# Coronary Microvascular Dysfunction: Is it a pre HFpEF syndrome?

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|---|---|
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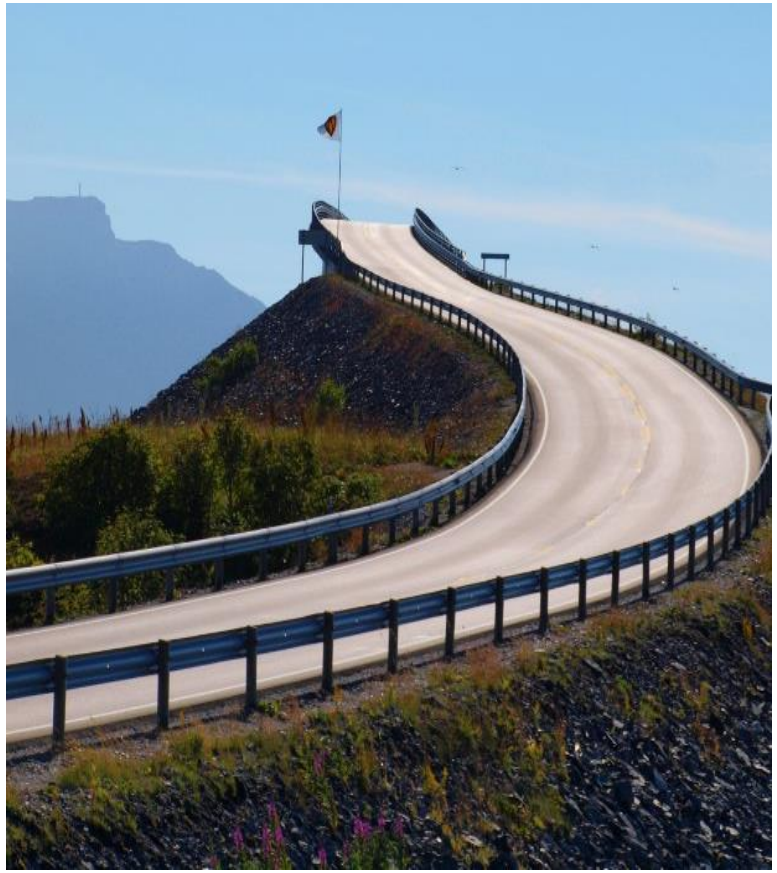
# Evidence linking ischemia due to CMD with HFpEF

Talking Points:

- General considerations
- Clinical phenotypes-CMD patients and HFpEF patients
- Clinical outcomes with CMD
- Mechanistic signals- paradigm shift:
  - Endothelium, microvasculature, cardiomyocyte function
  - Biomarkers of injury/dysfunction
- Hypothetical construct centering on inflammation and ischemia due to CMD as a “pre-HFpEF” condition

# Is ischemia due to coronary microvascular dysfunction “a bridge” to HFpEF?

# Or, is it a bridge to nowhere?



# Evidence linking ischemia due to CMD with HFpEF

## General considerations:

~3-4 M Americans with symptoms/signs of ischemia have ***no obstructive CAD*** (NHLBI-WISE, ACC-NCDR, PROMISE, VA-CART, etc.).

- Incur healthcare costs and disabilities similar to those with obstructive CAD, mostly due to ***hospitalizations for HF and angina*** (Shaw *Circulation* 2006, Gulati *Ann Int Med* 2009, Bakir *Int J Cardiol* 2017).
- Burdens confirmed by very large European and Canadian consecutive-case registries (Jesperson *EHJ* 2012, Sedlack *AHJ* 2014, Kissel *BMC Cardiovascular Disorders* 2018).
- Many have CMD with normal EF (Pepine *JACC* 2010, Murthy *Circulation* 2014, Pepine *JACC* 2015, Bairey Merz *Circulation* 2017, Taqueti *EHJ* 2018).

Hypothesis: ***Ischemia due to CMD represents a "pre-HFpEF" condition*** (*Pepine JACC:Cardiovascular Imaging 2014).*

# Microvascular Ischemia-HFpEF Hypothesis

*Pepine JACC:Cardiovascular Imaging 2014;7:362-5*

Risk conditions (hypertension, dyslipidemia, dysglycemia, psychosocial stress, estrogen loss, etc.) promote a pro-inflammatory, pro-oxidative state rendering the coronary microvasculature (including large artery vasa-vasorum) and myocardium vulnerable to dysregulation.

↓

Dysregulation of the coronary microcirculation, central nervous system and hypothalamic-pituitary-adrenal axis (endothelial dysfunction, vascular smooth muscle activation, sympathetic activation, epinephrine secretion, etc.) limit the ability to augment coronary flow, resulting in repeated and/or prolonged ischemia and stunning of the subendocardium and mid-wall (without symptoms).

↓

Ongoing ischemia-reperfusion facilitates ischemic preconditioning preserving cardiomyocyte contractile and coronary microvascular function against further ischemic injury but progressively impairing cardiomyocyte relaxation, leading to LV diastolic dysfunction with further coronary microvascular dysfunction.

↓

Clinically, this sequence contributes to LV diastolic dysfunction leading to heart failure with preserved ejection fraction (HFpEF) and eventually also impairs systolic function.

# Evidence linking ischemia due to CMD with HFpEF

## Multi-morbidity -- hallmark of CMD patients

*Multiple comorbid conditions:*

- Middle aged (40-65 yrs old)
- Women are the majority
- Hypertension (70-80%), other insulin resistant states (obesity, DM, etc.)
- Hypecholesteremia
- Chronic disorders [GI, neuropsych, lung, renal diseases (dysmotility, migraine, anxiety/depression, asthma, OSA, PAH, CKD, etc.)]
- Generally stable ***IHD symptoms*** with "exacerbations/flares" (ACS)
- Dyspnea, LV diastolic dysfunction (EDP, echo, cMRI)
- Coronary endothelial dysfunction (Ach) and VSM dysfunction (Ado)
- Central aortic stiffening

# Evidence linking ischemia due to CMD with HFpEF

## Multi-morbidity -- hallmark of HFpEF patients

Multiple comorbid conditions:

- Advanced age (>60 yrs old)
- Women are the majority
- Hypertension (80-90%)
- IHD in majority with HFpEF and HFmrEF (EF 40-49%)
- Chronic disorders (Obesity, CKD, DM, lung dis (OSA, PAH, etc.), anemia, AF, etc.
- Generally ***stable HF and/or IHD symptoms*** with "exacerbations" (HF, ACS)
- LV diastolic dysfunction (EDP, echo, cMRI)
- Coronary endothelial dysfunction (Ach) and VSM dysfunction (Adenosine)
- Central aortic stiffening

***Interestingly, "clinical phenotype" associated with HFpEF cardiac pathophysiology is remarkably similar to an older CMD patient!***

# HFpEF: is ischemia due to CMD the underlying mechanism?

*Paradigm shift in HFpEF pathophysiology*

- Suggested syndrome results from sequence of events initiated by ***comorbidity driven proinflammatory state linked with CMD*** promoting LVH, remodeling, fibrosis, stiffness. (Paulus and Tschöpe *JACC* 2013;62:263-71)
- Abnormal ex hemodynamics with reduced peak transcardiac $0_2$ gradient suggested ***impaired myocardial $O_2$ delivery*** as cause of abnormal diastolic flow reserve. (van Empel and Borlaug *J Am Heart Assoc* 2014;3:e001293)
- Hypothesis strengthened by postmortem demonstration that HFpEF pts have ***less coronary microvascular density*** vs pts with noncardiac death. (Mohammed and Redfield *Circulation* 2015;131:550-9)

# Evidence linking ischemia due to CMD with HFpEF

## Impaired CFR by Phase Contrast Cine-MRI in Patients with HFpEF

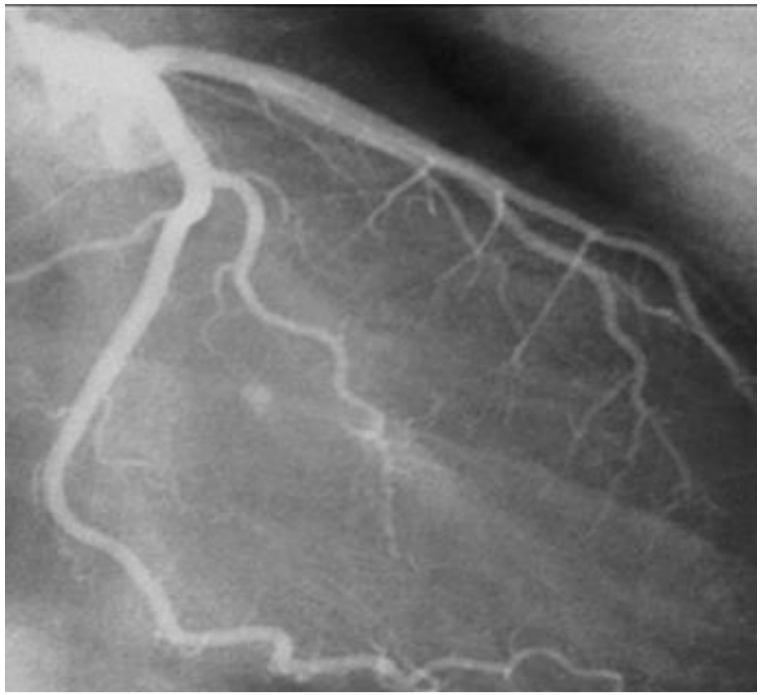
Kato, et al. *J Am Heart Assoc.* 2016 Feb; 5(2): e002649.

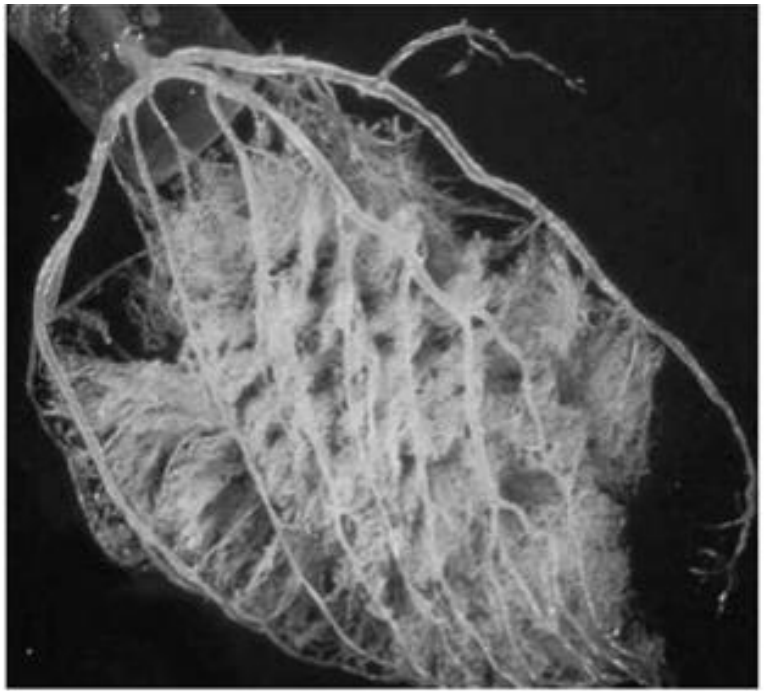
Coronary sinus (CS) phase contrast (PC) cine-MRI-CFR (index of LV microvascular function) 25 HFpEF pts (age 73±7 yrs), 13 pts HTN LVH (67±10 yrs), and 18 controls (65±15 yrs).
Breath-hold PC cine-MRI images of CS assessed blood flow at rest and during ATP infusion.
CFR =CS blood flow- during ATP infusion/at rest. Impaired CFR <2.5.

Majority (76%) of HFpEF pts had decreased CFR-vs HTN LVH pts and controls (CFR: **2.21**±0.55 in HFpEF vs **3.05**±0.74 in HTN LVH, **3.83**±0.73 in controls; *P*<0.001).
CFR independently correlated with serum BNP (*P*=0.007) and significantly lower in HFpEF pts vs HTN LVH pts and controls.

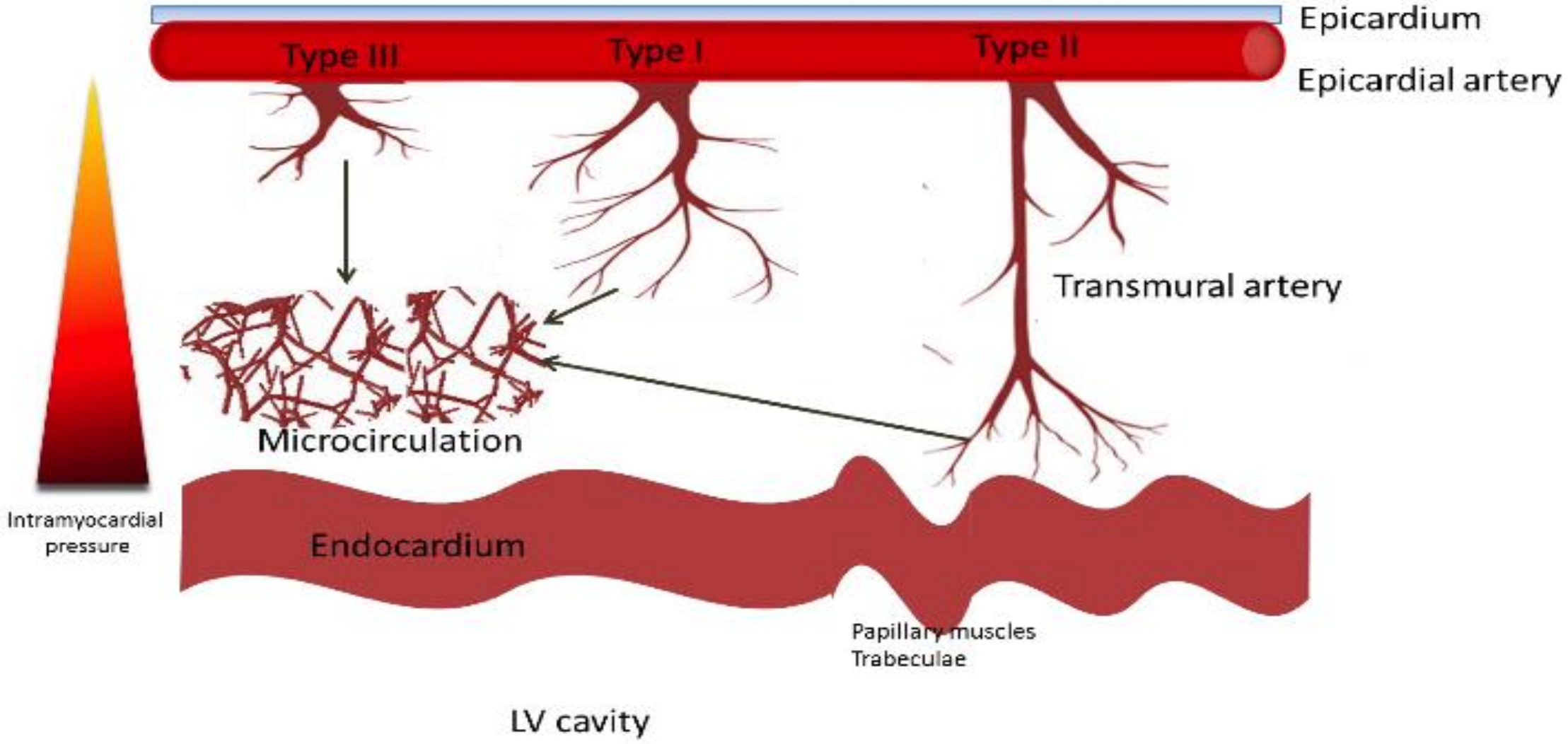
Concluded- ***impaired CFR*** a ***pathophysiological factor for HFpEF,*** related to ***disease severity***.

# Coronary macro and microvascular systems





***Coronary microvasculature*** constitutes ***>90% of the coronary vascular bed*** and regulates ***volume of blood flow*** (e.g. $O_2$ and nutrients with removal of waste products) and ***blood flow distribution***.




*Camici PG, Rimoldi O, Crea F: Coronary Microvascular Dysfunction. In Chronic Coronary Artery Disease a companion to Braunwald's Heart Disease; De Lemos JA and Omland T Editors; Elsevier Philadelphia 2018*

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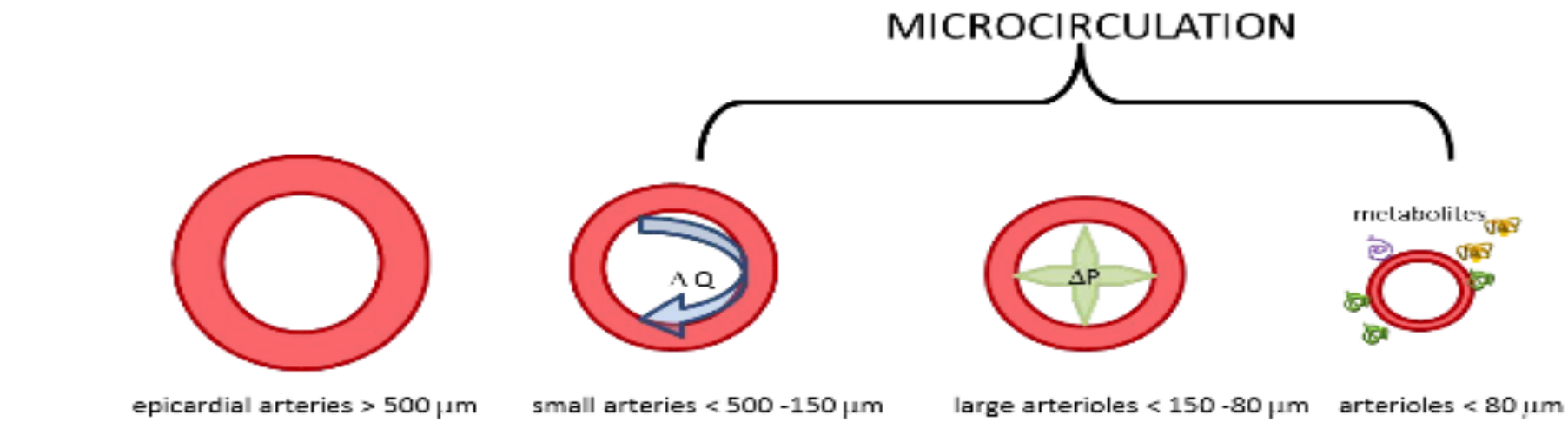
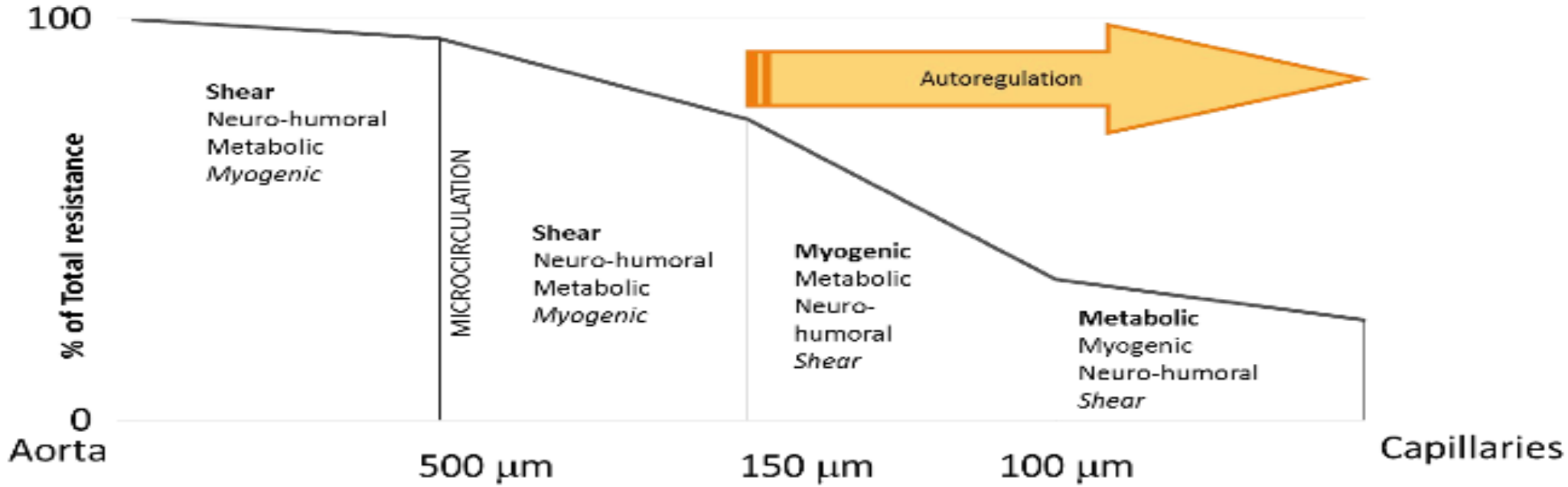

MICROCIRCULATION
ΔQ
ΔP
metabolites
epicardial arteries > 500 μm
small arteries < 500 -150 μm
large arterioles < 150 -80 μm
arterioles < 80 μm


100
0
% of Total resistance
Shear
Neuro-humoral
Metabolic
Myogenic
MICROCIRCULATION
Shear
Neuro-humoral
Metabolic
Myogenic
Autoregulation
Myogenic
Metabolic
Neuro-humoral
Shear
Metabolic
Myogenic
Neuro-humoral
Shear
Aorta
500 μm
150 μm
100 μm
Capillaries

# Taxonomy: Coronary Anatomy/Physiology and Ischemia Mechanisms

## *Coronary Macrocirculation*

Obstructive
- -Atherosclerosis (CAD)
- -Spasm
- -Dissection
- -Thromboembolism
- -Muscle bridging
- -Etc.

Non obstructive CAD
- -Same as above

## *Coronary Microcirculation*

### Structural Mechanisms
-Capillary rarefaction
-Arteriolar wall thickening
-Perivascular fibrosis
-Conduit vessel stiffening
-Intravascular micro-plugging
-Etc.

### Myocardial Mechanisms
-Hypertrophy (LVH)
-Infiltration
-Calcium overload
-Extramural compression
-Increased diastolic pressure
-Etc.

### Functional Mechanisms
-EC and/or VSMC dysfunction
- Atherosclerosis risk factors
- Inflammation
- Drugs
- Spasm
- Etc.

### Systemic Mechanisms
-Reduced Diastolic Pressure Time
-Anemia
-Hypoxemia
-Glycemia
-Carbon Monoxide
-Etc.

Pepine CJ, Douglas PS. Rethinking stable ischemic heart disease: is this the beginning of a new era?
*J Am Coll Cardiol.* 2012;60(11):951-6.

# HFpEF: is ischemia due to CMD the underlying mechanism?

## Recent support for CMD-impaired myocardial flow in HFpEF

Srivaratharajah *Circ Heart Fail*. 2016;9:e002562

- HFpEF- no obstructive CAD (n=78) or no HF controls (n=298), stratified for HTN (n=186). HFpEF pts more likely older, women w HTN, DM, HLD, AF, anemia and/or CKD.
- Global and regional stress/rest $MFR_{PET}$ : HFpEF pts -reduced global MFR (2.16±0.69) vs HTN controls (2.54±0.80, $p<0.02$) and normotensive controls (2.89±0.70, $p<0.001$).
- HFpEF pts had 2.62 fold greater odds of lower global MFR (RF adjusted).

***HFpEF, without obstructive CAD, is associated with reduced MFR independent of other risk factors.***

# HFpEF: is ischemia due to CMD the underlying mechanism?

## Considerable Evidence Linked Endothelium with LV Relaxation

- NO produced by endothelial cells lowers LV SP and increases LV diastolic distensibility.
- LV relaxation is modulated by interaction of coronary endothelium derived NO and prostaglandins.
- Endothelial dysfunction decreases LV diastolic distensibility.

*Circulation* 1994;89:2070-8. *Am J Physiol* 1994;267:H1804-13.

*Circulation* 1995;92:2119-26. *Cardiovasc Res* 1995;29:637-40.

*J Am Coll Cardiol* 1997;29:1332-8.

# HFpEF: is ischemia due to CMD the underlying mechanism?

*Biomarkers useful to inform mechanisms and determine prognosis*

- **NTproBNP**: HF diagnosis/management and prediction of IHD/CAD and stroke (*Lancet Diabetes Endocrinol* 2016;4:840-9).
- **IMA**: ischemia diagnosis/management but not cardiac specific.
- **hsTnI:** cardiomyocyte injury in IHD and other disorders (*Circulation* 2017;135:1911-21).
- **sST2 and galectin-3**: CV stress/tissue fibrosis and prognosis/disease progression (*Circulation* 2017;135:1911-21).

# HFpEF: is ischemia due to CMD the underlying mechanism?

***Hypoxic ventricular myocardial biopsies (***CABG pts without LV dysfunction), BNP expression, plasma BNP, and proBNP concentrations-all ***markedly increased***. (*FASEB J*. 2003;17:1105-7)

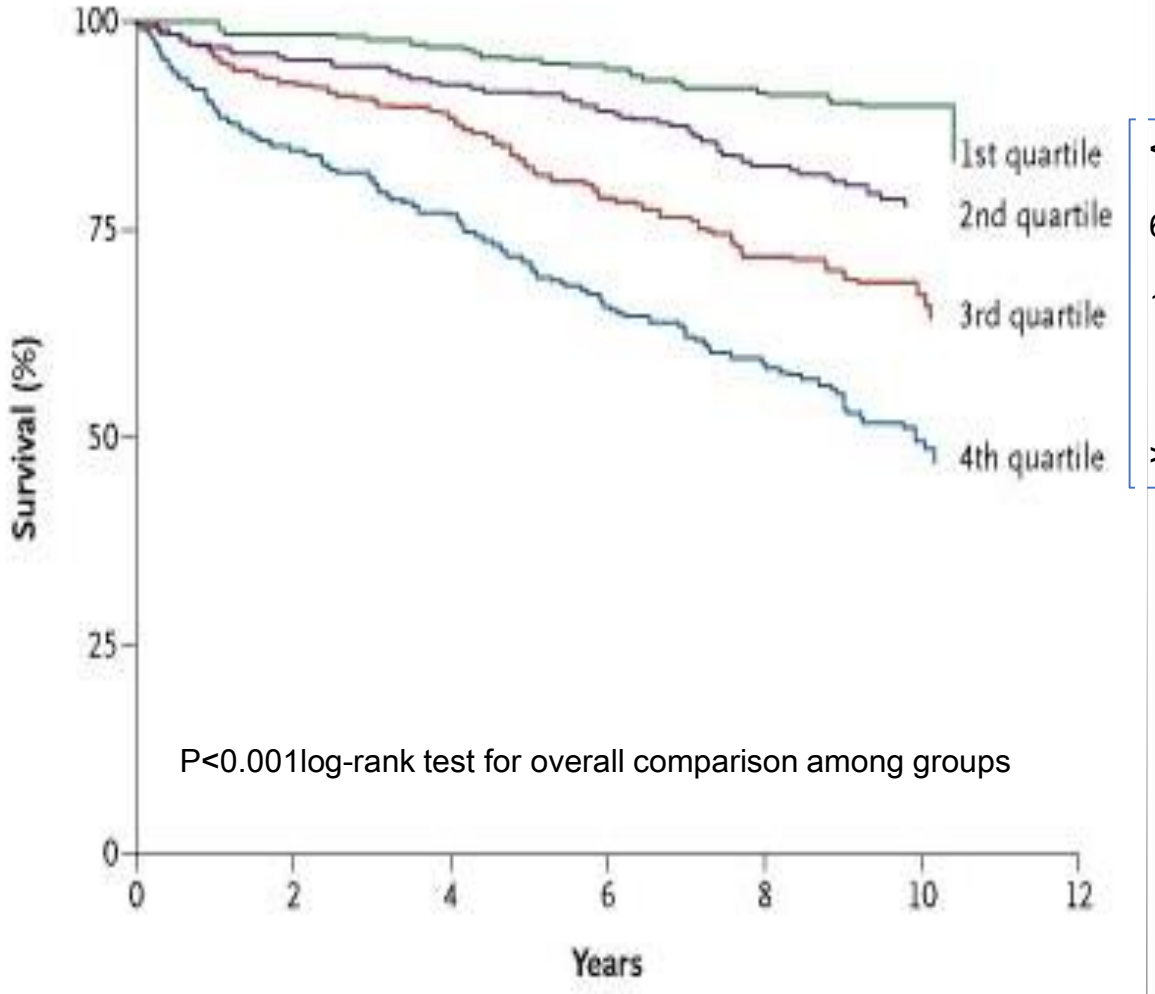
Surgical ***blood flow reduction*** in LV wall of pigs (myocardial ***$pO_2$ 46 to 13mmHg***) increased BNP mRNA expression. ProBNP peptide accumulated in medium of ventricular myocyte cultures indicating rapid release of newly synthesized proBNP peptide after myocardial hypoxia. (*FASEBJ.* 2004;18:1928-30)

***Hypoxia*** induces BNP release from human cardiomyocyte cell lines. HIF-1 inhibitor rotenone ***inhibited BNP***. (*Am J Physiol Heart Circ Physiol 2009;*297:H550-5).

***Myocardial ischemia***, ***even without LV dysfunction***, augments cardiac BNP gene expression, ***increases plasma BNP and proBNP concentrations***. Thus, elevated BNP and proBNP concentrations do not only reflect HF but also result from ***cardiac ischemia.***

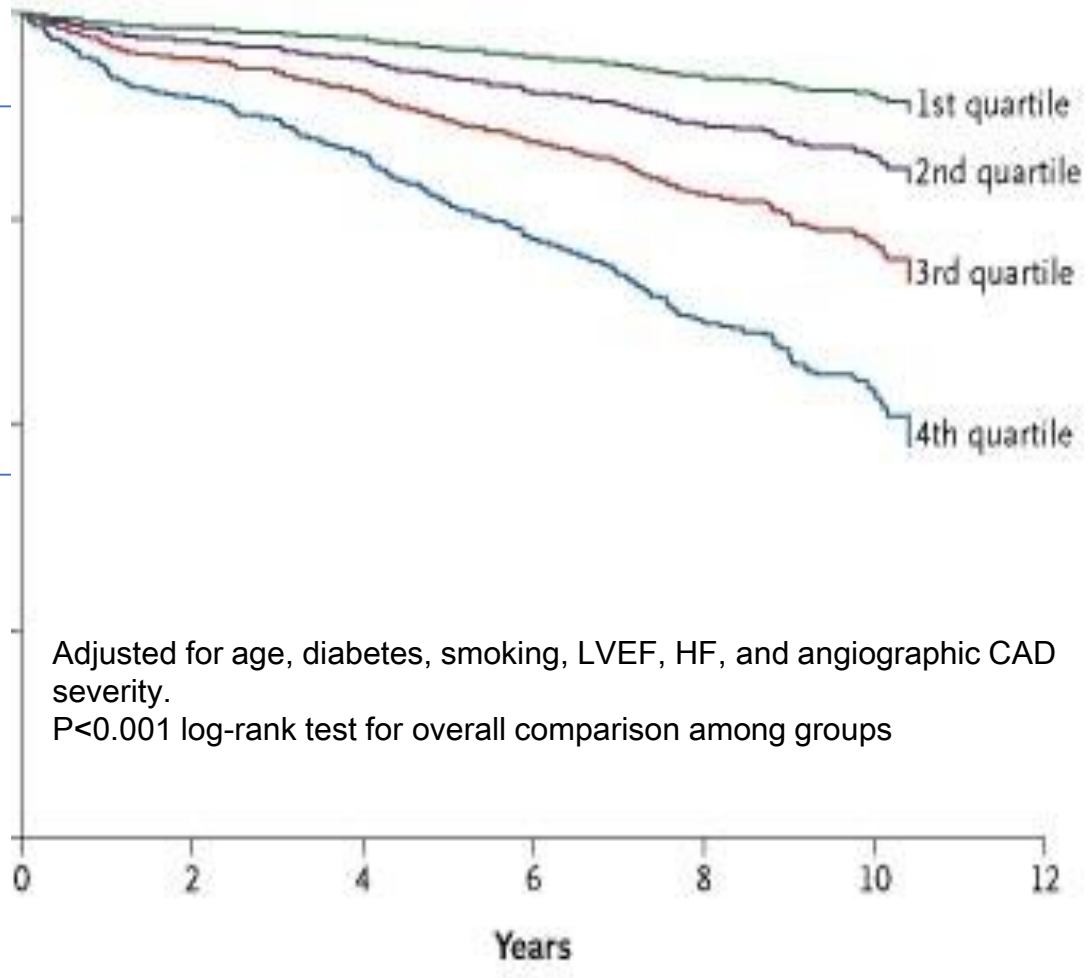
# Survival among Patients with Stable CAD by NT-pro-BNP Quartile

Kragelund C et al. *N Engl J Med* 2005;352:666-75




P<0.001log-rank test for overall comparison among groups

| | |
|---|---|
| 1st quartile | <64 pg/mL |
| 2nd quartile | 64-169 pg/mL |
| 3rd quartile | 170-455 pg/mL |
| 4th quartile | >455 pg/mL |




Adjusted for age, diabetes, smoking, LVEF, HF, and angiographic CAD severity.
P<0.001 log-rank test for overall comparison among groups

# CMD and future risk of HFpEF

Taqueti et al *European Heart Journal* 2018;39:840-9

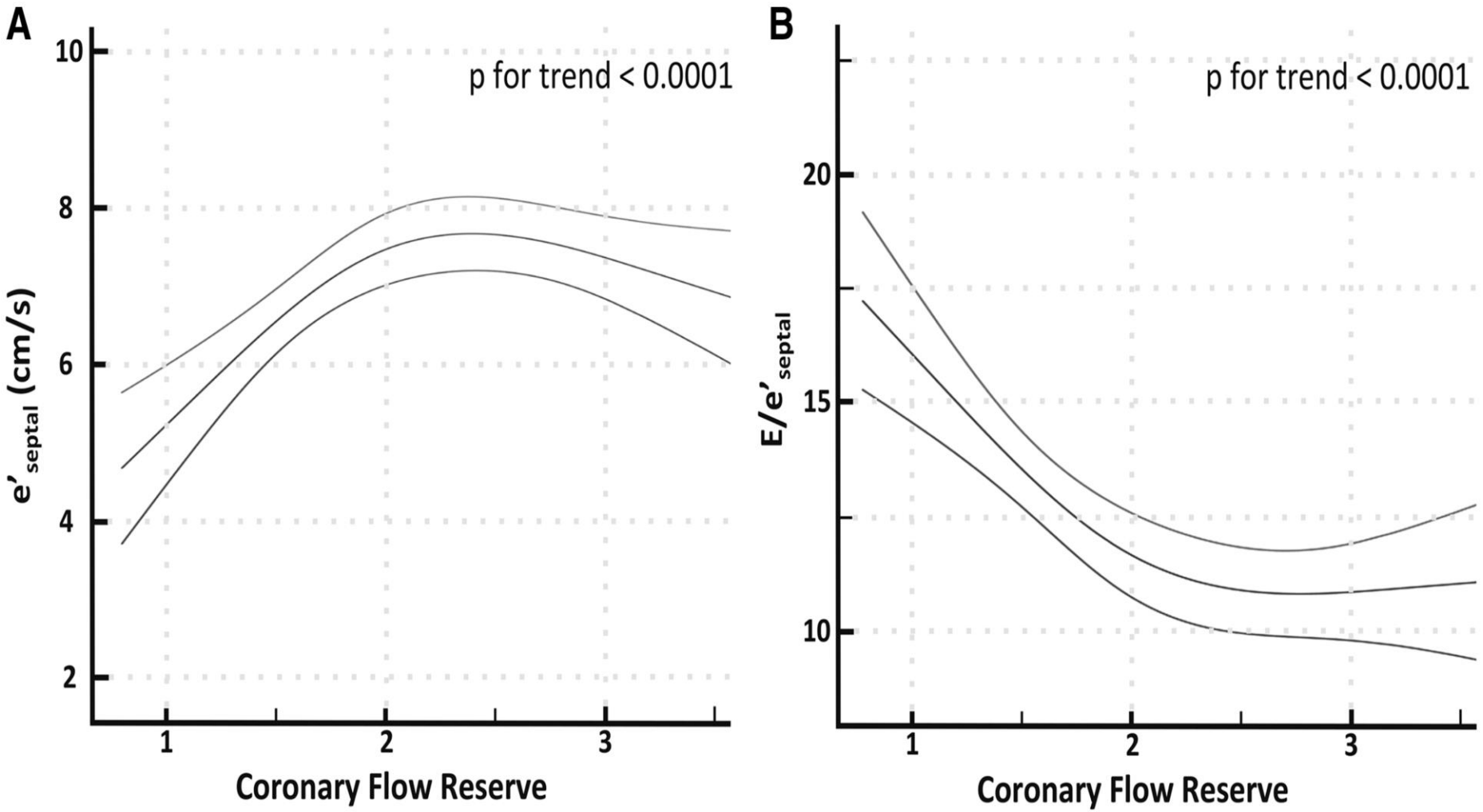
Consecutive pts (n=201) without flow-limiting CAD or reduced EF had stress myocardial perfusion PET, cTn, and TTE followed (median 4.1 yrs) for CV death and hosp for non-fatal MI or HF. CFR quantified as stress/rest MBF. Early diastolic flow (E) and relaxation (e0) velocities via transmitral and tissue Doppler, respectively.

Pts with impaired CFR (<2.0, n=108) had linearly decreasing e0 and increasing E/e0 consistent with worsening diastolic function (P for trend <0.0001). Detectable cTn associated with diastolic dysfunction only in presence of impaired CFR (interaction P = 0.002). Impaired CFR independently associated with diastolic dysfunction (E/e0septal > 15, adjOR 2.58, 95%CI 1.22-5.48) and CV adverse outcome or HFpEF hosp alone (adjHR 2.47,CI 1.09-5.62). ***Pts with both impaired CFR and diastolic dysfunction had >5-fold increased risk of HFpEF hosp (P <0.001).***

Symptomatic pts without overt CAD or HF, impaired CFR independently associated with diastolic dysfunction and adverse events, especially HFpEF hosp. ***Presence of both coronary microvascular and diastolic dysfunctions is associated with a markedly increased risk for HFpEF events***

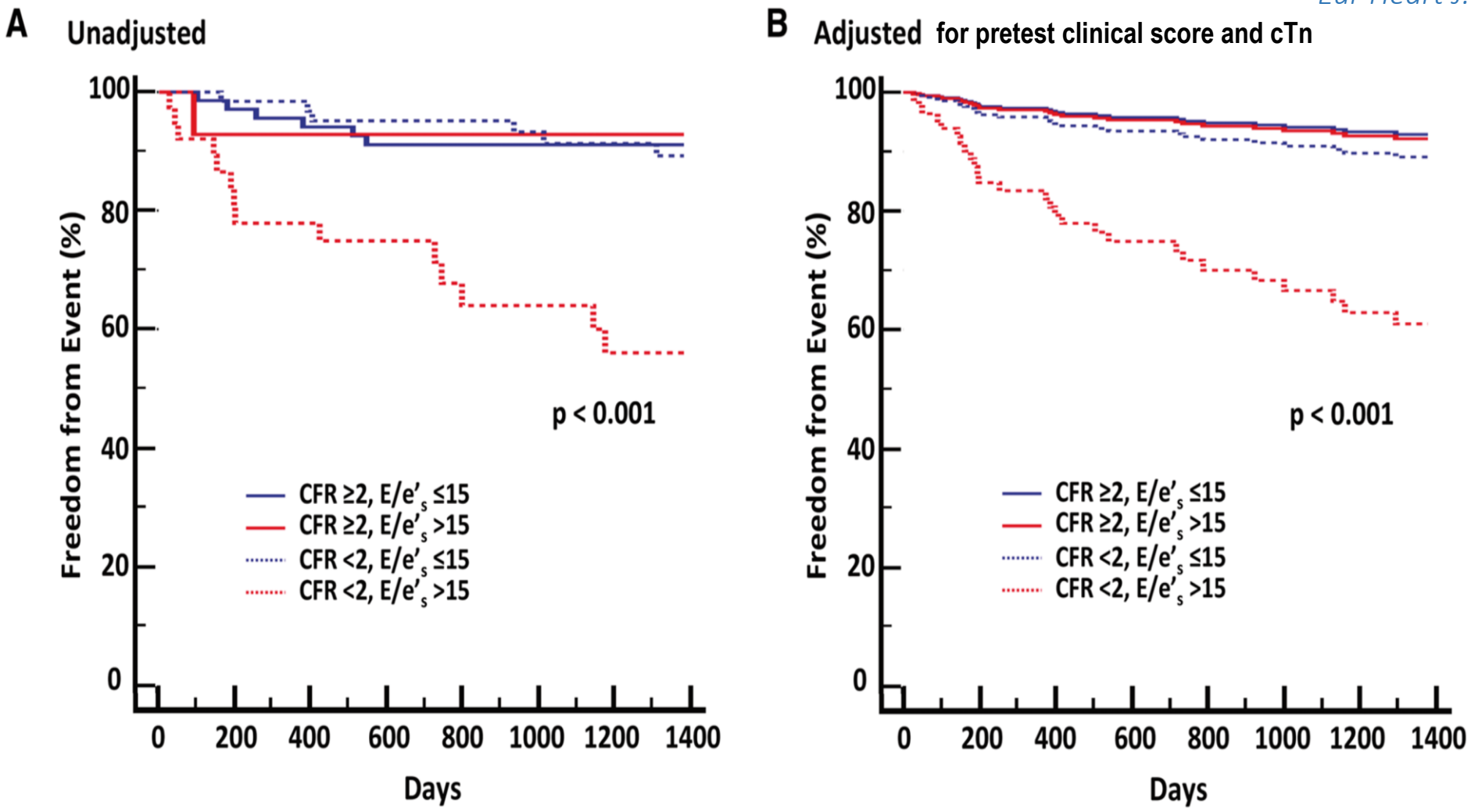
# Relationship between CFR and markers of diastolic dysfunction

*Eur Heart J.* 2018;39:840-9



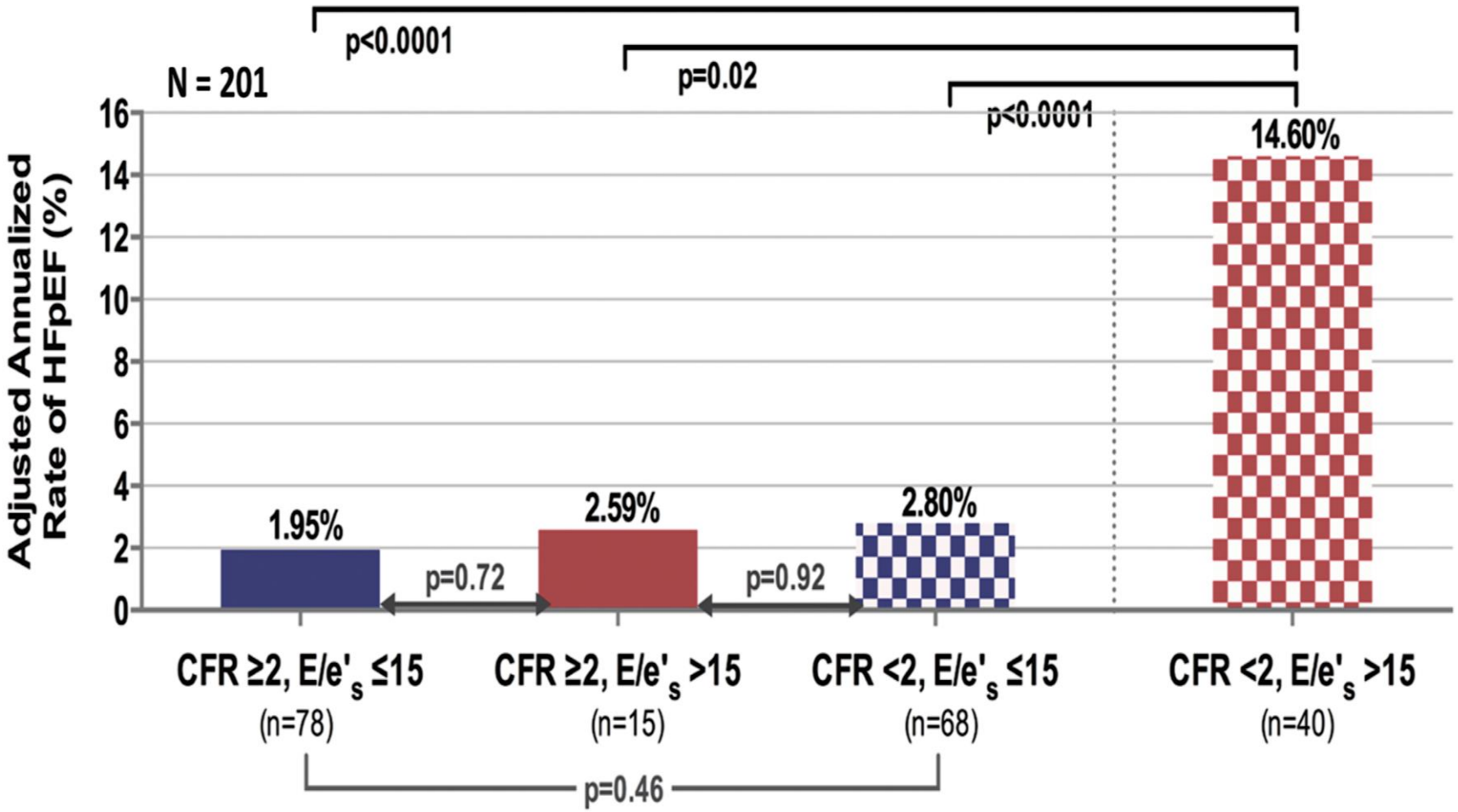
# Coronary microvascular dysfunction and HFpEF risk by CFR and diastolic dysfunction

*Eur Heart J.* 2018;39(10):840-9



# Coronary microvascular dysfunction and HFpEF risk

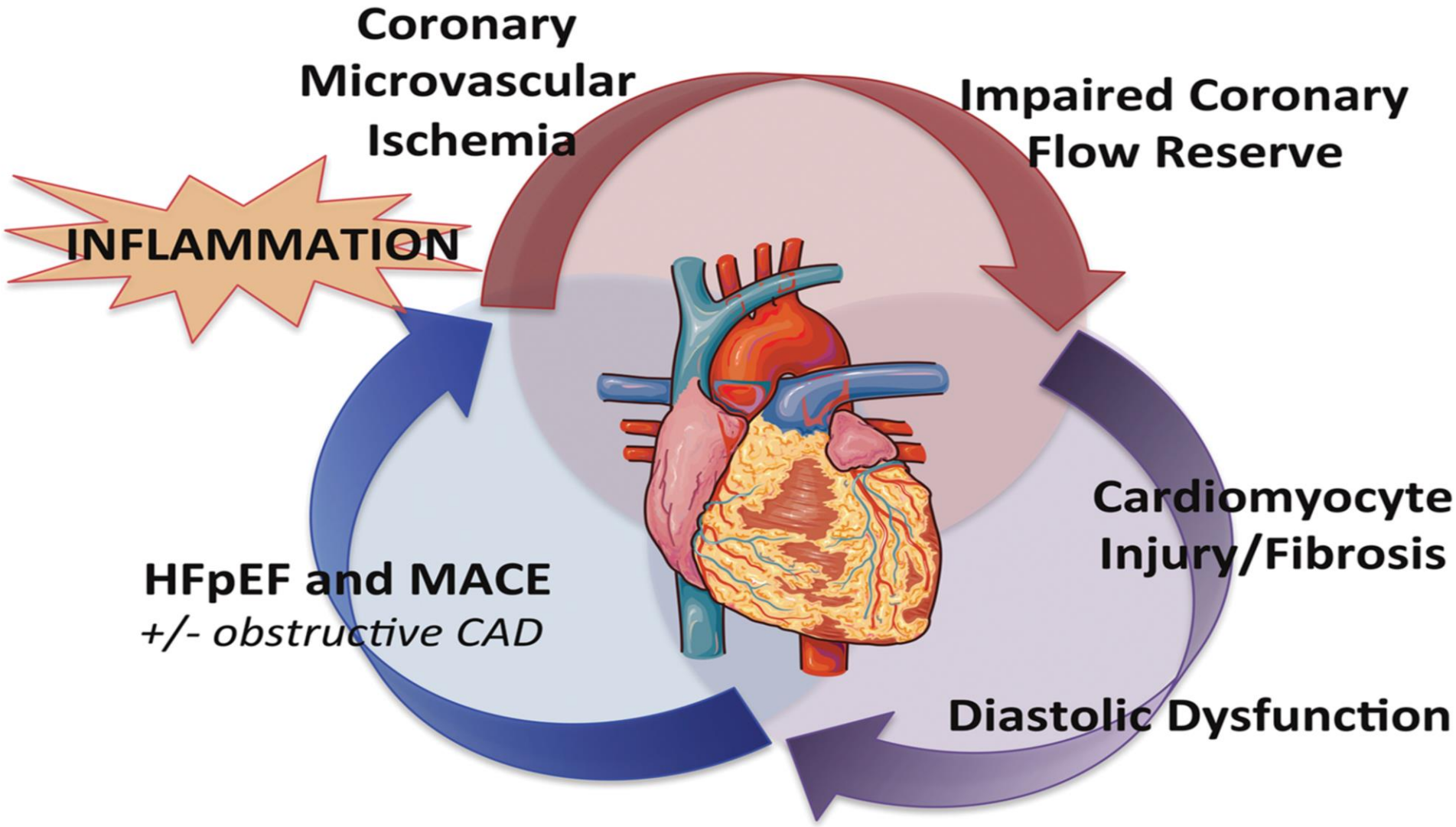
*Eur Heart J.* 2018;39:840-9




**Adjusted for pretest clinical score and cTn**

# Coronary microvascular dysfunction and HFpEF risk

*Eur Heart J.* 2018;39:840-9



# Prevalence and correlates of coronary microvascular dysfunction in HFpEF: PROMIS-HFpEF

Shah et al. *European Heart Journal*, 2018; 39, 3439-50.

Prospective multinational study of HFpEF pts fulfilling strict guideline criteria (unrevascularized CAD excluded). CFR by ado stress TTE Doppler and systemic endothelial function [reactive hyperemia index (RHI)] by peripheral arterial tonometry.

Among 202 HFpEF patients, 151 [75%] had CMD (CFR <2.5); they had higher prevalence of smoking (70% vs. 43%; $P = 0.0006$) and AF(58% vs. 25%; $P = 0.004$) vs no CMD. Worse CFR was associated with higher urinary albumin-to-creatinine ratio (UACR) and NTproBNP, with lower RHI, tricuspid annular plane systolic excursion, and RV free wall strain (age, sex, BMI, AF, DM, revasc CAD, smoking, LV mass, site- adjusted $P < 0.05$ for all).

First prospective, multi-center, multinational study to document: 1) high prevalence of CMD and 2) an association with systemic endothelial dysfunction (RHI, UACR) as well as markers of HF severity (NTproBNP and RV dysfunction). Microvascular dysfunction may be a promising therapeutic target in HFpEF.

# Stratified Medical Therapy Using Invasive Coronary Function Testing In Angina: CorMicA Trial Ford, et al DOI: 10.1016/j.jacc.2018.09.006

Pts with angina but no obstructive CAD (n=151) randomized to either ***intervention diagnostic procedure (IDP)*** stratified therapy based on results or ***sham procedure*** results not disclosed and standard care ***(SC). IDP included measurements of CFR, IMR and FFR with IV ado and IC Ach.*** Treatment according to ***ESC guidelines***: ***CMD- BB with nitrate contraindicated***; ***vasospastic angina- CA antagonist w/wo nitrate.***

***Results-*** mean age 61, ~ 3/4 women, 19% 10 yr CV event risk, angina questionnaire score reflected severe symptoms). ***At 6 mos***, IDP pts had ***less angina*** vs SC ($P = 0.001$), and angina occurred less often and was less severe. Majority of clinicians changed SC pts treatment vs none changed in IDP pts. Higher % of clinicians were certain of IDP vs SC pts diagnosis of microvascular angina or vasospastic angina (83% vs 18%; $P < 0.001$), were ~3X more likely to change angina therapy ($P < 0.001$). No serious AEs occurred.

”First trial” to investigate CMD testing, showed pts angina improved when g***iven an explanation for their symptoms followed by therapy tailored*** for a specific coronary disorder.

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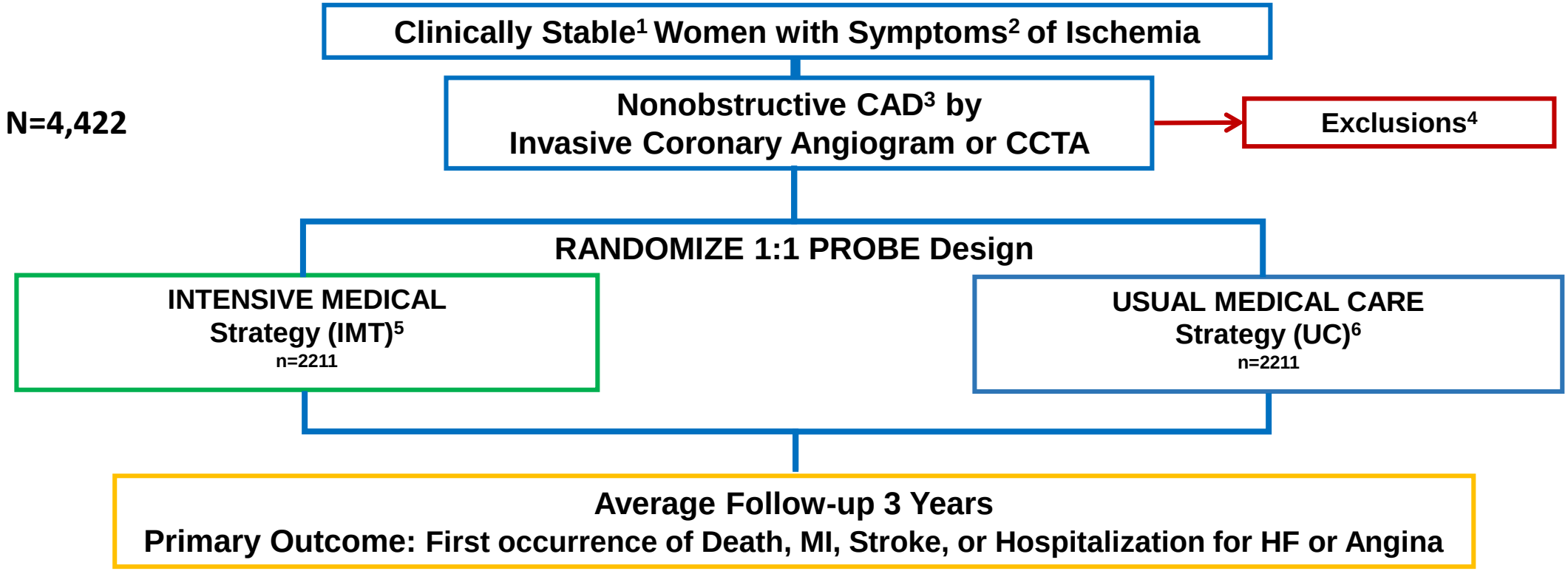
# The WARRIOR Trial

- The first randomized controlled trial (**W**omen's Ischemi**A** T**R**ial to **R**educe Events **I**n Non-**O**bst**R**uctive CAD [***WARRIOR***, *Clinicaltrials.gov* NCT03417388],
- Testing **Intense Medical Treatment (IMT)** to reduce adverse outcomes vs **Usual Care (UC),**
- Among 4422 women with angina and non-obstructive CAD highly suspect for CMD,
- Now enrolling.

# WOMEN'S ISCHEMIA TREATMENT REDUCES EVENTS IN NON-OBSTRUCIVE CAD

## WARRIOR (NCT #03417388)

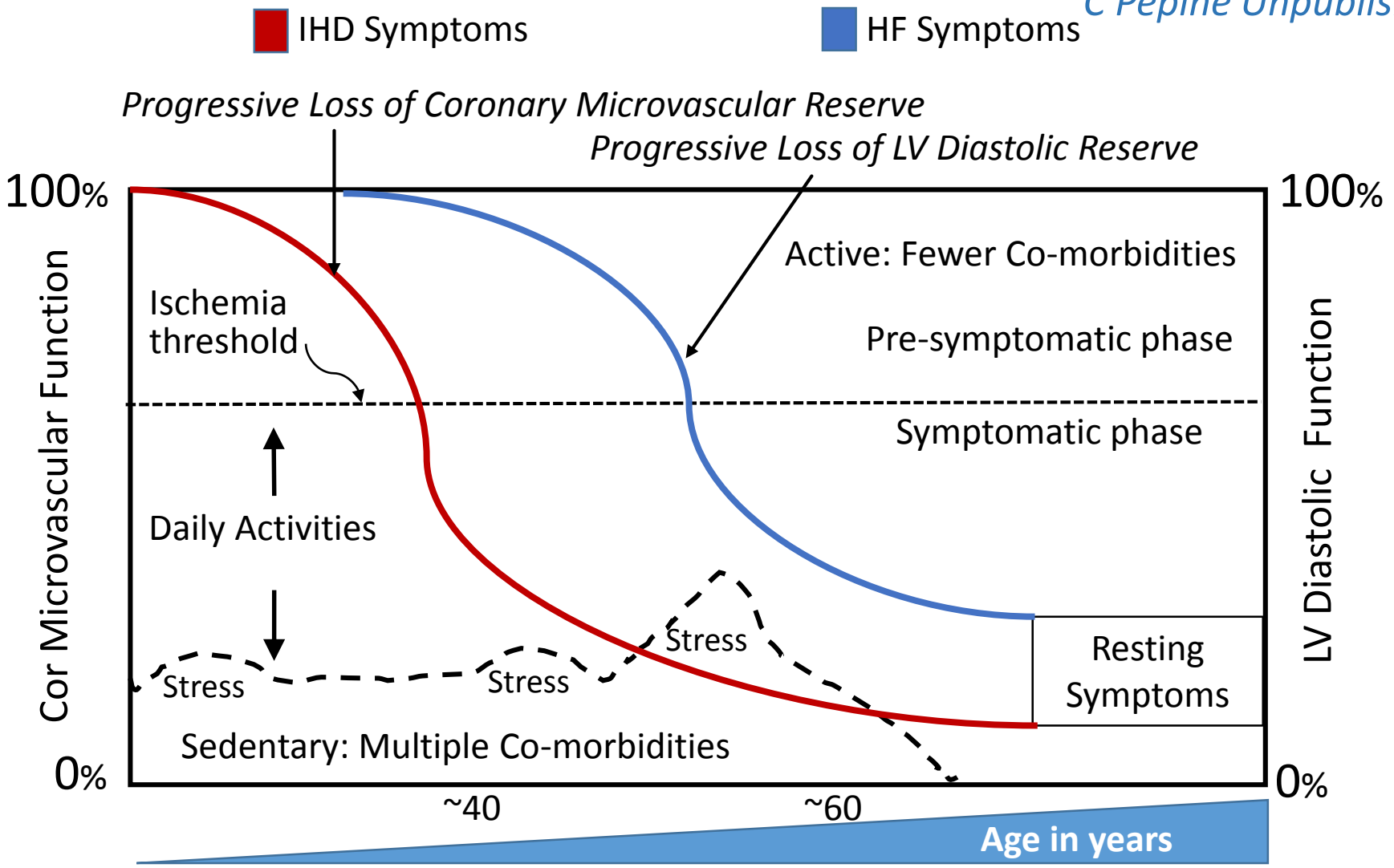
**Women's IschemiA TReatment Reduces Events In Non-ObstRuctiveCAD**




[1]No UAP, ACS, MI, etc. [2]Symptoms- angina or angina equivalent [3]<50% diameter stenosis [4]Exclude for Hx of non compliance, HIV, hepC, eGFR <30, liver disease, etc.
[5]IMT- Potent statin (or PCSK9 inhibitor) + ACE-I (or ARB if intolerant) [6]UC- Usual clinical care

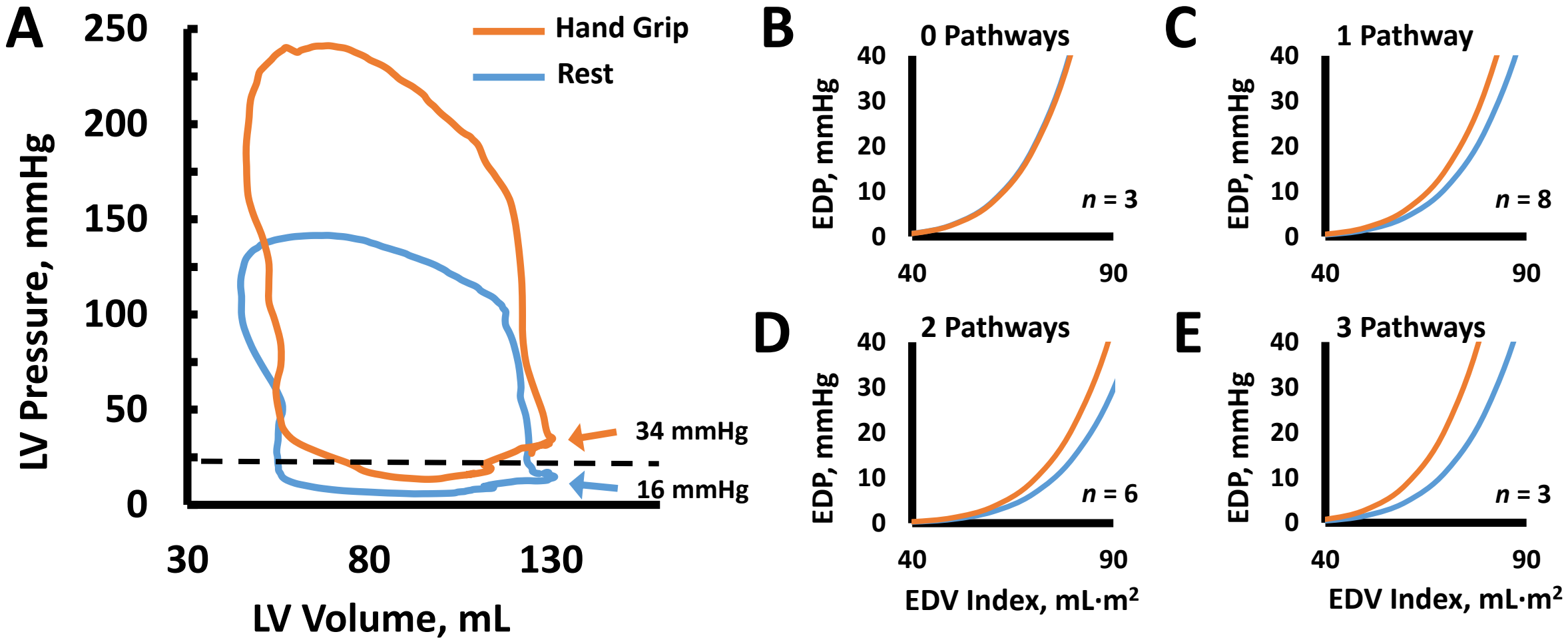
# Variable Clinical Course of CMD-Ischemia and HFpEF

*C Pepine Unpublished*



# CMD and LV End-diastolic pressure-volume relationships: WISE HFpEF

*Unpublished Data: Elliot, Pepine, Bairey-Merz*




**A:** Rest and 30% max isometric handgrip stress.

**B-E:** Coronary reactivity testing pathways with- IC Ado, Ach, and NTG End-diastolic P-V relationships single beat model (Klotz, Dickstein, Burkhoff. *Nature Protocols* 20017;2:2152-8).

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# Ischemia due to CMD and HFpEF

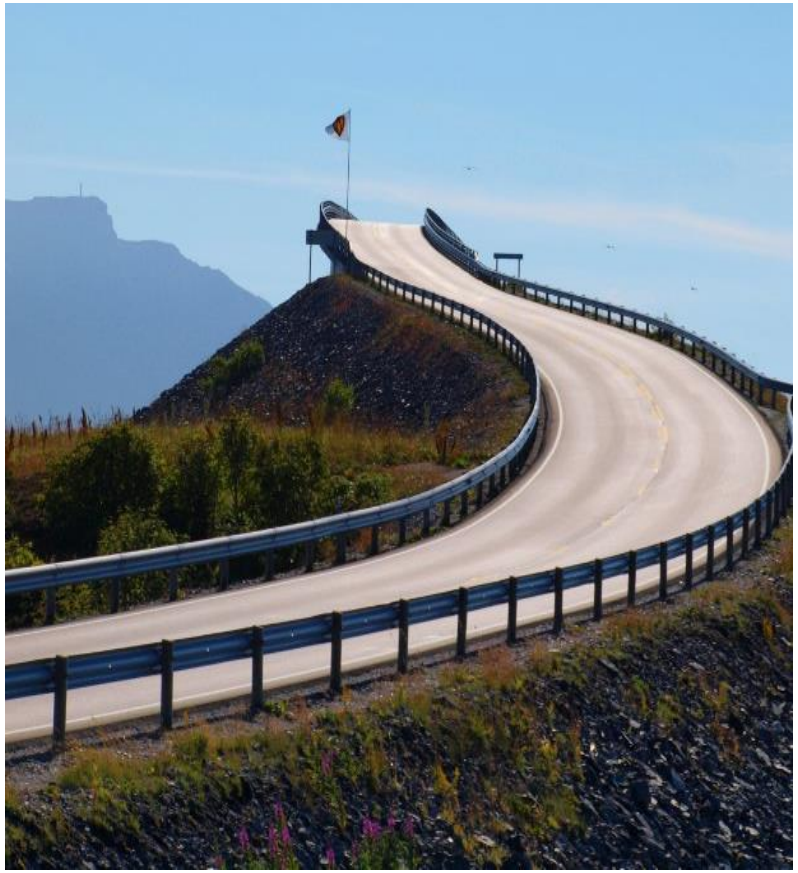
## Summary and Conclusions

Among pts with symptoms and signs of IHD without obstructive CAD, many have CMD and their outcomes are dominated by HFpEF.

CFR/MBF is reduced, NTpro-BNP and hscTn are elevated in ischemia and all are prognostic factors for risk in IHD, as well as HF, independent of traditional risk factors and indices.

Thus, ischemia due to impaired coronary microcirculation as a primary risk factor, or early marker for onset of a “pre-HFpEF” syndrome, seems appropriate. A new therapeutic target?

# Or, is it a bridge to nowhere?



## CENTRAL ILLUSTRATION: Key Questions With Critical Gaps Identified in HFpEF

### Key Questions with Critical Gaps Identified in HFpEF

**1 Is HFpEF a single entity or does it comprise many diseases?** ?

| Single Entity | Many Diseases |
|---|---|
| • Consistent patterns of signs/biomarkers/symptoms are observed across patients<br>• Hypothesis supporting a pro-inflammatory state could trigger cascade of events leading to multiple downstream disturbances | • High prevalence of non-cardiac comorbidities in this population<br>• Average older age in HFpEF suggests different physiologic processed "partnering" with senescence to produce HFpEF syndrome<br>• Still in search of high-fidelity HFpEF animal model |

**2 Should a HFpEF classification system be clinically or mechanistically based?** ?

| Clinically Based | Mechanistically Based |
|---|---|
| • Practical and allows for management decisions to be based on current knowledge of HFpEF phenotypes<br>• Can attempt to tease apart cardiac and vascular components based on clinical observations | • Can stimulate drug development<br>• Can assess dynamic contributions of different pathophysiological processes and their interactions |

**3 Do subpopulations of HFpEF patients respond to treatment differently and should they be studied separately?** ?

| Keep as Broad Group | Break into Individual Subpopulations |
|---|---|
| • HFrEF has diverse etiologies and this approach has worked to advance the field/improve patient outcomes<br>• Larger study size is more important to detect true signal in a population with more factors influencing risks for hospitalization and mortality | • Match appropriate therapy to the targeted pathophysiological subtype<br>• Hints from prior studies that diabetes/HFpEF and obesity, among other subgroups, may be targets of HFpEF prevention and/or treatment |

**4 Should HFpEF outcomes place increasing focus on quality-of-life metrics rather than mortality/heart failure hospitalizations?** ?

| Morbidity/Mortality Focus | Quality-of-Life Metrics |
|---|---|
| • Direct relevance to patients, health system, and payers in the current environment<br>• Has been the standard for HFrEF thus far | • Demonstrated to be feasible in recent HFpEF trials<br>• Can produce a more focused measure of treatment effect<br>• Allows for a patient-centered approach to HFpEF |

Parikh, K.S. et al. J Am Coll Cardiol HF. 2018;6(8):619–32.

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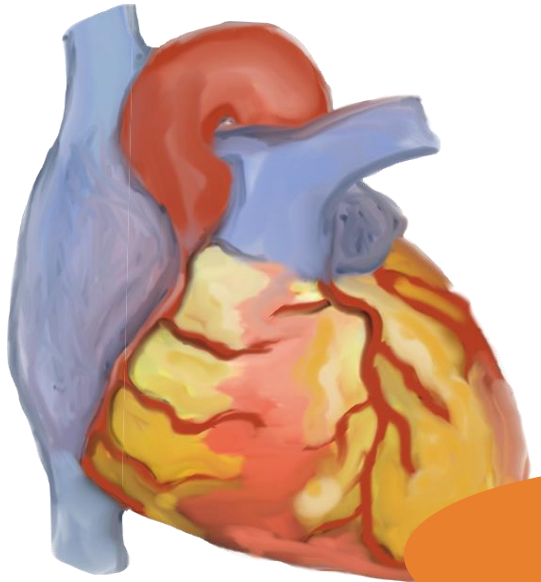
# Is Post-PCI Angina Mostly Due to CMD?

EHJ 2018 in press



**STRUCTURAL**

RESIDUAL DISEASE or
DISEASE PROGRESSION

IN-STENT RESTENOSIS
IN-STENT THROMBOSIS

DIFFUSE
ATHEROSCLEROSIS

INTRAMYOCARDIAL
BRIDGE

CORONARY
DISSECTION

**FUNCTIONAL**

**EPICARDIAL CORONARY ARTERY SPASM**

**CORONARY MICROVASCULAR DYSFUNCTION**

**~20-40% OF PATIENTS PRESENT WITH ANGINA AFTER »SUCCESSFUL» PCI AT 1-YEAR FOLLOW UP**

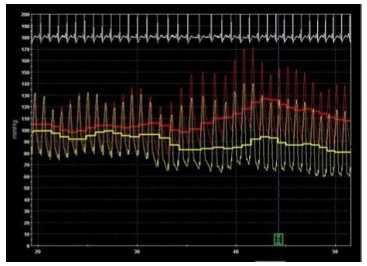
UFHealth

# DISEASE PROGRESSION OR RESIDUAL DISEASE

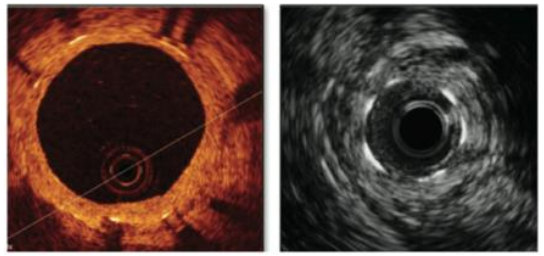
EHJ 2018 in press

**YES**

**FFR/NHPR**
(Assess intermediate stenoses)



**OCT/IVUS**
(Exclude subcritical unstable plaque)



**NO**

**ACH and/or ERGONOVINE**
(Testing for microvascular spasm)

**CFR/IMR**
(Probe microvascular reactivity)