Women and Coronary Artery Disease: Less is More?

Interventional Cardiology 2017
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Snow Mass March 5-10

Yolande Appelman MD, PhD,FESC
EAPCI-Women
Interventional Cardiologist
VU University Medical Center
Amsterdam

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Women's Day
Celebration
show your hands
show your heart

Cardiovascular disease

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- 1 in every 3 women dies of CVD or stroke
- 44 million women are affected by CVD in USA
- 80% can be prevented by lifestyle changes
- Cultural differences are often not accounted for
- Differences between men and women
  - Non obstructive CAD and MVD
  - SCAD
  - TakoTsubo
  - HFpEF

Gender differences CAD

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- Loss of sex hormones (oestrogen)
- Women at presentation 10 yrs older
- More riskfactors (HT, dyslipidemia, diabetics) and higher impact

- Female specific riskfactors

-
- Blood vessels
- smaller (macro and micro)/stiffer
- more inflamed/more diffuse
- microvascular dysfunction
- endothelial and smooth muscle cell dysfunction
- more plaque erosion (instead of plaque rupture)
- *less severe disease (gender paradox)!!*

Pepsine et al; JACC 2006;47 Suppl:S1-3
Shaw et al; JACC 2009;54:1561-75

Gender paradox

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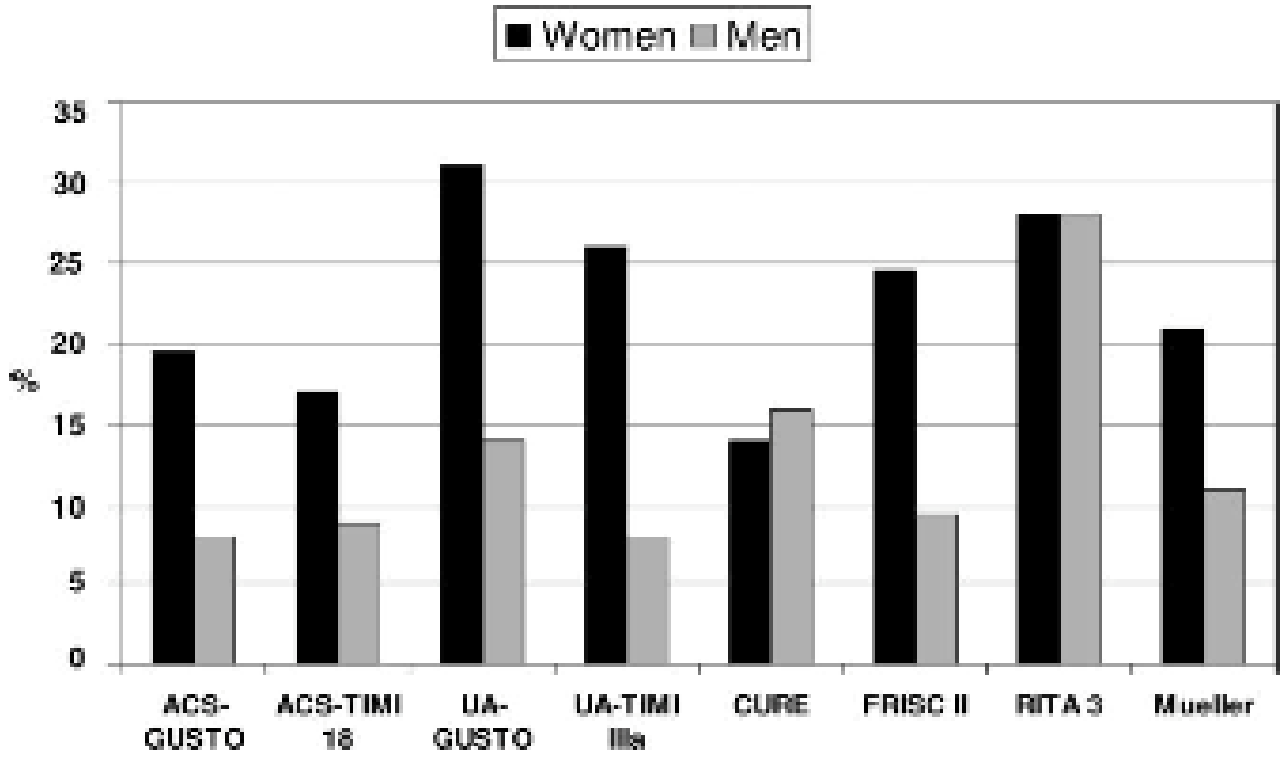
- *Less obstruction but higher mortality*



Anderson R. et al. Circulation 2007;115:823-826

Non-obstructive CAD

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Less is more in women?

- In 20-30% in patients undergoing CAG
- Higher prevalence (50-70%) in women
- In 60% due to abnormal epicardial and/or MVD
- In 60-80% atherosclerosis is found with IVUS/OCT
  - Increased mortality rate 1.5x
  - Increased rehospitalization rate 40%
  - Unneccesary repeat angiography 30%
  - Worse quality of life
  - Higher healthcare costs = obstructive CAD

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Science Times

The New York Times

In Heart Disease, the Focus Shifts to Women

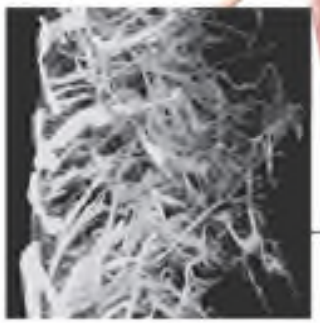
A Hidden Risk

While an angiogram, in which dye is injected into the coronary arteries, helps doctors to determine whether the blockages are forming in the larger vessels of the heart, the test does not reveal the smaller vessels, microvasculature. Blockages in these small vessels, which seem to be more common in women, can become an undetected threat.

TYPICAL ANGIOGRAM

Larger vessels stand out while smaller ones, because of their microscopic size and the motion of the heart, are lost in a blur.

MICROVASCULATURE



Other imaging techniques used on hearts removed from the body reveal the vast network of vessels unseen by the angiogram. This image shows the microvessels in a pig's heart.

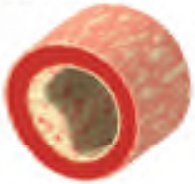
Coronary artery disease

HEALTHY ARTERY

The healthy artery allows unobstructed blood flow while maintaining an ideal blood pressure.

PLAQUE BUILDUP

Plaque deposit



Cholesterol and fatty molecules in the blood stick to the lining of the artery, forming a plaque deposit and narrowing the vessel.

HARDENED ARTERY

As the buildup continues, the arterial wall becomes inflamed and can thicken and harden, causing ischemia, or limited blood flow to the heart.

Thickened and hardened wall

Graham Roberts for The New York Times
Illustrations by Bryan Christie

By Denise Grady, April 18, 2006, The New York Times

Pathofysiology non-obstructive CAD

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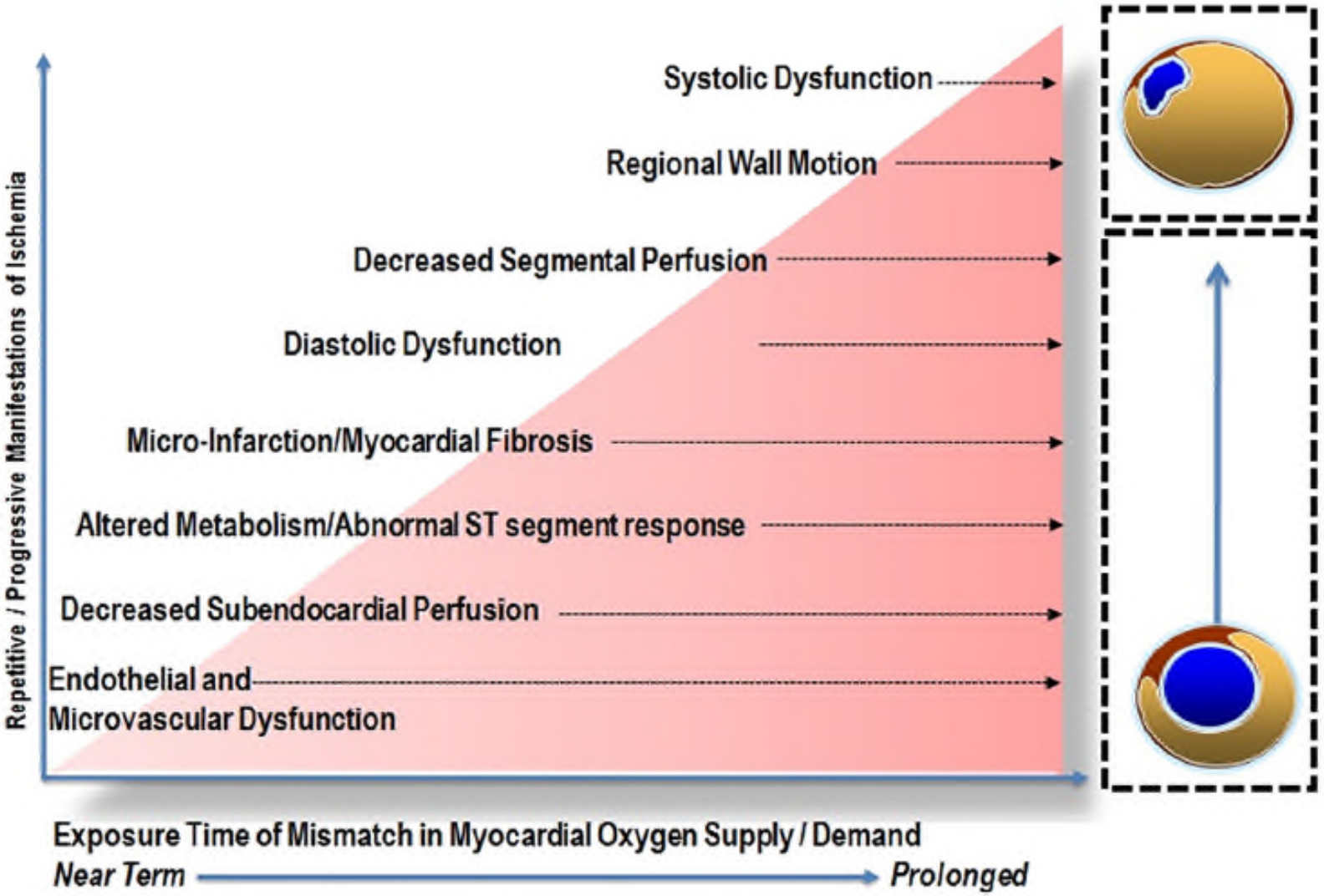
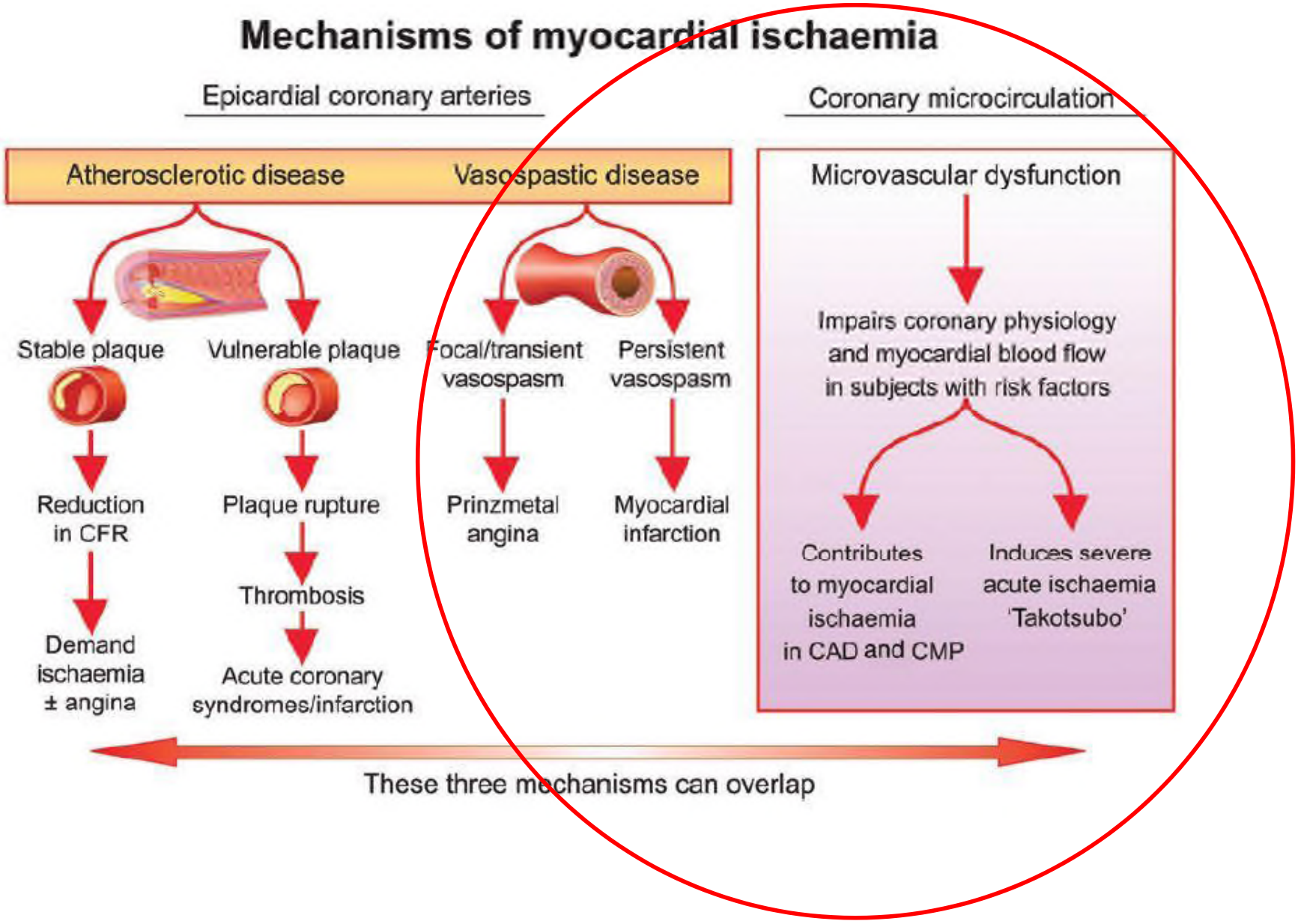


Shaw L et al; Women and ischemic heart disease: evolving knowledge JACC 2009;54:1561-75

Myocardial ischemia



Crea,Camici et al. EHJ.2014

Microvascular dysfunction

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Table 1. Clinical Classification of Coronary Microvascular Dysfunction.

Coronary microvascular dysfunction in the absence of obstructive CAD and myocardial diseases	This type represents the functional counterpart of traditional coronary risk factors (smoking, hypertension, hyperlipidemia, and diabetes and insulin-resistant states). It can be identified by noninvasive assessment of coronary flow reserve. This type is at least partly reversible, and coronary flow reserve can also be used as a surrogate end point to assess efficacy of treatments aimed at reducing the burden of risk factors.
Coronary microvascular dysfunction in the presence of myocardial diseases	This type is sustained in most instances by adverse remodeling of intramural coronary arterioles. It can be identified by invasive or noninvasive assessment of coronary flow reserve and may be severe enough to cause myocardial ischemia. It has independent prognostic value. It remains unclear whether medical treatment may reverse some cases. It is found with primary (genetic) cardiomyopathies (e.g., dilated and hypertrophic) and secondary cardiomyopathies (e.g., hypertensive and valvular).
Coronary microvascular dysfunction in the presence of obstructive CAD	This type may occur in the context of either stable CAD or acute coronary syndromes with or without ST-segment elevation and can be sustained by numerous factors. It is more difficult to identify than the first two types and may be identified through the use of an integrated approach that takes into account the clinical context with the use of a combination of invasive and noninvasive techniques. There is some early evidence that specific interventions might prevent it or limit the resultant ischemia.
Iatrogenic coronary microvascular dysfunction	This type occurs after coronary recanalization and seems to be caused primarily by vasoconstriction or distal embolization. It can be identified with the use of either invasive or noninvasive means on the basis of a reduced coronary flow reserve, which seems to revert spontaneously in the weeks after revascularization. Pharmacologic treatment has been shown to promptly restore coronary flow reserve, and it may also change the clinical outcome. The likelihood of distal embolization can be reduced by the use of appropriate devices during high-risk procedures.

Camici and Crea, NEJM 2007

Angina in non-obstructive CAD

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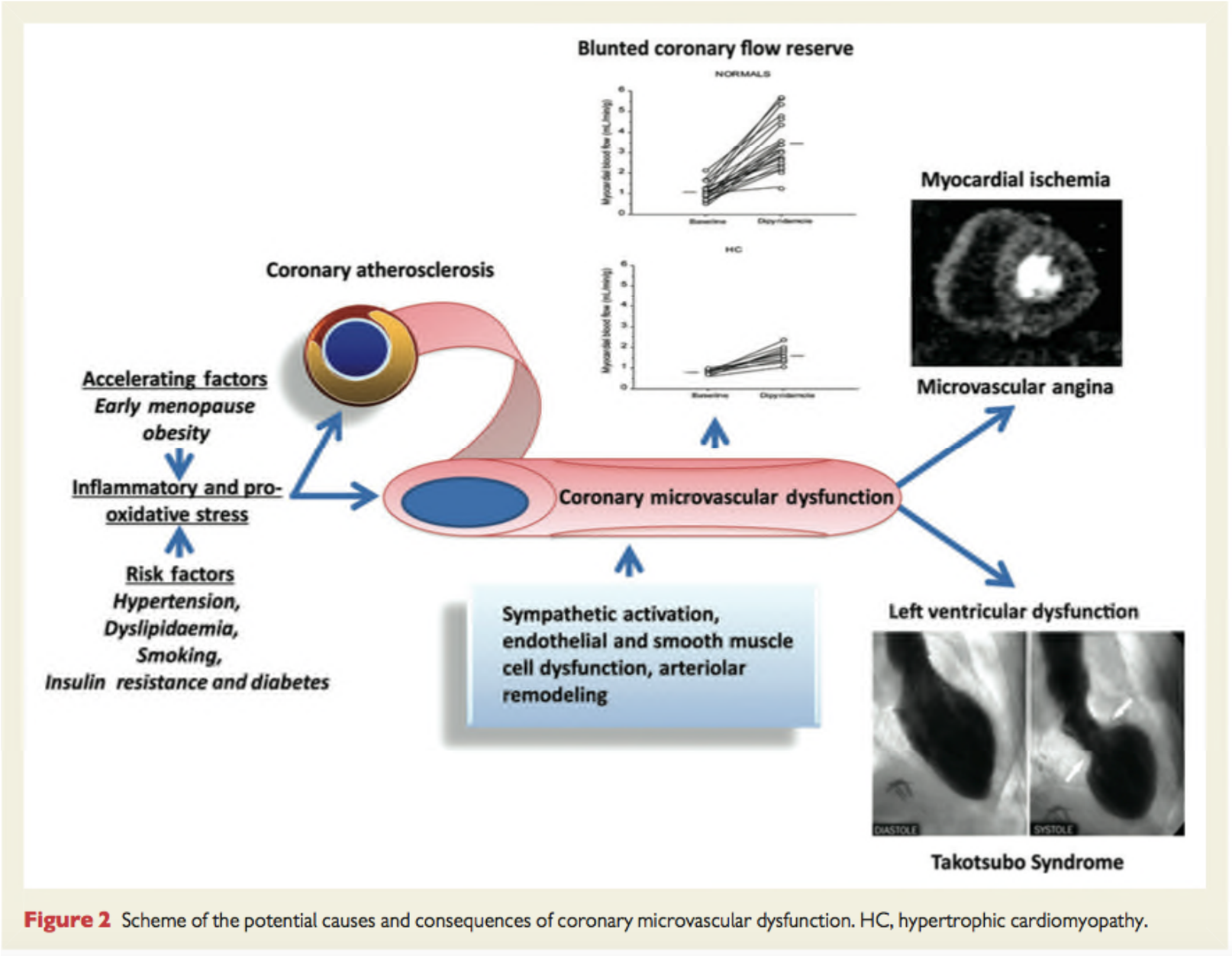

Figure 2 Scheme of the potential causes and consequences of coronary microvascular dysfunction. HC, hypertrophic cardiomyopathy.

Crea,Camici et al. EHJ.2014

Pathofysiology non-obstructive CAD

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- Organic non-atherosclerotic causes
  - ✓Coronary aneurysm
  - ✓Myocardial bridging
  - ✓Coronary anomalies
- Functional disorder = spasm = Prinzmetal angina
- Microcirculatory abnormalities = microvascular
  - ✓Endothelial dysfunction (NO reduced)
  - ✓Impairment of endothelium-independent vasodilation
- “True” syndrome X

Pathofysiology non-obstructive CAD

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How to diagnose angina related to non-obstructive coronary artery disease?

Depends on what you are looking for!

Spasm diagnosis

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- Intracoronary acetylcholine
  - Positive for epicardial coronary spasm if
    - >75% focal or diffuse coronary diameter reduction
    - Reproduction of angina and/or ischemic ECG changes
  - Positive for microvascular spasm if
    - Abcense of epicardial spasm
    - Reproduction of angina and/or ischemic ECG changes

Radico F JACC Cardiol Intv2014;7:453-63

Spasm diagnosis

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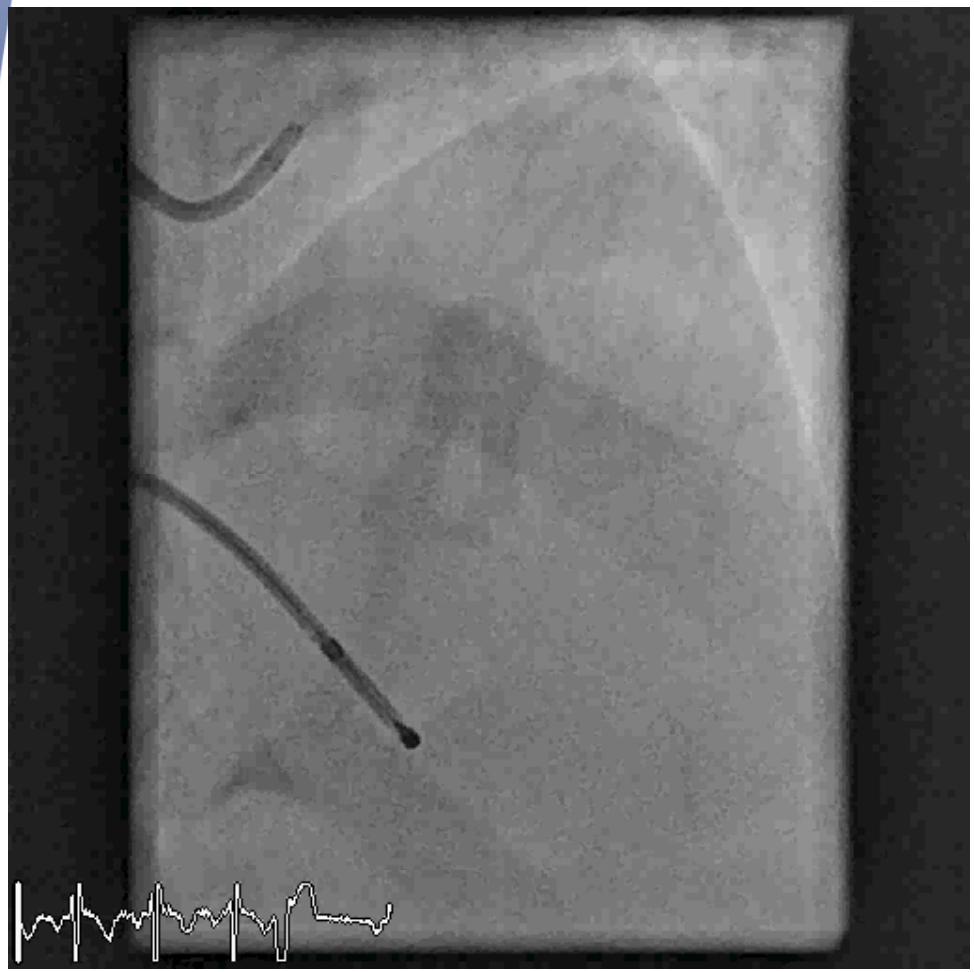

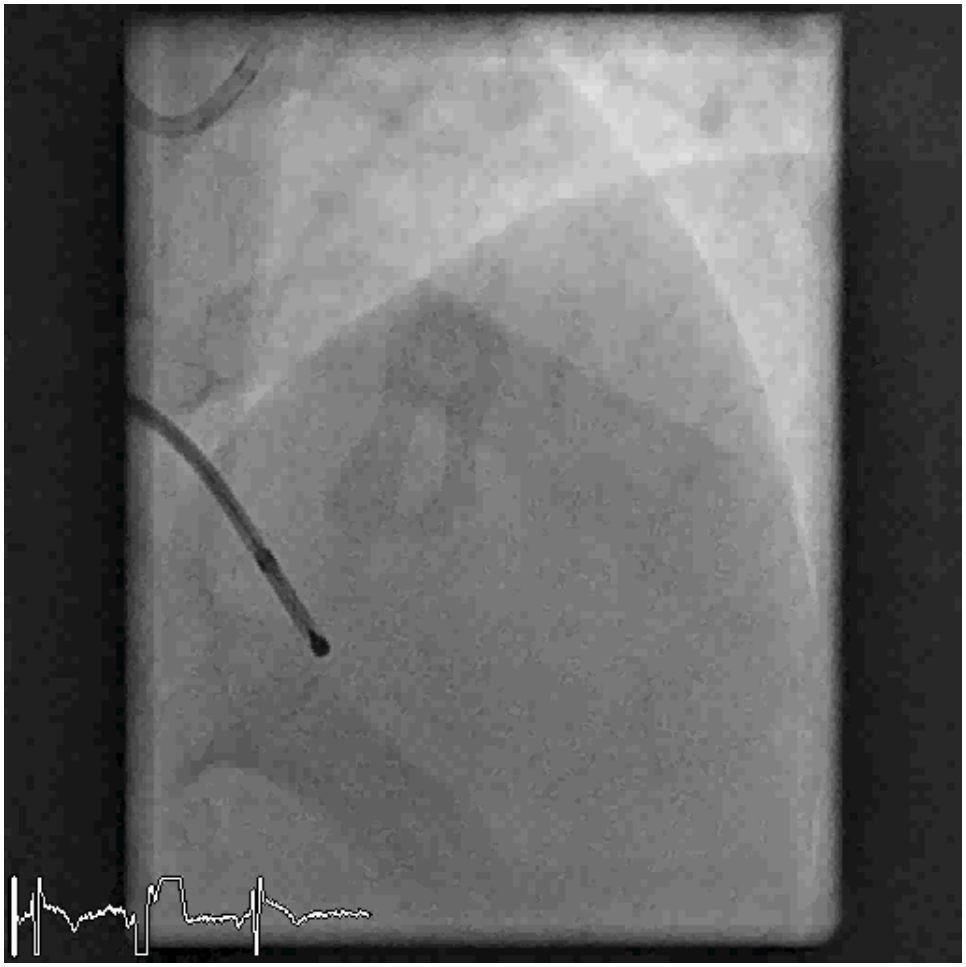

MVD diagnosis

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- Adenosine PET perfusion imaging
  - Microvascular endothelium-independent dysfunction if
    - CFR < 2.5 in absence of significant epicardial stenosis
    - Golden standard for absolute myocardial blood flow

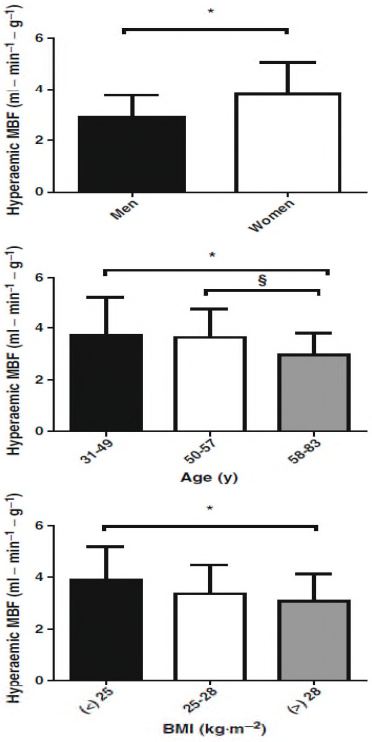

Table 4 Hyperaemic MBF ($ml \cdot min^{-1} \cdot g^{-1}$) in men and women. Values are means ± SD (range)

Parameter	Men	Women	*p*-value
Global[a]	2.90±0.85 (1.52–5.22)	3.78±1.27 (1.72–8.15)	<0.001
Vascular territory			
Left circumflex artery	2.99±0.99 (1.63–6.62)	3.84±1.23 (1.74–7.89)	<0.001
Right coronary artery	2.83±0.84 (1.43–5.41)	3.67±1.34 (1.83–8.85)	<0.001
Left anterior descending artery	2.92±0.86 (1.51–5.49)	3.85±1.35 (1.60–8.38)	<0.001
p-value	0.67	0.61	
Myocardial region			
Septum	2.78±0.78 (1.33–4.70)	3.76±1.40 (1.71–8.67)	<0.001
Inferior	2.95±1.05 (1.39–7.00)	3.70±1.30 (1.77–8.05)	<0.01
Lateral	2.99±1.00 (1.59–6.62)	3.84±1.23 (1.74–7.89)	<0.001
Anterior	2.98±0.98 (1.38–6.31)	3.92±1.58 (1.65–9.51)	<0.001
p-value	0.51	0.78	

[a]Mean MBF in whole left ventricle

Danad I, Appelman Y, Knaapen P Eur J Nucl Med Mol Imaging 2012

Diagnostic invasive assessment

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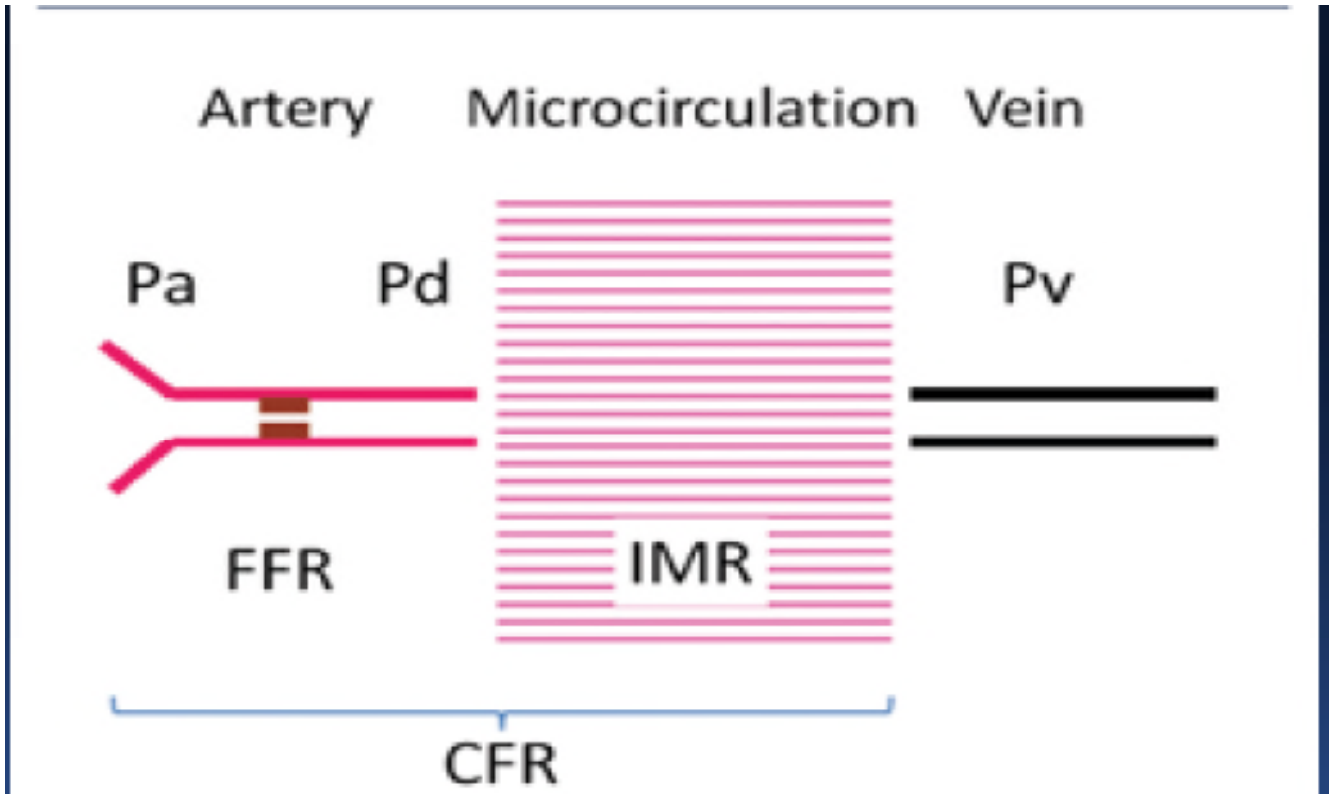
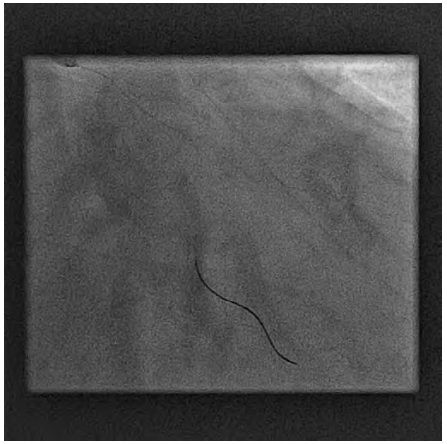


FFR = Fractional Flow Reserve

CFR = Coronary Flow Reserve

IMR = Index Microcirculatory Resistance



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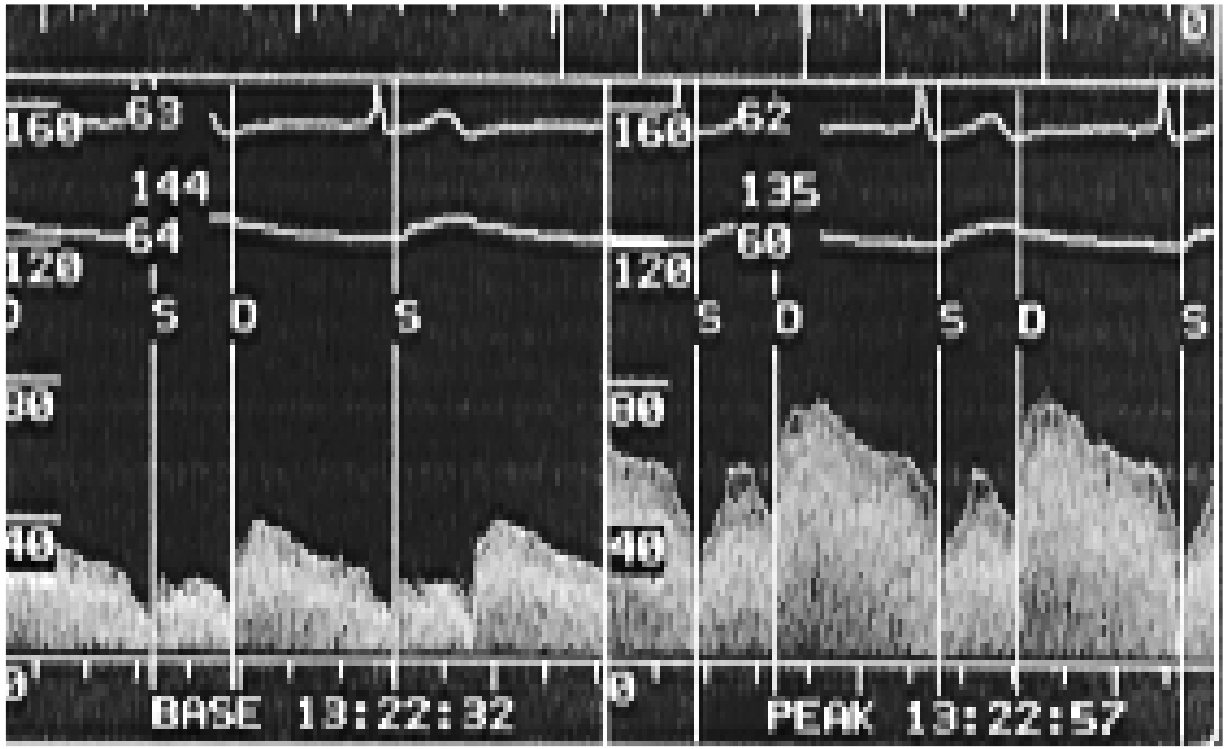
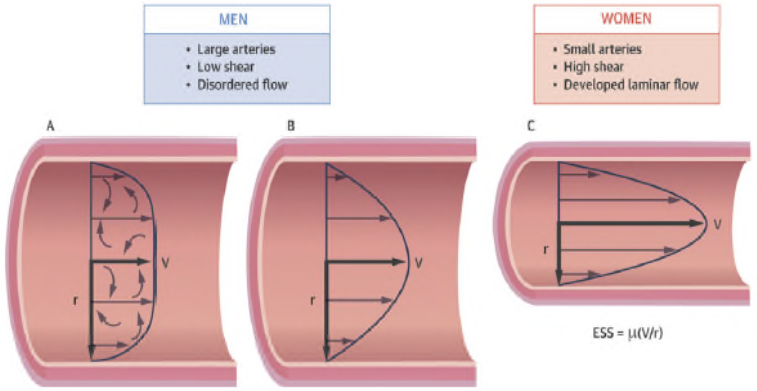
Coronary flow reserve (CFR)

baseline **hyperemia**



$$\text{CFR} = \frac{\text{hyperemia}}{\text{baseline}} \text{ flow velocity}$$

Imaging MVD and mechanism for male-female differences in CAD



Patel, M.B. et al. J Am Coll Cardiol Img. 2016; 9(4):465-82.

TABLE 1 Arterial Diameter, Myocardial Perfusion, LV Bed Size, and Shear

	Women	Men	p Value
Arterial diameter (mm)*			
LM	3.91 ± 0.67	4.35 ± 0.82	<0.001
LAD	3.24 ± 0.58	3.54 ± 0.67	<0.001
LCx	2.75 ± 0.64	3.18 ± 0.71	<0.001
RCA	3.26 ± 0.65	3.7 ± 0.70	<0.001
Mean size of all arteries	3.29	3.7	
Myocardial perfusion† (ml/min/g) for women (n = 1,150) and men (n = 3,178)			
Rest	0.97 ± 0.09	0.73 ± 0.04	<0.00001
Stress	2.36 ± 0.42	1.94 ± 0.4	<0.00001
CFR	2.57 ± 0.59	2.74 ± 0.71	<0.00001
Left ventricular bed size (g)‡			
LM	148	189	
LAD	99	127	
LCx	49	62	
RCA	49	63	
Mean size, all beds	86	110	
Shear (dynes/cm^2) for mean arterial size and female/male bed size above§			
LM	16.3	11.4	
LAD	19.2	14.1	
LCx	15.5	9.6	
RCA	9.4	6.2	
Mean size, all arteries	15.1	10.4	

*From Kucher et al. (9). †From Gould et al. (10,11) for patients with risk factors or documented coronary artery disease. ‡From Hiteshi et al. (7). §Assumes developed flow.

LAD = left anterior descending coronary artery; LCx = left circumflex; LM = left main; LV = left ventricular; RCA = right coronary artery.

Patel M, Gould K JACC Cardiovasc Imaging 2016

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Excess Cardiovascular Risk in Women Relative to Men Referred for Coronary Angiography Is Associated With Severely Impaired Coronary Flow Reserve, Not Obstructive Disease

Taqueti et al 2017 Circulation

Table 1. Baseline Characteristics of Patients, by Sex

Characteristic	Overall (N=329)	Sex		*P* Value*
		Women (n=140)	Men (n=189)	
Demographics				
Age,† y (Q1–Q3)	67 (59–75)	68 (59–76)	66 (59–75)	0.34
Nonwhite race (%)	79 (24.0)	44 (31.4)	35 (18.5)	0.009
Body mass index,† kg/m^2	29.9 (26.3–34.5)	31.0 (27.2–37.6)	28.9 (25.9–32.9)	0.002
Pretest clinical score,†‡ %	58.2 (28.4–84.8)	27.1 (13.1–45.7)	78.4 (59.3–91.4)	<0.001
Medical history				
Myocardial infarction, n (%)	108 (32.8)	37 (26.4)	71 (37.6)	0.04
Percutaneous coronary intervention, n (%)	105 (31.9)	35 (25.0)	70 (37.0)	0.02
Peripheral arterial disease, n (%)	48 (14.6)	22 (15.7)	26 (13.8)	0.64
Diabetes mellitus, n (%)	132 (40.1)	70 (50.0)	62 (32.8)	0.002
Hypertension, n (%)	290 (88.2)	129 (92.1)	161 (85.2)	0.06
Dyslipidemia, n (%)	241 (73.3)	105 (75.0)	136 (72.0)	0.61
Current smoker, n (%)	29 (8.8)	10 (7.1)	19 (10.1)	0.43
Renal hemodialysis, n (%)	11 (3.3)	3 (2.1)	8 (4.2)	0.37
Medications				
Antiplatelet therapy, n (%)	253 (76.9)	114 (81.4)	139 (73.5)	0.11
Statin, n (%)	231 (70.2)	99 (70.7)	132 (69.8)	0.90
β-Blocker, n (%)	229 (69.6)	98 (70.0)	131 (69.3)	0.90
Angiotensin inhibitor, n (%)	149 (45.3)	68 (48.6)	81 (42.9)	0.32
Nitroglycerin, n (%)	58 (17.6)	25 (17.9)	33 (17.5)	0.99
Diuretic, n (%)	108 (32.8)	51 (36.4)	57 (30.2)	0.24
Insulin, n (%)	62 (18.8)	38 (27.1)	24 (12.7)	0.002

Taqueti et al 2017 Circulation

Noninvasive imaging parameters				
Left ventricular ejection fraction,† %	57 (50–65)	62 (55–68)	54 (49–61)	<0.001
Left ventricular scar,† %	0 (0–2.9)	0 (0–2.9)	0 (0–4.4)	0.82
Left ventricular ischemia,† %	10.3 (5.9–16.2)	10.3 (5.1–17.7)	10.3 (5.9–16.2)	0.92
Stress global myocardial blood flow,† mL·g^{-1}·min^{-1}	1.6 (1.1–2.0)	1.7 (1.2–2.3)	1.5 (1.0–1.9)	<0.001
Rest myocardial blood flow,† mL·g^{-1}·min^{-1}	1.0 (0.8–1.2)	1.1 (0.9–1.3)	0.9 (0.7–1.1)	<0.001
Coronary flow reserve†	1.6 (1.2–2.0)	1.5 (1.2–1.9)	1.6 (1.2–2.0)	0.30
Impaired coronary flow reserve (<1.6)	163 (49.5)	76 (54.3)	87 (46.0)	0.15
Rubidium-82 radiopharmaceutical, %	293 (89.1)	127 (90.7)	166 (87.8)	0.48
Invasive angiography				
Coronary artery disease prognostic index†,§	32 (23–48)	32 (19–37)	37 (23–48)	<0.001
Nonobstructive disease (CADPI 0–19)	77 (23.4)	43 (30.7)	34 (18.0)	0.008
Any early revascularization¶ (%)	193 (58.7)	73 (52.1)	120 (63.5)	0.04
Percutaneous coronary intervention (%)	157 (47.7)	62 (44.3)	95 (50.3)	0.32
Coronary artery bypass surgery (%)	39 (11.9)	12 (8.6)	27 (14.3)	0.12

Taqueti et al 2017 Circulation

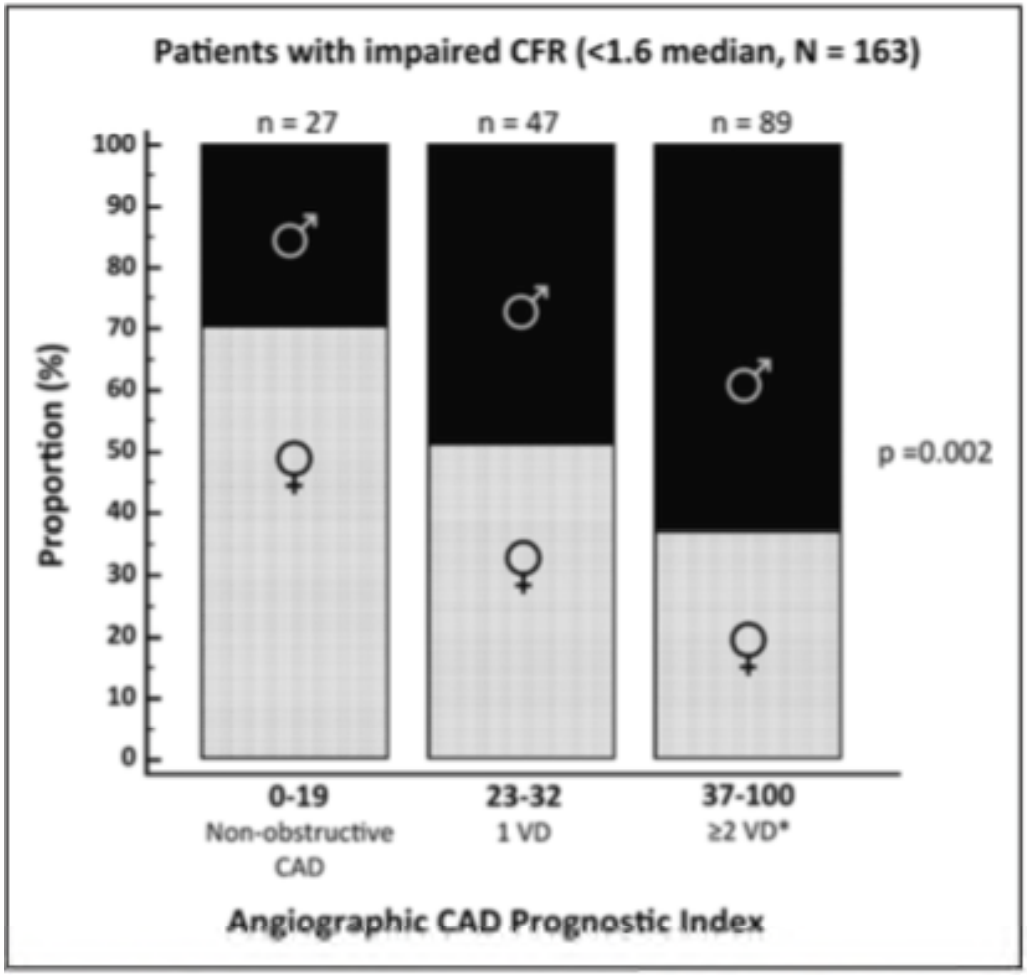

Figure 3. Patients with impaired coronary flow reserve (CFR) by coronary artery disease prognostic index (CADPI) and sex categories.

CFR in non-obstructive CAD

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Table 3. Multivariable-Adjusted Associations of Sex and Coronary Flow Reserve With Cardiovascular Events

	Female Sex		Coronary Flow Reserve*		Model Statistics	
Sequential Models for Total Cardiovascular Events	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Likelihood Ratio χ^2	*P* Value†
Multivariable model 1 Traditional clinical factors	2.21 (1.13–4.31)	0.02			34.45	<0.001
Multivariable model 2 +Invasive factors	2.05 (1.05–4.02)	0.03			47.58	0.02
Multivariable model 3 +Coronary flow reserve	1.81 (0.91–3.59)	0.10	1.69 (1.04–2.76)	0.03	52.45	0.03
+Interaction (CFR* × Sex)		0.04‡			112.07	<0.001
for CFR = 2.0	1.14 (0.49–2.72)					
for CFR = 1.6	1.69 (0.81–3.50)					
for CFR = 1.2	2.49 (1.16–5.38)					

Taqueti et al 2017 Circulation

CFR in non-obstructive CAD

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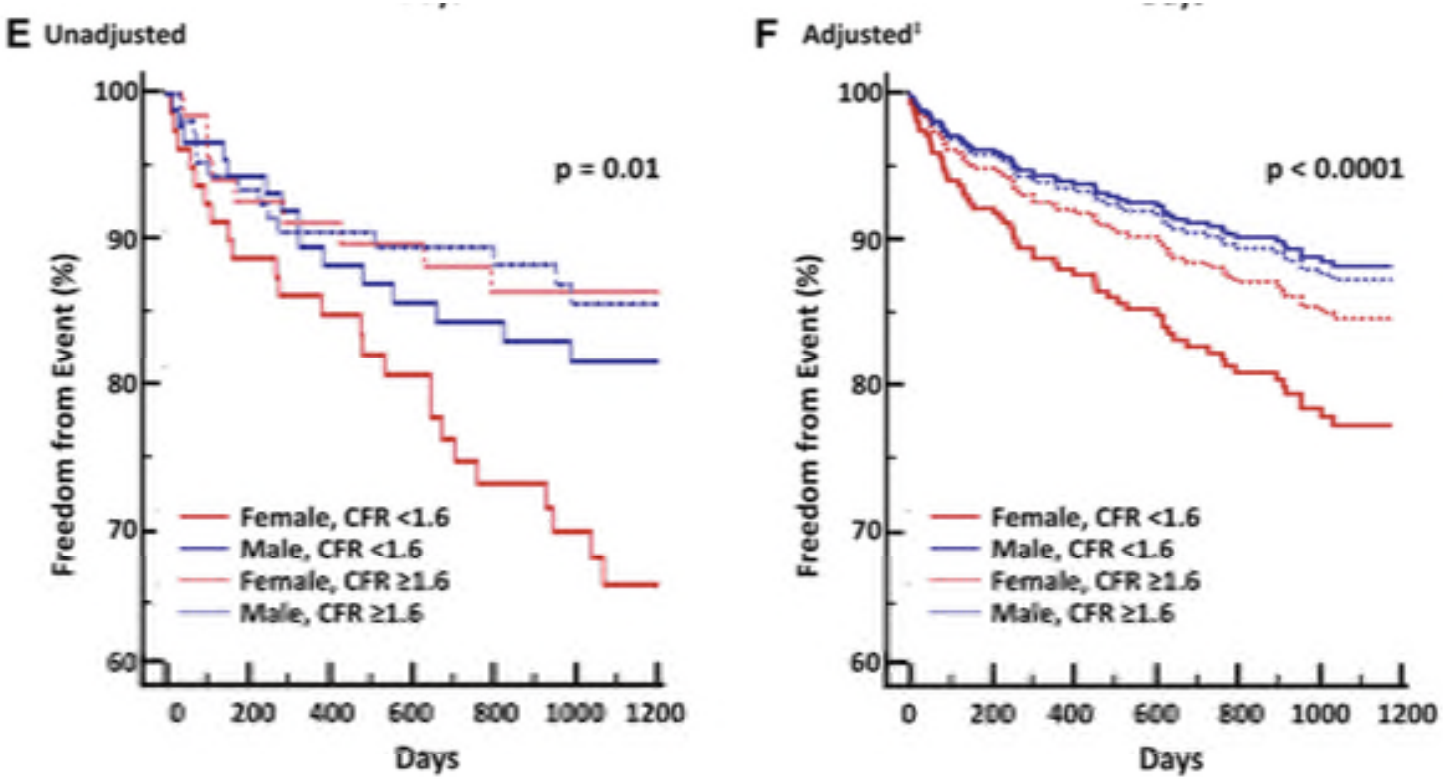

Taqueti et al 2017 Circulation

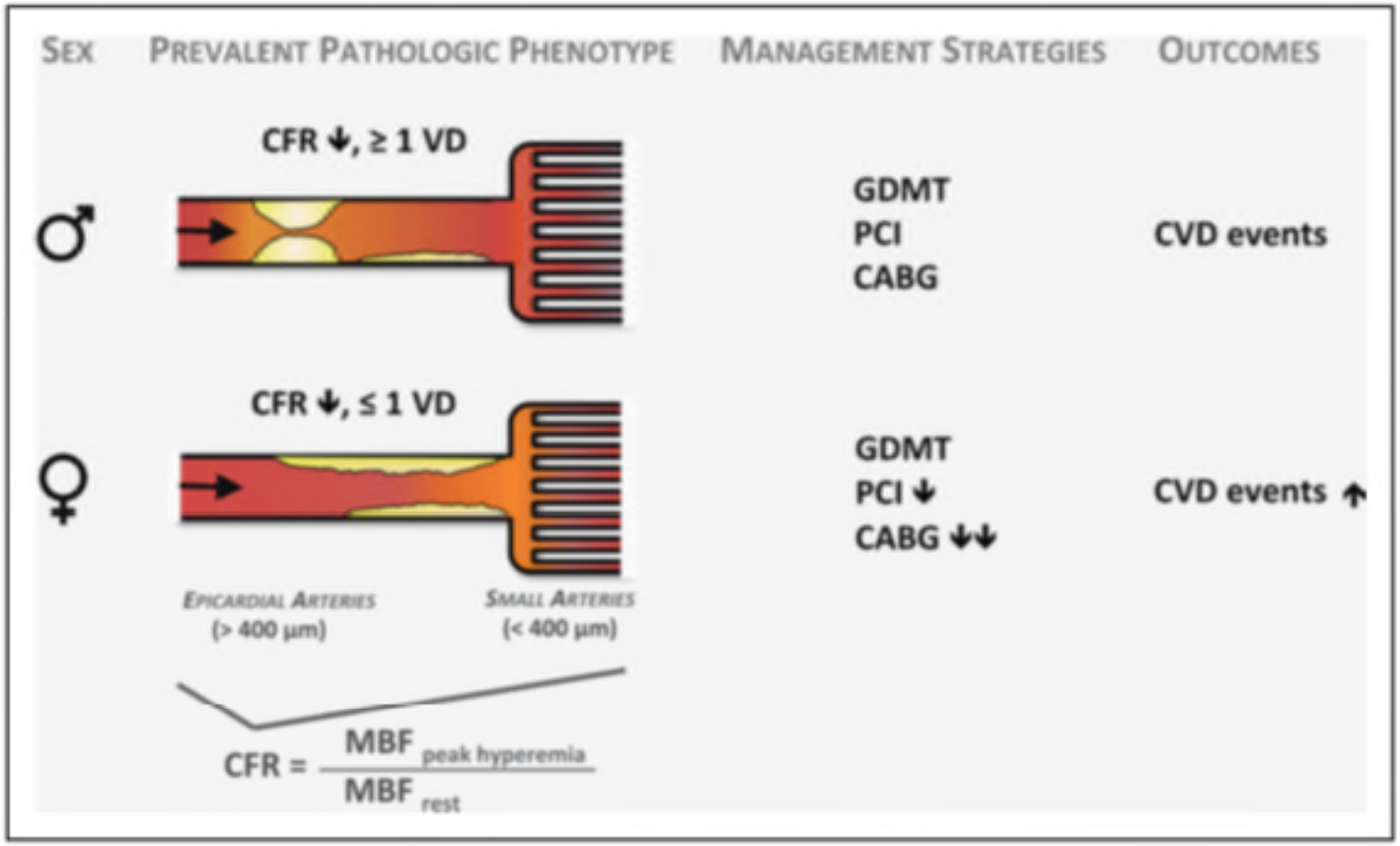

Figure 4. Conceptual model of prevalent pathological phenotypes in women and men with ischemic heart disease and possible impact on cardiovascular management strategies and outcomes.

- Women lower burden of CAD
- Women higher rate CV events
- Women excess CV events independently associated with severely impaired CFR
- Women have hidden biological risk of ischemic heart disease
- Women need new treatment strategies

Treatment ESC guidelines MVD

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Table 29 Treatment in patients with microvascular angina

Recommendations	Class [a]	Level [b]	Ref. [c]
It is recommended that all patients receive secondary prevention medications including aspirin and statins.	I	B	371
ß-blockers are recommended as a first line treatment.	I	B	372
Calcium antagonists are recommended if ß-blockers do not achieve sufficient symptomatic benefit or are not tolerated.	I	B	367
ACE inhibitors or nicorandil may be considered in patients with refractory symptoms.	IIb	B	368
Xanthine derivatives or non-pharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs.	IIb	B	373–375

LIFESTYLE MODIFICATION!

No study has evaluated the impact on MACE

ESC guidelines on management of stable CAD Eur Heart J 2013

Conclusions

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Women with angina indeed less = more

- Higher prevalence non-obstructive CAD
- 60% is caused by MVD
- CV riskfactors play an important role
- Lower CFR higher CV risk
- CFR hidden biological risk of ischemic disease
- Lack of evidence on treatment strategies
- Exact mechanisms remain elusive more research is needed

Thank you

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