



CPT ischemica al femminile: le sindromi aterosclerotiche e non, diagnosi e terapia uptodate

**CUORE & DONNA** 



SABATO 14 SETTEMBRE 2019 Teatro "G. MODENA", PALMANOVA (UD) Guglielmo Bernardi ARC (Associazione per la

Ricerca in Cardiologia) Pordenone

## Number of deaths from ten leading causes, by sex USA 2015



# Trends in awareness that heart disease is the leading cause of death in women



Mosca L, Circulation 2013;127:1254

#### **AHA Scientific Statement**

#### Acute Myocardial Infarction in Women A Scientific Statement From the American Heart Association

#### Laxmi S. Mehta, MD, FAHA, Chair; Theresa M. Beckie, PhD, FAHA, Co-Chair;

# ...CHD remains understudied, underdiagnosed, and undertreated in women.

Disease in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing, and Council on Quality of Care and Outcomes Research

*Abstract*—Cardiovascular disease is the leading cause of mortality in American women. Since 1984, the annual cardiovascular disease mortality rate has remained greater for women than men; however, over the last decade, there have been marked reductions in cardiovascular disease mortality in women. The dramatic decline in mortality rates for women is attributed partly to an increase in awareness, a greater focus on women and cardiovascular disease risk, and the increased application of evidence-based treatments for established coronary heart disease. This is the first scientific statement from the American Heart Association on acute myocardial infarction in women. Sex-specific differences exist in the presentation, pathophysiological mechanisms, and outcomes in patients with acute myocardial infarction. This statement provides a comprehensive review of the current evidence of the clinical presentation, pathophysiology, treatment, and outcomes of women with acute myocardial infarction. (*Circulation*. 2016;133:9) 6-947. DOI: 10.1161/CIR.00000000000351.)

## Cardiovascular disease mortality trends for ${\mathcal O}$ and in ${\mathcal Q}$

USA National Center for Health Statistics and National Heart, Lung, and Blood Institute



#### Benjamin EJ, Circulation. 2018;137:e67

# Trends in age-specific CHD mortality rates in age groups in USA



Wilmot KA, Circulation 2015;132:997

## Characteristics of IHD in women vs men

- Higher prevalence of angina
- Nonobstructive IHD
- Coronary microvascular dysfunction
- Spontaneous coronary artery dissection
- Stress-induced cardiomyopathy
- Heart failure with preserved ejection fraction

## Characteristics of IHD in women vs men

- Higher prevalence of angina
- Nonobstructive IHD
- Coronary microvascular dysfunction
- Spontaneous coronary artery dissection
- Stress-induced cardiomyopathy
- Heart failure with preserved ejection fraction

# Degree of CAD by sex and year of non-urgent invasive CA 11.223 pts (42% women)



one-third of men, but two-thirds of women, had no obstructive CAD



#### Jespersen L, EHJ 2012;33:734

# MACE-free survival by sex and vessel disease involvement on invasive CA 11.223 pts (42% women)



#### Jespersen L, EHJ 2012;33:734

#### Anatomy and function of the coronary circulation



De Bruyne B, JACC 2016;67:1170

# Arterial size, coronary blood flow, wall shear stress women versus men

	Women	Men	p Value	
Arterial diameter (mm)				
LM	$\textbf{3.91} \pm \textbf{0.67}$	$4.35\pm0.82$	<0.001	
LAD	$\textbf{3.24} \pm \textbf{0.58}$	$\textbf{3.54} \pm \textbf{0.67}$	<0.001	
LCx	$\textbf{2.75} \pm \textbf{0.64}$	$\textbf{3.18} \pm \textbf{0.71}$	<0.001	
RCA	$3.26\pm0.65$	$\textbf{3.7} \pm \textbf{0.70}$	<0.001	
Mean size of all arteries	3.29	3.7	Crea ella ri a rita ria a	
Myocardial perfusion (ml/min/g) for women $(n = 1,150)$ and men $(n = 3,178)$	>		Smaller afteries	
Rest	$\textbf{0.97} \pm \textbf{0.09}$	$\textbf{0.73} \pm \textbf{0.04}$	<0.00001	
Stress	$\textbf{2.36} \pm \textbf{0.42}$	$\textbf{1.94} \pm \textbf{0.4}$	<0.00001	
CFR	$\textbf{2.57} \pm \textbf{0.59}$	$\textbf{2.74} \pm \textbf{0.71}$	<0.00001	
Left ventricular bed size (g)			higher flow	
LM	148	189	Tigrici now	
LAD	99	127		
LCx	49	62		
RCA	49	63		
Mean size, all beds	86	110		
Shear (dynes/cm <sup>2</sup> ) 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		4
Mean size, all arteries	15.1	10.4	higher endothelial she	ar str

#### Patel MB, JACC Img 2016;9:465

Small arteries with high flow have fully developed flow profiles and high endothelial shear stress



Patel MB, JACC Img 2016;9:465

# Average calculated endothelial shear stress & different manifestations of CAD



# Adjusted cumulative rate of MACE by sex and CFR in pts with normal myocardial perfusion

2.783 consecutive pts with suspected or known CAD referred for PET



Both women and men with CFR <2 experienced worse outcomes but this phenotype was twice as prevalent in women as in men

Murthy VL, Circulation 2014;129:2518

# Log adjusted hazard for MACE in $\hfill \phi$ versus $\hfill \phi$ varies as a function of CFR

329 consecutive pts (43% Q ), EF >40%, referred for invasive CA after PET stress test (median FU 3 y)



Taqueti VR, Circulation 2017;135:566

Difficulties in interpretation of noninvasive diagnostic testing in women

- Relatively low prevalence of obstructive CAD below 60 years
- Non-specific ECG changes at rest
- Lower exercise capacity

Lower sensitivity and specificity

### Effect of gender on the investigation and management of new-onset stable angina Euro Heart Survey of Stable Angina



Daly C, Circulation. 2006;113:490

# Diagnostic value of various stress testing modalities in women

Stress Testing Modality	Sensitivity	Specificity	NPV	PPV
Exercise ECG	31–71	66-78	78	47
Exercise echocardiography	80-88	79–86	98	74
Exercise SPECT	78–88	64–91	99	87
Pharmacological echocardiography	76–90	85–94	68	94
Pharmacological SPECT	80–91	65-75	90	68
Values are percentages. Pl	PV indicates pos	sitive predictive	value.	

Kohli P, Circulation. 2010;122:2570

# Sex differences in functional testing and CT angio in pts with suspected CAD PROMISE Study 8.966 pts





Pagidipati NJ, JACC. 2016;67:2607

#### Sex differences in functional testing and CT angio in pts with suspected CAD PROMISE Study 8.966 pts



# Indications to stress testing/imaging or coronary computed tomography angiography in women with ischaemic symptoms

	Exe	ercise status	ECG interpretable	Pretest prob	ability of IHD	
Test	Abl	e Unable	Yes N	No Low	Intermediate	High
Exercis Exercis Exercis Pharma Pharma	Current ESC techniques ( with a prefer younger wor	guidelines when avail ence for no nen	s advise s able) as on radiati	stress ima first test o on diagno	aging of choice, ostics in	× × × ×
Pharma	icological stress CMR	х	Any		х	x
CCTA	Any	/	Any		(x)	×

CCTA: coronary computed tomography angiography. CMR: cardiac magnetic resonance IHD: ischaemic heart disease. MPI: myocardial perfusion imaging

Regitz-Zagrosek V, EHJ 2016;37:24

Diagnostic stress tests in pts with microvascular disfunction according to coronary flow velocity reserve level *iPOWER Study* 

	CFVR≤2.0 (n=241)	2 <cfvr≤2.5 (n="318)&lt;/th"><th>CFVR&gt;2.5 (n=360)</th><th>P Value</th></cfvr≤2.5>	CFVR>2.5 (n=360)	P Value
Positive exercise test (n=317)	22 (28)	37 (33)	40 (32)	0.52
Positive SPECT (n=99)	11 (33)	12 (36)	8 (24)	0.41
	n (%)	n (%)	n (%)	

Mygind ND, J Am Heart Assoc 2016;5:e003064

## Coronary flow reserve (CFR) evaluation

#### Non-invasively

- Transthoracic doppler echocardiography by imaging LAD
- Magnetic resonance imaging (myocardial perfusion index)
- PET (<sup>82</sup>Rubidium, <sup>13</sup>N-Ammonia)

#### In the cath. Lab. using intravenous adenosine

- Intracoronary pressure & thermodilution to calculate the index of microcirculatory resistance (IMR)
- Doppler flow velocity to calculate hyperemic microvascular resistance (HMR)
- Intracoronary thermodilution and doppler allow the calculation of coronary flow reserve (CFR)
- values of IMR  $\leq$  25 units, CFR <2.0

#### Stratified medical therapy using invasive coronary function testing in angina The CorMicA TrialA, 391 pts enrolled, 151 (39%) with no obstructive CAD randomized



#### Ford TJ, JACCardiol 2018;72:2841

## Microvascular angina to be considered

- Typical chest pain
- (Abnormal non-invasive functional tests)
- Normal or mild, functionally nonsignificant stenosis (ICA or CTA)

## Mechanisms in ACS (I)

NB may overlap and coexist in some patients



Crea F, Libby P, Circulation 2017;136:1155

## Mechanisms in ACS (II)

NB may overlap and coexist in some patients



# Extension of coronary atherosclerosis in fatal cases of IHD women vs men, autopsy study



#### Smilowitz NR, Am Heart J 2011;161:681

#### Sex differences in short-term all-cause mortality in STEMI pts treated by PCI Meta-analysis (18.555 Q & 49.981 Ő)

#### Adjusted in-hospital all-cause mortality

Source	log (RR)	Favors	Favors	Weight
Porger and Prown 6 2006	0.222			6.0
Berger and Brown, 2000	0.225			0.9
De Luca et al, <sup>9</sup> 2004	0.95			11.3
Eitel et al, <sup>10</sup> 2012	0.66			- 6.4
Hurtado-Martinez et al, <sup>16</sup> 2006	0.92			- 8.8
Jackson et al, <sup>17</sup> 2011	0.26			5.7
Kosuge et al, <sup>18</sup> 2006	0.0099			7.2
Srimahachota et al, <sup>22</sup> 2004	0.765	·		- 5.8
Vakili et al, <sup>24</sup> 2001	0.83			9.6
Valente et al, <sup>27</sup> 2012	-0.612	· · · · · · · · · · · · · · · · · · ·	<u>:</u>	8.5
Yamane et al, <sup>28</sup> 2011	0.667		<b></b>	12.9
Zanchi et al, <sup>25</sup> 2009	0.14			4.8
Zhang et al, <sup>26</sup> 2010	-0.26	·	<u> </u>	12.1
Total			$\diamond$	100.0
Heterogeneity: $\tau^2 = 0.17$ ; $\chi^2_{11} = 25.28$ , (P Test for overall effect: Z = 2.38 (P = .02)	2=.008);	0.1 1	.0	 10

Pancholy SB, JAMA Intern Med 2014;174:1822

KK IV, Kandom (95% CI)

#### Sex differences in one-year all-cause mortality in STEMI pts treated by PCI Meta-analysis (18.555 $\bigcirc$ & 49.981 $\circlearrowright$ )



Unadjusted

#### Adjusted

Fourse	RR IV, Random	Favors Favors	Weight,
Source	(95% CI)	women Men	70
De Luca et al, <sup>9</sup> 2004	1.41 (0.86-2.30)		16.2
De Luca et al, <sup>30</sup> 2010	1.01 (0.56-1.81)		13.1
Mehilli, <sup>40</sup> 2002	0.65 (0.48-0.87)		25.0
Mrdovic et al, <sup>33</sup> 2013	0.74 (0.51-1.08)	- <b>B</b> +	21.1
Velders et al, <sup>38</sup> 2013	1.02 (0.75-1.38)		24.4
Total	0.90 (0.69-1.17)	$\diamond$	100.0
Heterogeneity: $\tau^2 = 0.05$ ; $\chi^2_4 = 9.46$ , (P = .05);	2		
Test for overall effect: $7 = 0.80$ (P = 42)	Г		
rescribit overall effect. 2 = 0.00 (r = .42)	0.1	1 1.0	10
		RR IV. Random (95% CI)	

#### Pancholy SB, JAMA Intern Med 2014;174:1822

Role of gender on outcomes of young AMI patients VIRGO study, 1.465 pts 18-55 y

## Women more likely to

- Present with atypical chest pain/no symptoms
- Present > 6 hours after symptom onset
- Be untreated compared with young men
- Exceed in-hospital and transfer time guidelines for PCI
- Exceed door-to-needle times

# Sequential logistic regression for the effect of sex on exceeding recommended guidelines VIRGO study



#### D'Onofrio G, Circulation 2015;131:1324

# Early invasive vs conservative treatment in women and men with NSTEMI Meta-analysis (8 trials, 3075 오 7075 ♂)



#### Comparison of 3-year outcomes by gender for CABG and PCI with DES 4.532 Q & 11.768 of from three NY State Registries

#### Kaplan-Meier survival curves



#### Hannan EL, Ann Thorac Surg 2015;100:2227

#### In-hospital mortality trend by gender after CABG 2003 – 2012, US Nationwide Inpatient Sample (NIS) database, 623.423 〇 1.649.575 〇



#### Swaminathan RV, AJC 2016;118:362

#### Unadjusted in-hospital clinical outcomes by gender after CABG NIS database, 623.423 Q 1.649.575 of



#### Swaminathan RV, AJC 2016;118:362

# Gender differences of in-hospital outcomes in pts undergoing PCI in the DES era 44.967 procedures



Kim HL, Medicine 2019;98:20

# PCI for STEMI in the New Jersey statewide database

12.878 women and 27.337 men



# Sex-specific differences in the pharmacokinetic profiles of drugs

- Intestinal absorption of medications slower
  - Reduced gastric acid secretion and gastrointestinal motility
- Smaller distribution volume
  Overall impact of differences on clinical
  efficacy has been shown to be marginal

#### metabolic enzymes

- Higher activity of CYP1A2, CYP2E1, p-glycoprotein and isoforms of glucuronyltransferases and sulfotransferases
- CYP2D6 and CYP3A have in general a slightly higher activity in women of childbearing years (21, 24, 25).
- Glomerular filtration rate 10 25% lower even adjusting for body size

Stolarz AJ, Cardiovasc Drugs Ther 2015;29:403

### Frequency of use of evidence-based medical therapy according to gender after presentation to a cardiologist *The Euro Heart Survey of Stable Angina*

Medication	Overall (n=3779)	Male (n=2197)	Female (n=1582)	<i>P</i> , Male vs Female
Antiplatelet	3058	1851	1207	<0.001
	81%	84%	76%	
Aspirin	2942	1784	1158	< 0.001
	78%	81%	73%	
Lipid-lowering drug	1892	1156	736	< 0.001
	50%	53%	47%	
Statin	1830	1117	713	< 0.001
	48%	51%	45%	
β-Blocker	2513	1479	1034	0.21
	67%	67%	65%	
No. of antianginal drugs, mean (SD)	1.6 (0.9)	1.7 (0.9)	1.6 (0.9)	0.05

#### Daly C, Circulation. 2006;113:490

#### Factors affecting prescription of OMT to women

![](_page_41_Figure_1.jpeg)

#### Davis E, Int J Cardiol 2017;227:840

## Characteristics of IHD in women vs men

- Higher prevalence of angina
- Nonobstructive IHD
- Coronary microvascular dysfunction
- Spontaneous coronary artery dissection
- Stress-induced cardiomyopathy
- Heart failure with preserved ejection fraction

#### **Spontaneous coronary artery dissection (SCAD)** *Epicardial vessel disease not associated with atherosclerosis, trauma nor iatrogenic*

![](_page_43_Picture_1.jpeg)

#### Hayes SN, Circulation. 2018;137:e523

# Epidemiology of SCAD

- 1% to 4% of ACS cases overall (true prevalence uncertain – underdiagnosed condition)
- Patients with few or no traditional cardiovascular risk factors
- Average age of women with SCAD ranges from 45 to 53 years, up to 35% women ≤50 years of age
- Most common cause of pregnancy-associated MI (43%)
- Mid-distal LAD 32% 46% of cases

### Conditions and factors associated with SCAD (I)

Associated Condition or Factor	Reported Prevalence in Cohort Studies, %
Fibromuscular dysplasia	25–86
Pregnancy	2–8
Multiparity (≥4 births)	8.9–10
Inherited arteriopathy and connective tissue disorder	1.2–3.0
Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, α <sub>1</sub> - antitrypsin deficiency, polycystic kidney disease	

Hayes SN, Circulation. 2018;137:e523

### Conditions and factors associated with SCAD (II)

Associated Condition or Factor	Reported Prevalence in Cohort Studies, %
Exogenous hormones	10.7–12.6
Oral contraceptives, postmenopausal therapy, infertility treatments, testosterone, corticosteroids	
Systemic inflammatory disease	<1-8.9
Systemic lupus erythematosus, Crohn disease, ulcerative colitis, polyarteritis nodosa, sarcoidosis, Churg-Strauss syndrome, Wegener granulomatosis, rheumatoid arthritis, Kawasaki disease, celiac disease	

Hayes SN, Circulation. 2018;137:e523

# Precipitating factors for SCAD > 50% of pts

- Intense exercise (isometric or aerobic)
- Intense Valsalva
- Retching, vomiting, bowel movement, coughing, lifting heavy objects
- Intense emotional stress

- Labor and delivery
- Drugs (cocaine, amphetamines)
- Exogenous hormones/hormone modulators
- β-hCG injections, corticosteroid injections, clomiphene

#### Frequency of presenting symptoms of SCAD

![](_page_48_Figure_1.jpeg)

Luong C, Catheter Cardiovasc Interv 2017;89:1149

## SCAD treatment

- Conservative management first choice
- Discontinuation of anticoagulation if no other indications
- No firm data on DAPT (individualized treatment)
- β-blocker potentially useful (but limited by adverse effects)
- ACE-Inhibitors, ARB, statins, based on guidelines
- Antianginal therapy... often empirical

## Characteristics of IHD in women vs men

- Higher prevalence of angina
- Nonobstructive IHD
- Coronary microvascular dysfunction
- Spontaneous coronary artery dissection
- Stress-induced cardiomyopathy
- Heart failure with preserved ejection fraction

## Takotsubo syndrome TTS

- Acute coronary syndrome characterized by severe left ventricular dysfunction that typically recovers spontaneously within days or weeks
- ~ 90% of pts postmenopausal women
- Normal coronary arteries or nonobstructive CAD (~ 85% of pts)
- Modest increases in biomarkers of myocardial damage
- Disparity biomarker elevation/extent of myocardial dysfunction
- Significantly elevated BNP (ventricular stretching)

# Plasma norepinephrine levels in pts with TTS and pts with Killip class III AMI

![](_page_52_Figure_1.jpeg)

#### Wittstein IS, NEJM 2005;352:539

## TTS symptoms

#### Most common

- Chest pain, dyspnea
- Possible
  - Syncope, pulmonary edema

#### Rare

 Cardiac arrest, cardiogenic shock, serious ventricular arrhythmias

#### Also reported

 Generalized weakness, unexplained cough, fever

#### Stressors identified to precede TTS 80% ~ of pts

- Unexpected death of a relative/friend
- Suppressed terror
- Natural disasters
- Strenuous physical stress
- Positive life event (happy heart syndrome)

### **In-hospital mortality rate in TTS** *Meta-analysis of 37 studies, 2.120 pts, 11 countries, mean age 68 years, female 87%*

Grouping	Number of Studies	In-Hospital Death, % (95% CI)	I <sup>2</sup>
Total	37	4.5 (3.1-6.2)	60.8
Retrospective studies	18	4 (2.1-6.4)	54.6
Prospective studies	12	4.8 (2.3-8.2)	71.5
Single-center studies	28	4.9 (3.1-7.1)	58.5
Multicenter studies	7	3.8 (1.4-7.1)	74.8

Mortality 4.5% overall

- 38% cardiac complications
  - 62% underlying co-morbidity

## Treatment of TTS Acute phase

- No randomized clinical trials on specific treatment
- Mainly supportive aiming to reduce life threatening complications
- Non beneficial drugs
  - B-blockers
- Beneficial drugs
  - Antiplatelet, ACEI/ARB, levosimendan (probably)

Kato K , Heart 2017;103:1461

## Treatment of TTS Non acute phase

- No randomized clinical trials on specific treatment
- Non beneficial drugs
  - β-Blockers, statins, aspirin
- Possibly beneficial drugs
  - angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

## Conclusioni (I)

- Nella cardiopatia ischemica, le donne si presentano con un maggior carico di sintomi e comorbidità rispetto agli uomini e vanno incontro ad una prognosi peggiore
- Tra le cause spiccano il sottoutilizzo di terapie mediche basate sull'evidenza, ritardi nella presentazione, nella diagnosi, nel trattamento e la mancanza di dati generespecifici
- La presenza di una placca ostruttiva non è condizione necessaria né sufficiente per spiegare sintomi e manifestazioni cliniche e il riscontro di una coronarografia normale non è sinonimo di una normale circolazione coronarica... specialmente nelle donne

## Conclusioni (II)

- Differenze anatomiche, funzionali e una diversa sensibilità ai mediatori dell'infiammazione possono comportare lo sviluppo di forme di coronaropatia diffusa con un maggiore peso della disfunzione vasomotoria rispetto alla classica ostruzione focale... specialmente nelle donne
- Queste forme non comportano una prognosi migliore rispetto a quelle ostruttive... specialmente nelle donne
- I test diagnostici non devono limitarsi a rilevare l'assenza di malattia ostruttiva epicardica che rappresenta solo uno dei numerosi possibili fattori che contribuiscono all'ischemia miocardica
- Sono necessari ulteriori studi per chiarire la fisiopatologia della CAD nelle donne con l'obiettivo di individuare linee guida specifiche per migliorarne il trattamento e la prognosi

![](_page_60_Picture_0.jpeg)