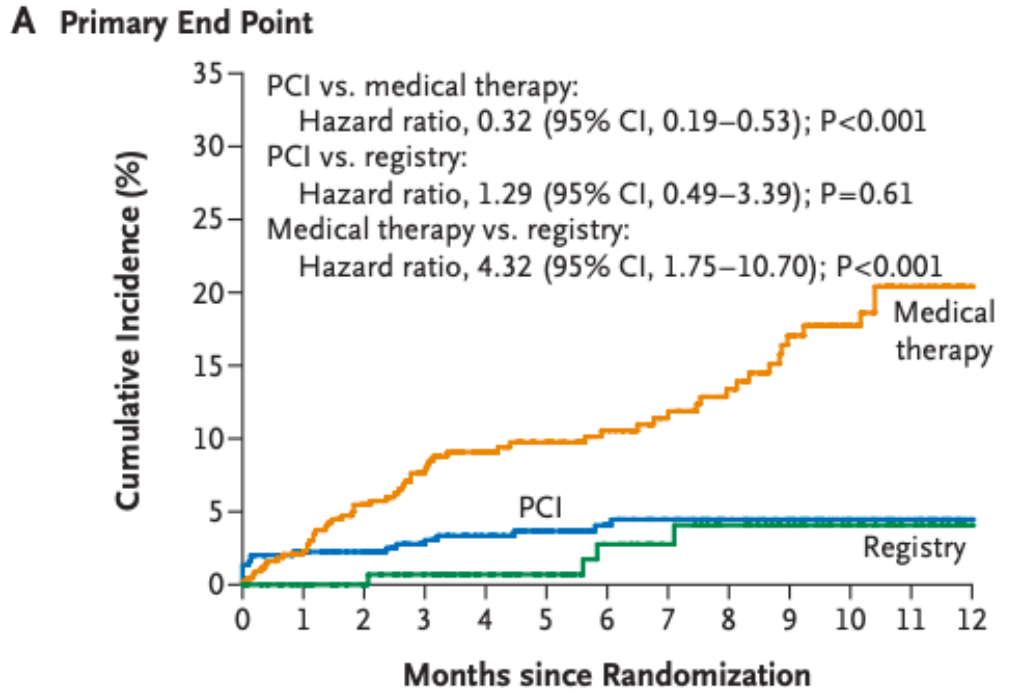
# Background - FFR and HFrEF

In FAME and FAME 2 trials LVEF<30% was an exclusion criteria




**No. at Risk**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Medical therapy | 441 | 414 | 370 | 322 | 283 | 253 | 220 | 192 | 162 | 127 | 100 | 70 | 37 |
| PCI | 447 | 414 | 388 | 351 | 308 | 277 | 243 | 212 | 175 | 155 | 117 | 92 | 53 |
| Registry | 166 | 156 | 145 | 133 | 117 | 106 | 93 | 74 | 64 | 52 | 41 | 25 | 13 |

Witt et al., for the FAME 2 Trial Investigators. Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease. N Engl J Med 2012;

# Background - FFR and HFrEF

**Table 1** Clinical and angiographic characteristics of the propensity-matched population

| | FFR-guided ($n = 433$) | Angio-guided ($n = 866$) | *P*-value |
|---|---|---|---|
| Age, years | 66.3 ± 10.8 | 66.7 ± 10.6 | 0.51 |
| Male sex | 351 (81%) | 691 (80%) | 0.59 |
| Smoking habit | 242 (56%) | 472 (54%) | 0.63 |
| PVD | 46 (11%) | 95 (11%) | 0.92 |
| Diabetes mellitus | 111 (26%) | 237 (27%) | 0.51 |
| IDDM | 26 (6%) | 56 (6%) | 0.75 |
| Hypertension | 212 (49%) | 419 (48%) | 0.84 |
| Hyperlipidaemia | 249 (57%) | 485 (56%) | 0.61 |
| Family history CAD | 112 (26%) | 216 (25%) | 0.72 |
| Previous CABG | 45 (10%) | 90 (10%) | 1.00 |
| Previous PCI | 79 (18%) | 158 (18%) | 1.00 |
| Atrial fibrillation | 36 (8%) | 75 (9%) | 0.83 |
| LVEF | 39.4% ± 9% | 39.1% ± 9% | 0.51 |
| LVEDVi, mL | 106 ± 38 | 106 ± 40 | 0.54 |
| LVESVi, mL | 65 ± 29 | 65 ± 35 | 0.88 |
| N° diseased vessels | 2.00 ± 0.85 | 1.97 ± 0.84 | 0.54 |
| 1-vessel disease | 154 (36%) | 315 (36%) | 0.92 |
| 2-vessel disease | 124 (29%) | 259 (30%) | |
| 3-vessel disease | 155 (36%) | 292 (34%) | |
| Diameter stenosis | 62% ± 23% | 63% ± 20% | 0.41 |
| Stenosis location | | | |
| LMCA | 43 (10%) | 112 (13%) | 0.11 |
| LAD | 348 (80%) | 636 (74%) | 0.007 |
| LCX | 240 (55%) | 498 (58%) | 0.43 |
| RCA | 237 (55%) | 492 (57%) | 0.45 |

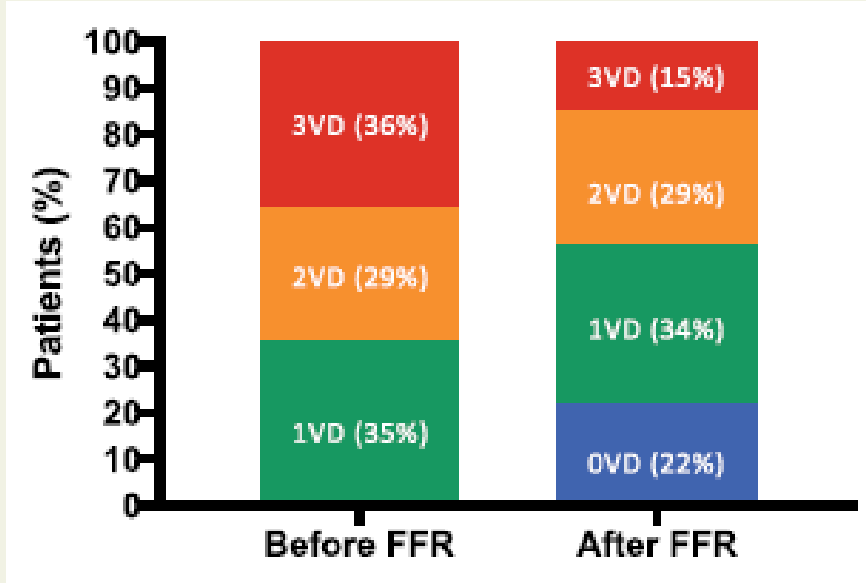



**Figure 1** Downgrading in the number of diseased vessels after fractional flow reserve measurement. VD, vessel disease.

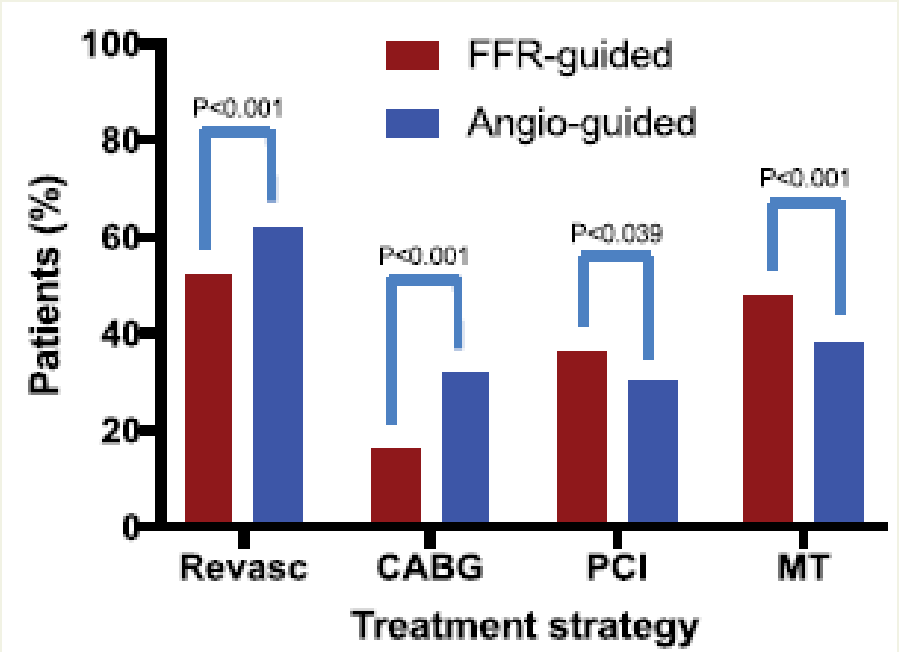



**Figure 2** The difference in treatment strategies between fractional flow reserve- and Angiography-guided group. CABG, coronary artery bypass grafting; MT, medical therapy; PCI, percutaneous coronary intervention; Revasc, revascularization.

G Di Gioia et al. European Heart Journal (2020) 41, 1665–1672

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# Background - FFR and HFrEF

**Table 4** Clinical outcomes at 1 and 5 years

| Endpoint | 1 year | | HR (95% CI) | *P*-value | 5 years | | HR (95% CI) | *P*-value |
|---|---|---|---|---|---|---|---|---|
| | FFR-guided, *n* (%) | Angio-guided, *n* (%) | | | FFR-guided, *n* (%) | Angio-guided, *n* (%) | | |
| MACCE | 59 (14) | 181 (21) | 0.60 (0.45–0.80) | 0.001 | 172 (40) | 389 (46) | 0.81 (0.67–0.97) | 0.019 |
| All-cause death | 24 (6) | 107 (13) | 0.42 (0.27–0.66) | <0.001 | 96 (22) | 272 (31) | 0.64 (0.51–0.81) | <0.001 |
| MI | 8 (2) | 30 (3) | 0.52 (0.221.22) | 0.13 | 22 (5) | 54 (6) | 0.73 (0.43–1.25) | 0.25 |
| Revascularization | 36 (8) | 71 (8) | 0.91 (0.61–1.38) | 0.54 | 77 (18) | 126 (15) | 1.13 (0.85–1.50) | 0.40 |
| Stroke | 1 (0) | 12 (2) | 0.84 (0.62–0.96) | 0.03 | 11 (3) | 28 (3) | 0.68 (0.37–1.65) | 0.51 |
| HF hospitalization | 15 (3) | 45 (5) | 0.64 (0.34–1.21) | 0.16 | 42 (10) | 106 (13) | 0.75 (0.51–1.10) | 0.15 |
| Unplanned cardiac hospitalization | 30 (7) | 85 (10) | 0.65 (0.41–1.03) | 0.065 | 87 (20) | 200 (24) | 0.81 (0.62–1.05) | 0.11 |

HF, heart failure; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction.

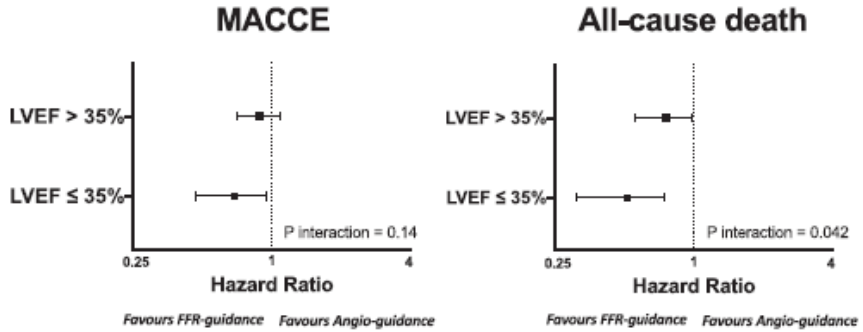
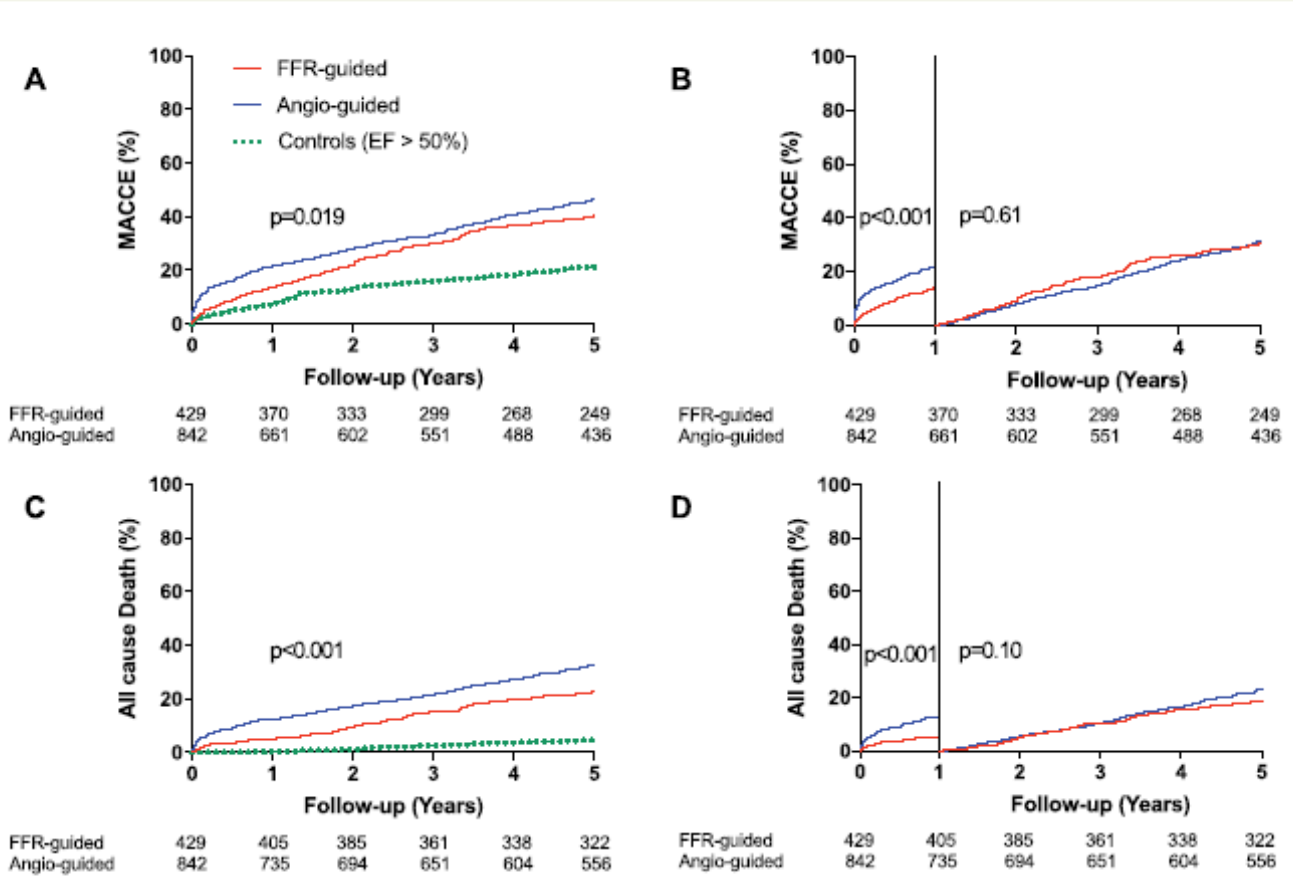



**Figure 3** Impact of fractional flow reserve on MACCE and all-cause death in patients with LVEF ≤35% and with LVEF 36–50%.




**Take home figure** Cumulative incidences and landmark analysis for MACCE and all-cause death. cumulative incidence of MACCE (*A*) and all-cause death (*C*); landmark analysis before and after 1 year timepoint for MACCE (*B*) and all-cause death (*D*). The dotted green line represents the control cohort with preserved LVEF, for visual comparison. *P*-values are referred to the fractional flow reserve-guided and the Angiography-guided groups.

G Di Gioia et al. European Heart Journal (2020) 41, 1665–1672

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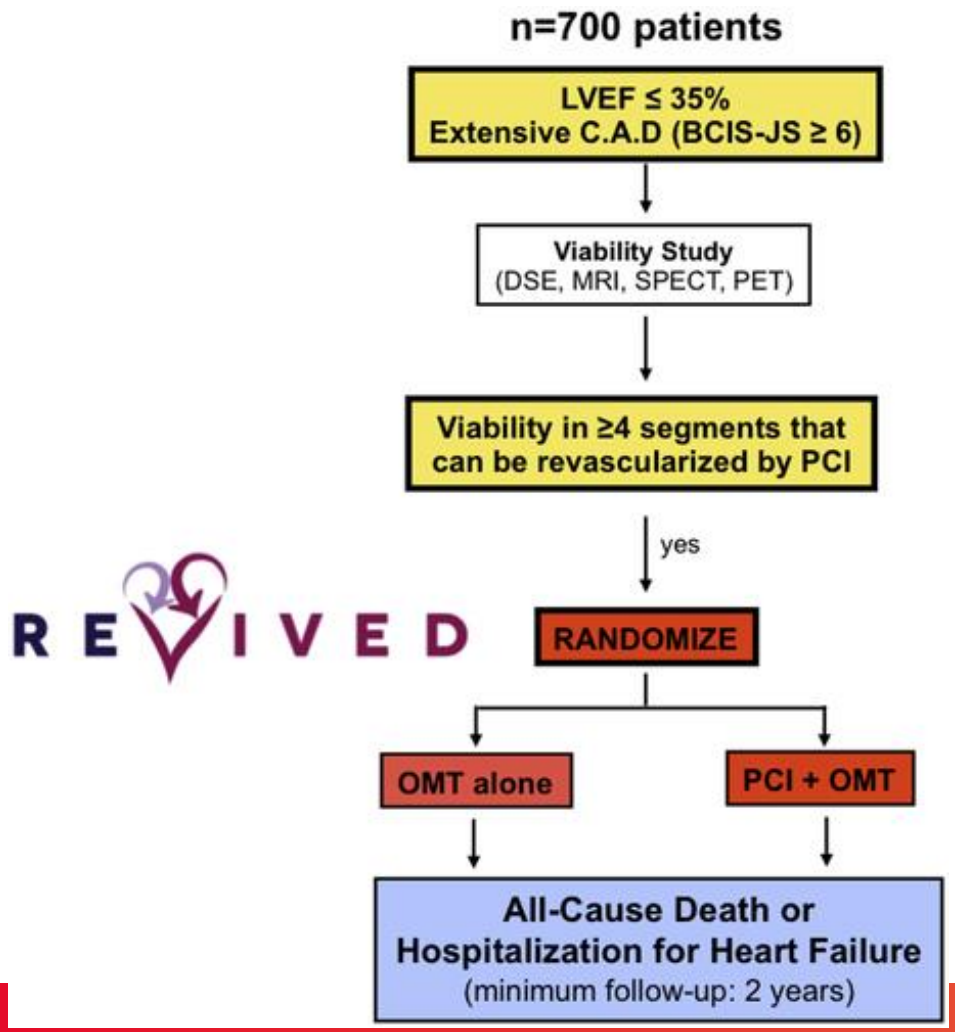
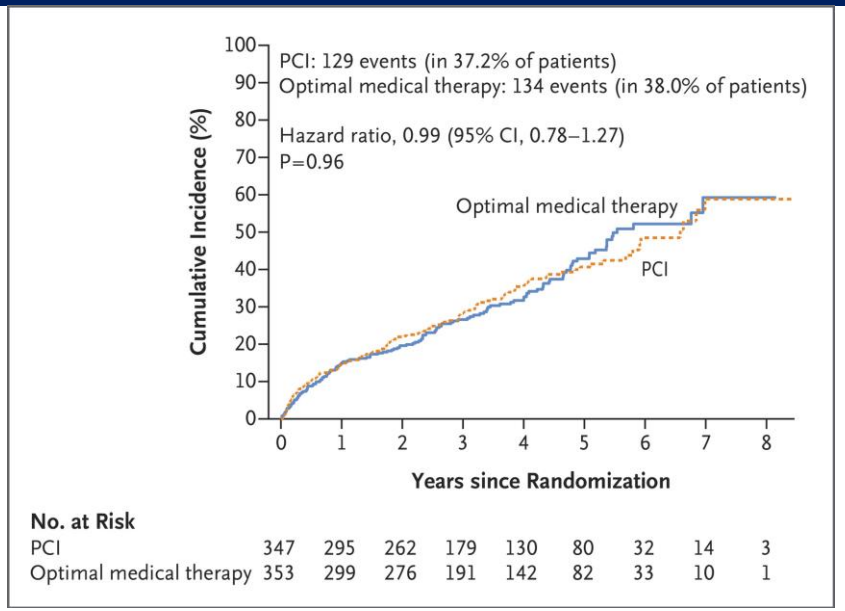
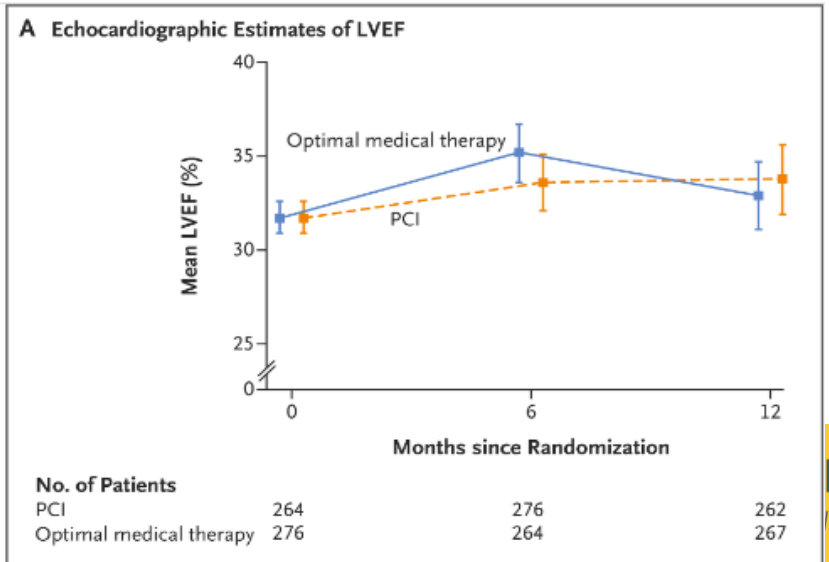
# Background – PCI and HFrEF

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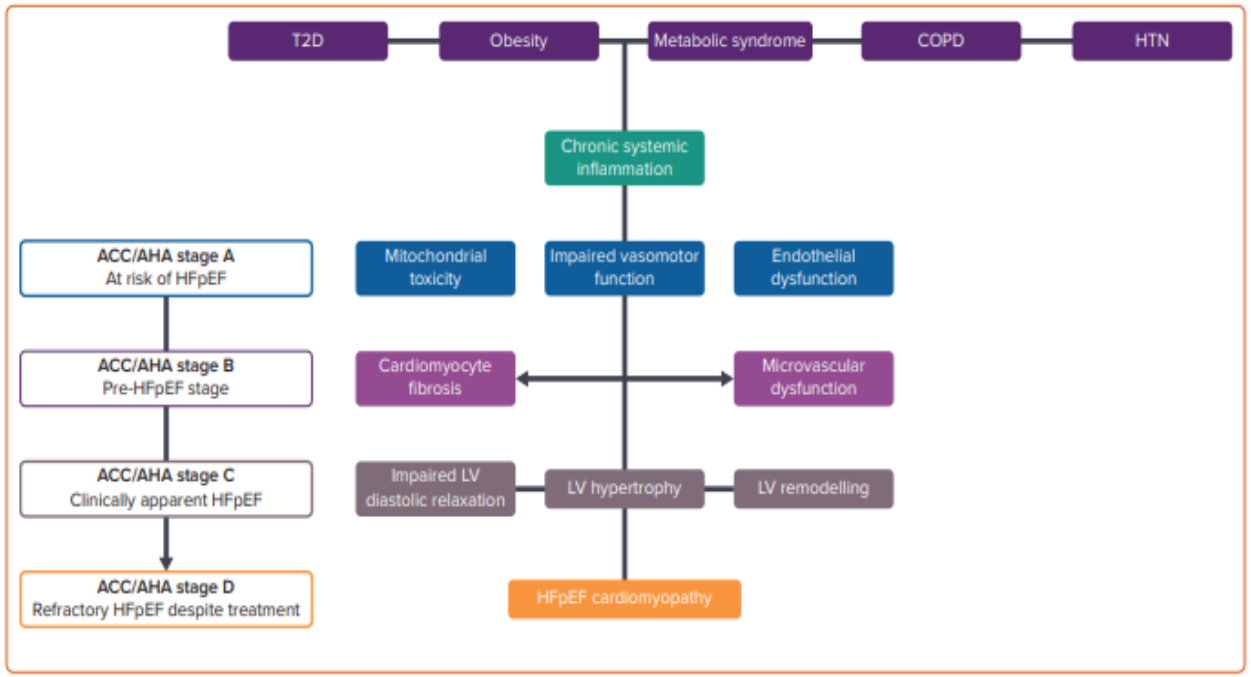
# Background - Microvascular dysfunction and HFpEF



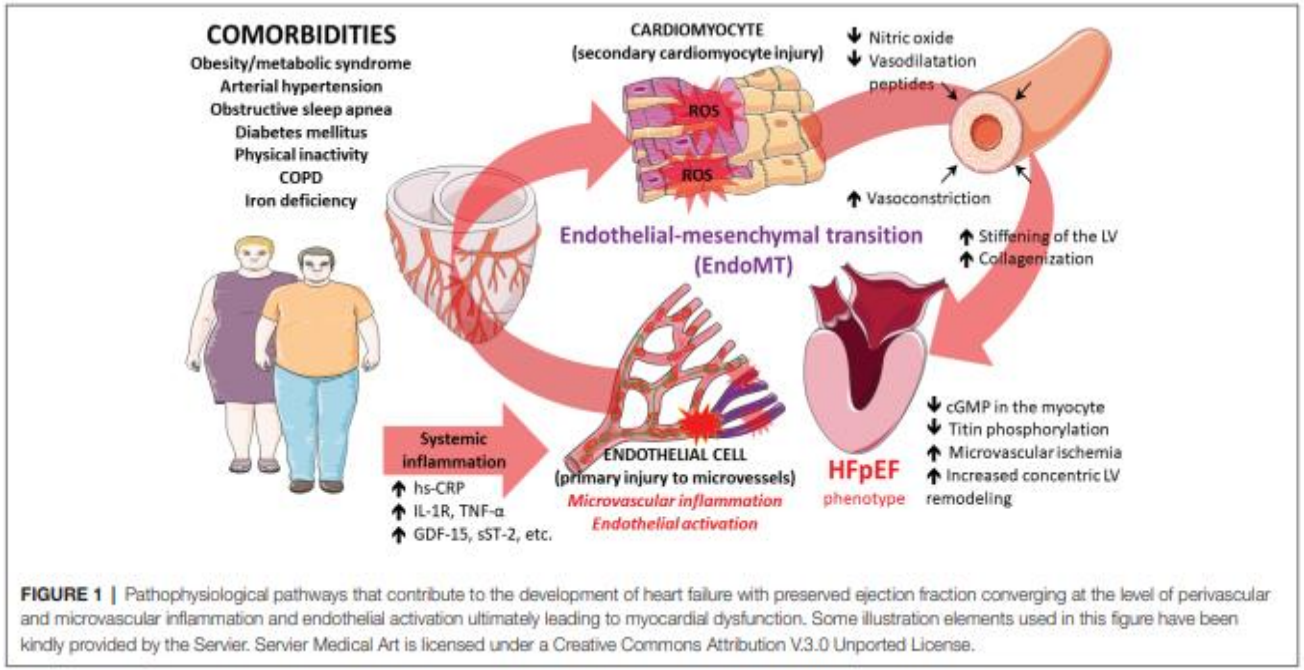




**FIGURE 1** | Pathophysiological pathways that contribute to the development of heart failure with preserved ejection fraction converging at the level of perivascular and microvascular inflammation and endothelial activation ultimately leading to myocardial dysfunction. Some illustration elements used in this figure have been kindly provided by the Servier. Servier Medical Art is licensed under a Creative Commons Attribution V.3.0 Unported License.

JRD Clarke et al. J. Clin. Med. 2020, 9(1), 86; https://doi.org/10.3390/jcm9010086

F Diez-Delhoyo. Trends Cardiovasc Med. 2020 Aug;30(6):346-352.

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# Background - Mycrovascular dysfunction in HFpEF and CMR evaluation

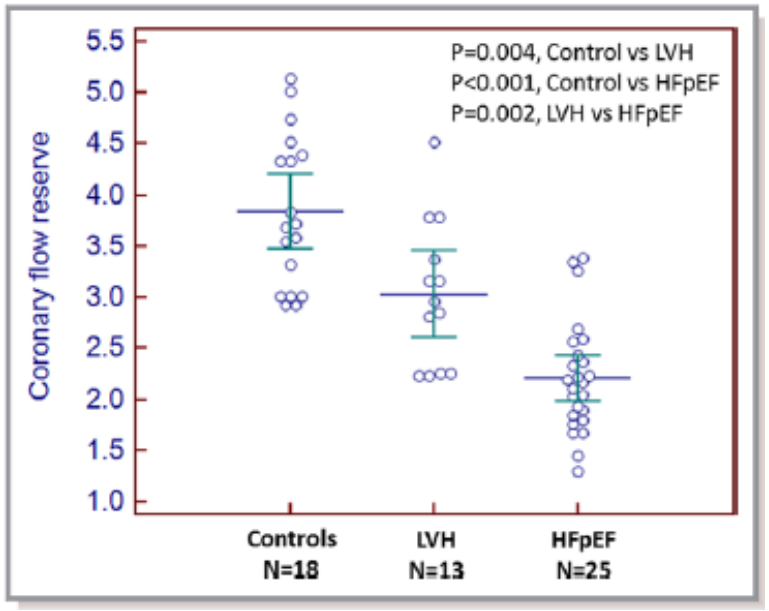



**Table 5.** Multivariable Linear Regression Analysis of the Relationship Between Serum Brain Natriuretic Peptide Level and Cardiac Functional Parameters

| | β | SE | 95% CI for β | *P* Value |
|---|---|---|---|---|
| Coronary flow reserve | −68.0 | 24.0 | −116.2 to −19.7 | 0.007 |
| LVEF | 0.98 | 2.61 | −2.9 to 9.4 | 0.30 |
| E/e′ | −0.59 | 4.08 | −8.7 to 7.5 | 0.88 |
| LA dimension | 3.22 | 3.09 | −4.2 to 6.2 | 0.70 |

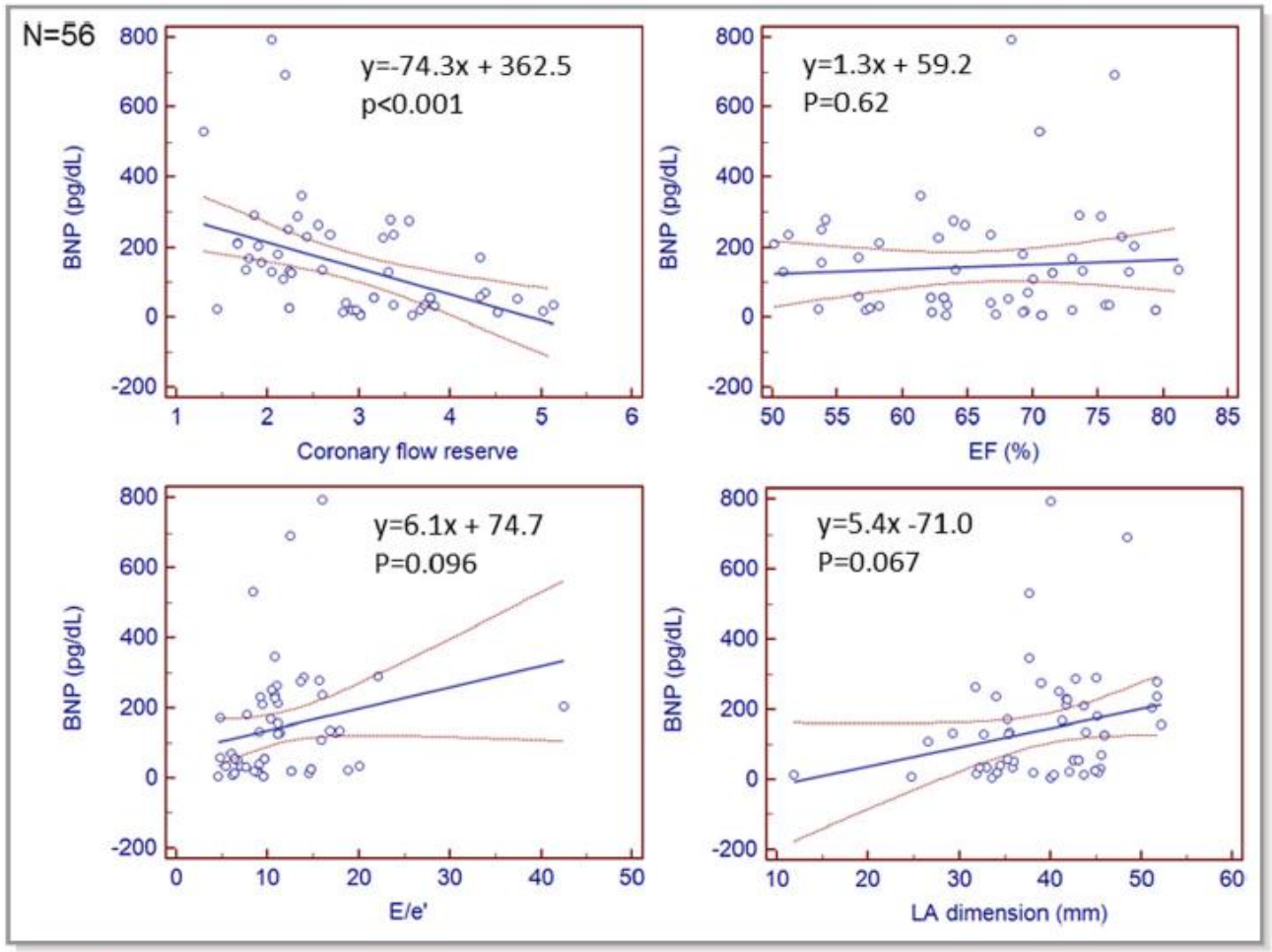



**Figure 5.** Relationship between serum BNP and cardiac functional parameters. Significant negative correlation is noted between serum BNP and coronary flow reserve. No significant relationship is noted between BNP and EF, BNP and E/e′, BNP, and LA dimension. BNP indicates brain natriuretic peptide; EF, ejection fraction; LA, left atrium.

S Kato et al J Am Heart Assoc. 2016;5:e002649

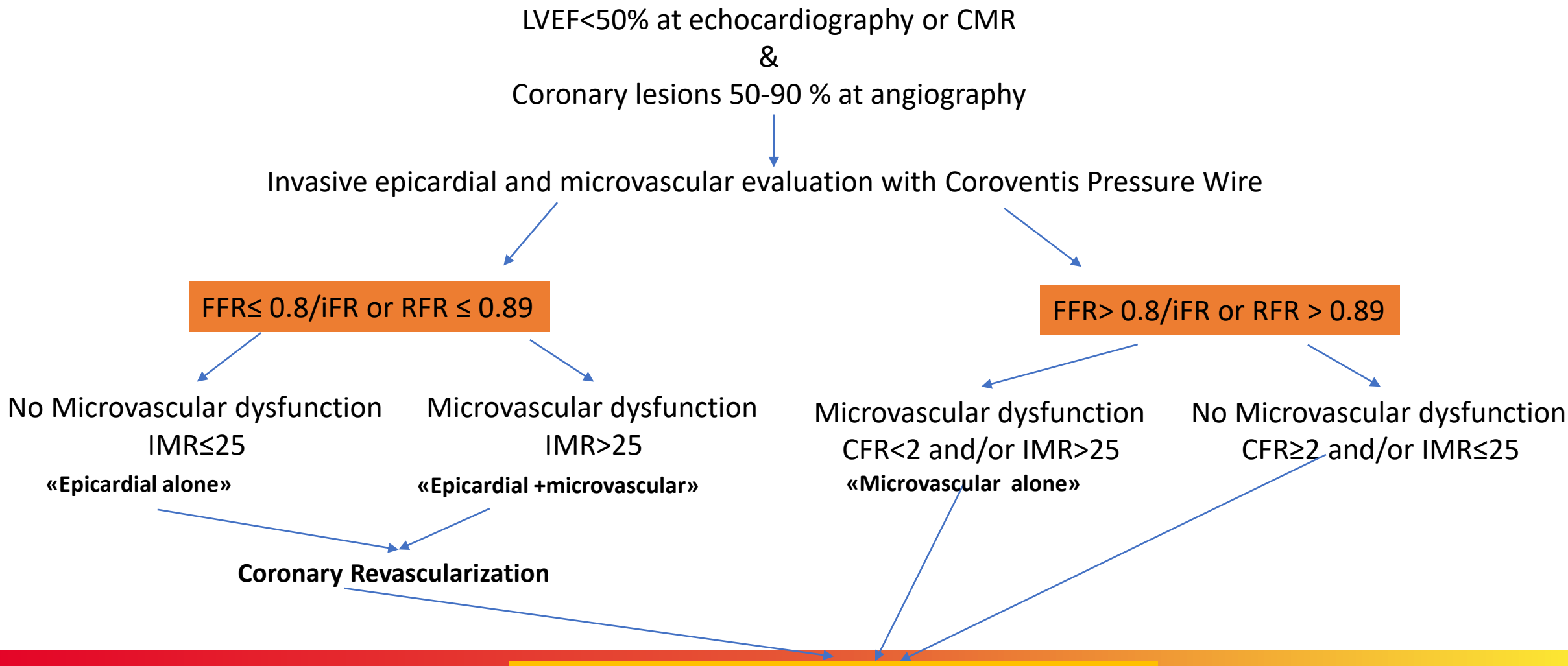
# Study overview

**REDUCE-CMD Registry**

A prospective, multicenter, registry

Aim: to evaluate microvascular and epicardial physiology in patients with reduced left ventricular ejection fraction (<50%) and intermediate coronary stenosis in proximal or mid segment

# Study design

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# Follow-up and outcomes

**Primary endpoint:** improvement of EF from baseline (%)

**Secondary study endpoints will be:**

- MACCE: all-cause mortality, myocardial infarction (MI), coronary revascularization, stroke, hospitalization due to heart failure
- Hospitalization due to heart failure
- All-cause and cardiovascular mortality
- Myocardial infarction (MI)
- Angina CCS class and NYHA class
- Left ventricular remodeling and strain analysis
- Diuretic dose at follow-up visit

# Inclusion criteria

**Inclusion criteria:**

- Males or females non-pregnant
- Written informed consent
- LVEF< 50% evaluated at baseline with echocardiography or C-MR
- At least one coronary stenosis between 50 and 90% at coronary angiogram

# Exclusion Criteria

**Exclusion criteria:**

- ACS within 4 weeks Acute decompensated heart failure requiring inotropes/ventilation/mechanical circulatory support (MCS) within 72 hours Sustained ventricular tachycardia/fibrillation (VT/VF) within 72 hours Left main disease >=50%
- Severe valve disease requiring valve surgery
- Any contraindications to PCI
- Age < 18 years
- Life expectancy < 1 year due to noncardiac pathology

# Sample size calculation

In a previous study LVEF recovery >5% was associated to improved prognosis and that occurred in 30% of patients with LVEF<50% prior to myocardial revascularization

Considering this event rate, a number of event per variable (EPV) of 10 and 6 possible predictive variables, to collect 60 events a population study of **200 patients** should be needed

Possible variable of interest are IMR, CFR, DM, age, eGFR, SYNTAX score

RS Velagalet et al Circulation Cardiovascular intervention. 2022;15:e011284.
P Peduzzi et al J Clin Epidemiol . 1996 Dec;49(12):1373-9.

# Sample size calculation

Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

## Change in Left Ventricular Ejection Fraction With Coronary Artery Revascularization and Subsequent Risk for Adverse Cardiovascular Outcomes

Raghava S. Velagaleti, MD, MPH; Joy Vetter, MA, MPH; Rachel Parker, MPH; Katherine E. Kurgansky, MPH; Yan V. Sun, PhD; Luc Djousse, MD, DSc; J. Michael Gaziano, MD; David Gagnon, MD, PhD*; Jacob Joseph, MD*

**BACKGROUND:** Coronary revascularization is recommended to treat ischemic cardiomyopathy. However, the relations of revascularization-associated ejection fraction (EF) change to subsequent outcomes have not been elucidated.

**METHODS:** In 10 071 veterans (mean age 67 years; 1% women; 15% non-White) who underwent a first percutaneous coronary intervention (PCI) or coronary artery bypass grafting between January 1, 1995, and December 31, 2010, and had prerevascularization and postrevascularization EF measured, we calculated delta-EF (postprocedure EF−preprocedure EF). We related delta-EF as a continuous measure and as categories (≤−5, −5<delta-EF<0, delta-EF=0, 0<delta-EF<5, and delta-EF≥5) to death (using Cox regression) and heart failure hospitalization days (using negative binomial regression) in multivariable-adjusted models, for total sample, and PCI and coronary artery bypass grafting strata.

**RESULTS:** Over follow-up (mean/maximum 5/14 years) 56% died. Each 5% improvement in delta-EF was associated with statistically significant reductions in death and heart failure hospitalization days of 5% (95% CI, 3%–7%) and 10% (95% CI, 5%–15%), respectively, in the total sample and 6% (95% CI, 4%–8%) and 10% (95% CI, 5%–16%), respectively, in the PCI subgroup. Patients in the highest delta-EF category had 27% (95% CI, 19%–34%) lower mortality (30% [95% CI, 21%–37%] lower in PCI stratum) and ≈40% lower heart failure hospitalization days in total sample and PCI stratum, compared with those in the lowest category. Relations of delta-EF and outcomes in coronary artery bypass grafting subgroup did not reach statistical significance.

**CONCLUSIONS:** Revascularization-associated EF improvement was associated with significant reductions in mortality and heart failure hospitalization burden, particularly in the PCI subgroup.

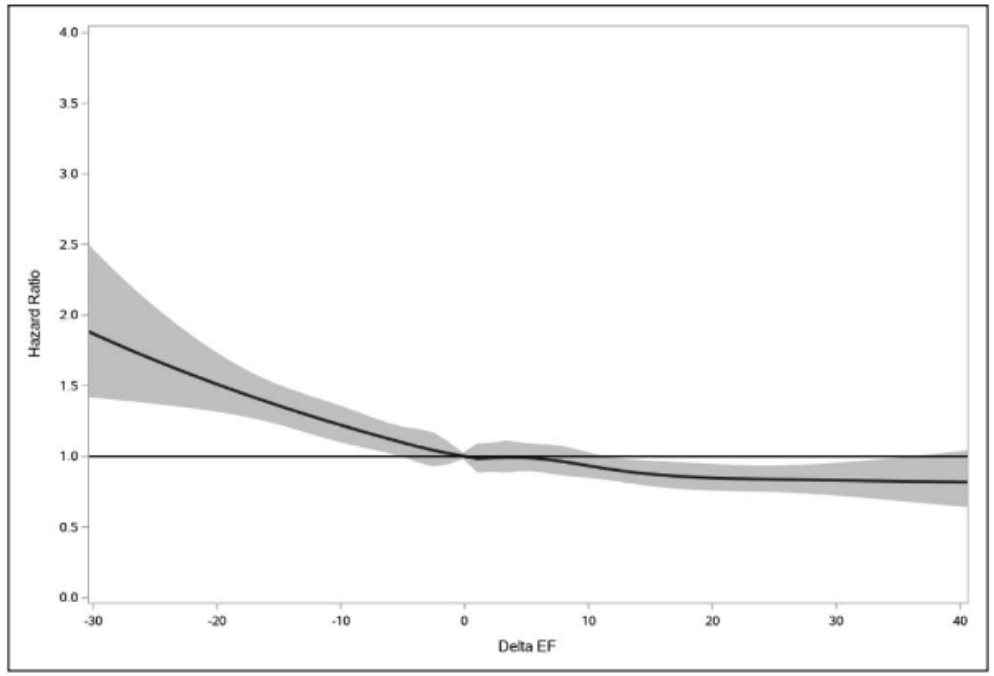


**Figure 2. Cubic spline relating delta-ejection fraction (EF) to mortality.**
The spline was created using a SAS macro, specifying 9 knots placed based on Harrell's approach, with 3 degrees of freedom, and a reference value of no change in EF.

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# Study roadmap