DIFFERENZE DI GENERE NELLE MALATTIE CARDIOVASCOLARI

Corso “Medicina di Genere: la cultura delle differenze”

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DIFFERENCES IN THE USE OF PROCEDURES BETWEEN WOMEN AND MEN HOSPITALIZED FOR CORONARY HEART DISEASE

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SEX DIFFERENCES IN THE MANAGEMENT OF CORONARY ARTERY DISEASE

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THE YENTL SYNDROME

YENTL, the 19th-century heroine of Isaac Bashevis Singer's short story,[1] had to disguise herself as a man to attend school and study the Talmud. Being "just like a man" has historically been a price women have had to pay for equality. Being different from men has meant being second-class and less than equal for most of recorded time and throughout most of the world. It may therefore be sad, but not surprising, that women have all too often been treated less than equally in social relations, political endeavors, business, education, research, and health care.

Bernardine Healy. N Engl J Med 1991;325:274-276

"Sex and gender medicine": il principio della medicina di genere

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"Sex and gender medicine" is the original name of gender medicine. It is important to define medical concepts without ignoring key terminology. The purpose of "sex and gender medicine" is to focus on both sex and gender differences, to analyze how these two sides of the human being overlap and, finally, to improve their medical understanding. On the one hand sex, besides defining male and female, refers to the biological differences among humans, animals, tissues and cells. On the other, the concept of gender is applicable only to humans, and includes identity, roles and relations in the society. However, despite its 20 years of history, gender medicine is still little known. Biological differences among cardiovascular diseases are ignored. Symptoms and their expressions, which may be different in women, are often described as "atypical" because of the masculine vision of the heart attack and pain. Similarly, anxious syndrome is often conceived as the first reason to explain chest discomfort in women. In reality, prejudices and vagueness around women still dominate prevention and medical treatment. Our objective is to distinguish the concepts of sex and gender in order to understand the best way to face differences and medical knowledge in both.

Key words. Cardiovascular disease; Gender; Sex.

SEX AND GENDER

Scusatemi se da cardiologo di provincia, per di più superanziano, mi riesce difficile di capire perché il binomio "sex and gender", sesso e genere, non lo si possa attribuire agli animali, ma solo alla specie umana. Lo afferma un gruppo di cardiologi svizzeri della Fondazione Cardiocentro Ticino di Lugano in una pubblicazione sul *Giornale Italiano di Cardiologia*[1]. Iniziando a leggerlo mi confortava il fatto che a coordinare quel "Questionario Aperto" fosse un famoso ricercatore italiano, incomparabile nell'interpretare i risultati delle ricerche mediche e poi a riferirceli in numeri e statistiche. Questa volta però, credo si sia lasciato travolgere da un entusiasmo dei coautori ticinesi.

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Gender Difference in COVID-19

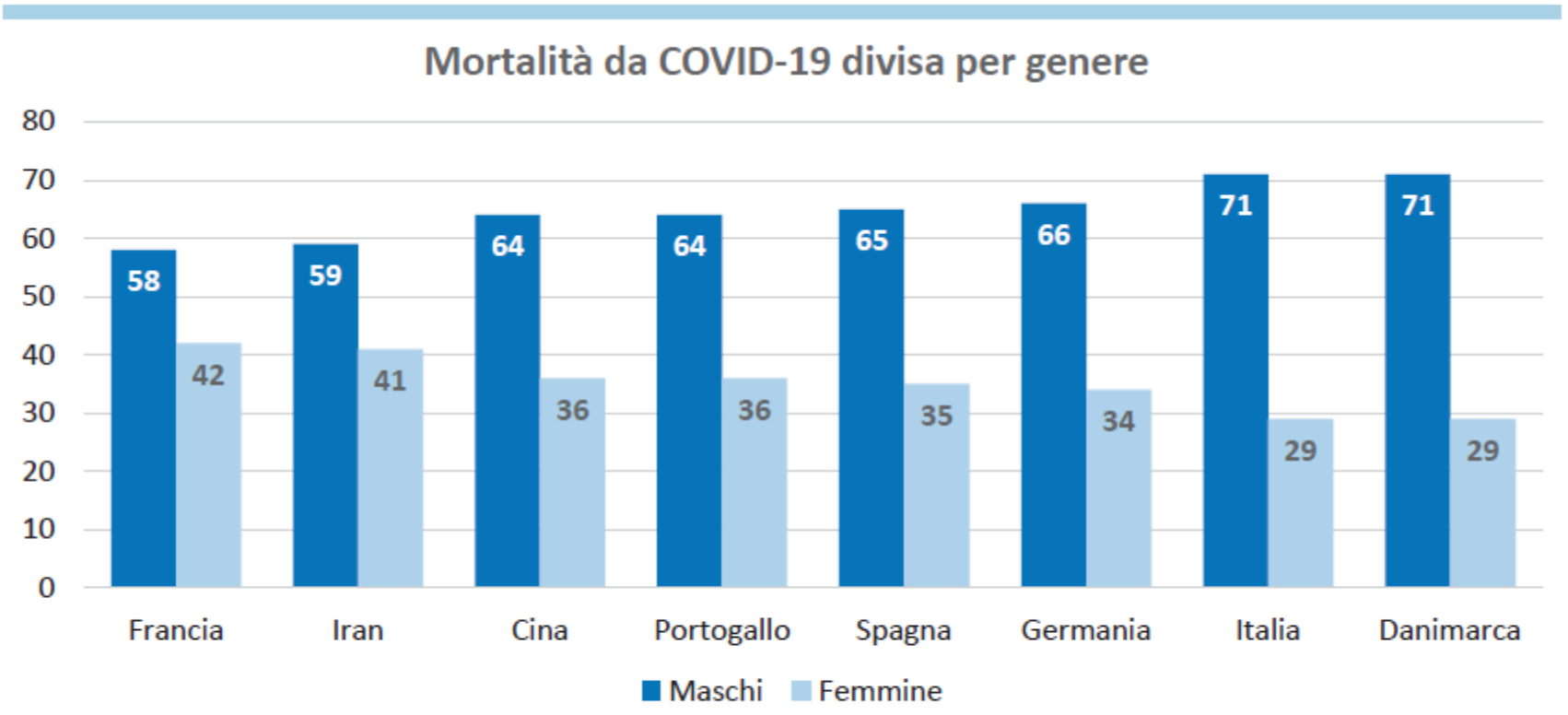

Figura 2. Decessi da COVID-19 divisi per genere, secondo i dati del Wall Street Journal Global Health 50/50 (27 marzo 2020).

Lodi E et al. G Ital Cardiol 2020; 21: 570-574

L’infarto miocardico è sempre stato considerato una malattia al maschile

Percezione sbagliata che la cardiopatia ischemica non sia una malattia delle donne

- Le malattie CV colpiscono sia gli uomini che le donne
- Dopo i 75 anni la prevalenza di malattia CV è superiore nelle donne rispetto agli uomini
- Le malattie CV sono la principale causa di morte nella donna
- Di tutte le morti prima dei 75 anni quelle causate da malattie CV sono il 42% nelle donne e 38% negli uomini

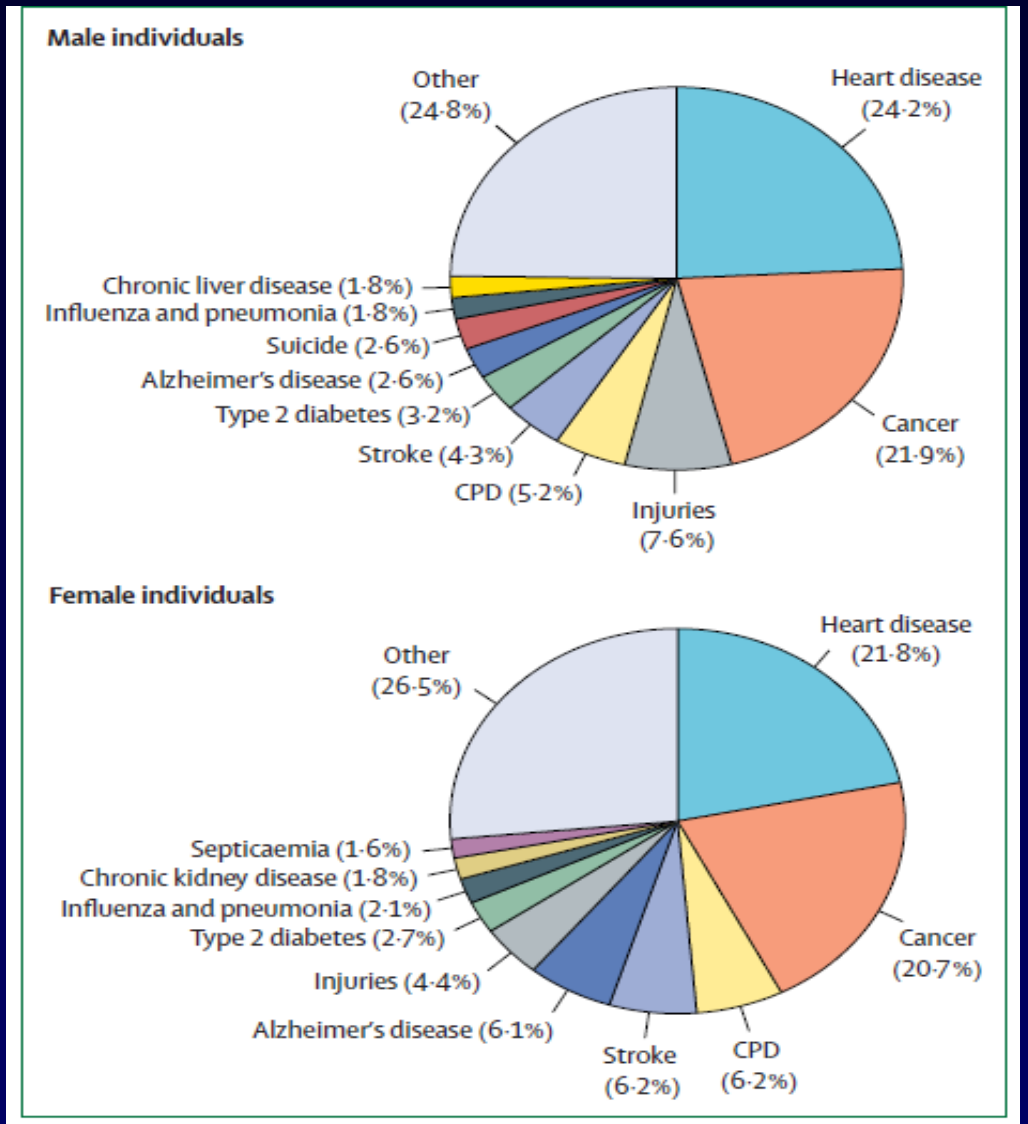

Figure 3: Percent distribution of the ten leading causes of death, by sex: USA, 2017

Mauvais-Jarvis et al. Lancet August 22, 2020

CORRIERE DELLA SERA

L'infarto per le donne è la prima causa di morte. Ma loro non lo sanno

Le donne sviluppano malattie cardiache con un ritardo di 10 anni rispetto agli uomini, ma quando succede avviene in maniera più grave. Diventano ipertese e diabetiche prima degli uomini e basta fumare un terzo delle sigarette per gli stessi danni

SILVIA TURIN

di **Silvia Turin Silvia Turin**

(Getty Images)

Una donna su due è a rischio infarto dopo i 50 anni, o quanto meno a rischio di malattie cardiovascolari che, per le signore over 50, rappresentano la prima causa di mortalità (nel 55% dei casi contro il 43% degli uomini secondo una stima dell'Osservatorio Nazionale salute della donna) superando di gran lunga tutte le forme di neoplasie, compreso il cancro al seno. Non solo, dopo i 60 anni il 32% dei casi di infarto riguarda una donna e la percentuale cresce con l'aumentare dell'età.

MORTALITÀ (DOPO ATTACCO CARDIACO) PIÙ DEGLI UOMINI Il guaio è che le donne non capiscono di essere in pericolo: 7 su 10 pensano che l'attacco cardiaco sia un problema solo maschile. Se si considera poi che l'infarto femminile è spesso atipico, perché i sintomi non sono quelli classici (si veda scheda allegata), si capisce perché dopo un attacco cardiaco il 38% delle donne muore entro un anno contro il 25% degli uomini, o perché un secondo evento colpisca il 35% delle femmine e solo il 18% dei maschi.

DOPO I 50 ANNI RISCHIO MAGGIORE CHE PER GLI UOMINI Sono i dati raccolti in quasi due anni di attività dal "Monzino Women", il primo centro italiano dedicato al cuore delle donne del Centro Cardiologico Monzino di Milano: il 30% delle donne visitate senza sintomi e precedenti, ha un rischio elevato soprattutto per pressione e colesterolo alti, ma anche per stress, ansia e depressione. «Le donne hanno impegni gravosi e non delegano, il risultato è una pressione emotiva cronica — dice **Daniela Trabattoni**, responsabile del centro —. La difficoltà nel gestire lo stress porta a un incremento in circolo di noradrenalina, adrenalina, ormone della crescita, corticotropina che hanno effetti sul cuore: salgono pressione e frequenza cardiaca, aumenta l'aggregazione piastrinica (che favorisce la formazione di trombi, *ndr*). Tutti elementi che aumentano il rischio cardiovascolare: le donne diventano ipertese e diabetiche prima degli uomini, ancor di più se hanno abitudini scorrette. A lei, per esempio, basta fumare un terzo delle sigarette di lui per avere lo stesso impatto su cuore e vasi».

INFARTO: SINTOMI DIVERSI Le donne sviluppano malattie cardiache con un ritardo di 10 anni rispetto agli uomini, ma quando succede avviene in maniera più grave che nell'uomo. Con l'arrivo della menopausa il rischio cardiovascolare della donna diventa pari, se non addirittura maggiore a quello degli uomini. Perché succede? Crollano drasticamente gli ormoni estrogeni e viene a mancare la loro attività protettiva sul sistema cardiovascolare. In Italia il 58% delle donne in menopausa sono ipertese, il 51% ha il colesterolo alto, il 67% è sovrappeso o obesa. I sintomi della insufficienza cardiaca nel gentil sesso poi cambiano: respiro corto anche a riposo, sensazione di stretta o dolore al petto mai sentiti prima, vertigini, nausea, vomito, stordimento, sudore freddo e sensazione simile a quando si ha la febbre, spossatezza estrema, dolore al braccio, alla schiena, al collo. Conoscere bene il proprio corpo aiuta a intercettare per tempo un problema.

Medicina di Genere in Cardiologia

Le differenze di genere

- Fattori di rischio cardiovascolare
- La malattia coronarica
- Lo scompenso cardiaco
- La fibrillazione atriale

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Fattori di rischio coronarico

I fattori di rischio hanno un impatto differente nella donna

- Età → - effetto protettivo degli estrogeni che posticipano l'età di insorgenza di malattie CV di una decina di anni
  - le donne vivono di più
- Familiarità
- Diabete
- Ipertensione arteriosa
- Fumo di sigaretta
- Dislipidemia
- Obesità

I fattori di rischio

- Età
- Familiarità
- Diabete → nella donna più pericoloso per le complicanze cardiovascolari : la donna diabetica sviluppa maggiormente malattia coronarica e scompenso cardiaco rispetto all'uomo.
- ipertensione arteriosa

Am Heart J. 2013 Jun;165(6):972-8. doi: 10.1016/j.ahj.2013.02.024. Epub 2013 Apr 6.

Gender differences in clinical outcomes among diabetic patients hospitalized for cardiovascular disease.

Flink L[1], Mochari-Greenberger H, Mosca L.

- Obesità

I fattori di rischio

- Età →
- Familiarità
- Diabete
- Ipertensione arteriosa → prevalenza più alta nelle donne anziane contribuendo all'aumento di comorbidità (rischio di ictus e rischio di fibrillazione atriale)
- Fumo di sigaretta
- Dislipidemia
- Obesità

I fattori di rischio

- Età
- Familiarità
- diabete
- ipertensione arteriosa
- Fumo di sigaretta → in aumento nelle donne;

  il rischio CV legato al fumo agisce sinergicamente con l'uso di contraccettivi orali
- Dislipidemia
- Obesità

I fattori di rischio

- Età
- Familiarità
- Diabete
- Ipertensione arteriosa
- Fumo di sigaretta
- Dislipidemia

- Obesità → La sindrome metabolica ha una prevalenza nella donna con età superiore a 65 anni del 60% rispetto al 35% nell'uomo

AHA Guideline

Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women—2011 Update

A Guideline From the American Heart Association

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Nuovi fattori di rischio al femminile

- Marker infiammatori
- Fenomeni a carattere autoimmune (artrite reumatoide, tiroiditi più frequenti nella donna)
- Alterata reattività vascolare (disfunzione endoteliale)
- Fattori protrombotici
- Stato psico-sociale (solitudine, depressione etc)

Scarsa consapevolezza della malattia e dei fattori di rischio cardiovascolare

Canadian Journal of Cardiology 30 (2014) 827–834

CJC Canadian Journal of Cardiology
Journal canadien de cardiologie

Clinical Research

Perceived vs Actual Knowledge and Risk of Heart Disease in Women: Findings From a Canadian Survey on Heart Health Awareness, Attitudes, and Lifestyle

Lisa A. McDonnell, MSc, MBA, Andrew L. Pipe, MD, Courtney Westcott, MSc, Sue Perron, BEPS, Deborah Younger-Lewis, RN, BScN, Nadine Elias, BSc, Jessica Nooyen, MHK, and Robert D. Reid, PhD, MBA

Division of Prevention and Rehabilitation, University of Ottawa Heart Institute, Ottawa, Ontario, Canada

Methods

A cross-country survey using an adaptation of an instrument used in the United States was undertaken in spring of 2013. Based on online (208) and telephone (1446) responses from a randomly selected sample of women aged 25 or older, a total sample of 1654 weighted percentage estimates were produced. The overall response rate was 12.5%.

Results

Just under half of women were able to name smoking as a risk factor of heart disease, and less than one quarter named hypertension or high cholesterol. Fewer than half of women knew the major symptoms of heart disease. Most women prefer to receive information on heart health from their doctor, but only slightly more than half report that their doctor includes discussion of prevention and lifestyle during clinical consultations.

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Il dolore della sindrome coronarica acuta nella donna

Caratteristiche del dolore differenti

- Sede (spesso localizzato al dorso, al collo)
- Tipologia (sintomi aspecifici, più frequente dispnea, nausea, debolezza)

La componente “dolore toracico da sforzo” è prevalentemente maschile

L’anatomia coronarica è diversa nella donna

- Coronarie piu’ piccole
- Maggiore frequenza di lesioni multiple o diffuse

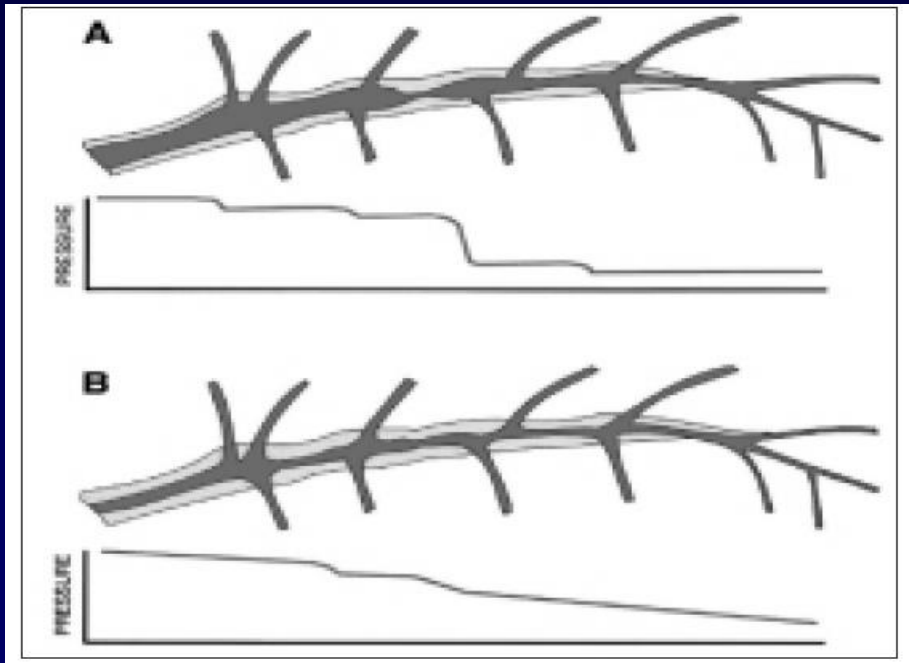


Figura 19. *Rappresentazione schematica di una riduzione di calibro di un vaso segmentaria* (A) *e diffusa* (B), *con il relativo andamento della pressione. Da Gould*[69]*, modificata.*

Women Less Likely to Be Treated for Heart Attack Symptoms

FEBRUARY 19, 2018
Kevin Kunzmann
@NotADoctorKevin


Gail D'Onofrio, MD

Younger women who report the common symptoms of a heart attack are more likely to be dismissed for treatment of the condition, according to a new study.

The Yale School of Public Health has found significant differences between genders of patients who were 55 years and younger and were hospitalized for acute myocardial infarction (AMI) following self-reported symptoms. Their analysis of 2985 patients (2009 women; 976 men) from 103 hospitals found that most patients reported chest pain, pressure, tightness, or discomfort as their primary AMI symptom, regardless of gender (87% of all women; 89.5% of all men).

However, women were more likely to reporter symptoms associated with a heart attack — indigestion, shortness of breath, palpitations, or pain in their jaw, neck, or arms — than men were. At least 3 of these symptoms were present in 61.9% of women, versus just 54.8% of men ($P < 0.001$).

Women were also more likely to believe these symptoms, when present, were associated with stress or anxiety (20.9% versus 11.8%; $P < 0.001$), while men were more likely to perceive such symptoms as a muscle-related condition. Women were more likely to have sought medical care for similar symptoms prior to the hospitalization (29.5% versus 22.1%; $P < 0.001$).

Even with a more frequent rate of symptoms and medical attention, women were more likely to be told by their health care provider that these symptoms were not heart-related (53% versus 37%; $P < 0.001$).

The analysis comes from the National Institutes of Health (NIH)-funded project "Variation In Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO)." The group sought the varied outcomes of women's heart disease different from that of men, and how do both inherent factors — genes, demographic, psychosocial, and behavioral makeup — and clinical factors — assessment, treatment, and perception — change the results of women's heart disease.

More than 8000 annual deaths in the US are due to heart disease in women aged 55 years and younger — a demographic which is about twice as likely of dying in the hospital from a heart attack than similarly aged men. For those who survive, conditions do not improve: female heart attack patients' subsequent risk of death is about 50% greater than that of men.

More particularly, non-Hispanic black women in the US are at a significantly greater risk of cardiovascular disease that leads to death. In 2015, coronary heart disease accounted for 86.7 deaths per every 100,000 population in black women. In white women, it accounted for 71.2 deaths per 100,000 population, and in Hispanic women, it accounted for 56 deaths per 100,000 population.

Stroke also accounted for 47.9 deaths per 100,000 population in black women, while accounting for just 36.2 deaths per 100,000 population in white women and 30.4 deaths per 100,000 population in Hispanic women.

This subset of data analysis brings more weight to the plight of females who suffer from heartdisease. Gail D'Onofrio, MD, study co-author and chair of the Department of Emergency Medicine at Yale School of Medicine, said that it's important to emphasize that most of that the analyzed women had multiple cardiac risk factors prior to their AMI.

Circulation

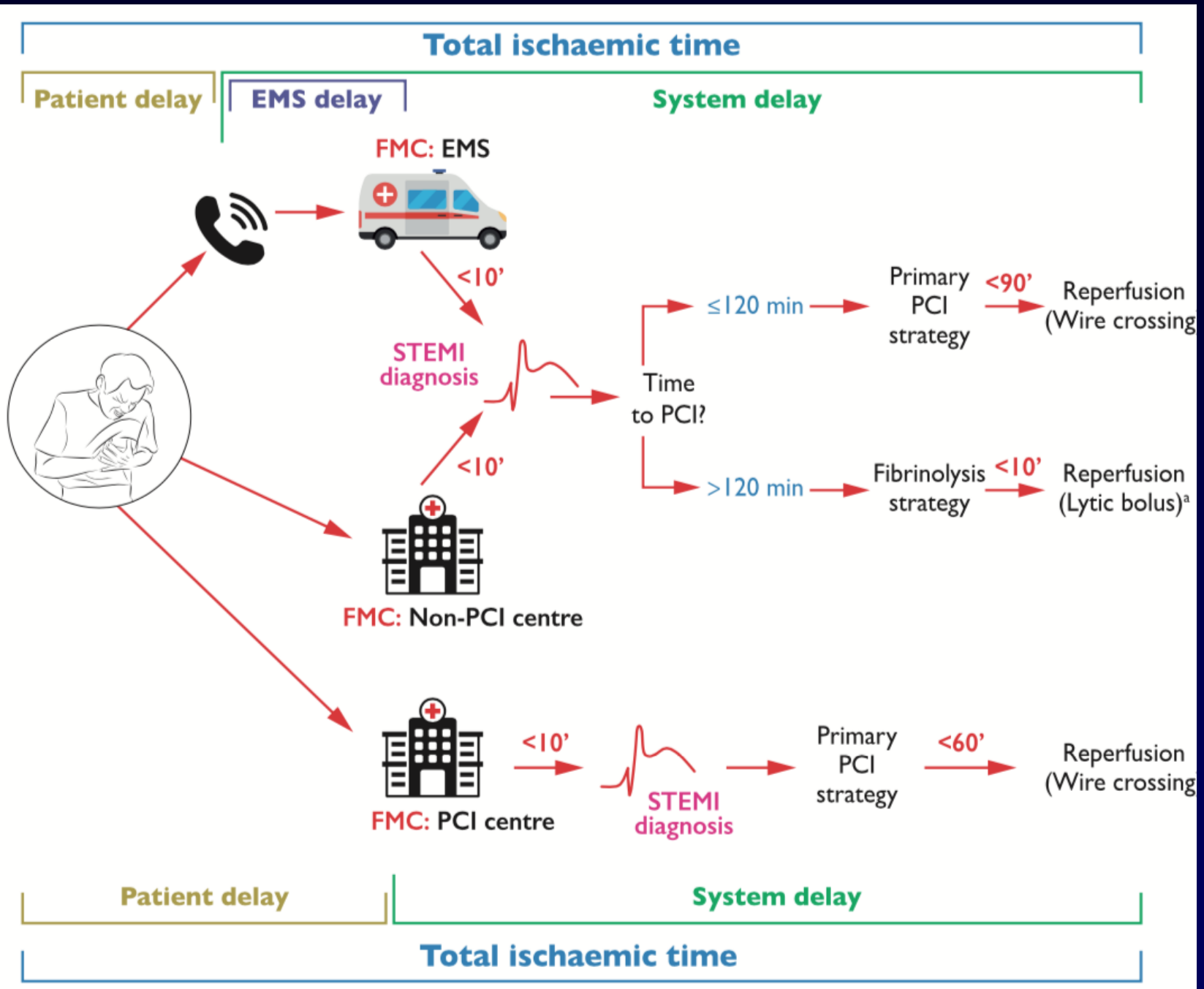
ORIGINAL RESEARCH ARTICLE

Sex Differences in the Presentation and Perception of Symptoms Among Young Patients With Myocardial Infarction

Evidence from the VIRGO Study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients)

Judith H. Lichtman, PhD
Erica C. Leifheit, PhD
Basmah Safdar, MD
Haikun Bao, PhD
Harlan M. Krumholz, MD
Nancy P. Lorenze, DNSc
Mitra Daneshvar, MD
John A. Spertus, MD
Gail D'Onofrio, MD

Circulation. 2018;137:781–790.


Total ischaemic time
Patient delay
EMS delay
System delay
FMC: EMS
<10'
STEMI diagnosis
Time to PCI?
≤120 min
Primary PCI strategy
<90'
Reperfusion (Wire crossing
>120 min
Fibrinolysis strategy
<10'
Reperfusion (Lytic bolus)a
<10'
FMC: Non-PCI centre
FMC: PCI centre
<10'
STEMI diagnosis
Primary PCI strategy
<60'
Reperfusion (Wire crossing
Patient delay
System delay
Total ischaemic time

ORIGINAL RESEARCH

Sex Differences in Prehospital Delays in Patients With ST-Segment–Elevation Myocardial Infarction Undergoing Percutaneous Coronary Intervention

Julia Stehli, MD; Diem Dinh, PhD; Misha Dagan, MMed(Epi), MD; Stephen J. Duffy, MBBS, PhD; Angela Brennan, RN; Karen Smith, PhD; Emily Andrew, MBiostat; Ziad Nehme, PhD; Christopher M. Reid, PhD; Jeffrey Lefkovits, MBBS; Dion Stub, MBBS, PhD; Sarah Zaman, MBBS, PhD

CONCLUSIONS: Female patients with ST-segment–elevation myocardial infarction experienced excess delays in patient delays, prehospital system delays, and hospital delays, even after adjustment for confounders. Prehospital system and hospital delays resulted in an adjusted excess delay of 10 minutes compared with men.

Sex Differences in Delays in Patients With STEMI

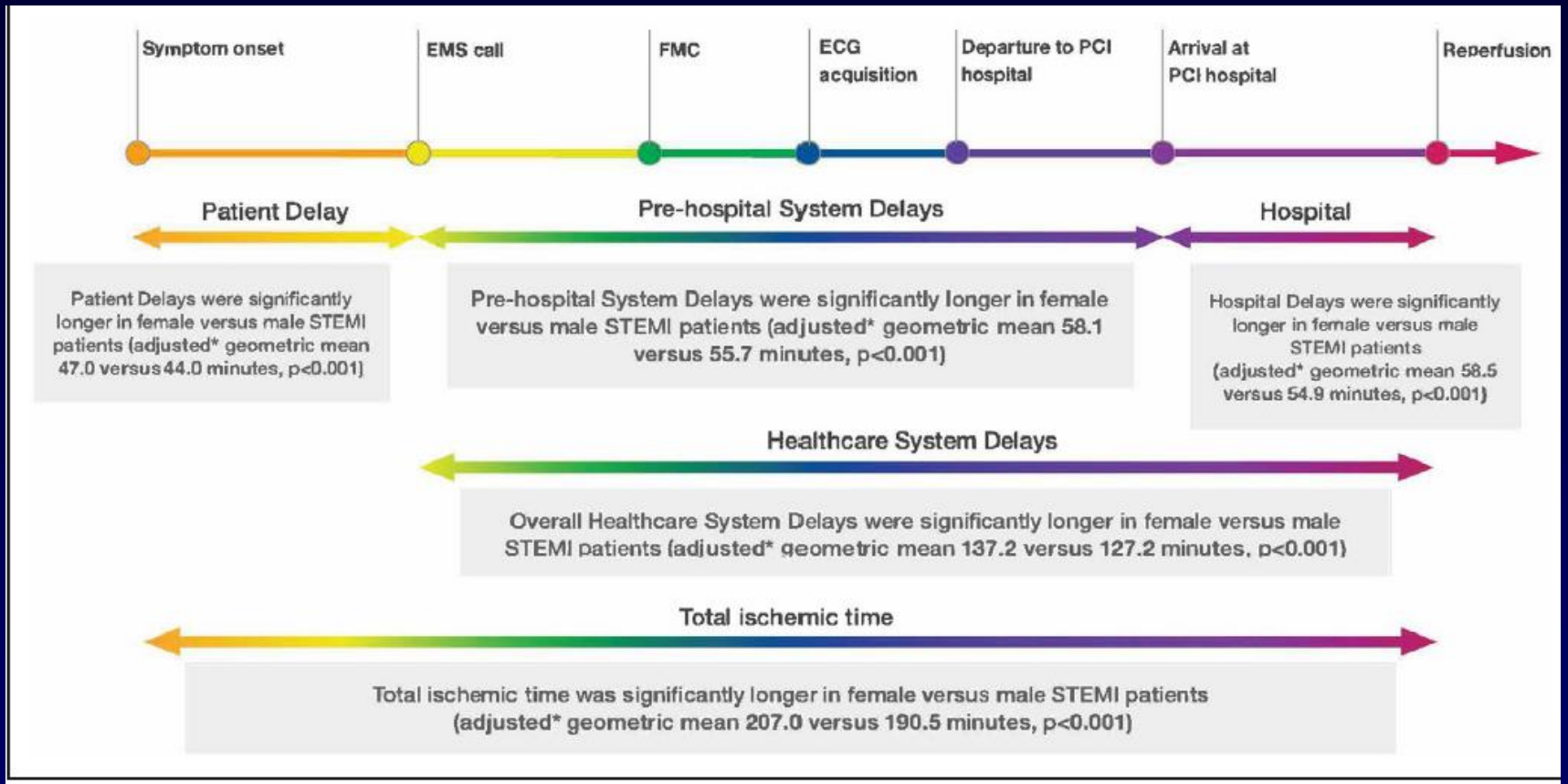


Figure 3. Sex discrepancies in patient, prehospital, and hospital reperfusion delays in patients with STEMI transported b EMS.

Julia Stehli et al. J Am Heart Assoc 2021

Gender differences in patient and system delay for primary percutaneous coronary intervention: current trends in a Swiss ST-segment elevation myocardial infarction population.

Meyer MR[1,2], Bernheim AM[1], Kurz DJ[1], O'Sullivan CJ[1], Tüller D[1], Zbinden R[1], Rosemann T[2], Eberli FR[1].

CONCLUSIONS:: STEMI-related ischaemic time in women remains greater than in men due to persistently greater patient delays. In contrast to men, clinical signs of ongoing chest discomfort do not predict delays in women, suggesting that female STEMI patients are less likely to attribute symptoms to a condition requiring urgent treatment.

Eur **Heart** J Acute Cardiovasc Care. 2018 Nov 8:2048872618810410.

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

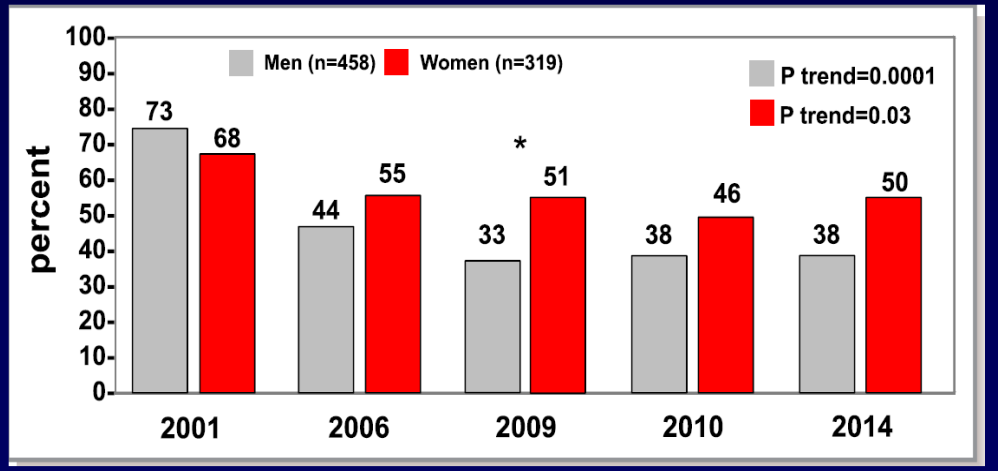
Contemporary Trends and Age-Specific Sex Differences in Management and Outcome for Patients With ST-Segment Elevation Myocardial Infarction

Leonardo De Luca, MD, PhD, FACC, FESC; Marco Marini, MD; Lucio Gonzini, BSc; Alessandro Boccanelli, MD; Gianni Casella, MD; Francesco Chiarella, MD; Stefano De Servi, MD, FESC; Antonio Di Chiara, MD; Giuseppe Di Pasquale, MD, FACC, FESC; Zoran Olivari, MD; Giorgio Caretta, MD; Laura Lenatti, MD; Michele Massimo Gulizia, MD, FACC, FESC; Stefano Savonitto, MD, FESC

J Am Heart Assoc 2016;5:e004202

In-hospital mortality rates over time according to age classes

In-hospital mortality rates among men and women with cardiogenic shock over the observation time



De Luca L et al. J Am Heart Assoc 2016;5:e004202

Original article

FIC Federazione Italiana di Cardiologia
Italian Federation of Cardiology

Sex differences in the management of acute coronary syndromes in Italy: data from the MANTRA registry

Silvia Zagnoni[a], Gianni Casella[a], Maria G. Pallotti[a], Lucio Gonzini[b], Maurizio G. Abrignani[c], Pasquale Caldarola[d], Giuseppe Romano[e], Luigi Oltrona Visconti[f], Marino Scherillo[g], Giuseppe Di Pasquale[a], on behalf of the MANTRA Investigators*

Fewer women underwent reperfusion in ST-elevation myocardial infarction and coronary angiography during hospitalization in Non-ST-elevation ACS

	Global population ($n=6394$)			STEMI ($n=2858$)			NSTEACS (n = 3536)		
Parameter	Women ($n=1894$)	Men ($n=4500$)	*P*	Women ($n=767$)	Men ($n=2091$)	*P*	Women ($n=1127$)	Men ($n=2409$)	*P*
Reperfusion therapy									
Primary PCI, %	–	–	–	56.3	66.4	<0.0001	–	–	–
Thrombolysis, %	–	–	–	11.7	17.7		–	–	–
None, %	–	–	–	32.0	15.9		–	–	–
Revascularization strategies									
Angiography performed, %	76.9	85.6	<0.0001	83.8	90.8	<0.0001	72.2	81.1	<0.0001
PCI, %	56.2	69.8	<0.0001	70.8	82.8	<0.0001	46.2	58.5	<0.0001
CABG, %	2.9	4.4	0.003	1.0	2.3	0.04	4.1	6.3	0.007

J Cardiovasc Med 2017; 18:178 - 184

Outcome results according to sex and type of ACS

Parameter	Global population ($n=6394$) Women ($n=1894$)	Men ($n=4500$)	P	STEMI ($n=2858$) Women ($n=767$)	Men ($n=2091$)	P	NSTEACS ($n=3536$) Women ($n=1127$)	Men ($n=2409$)	P
In-hospital events									
Total death, %	5.3	2.4	<0.0001	8.1	2.8	<0.0001	3.5	2.1	0.01
Reinfarction or infarction, %	1.7	1.9	0.65	1.7	1.7	0.97	1.8	2.1	0.50
Heart failure or worsening, %	13.3	7.9	<0.0001	16.4	8.3	<0.0001	11.2	7.5	0.0003
Shock or Killip IV, %	3.6	2.1	0.0003	5.2	2.4	0.0002	2.6	1.8	0.12
Any stroke, %	1.0	0.5	0.03	0.9	0.7	0.60	1.1	0.3	0.007
Major TIMI bleedings, %	2.1	0.9	<0.0001	3.1	0.8	<0.0001	1.4	1.0	0.22
Cumulative 6-month events									
Total death, %	10.6	5.5	<0.0001	13.4	5.7	<0.0001	8.7	5.4	0.0002
Hospitalization for reinfarction, %	4.0	3.4	0.23	4.0	3.1	0.22	4.0	3.7	0.62
Death or reinfarction, %	13.4	8.3	<0.0001	16.2	8.4	<0.0001	11.5	8.3	0.003
Heart failure or worsening, %	15.7	9.4	<0.0001	18.6	9.8	<0.0001	13.8	9.1	<0.0001
Any stroke, %	1.5	0.9	0.06	1.2	1.1	0.87	1.7	0.8	0.02
Major TIMI bleedings, %	2.5	1.2	<0.0001	3.4	1.0	<0.0001	2.0	1.3	0.16

Table 5 Independent predictors of in-hospital TIMI major bleeding

Predictors	OR (CI 95%)	P
Weight (Kg)	0.97 (0.95–0.99)	0.003
Female sex	1.80 (1.09–2.96)	0.02
Peripheral artery disease[a]	2.95 (1.83–4.78)	<0.0001
Switching anticoagulant therapy[b]	2.62 (1.36–5.05)	0.004
Creatinine ≥2 mg/dl on admission	3.68 (1.84–7.33)	0.0002
Intraortic balloon pump implantation	4.44 (1.85–10.69)	0.0009

CI, confidence interval; OR, odds ratio. [a]Stroke/transient ischemic attack/peripheral vascular disease. [b]Patients treated with more than 2 anticoagulants (unfractionated heparin, low molecular weight heparin, fondaparinux or bivalirudin).

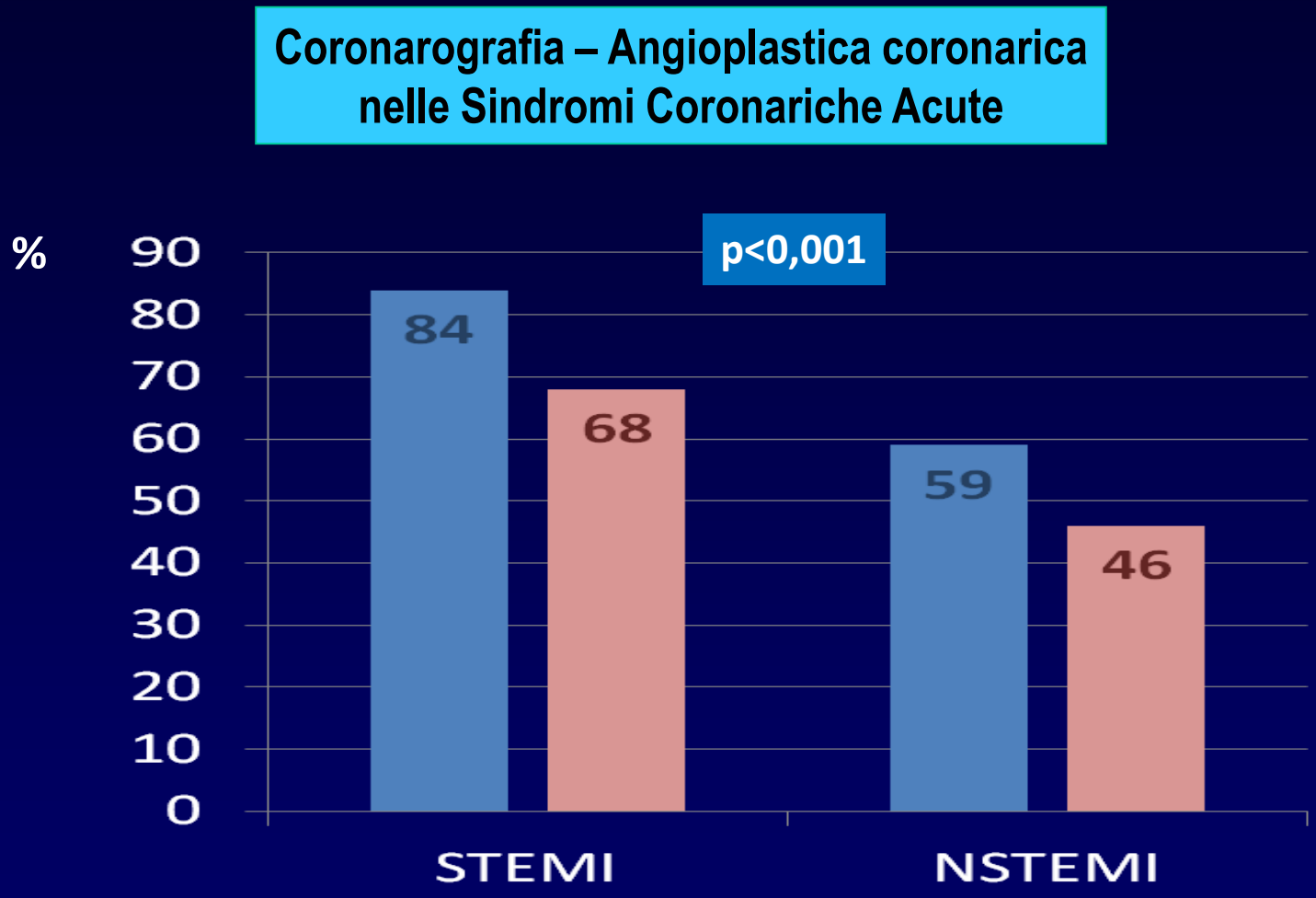
Zagnoni S, Di Pasquale G et al. J Cardiovasc Med 2017; 18:178-184

Multivariate Model for Major Bleeding in Patients with NSTEMI

Variable	Adjusted OR	P-value
Age (per 10y increase)	1.22	0.0002
Female sex	1.36	0.0116
History of renal insufficiency	1.53	0.0062
History of bleeding	2.18	0.014
GPIIb/IIIa blockers	1.86	<0.001
Percutaneous interventions	2.24	<0.0001

Moscucci M. et al. for the GRACE Investigators Eur Heart J 2003;24:1815-1823

Undertreatment delle donne nel registro MANTRA dell'ANMCO



Casella G, Di Pasquale G et al.
Eur Heart J Acute Cardiovasc Care 2013

Due presentazioni della malattia coronarica tutte al femminile

- Sindrome X → angina microvascolare
- Tako - Tsubo → “crepacuore”

Sindrome X **Sindrome di Tako-Tsubo**

Comune substrato anatomico

assenza di malattia ateromasica critica
delle arterie coronarie *epicardiche*

Angina Microvascolare (Sindrome X)

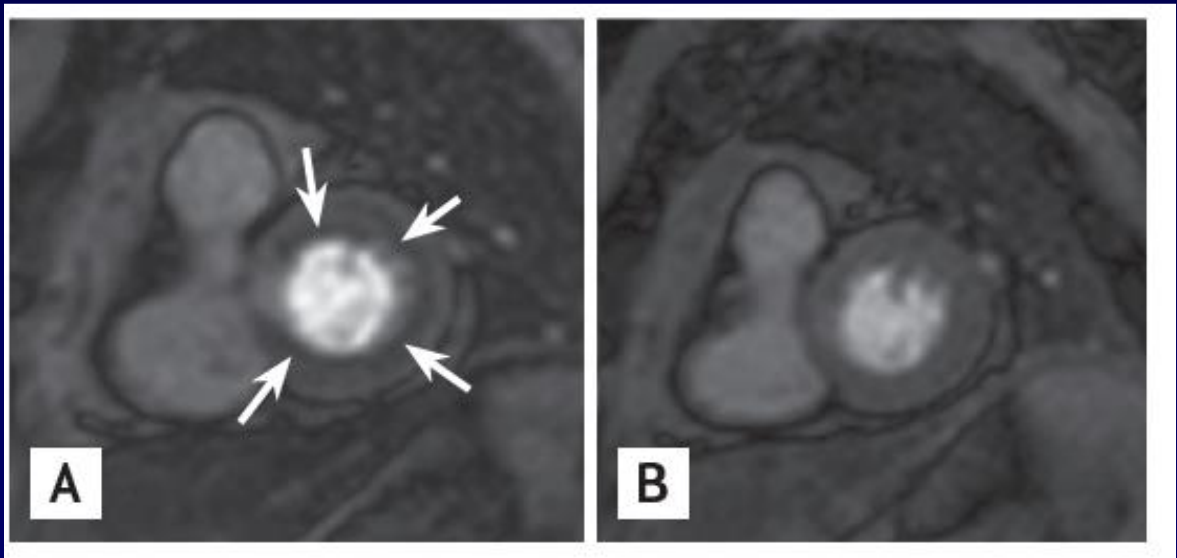
Caratterizzata da :

- dolore toracico cardiaco
- ischemia alla prova da sforzo
- assenza di malattia coronarica

Microvascular angina: angina that predominantly affects women

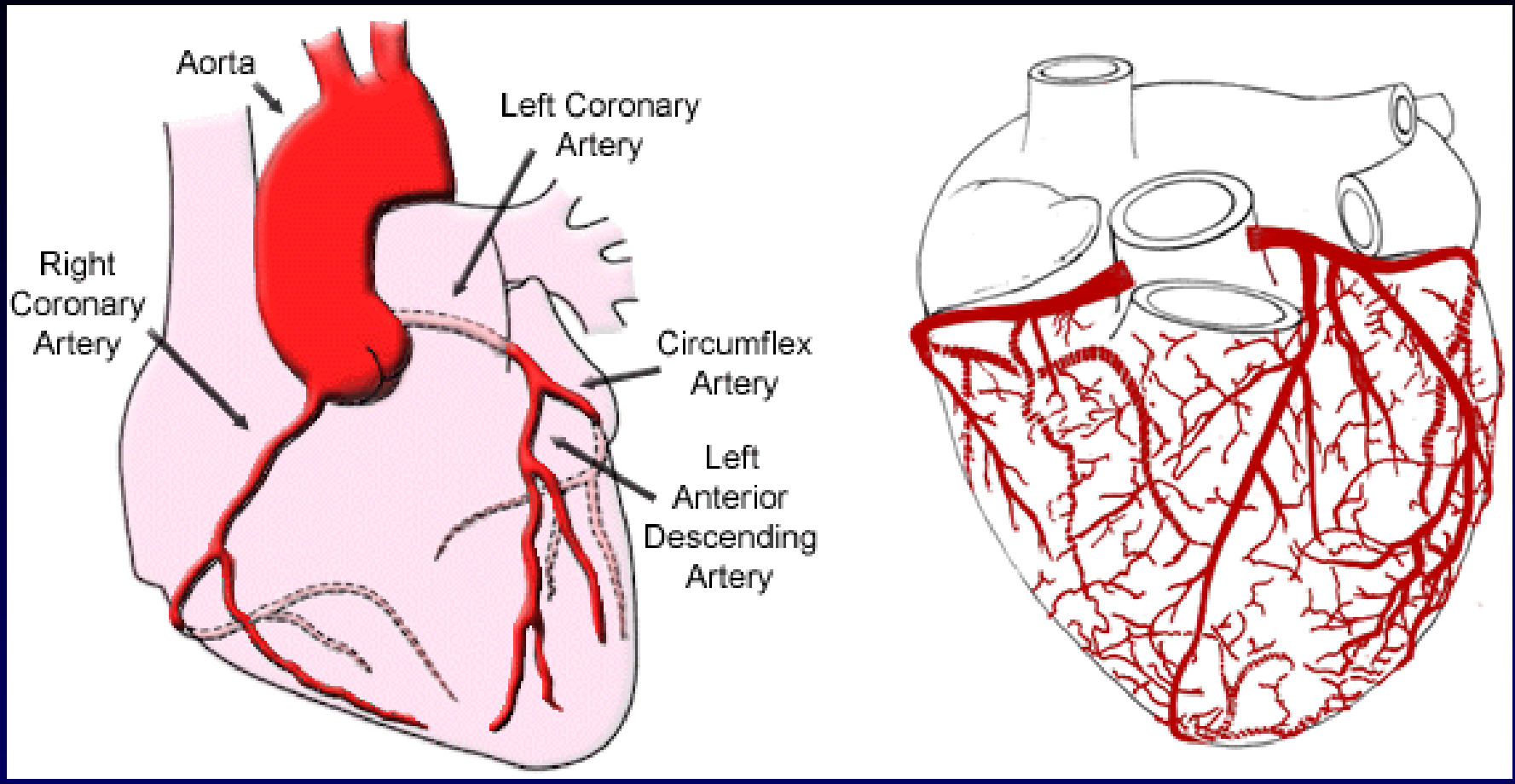
Jin Joo Park[1], Sung-Ji Park[2], and Dong-Ju Choi[1,3]

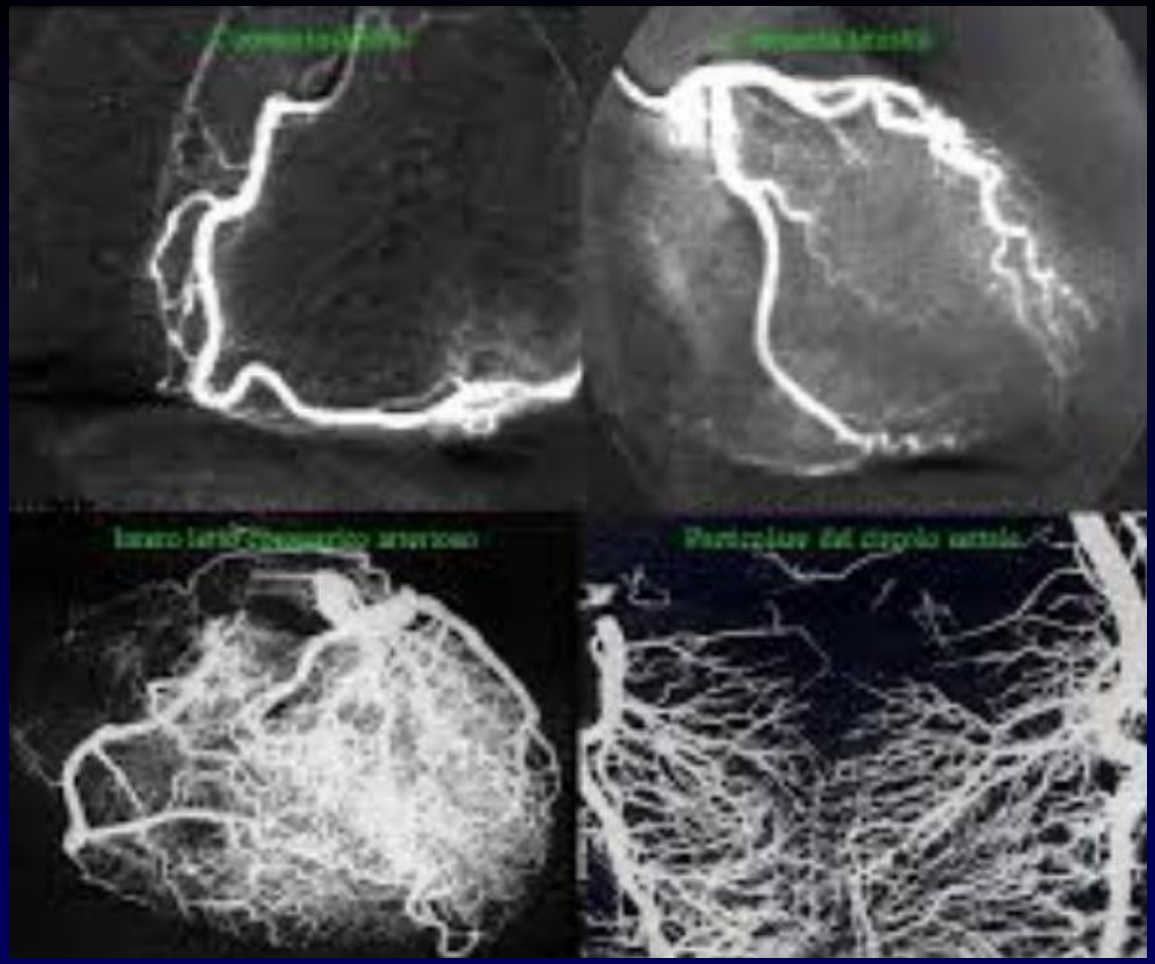
- Assenza di restringimenti coronarici
- Sintomi di angina spesso resistente ai farmaci
- Frequenti ricoveri in ospedale e nuove coronarografie

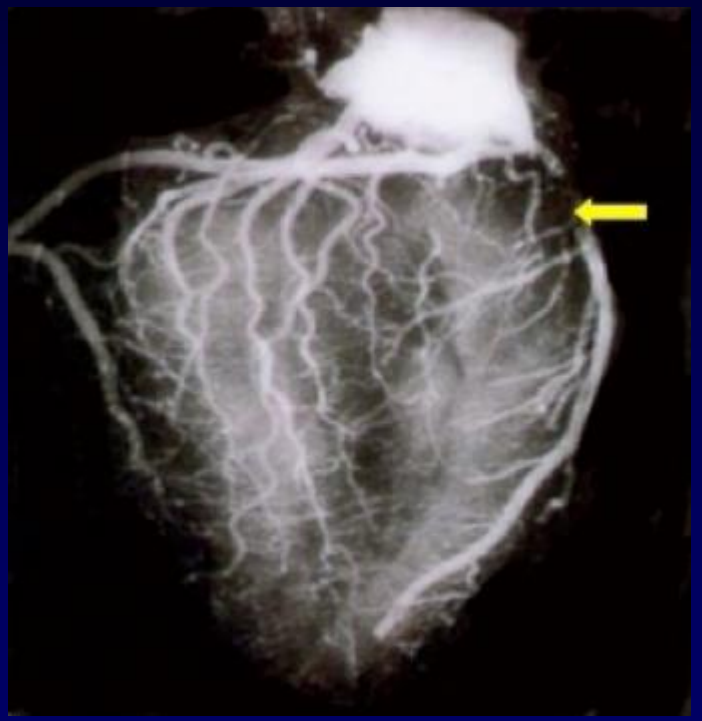


Adenosine-perfusion MR imaging in patients with microvascular angina. (A) Stress perfusion image: inducible myocardial perfusion defect (> 25% of myocardium, arrows) (B) Rest perfusion image, no perfusion defect

Korean J Intern Med 2015;30:140-147

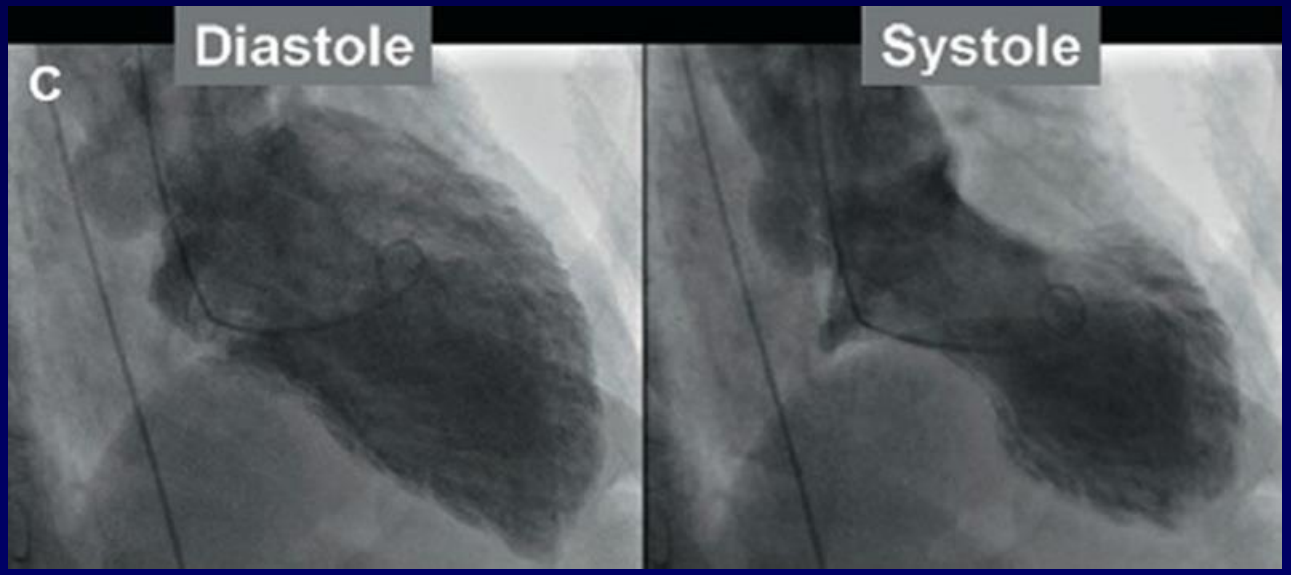

Aorta
Left Coronary Artery
Right Coronary Artery
Circumflex Artery
Left Anterior Descending Artery





Sindrome di Tako-Tsubo

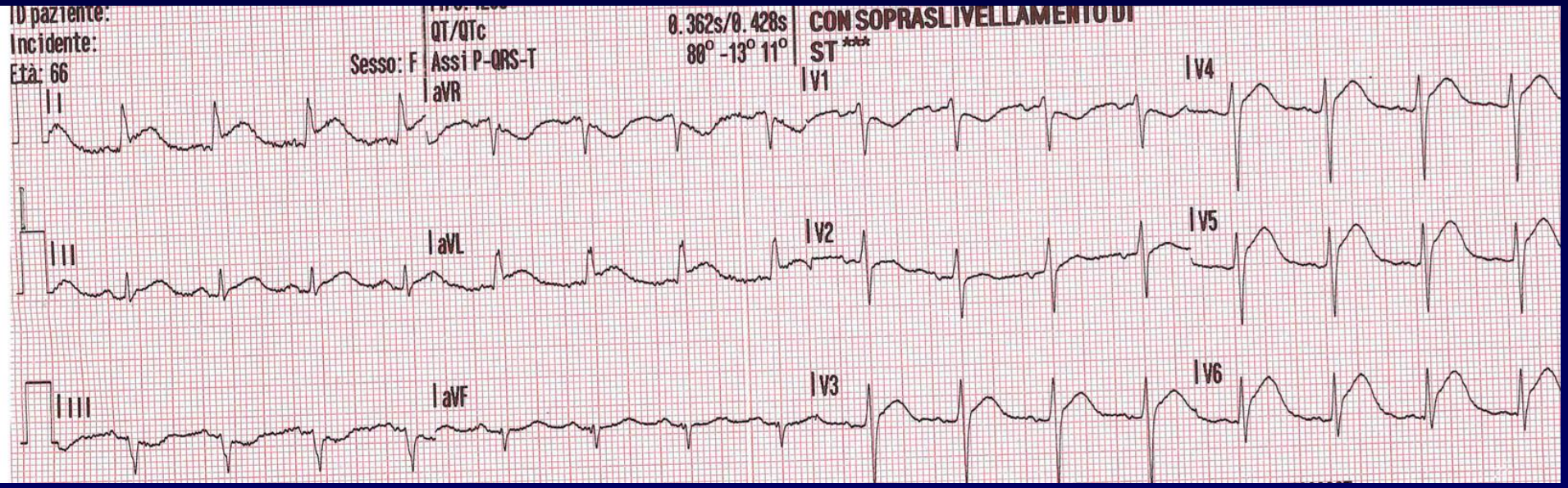
- Transitoria disfunzione cardiaca in assenza di lesioni coronariche
- Aspetto balloniforme della parte apicale del cuore
- Forte prevalenza femminile, specie in postmenopausa
- Forte associazione con stress emotivi o fisici

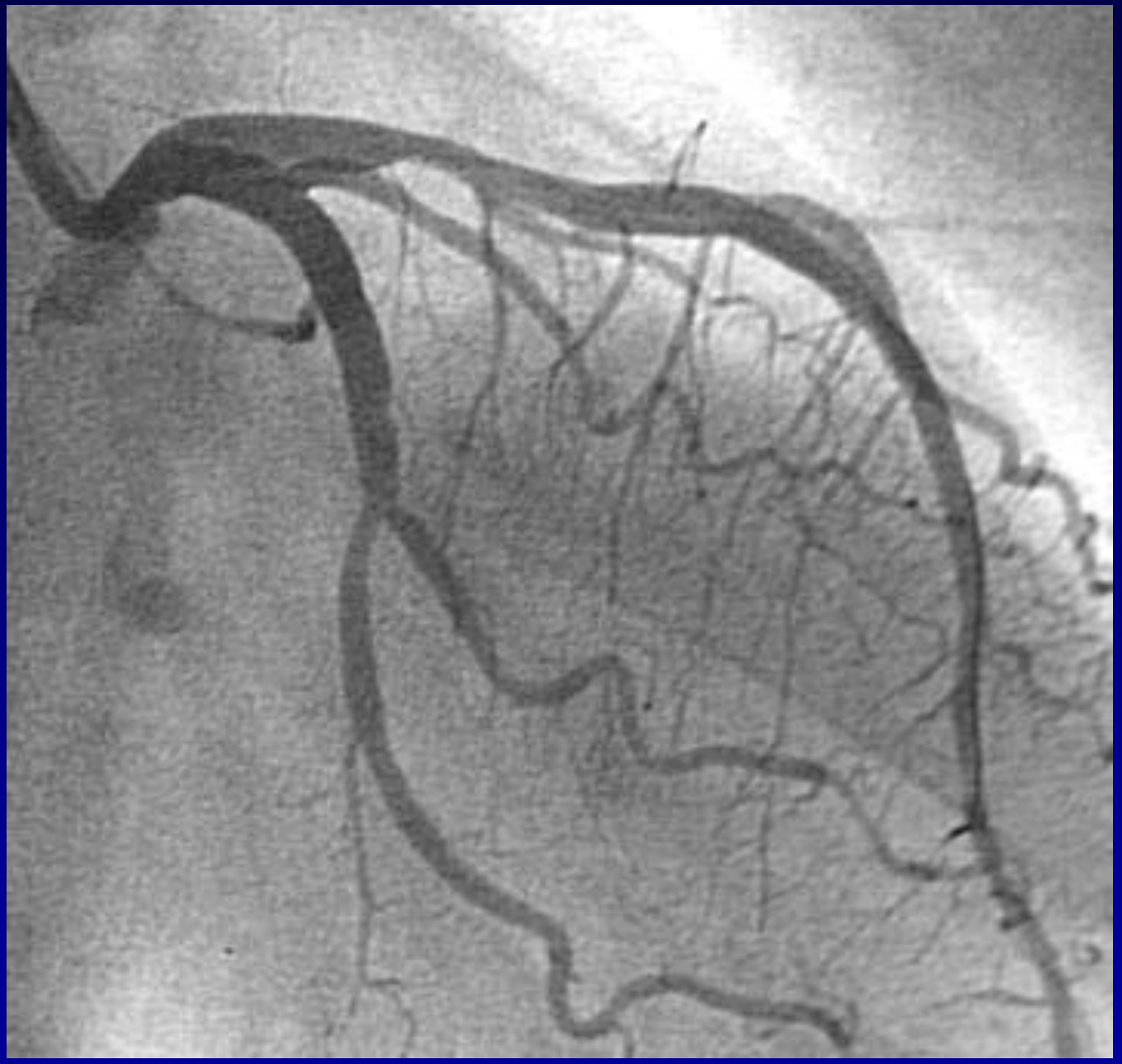


Caso Clinico Sig.ra Marta

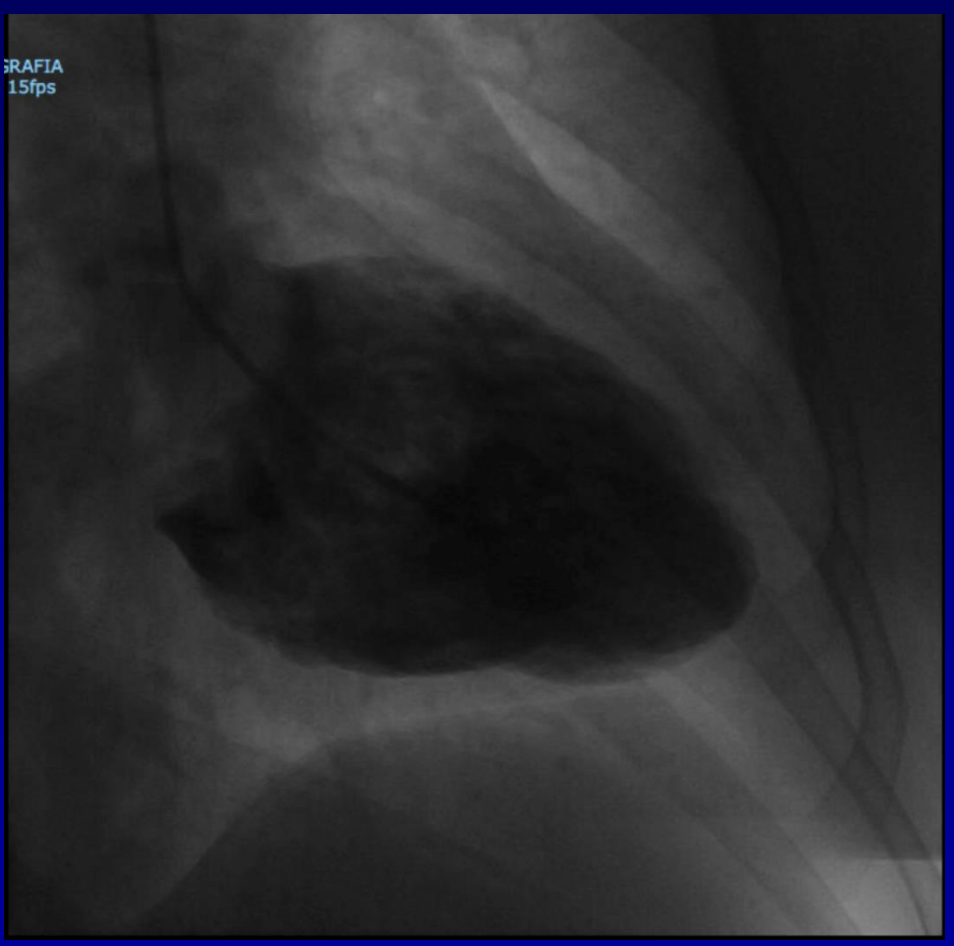
- Donna di 66 anni con sindrome ansioso-depressiva
- Assenza di FR coronarico
- Il 3.2.2018 trova il figlio di 29 anni morto nel letto
- Insorgenza improvvisa di violento dolore costrittivo retrosternale
- Immediata attivazione del 118

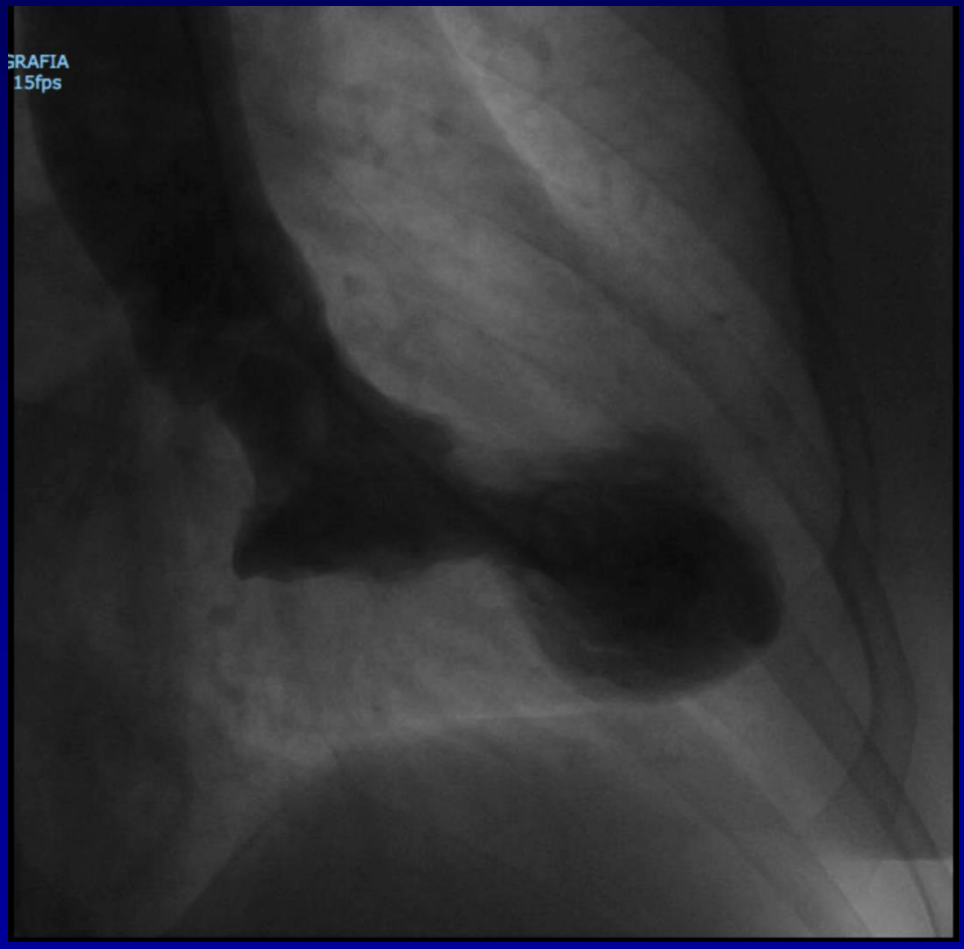
ECG teletrasmesso all'UTIC dell'Ospedale Maggiore di Bologna 3.2.2019 ore 12.51



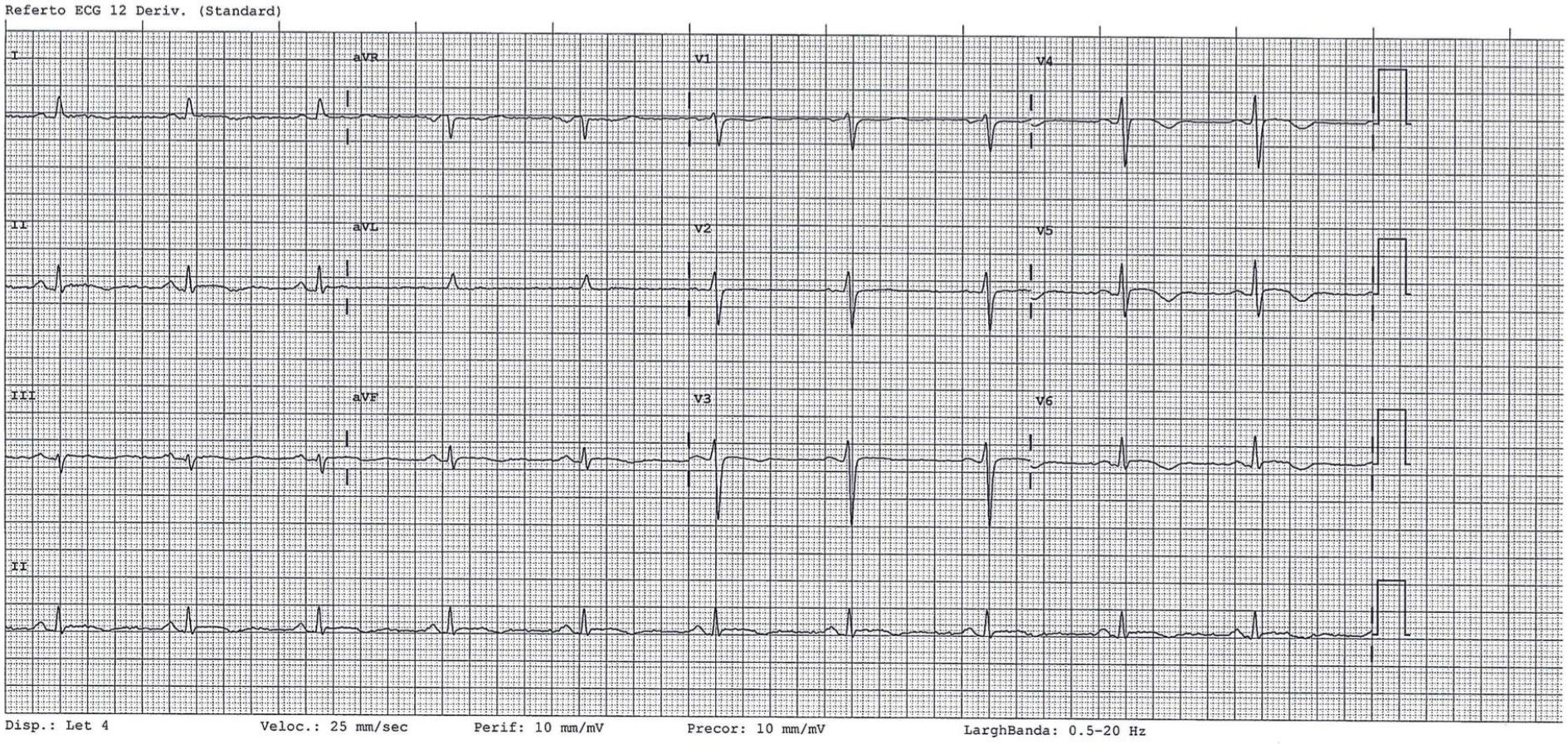


Ventricolografia: 3.2.2019 ore 14.16





ECG: 4.2.2019


Referto ECG 12 Deriv. (Standard)
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
Disp.: Let 4
Veloc.: 25 mm/sec
Perif: 10 mm/mV
Precor: 10 mm/mV
LarghBanda: 0.5-20 Hz

Caso Clinico Sig.ra Marta

- Decorso clinico non complicato
- Dimessa in 5a giornata
- Al controllo ad 1 mese e 12 mesi: ECG normale e normale funzione VS all'ecocardiogramma

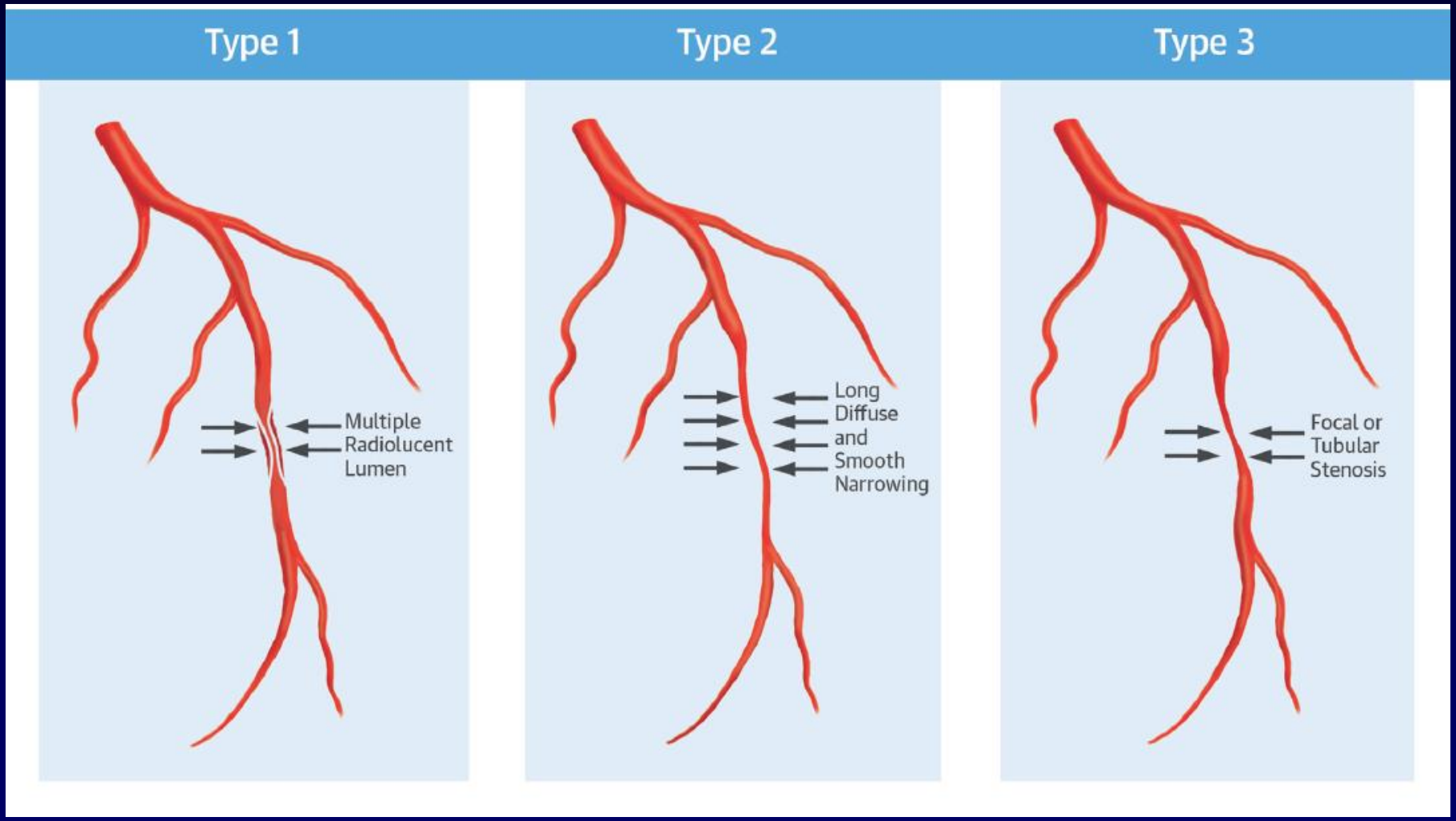
Spontaneous Coronary Artery Dissection

Clinical Outcomes and Risk of Recurrence

Jacqueline Saw, MD,[a] Karin Humphries, DSc,[b] Eve Aymong, MD,[c] Tara Sedlak, MD,[a] Roshan Prakash, MBBS,[a] Andrew Starovoytov, MD,[a] G.B. John Mancini, MD[a]

J Am Coll Cardiol 2017;70:1148

Dissezione coronarica spontanea



Saw et al. J Am Coll Cardiol 2017:1148

TABLE 1 Baseline Characteristics

	Patients (N = 327)
Age, yrs	52.5 ± 9.6
Female	297 (90.8)
Body mass index, kg/m^2	24.4 (21.5-28.3)
Race	
Caucasian	268 (82.0)
East Asian	35 (10.7)
South Asian	17 (5.2)
African Canadian	3 (0.9)
First nation	2 (0.6)
Diabetes mellitus	15 (4.6)
Dyslipidemia	84 (25.7)
Hypertension	119 (36.4)
Current smoker	32 (9.8)
Family history of coronary artery disease	109 (33.3)
Previous MI	3 (0.9)
Cerebrovascular disease	13 (4.0)
Hypothyroidism	43 (13.1)
Postmenopausal	169* (56.9)
Migraines	119 (36.4)
Depression	74 (22.6)
Anxiety	44 (13.5)

HealthDay
News for Healthier Living

Why Bystanders Are Less Likely to Give CPR to Women

By Amy Norton
HealthDay Reporter

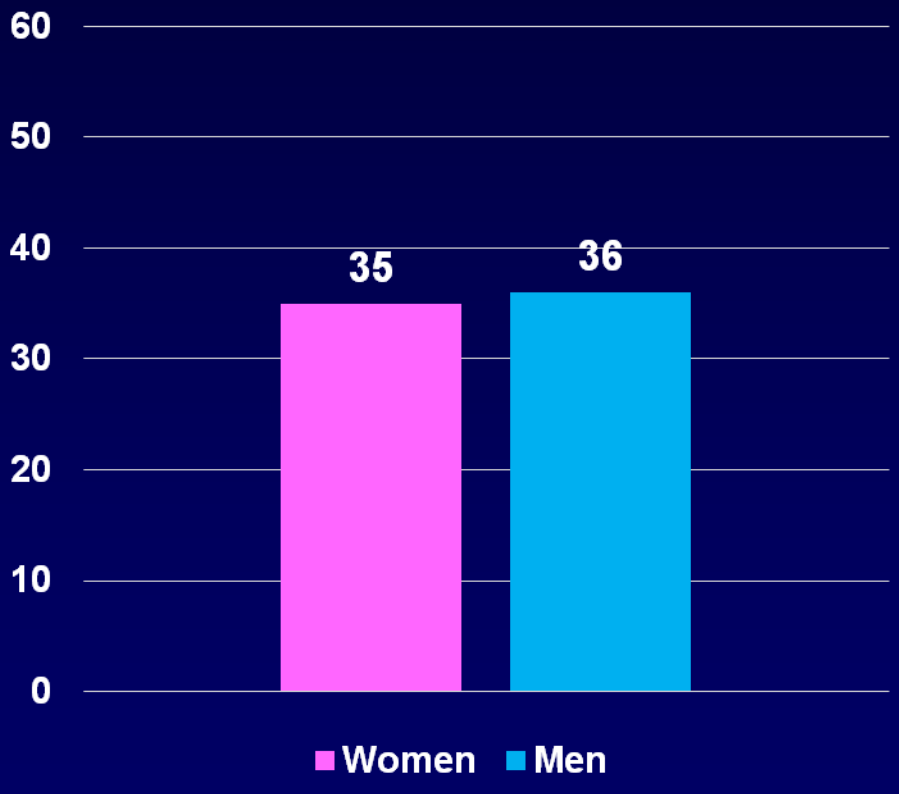
MONDAY, Nov. 5, 2018 (HealthDay News) -- Some bystanders may avoid performing CPR on women because they fear hurting them, or even being accused of sexual assault, preliminary research suggests.

In two new studies, researchers tried to dig deeper into a puzzling pattern that has been seen in past research: Women are less likely than men to receive bystander CPR if they go into cardiac arrest in a public place.

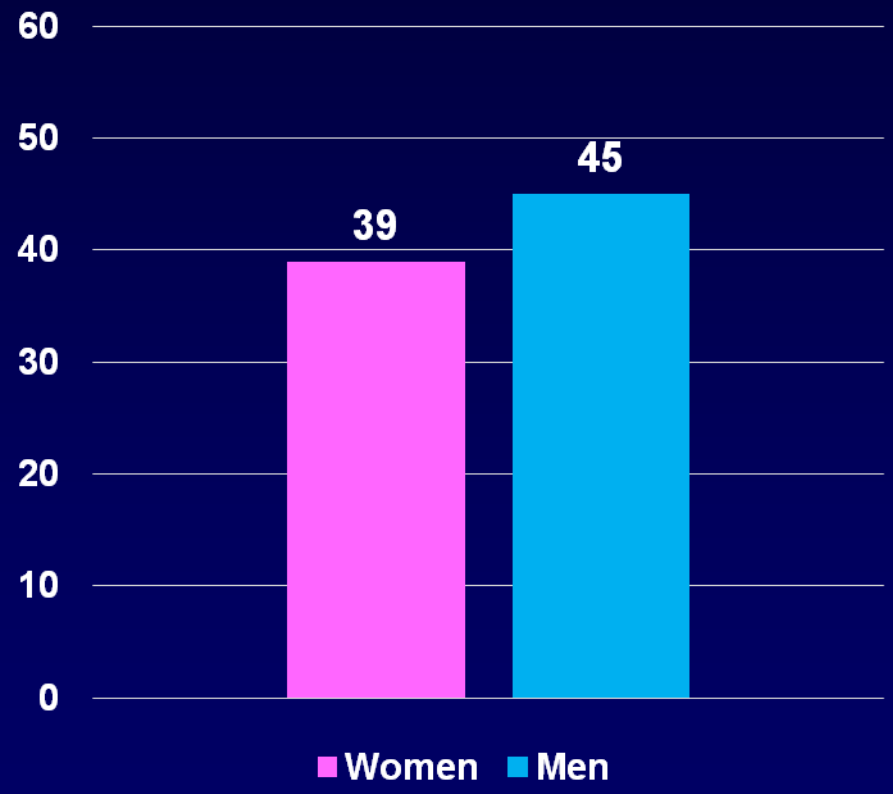
Women less likely to get CPR from bystanders

19.331 Out of Hospital Cardiac Arrests in US-Canada

Bystander CPR at home



CPR in public setting

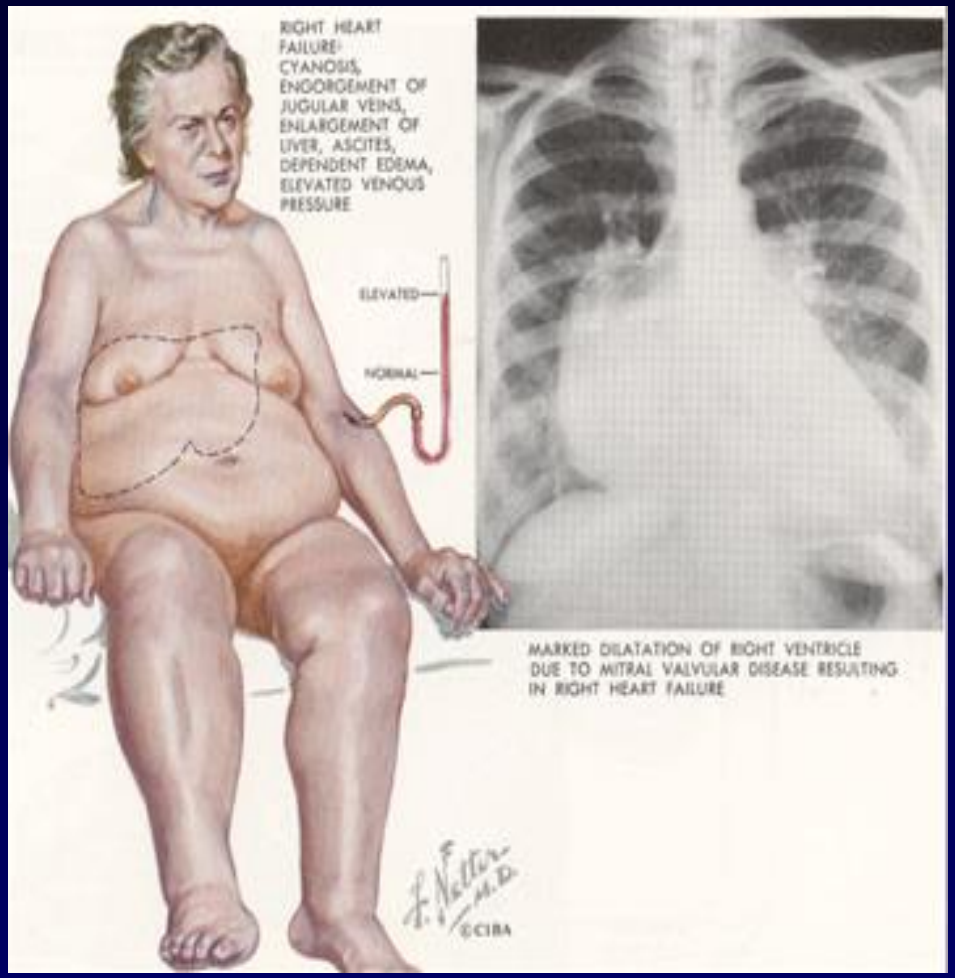


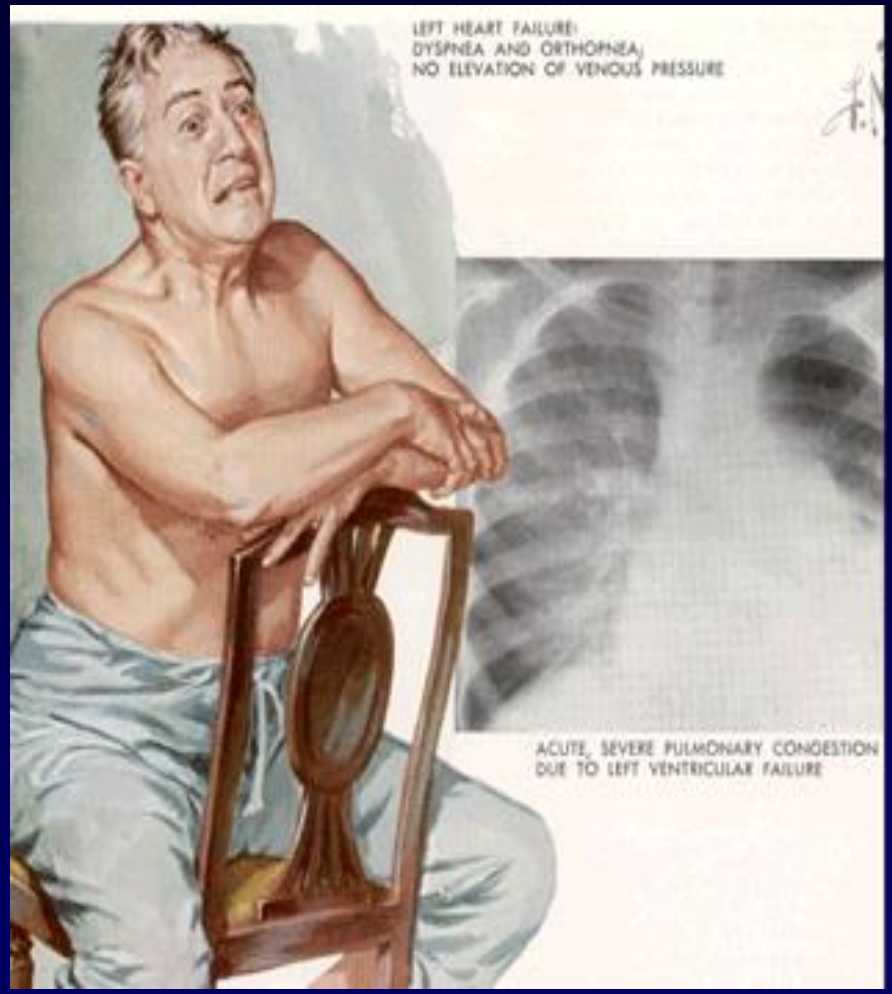
AHA Scientific Sessions, November 2018

Medicina di Genere in Cardiologia

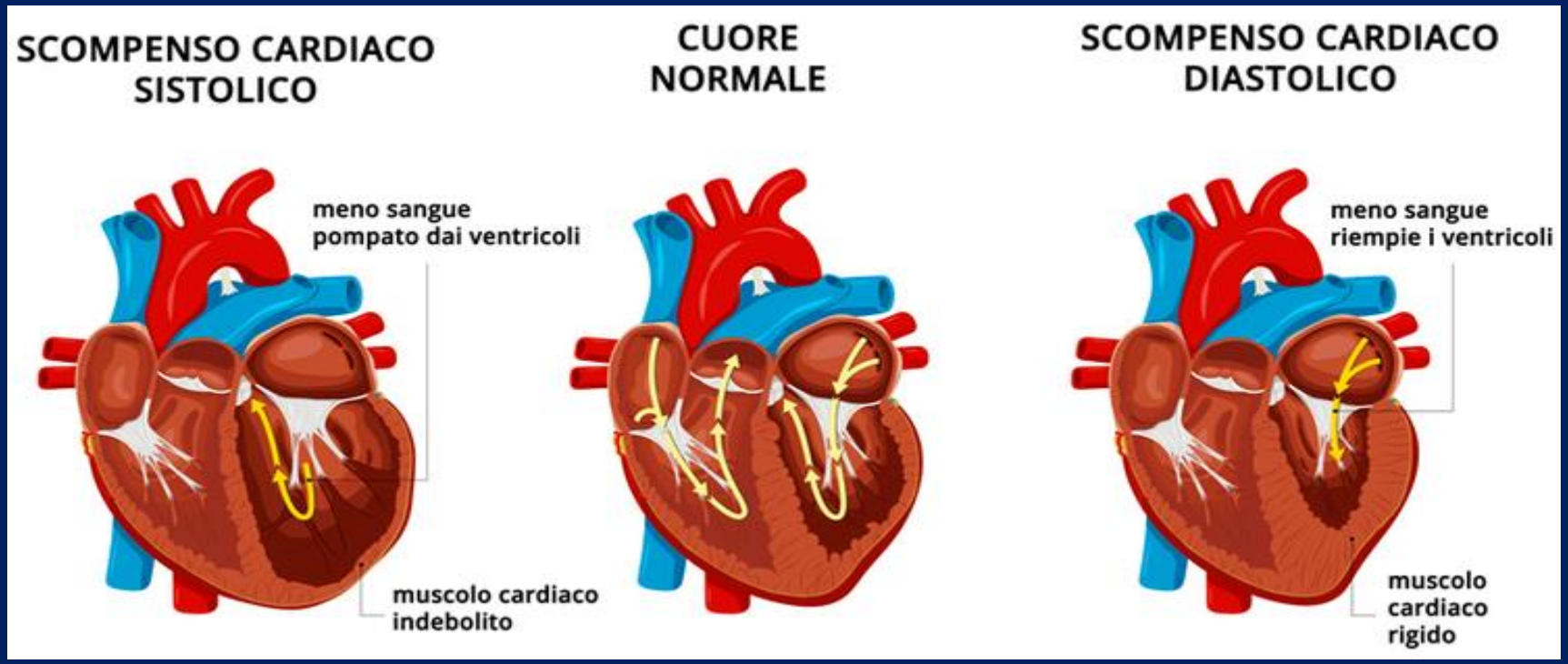
Le differenze di genere

- Fattori di rischio cardiovascolare
- La malattia coronarica
- Lo scompenso cardiaco
- La fibrillazione atriale


RIGHT HEART FAILURE: CYANOSIS, ENGORGEMENT OF JUGULAR VEINS, ENLARGEMENT OF LIVER, ASCITES, DEPENDENT EDEMA, ELEVATED VENOUS PRESSURE
ELEVATED
NORMAL
MARKED DILATATION OF RIGHT VENTRICLE DUE TO MITRAL VALVULAR DISEASE RESULTING IN RIGHT HEART FAILURE
F. Netter M.D.
©CIBA


LEFT HEART FAILURE: DYSPNEA AND ORTHOPNEA; NO ELEVATION OF VENOUS PRESSURE
ACUTE, SEVERE PULMONARY CONGESTION DUE TO LEFT VENTRICULAR FAILURE

Nella donna prevale lo scompenso cardiaco con funzione di pompa conservata



- La diagnosi è più difficile rispetto allo SC con funzione di pompa ridotta
- I farmaci sono meno efficaci

International Journal of Cardiology 255 (2018) 145–151

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Sex-related differences in chronic heart failure

Alberto Aimo [a,b,*], Giuseppe Vergaro [c], Andrea Barison [c], Silvia Maffei [c], Chiara Borrelli [a], Doralisa Morrone [b], Matteo Cameli [d], Alberto Palazzuoli [d], Giuseppe Ambrosio [e], Stefano Coiro [e], Ketty Savino [e], Elisabetta Cerbai [f], Rossella Marcucci [f], Roberto Pedrinelli [b], Luigi Padeletti [f], Claudio Passino [a,c], Michele Emdin [a,c], on behalf of the Società Italiana di cardiologia, sezione tosco-umbra

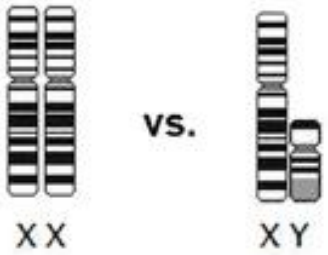
Epidemiology and clinical presentation

- ↑ **age** at diagnosis
- = **hospitalization** rates, ↑ hospital stay duration
- ↑↑ **HFpEF**
- ↑ **signs and symptoms**
- ↓ **quality of life**, functional impairment

Better prognosis for

> all-cause death,
> CV death,
> HF hospitalization,

independent of etiology



Etiology and comorbidities

- ↑ **CV risk factors** (>>diabetes mellitus, hypertension)
- ↓ **ischemic** etiology (especially in younger women)
- different **causes of non-ischemic** HF (↑ hypertension, ↓ viral)
- ↑ **AF**
- ↓ **CAD**, peripheral **vasculopathy**, **COPD**.

Therapy

- ↑ prognostic benefit from ARBs
- ↑ response to CRT
- ↓ rates of ICD and HT

A. Aimo et al. / International Journal of Cardiology 255 (2018) 145–151

TABLE 2 Heart failure trials: number and percent of women enrolled in each and LVEF for entry

Study	% Women	No. of Women	LVEF
A-HeFT	40	420	≤35%
CHARM–Overall	32	2400	Any
CHARM–Preserved	40	1212	>40%
CIBIS II	19	515	≤35%
COMPANION	32	493	≤35%
CONSENSUS	30	75	Unknown
COPERNICUS	20	469	<25%
DIG	22	1520	≤45%
ELITE-I	33	240	≤40%
ELITE-II	31	966	≤40%
MADIT II	16	192	≤30%
MERIT-HF	23	898	≤40%
MIRACLE	32	145	≤35%
PARADIGM	22	1832	≤40%
RALES	27	446	≤35%
SCD HeFT	23	588	≤35%
SOLVD-Prevention	11	484	≤35%
SOLVD-Treatment	20	505	≤35%
Val-HEFT	20	1003	<40%
V-HeFT I II III	0	0	<45%
WARCEF	20	339	<40%
HF ACTION	29	653	≤35%

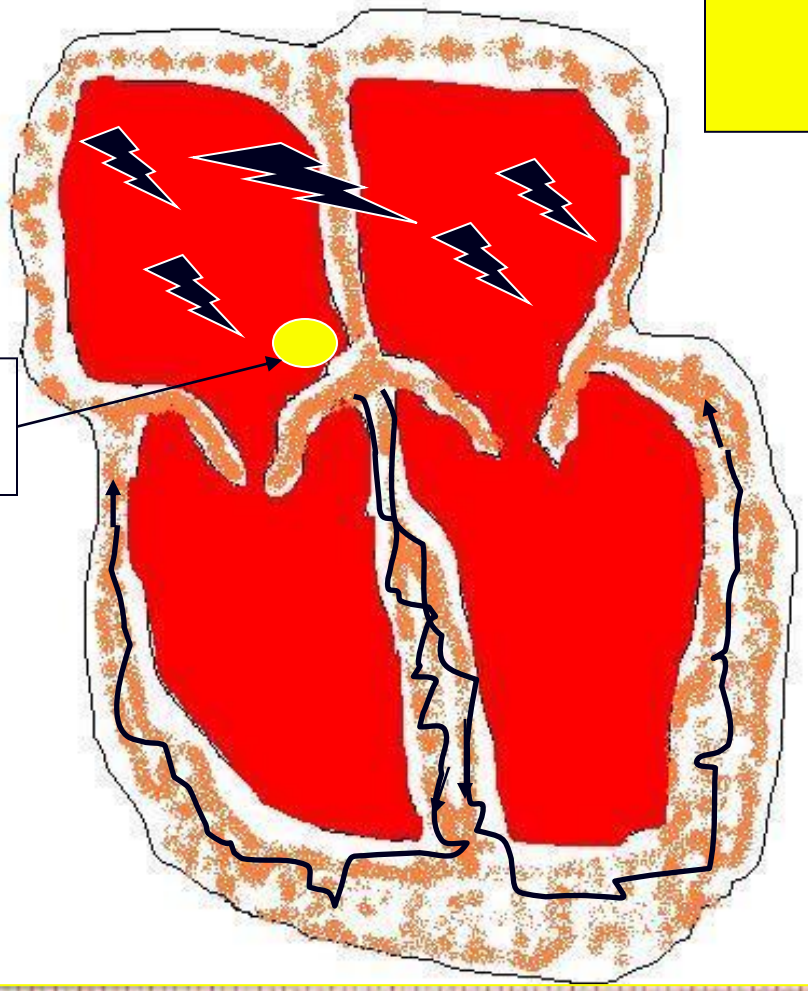
Le donne sono meno rappresentate nei trial clinici

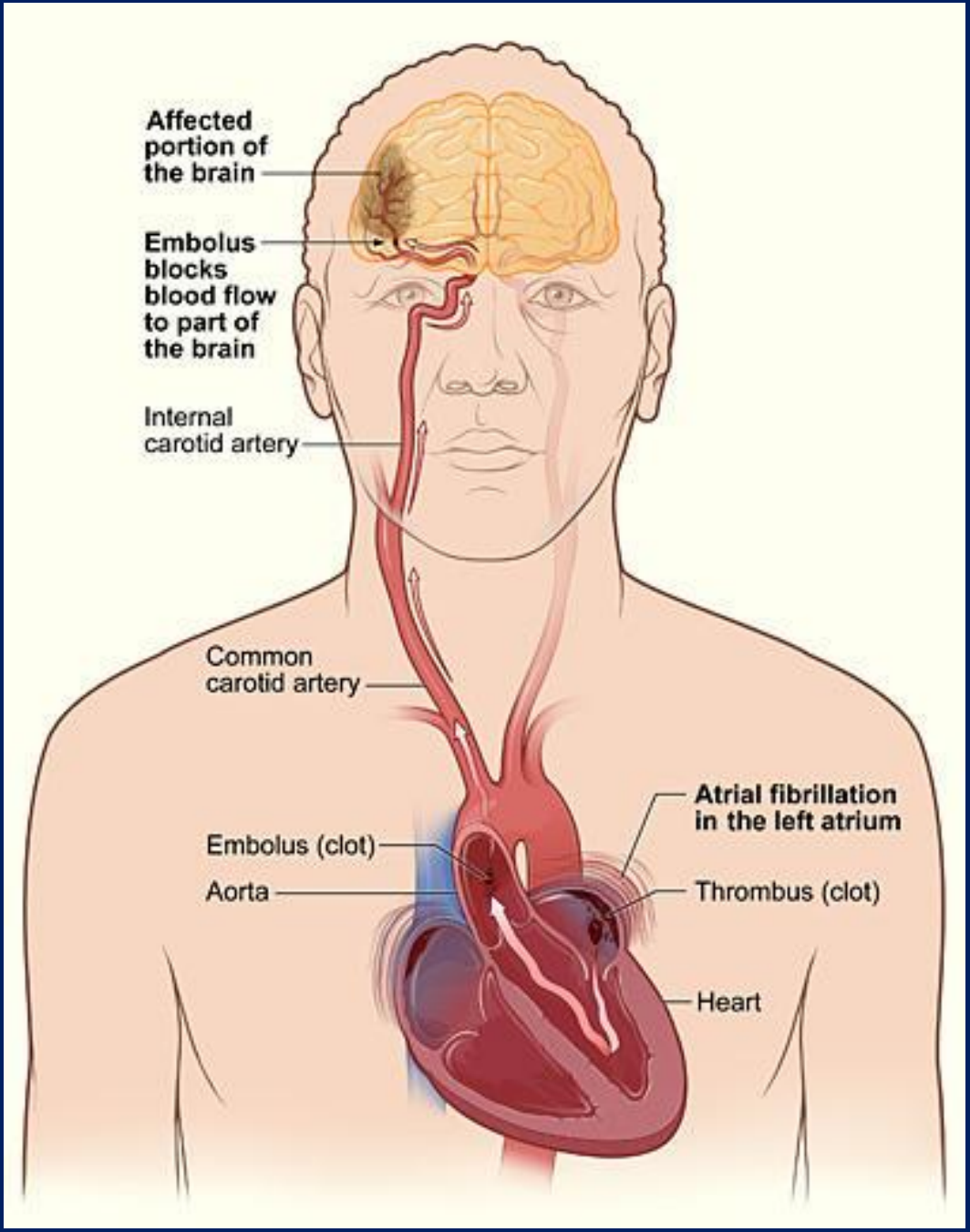
Medicina di Genere in Cardiologia

Le differenze di genere

- Fattori di rischio cardiovascolare
- La malattia coronarica
- Lo scompenso cardiaco
- La fibrillazione atriale

FIBRILLAZIONE ATRIALE




Affected portion of the brain
Embolus blocks blood flow to part of the brain
Internal carotid artery
Common carotid artery
Atrial fibrillation in the left atrium
Embolus (clot)
Aorta
Thrombus (clot)
Heart

Medicina di Genere in Cardiologia

Fibrillazione atriale e gender

- **Sesso femminile fattore di rischio per stroke**
- **Sesso femminile “risk modifier” per stroke**
- **Sesso femminile e terapia anticoagulante orale**

Gender Differences of TE Risk in AFib

Study	Event rate (%/year)	Thromboembolic risk	Ref.
Analysis of nonanticoagulated patients			
Randomized trials			
AFI	F: 5.8 M: NR	1.2 (0.8–1.8)† p = 0.18	[20]
SPAF	F: 4.4 M: 2.1	1.6 (NR)† p = 0.01	[14]
Observational studies			
ATRIA	F: 3.5 M: 1.8	1.6 (1.3–1.9)†	[22]
Framingham		1.9 (1.2–3.1)‡	[12]
Copenhagen City Heart	F: 5.17 M: 1.98	2.6 (1.3–5.4)‡	[21]
Euro Heart Survey	F: 2.2 M: 1.2	1.83 (1.10–3.03)§ p = 0.019	[32]

Madias & Trohman, Women's Health 2011;7:375-382

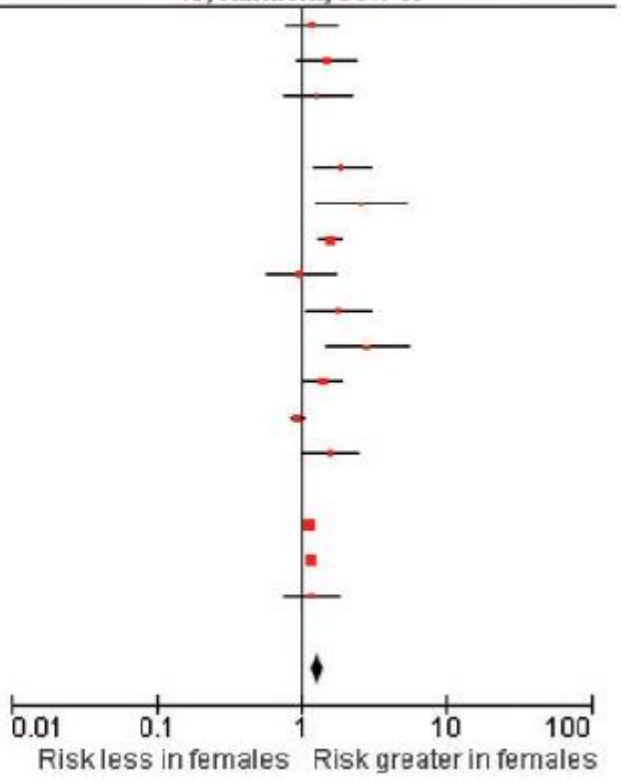
Risk of stroke in female AF patients

Meta-analysis of 17 studies, 5 RCTs and 12 observational studies

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
AFI 1994	0.18	0.21	4.9%	1.20 [0.79, 1.81]	1994
EAFT 1995	0.41	0.24	4.0%	1.51 [0.94, 2.41]	1995
Stollberger 1998	0.26	0.27	3.3%	1.30 [0.76, 2.20]	1998
SPAF 1999	0.47	0		Not estimable	1999
Framingham 2003	0.65	0.24	4.0%	1.92 [1.20, 3.07]	2003
Copenhagen City 2004	0.96	0.37	2.0%	2.61 [1.26, 5.39]	2004
ATRIA 2005	0.47	0.09	11.5%	1.60 [1.34, 1.91]	2005
BAFTA 2007	-0.01	0.28	3.1%	0.99 [0.57, 1.71]	2007
Euro Heart study 2007	0.6	0.26	3.5%	1.82 [1.09, 3.03]	2007
Poli 2009	1.06	0.34	2.3%	2.89 [1.48, 5.62]	2009
SPORTIF 2010	0.36	0.15	7.4%	1.43 [1.07, 1.92]	2010
van Staa 2011	-0.05	0.06	13.8%	0.95 [0.85, 1.07]	2011
Olesen 2011	0.47	0.23	4.3%	1.60 [1.02, 2.51]	2011
Mikkelsen 2012	0	0		Not estimable	2012
Tsadok 2012	0.13	0.03	15.8%	1.14 [1.07, 1.21]	2012
Friberg 2012	0.17	0.03	15.8%	1.19 [1.12, 1.26]	2012
Poli 2013	0.18	0.23	4.3%	1.20 [0.76, 1.88]	2013
Total (95% CI)			**100.0%**	**1.31 [1.18, 1.46]**	

Heterogeneity: Tau² = 0.02; Chi² = 49.13, df = 14 (P < 0.00001); I² = 72%

Test for overall effect: Z = 4.94 (P < 0.00001)



Wagstaff AJ et al. J Med 2014; 107:955-967

CHA_2DS_2 - VASc Score

Risk Factor	SCORE
Congestive heart failure / LV disfunction	+ 1
Hypertension	+ 1
Age ≥ 75 years	+ 2
Diabetes mellitus	+ 1
Stroke / TIA / systemic embolism	+ 2
Vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque)	+ 1
Age 65 - 74 years	+ 1
Sex category (ie female gender)	+ 1

Lip GYH et al. Chest 2010;137:263-72

Excess stroke risk in women with AFib

Possible mechanistic reasons

- reduced renal reserve
- endothelial dysfunction
- prothrombotic factors
- hormone replacement therapy
- poorer quality OAC control
- less optimal treatment of underlying CV disease

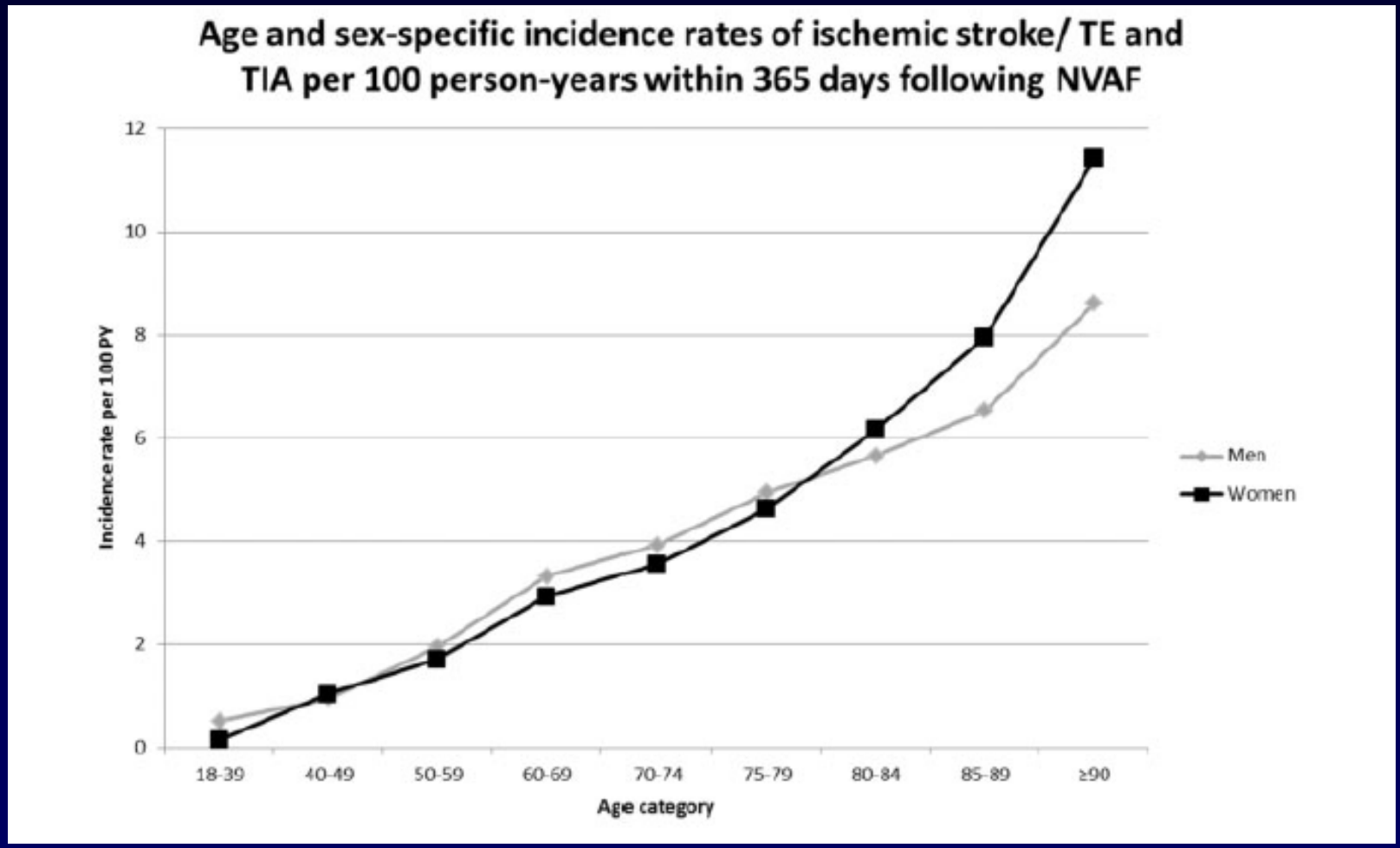
European Heart Journal (2017) **38**, 1473–1479
doi:10.1093/eurheartj/ehw613

CLINICAL RESEARCH
Atrial fibrillation

Revisiting sex differences in outcomes in non-valvular atrial fibrillation: a population-based cohort study

Christel Renoux[1,2,3]*, Janie Coulombe[1], and Samy Suissa[1,3]

Retrospective cohort study of 147.662 patients with NVAF with a mean follow-up of 2.9 years.



Renoux C et al. Eur Heart J 2017;38:1473-1479

Medicina di Genere in Cardiologia

Fibrillazione atriale e gender

- Sesso femminile fattore di rischio per stroke
- **Sesso femminile "risk modifier" per stroke**
- Sesso femminile e terapia anticoagulante orale

Circulation

ORIGINAL RESEARCH ARTICLE

Female Sex Is a Risk Modifier Rather Than a Risk Factor for Stroke in Atrial Fibrillation

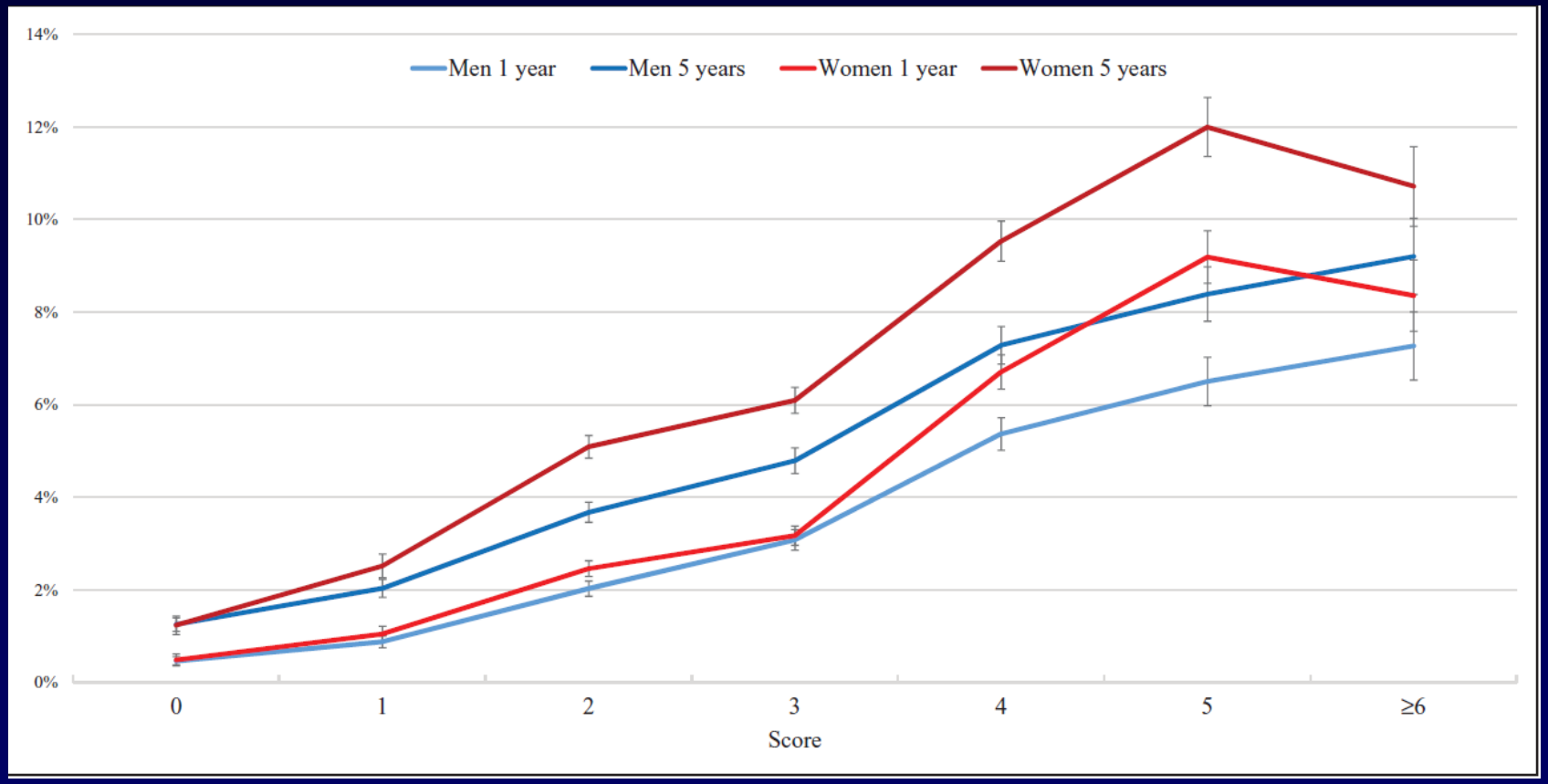
Should We Use a CHA_2DS_2-VA Score Rather Than CHA_2DS_2-VASc?

Peter Brønnum Nielsen, MSc, PhD
Flemming Skjøth, MSc, PhD
Thure Filskov Overvad, MD, PhD
Torben Bjerregaard Larsen, MD, PhD
Gregory Y. H. Lip, MD

Circulation 2018;137:832-840

Risk of TE by Sex According to CHA_2DS_2 - VA

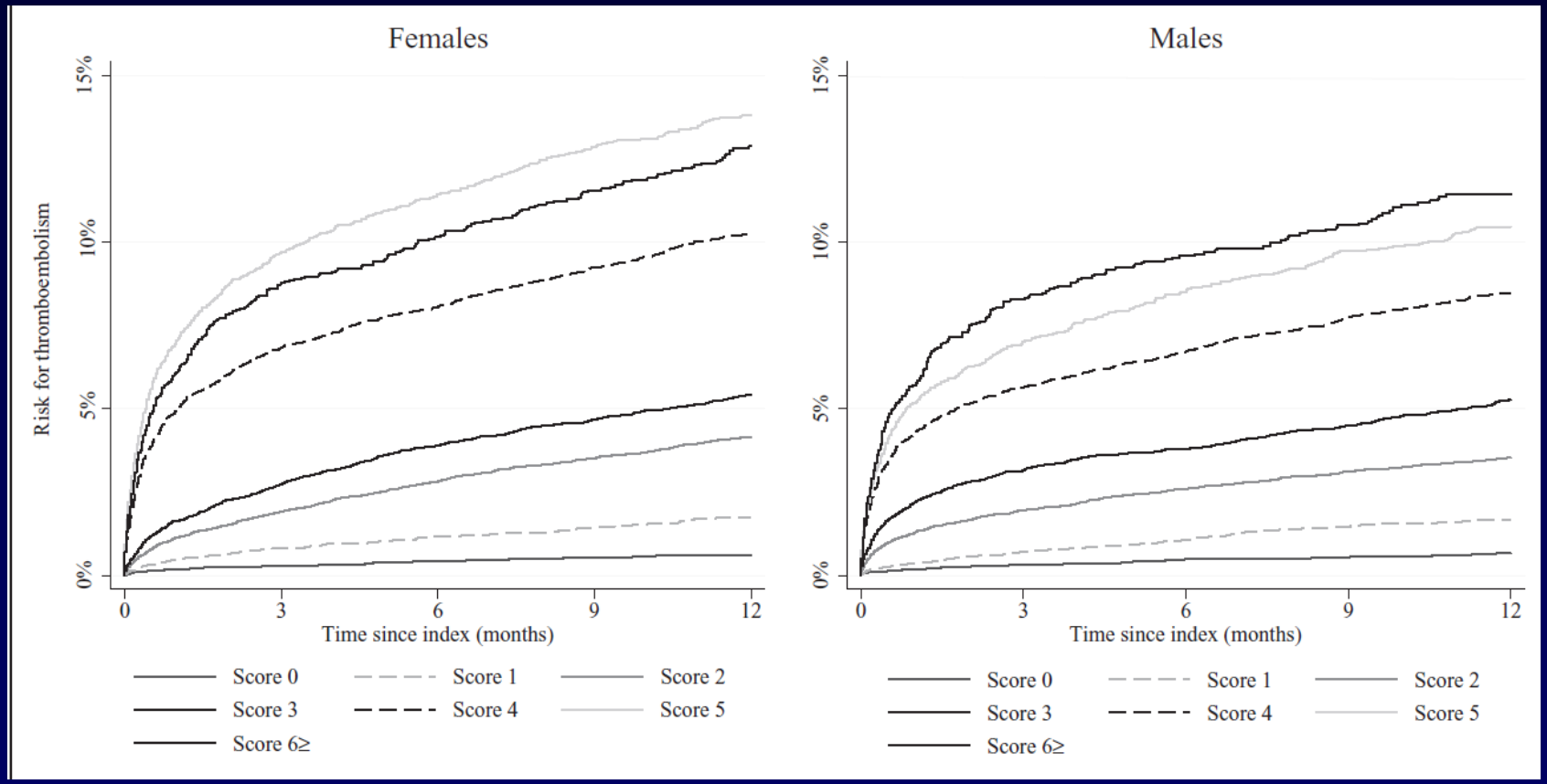
A total of 239.671 AF patients from 3 Danish Nationwide registries



Nielsen PB et al. Circulation 2018,137:832-840

Thromboembolism risk according to CHA_2DS_2-VA

A total of 239.671 AF patients from 3 Danish Nationwide registries



Nielsen PB et al. Circulation 2018,137:832-840

Medicina di Genere in Cardiologia

Fibrillazione atriale e gender

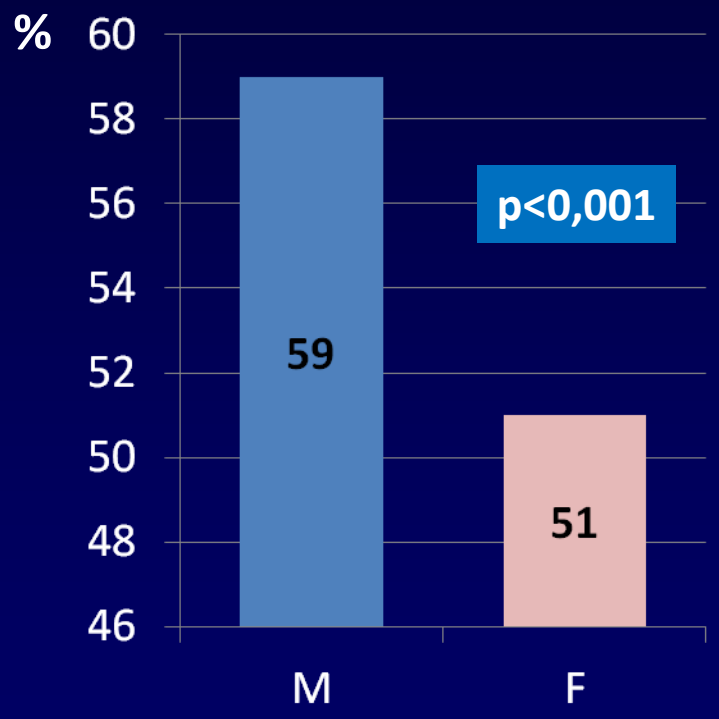
- Sesso femminile fattore di rischio per stroke
- Sesso femminile “risk modifier” per stroke
- **Sesso femminile e terapia anticoagulante orale**

Le donne sono meno curate……

Le donne sono meno curate……?

Undertreatment delle donne in due registri italiani dell'ANMCO

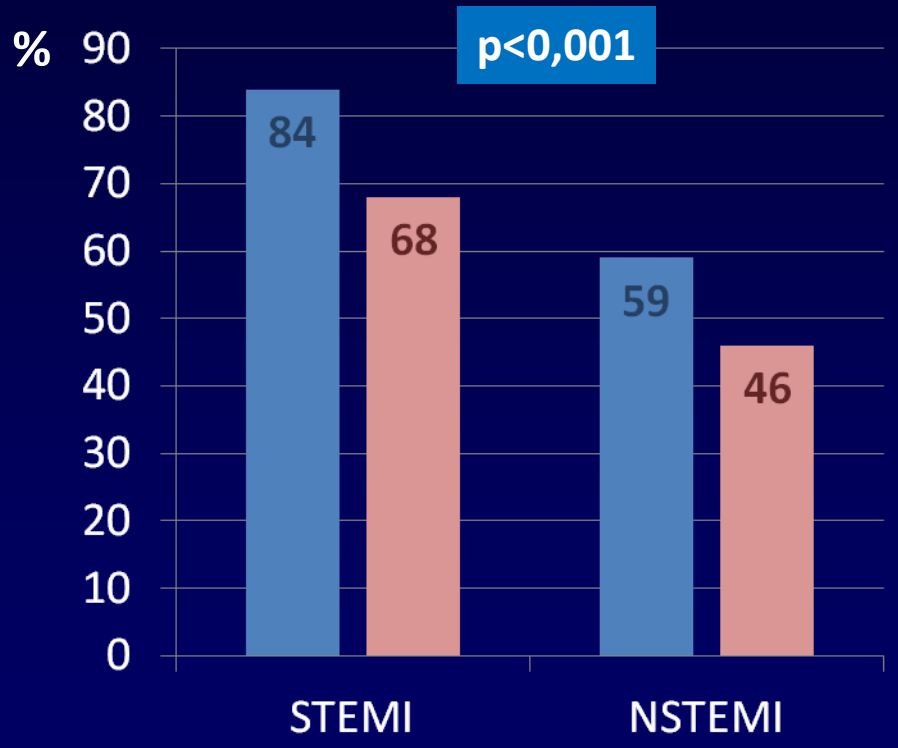
Terapia anticoagulante orale nella FA



ATA-AF 2012

Di Pasquale G et al. Int J Cardiol 2012

Coronarografia – Angioplastica coronarica nelle Sindromi Coronariche Acute



MANTRA 2012

Casella G, Di Pasquale G et al.
Eur Heart J Acute Cardiovasc Care 2013

pagepress

Italian Journal of Medicine 2016; volume 10:207-212

Sex-gender and atrial fibrillation treatment in the AntiThrombotic Agents in Atrial Fibrillation (ATA-AF) study

Cecilia Politi,[1] Tiziana Ciarambino,[1] Letizia Riva,[2] Stefania Frasson,[3] Donata Lucci,[4] Gualberto Gussoni,[3] Lucio Gonzini,[4] Mauro Campanini,[5] Michele Gulizia,[6] Giuseppe Di Pasquale,[2] Giovanni Mathieu,[7] on behalf of ATA-AF Steering Committee and Investigators

[1]Department of Internal Medicine, F. Veneziale Hospital, Isernia; [2]Unit of Cardiology, Maggiore Hospital, Bologna; [3]Clinical Research Department, FADOI Foundation Research Center, Milan; [4]ANMCO Research Centre, Florence; [5]Department of Internal Medicine, Maggiore della Carità Hospital, Novara; [6]Unit of Cardiology, Garibaldi-Nesima Hospital, Catania; [7]Department of Internal Medicine, E. Agnelli Hospital, Pinerolo (TO), Italy

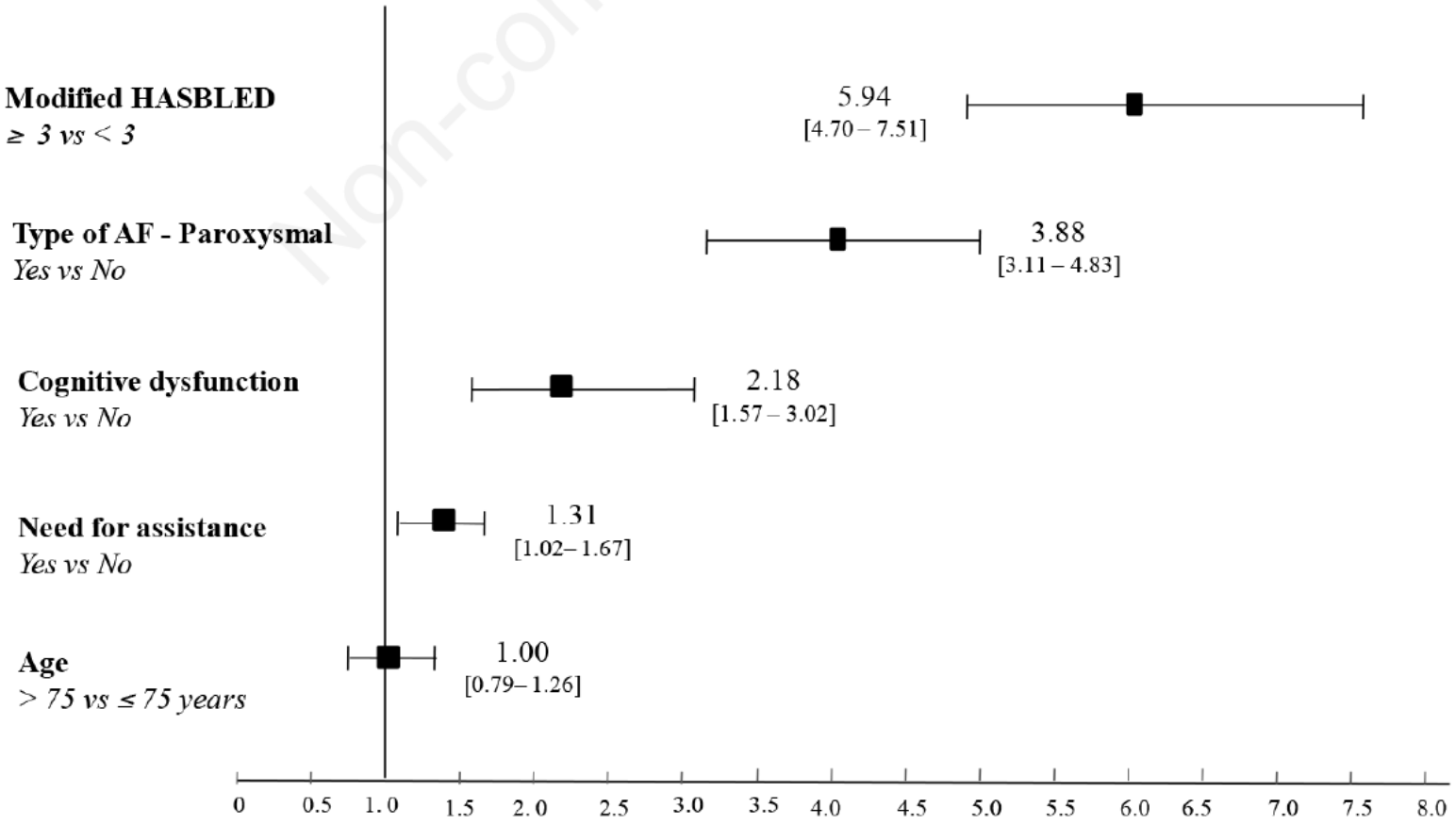
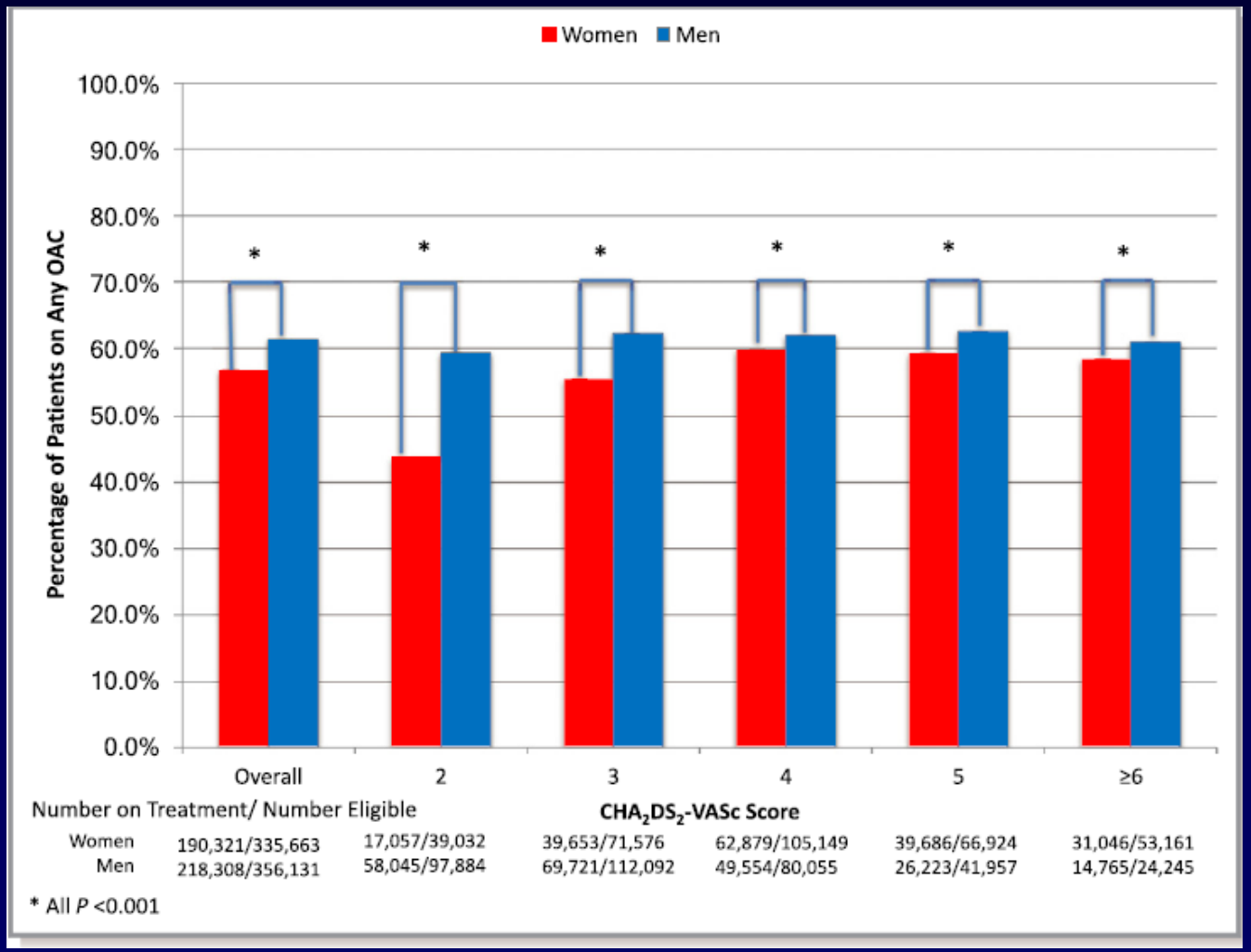


Figure 1. Predictors of non-prescription of oral anticoagulants in female non-valvular atrial fibrillation (AF) patients. Results of multivariable logistic regression analysis.

Politi C et al. Ital J Med 2016;10:207-212

Sex Differences in Oral Anticoagulant Use in the NCDR US PINNACLE Registry (848.931 pts with first documented AF)



Thompson LE et al. J Am Heart Assoc 2017

Gender gap in OAC prescription among women

The reluctance of physicians and patients to use warfarin anticoagulation in women may be due to an increased risk of bleeding.

Volgman AS et al. Gend Med 2009;6:419-432

Gender Differences of bleeding risk on VKA Rx

3015 AF pts who started VKA after the age of 80 years

Table 3
Distribution of adverse events in relation to gender.

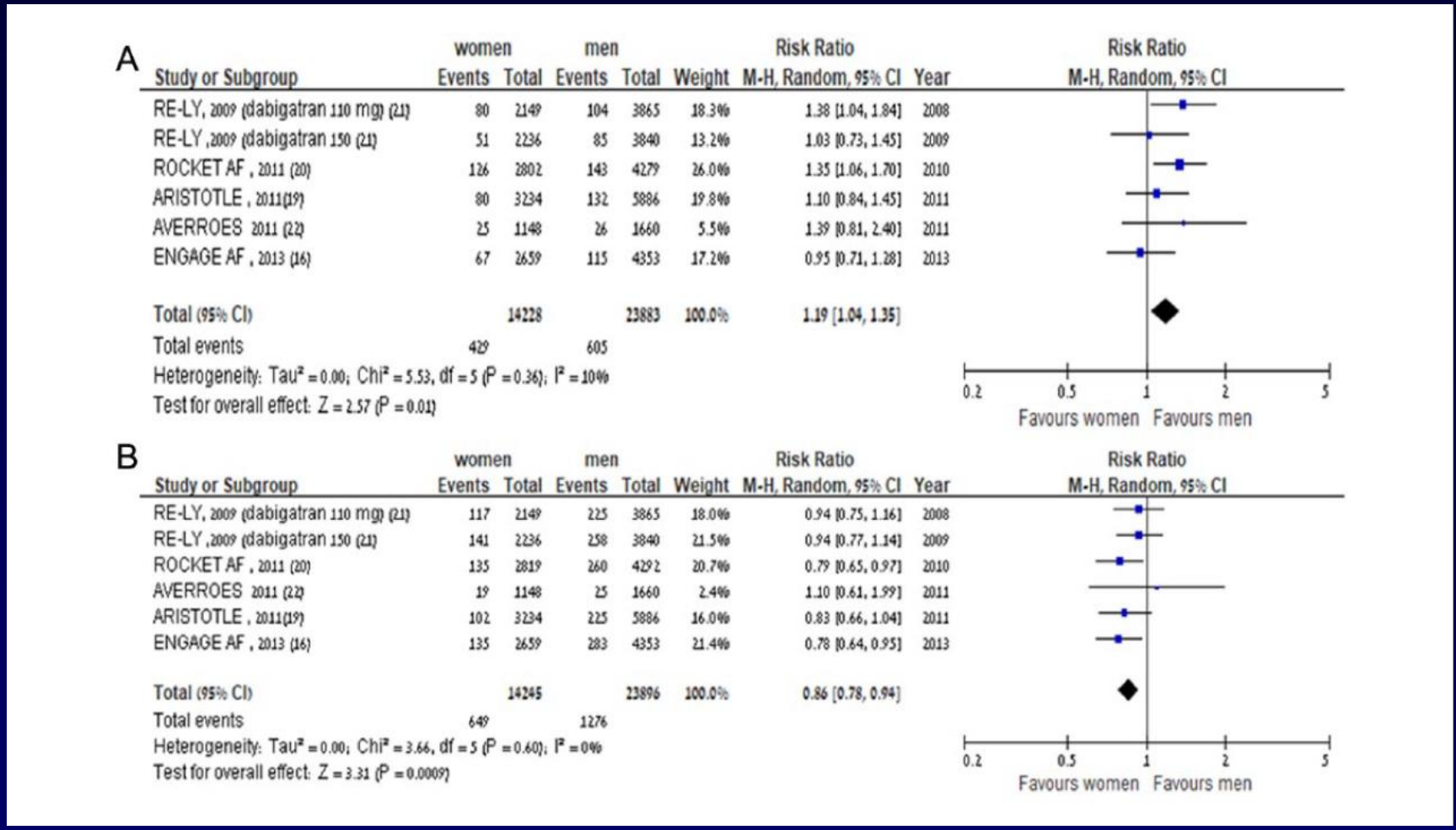
	Males N (x100 pt-years)	Females N(x100 pt-years)	RR (95%CI)	p value
Major bleedings	75 (2.2)	57 (1.4)	1.6 (1.1–2.3)	0.001
Cerebral bleedings	23 (0.7)	19 (0.5)	1.4 (0.7–2.8)	0.2
GI bleeding	30 (0.9)	21 (0.5)	1.7 (0.9–3.1)	0.06
Fatal Bleedings	13 (0.4)	12 (0.3)	1.3 (0.5–3.1)	0.5
Stroke/TIA	45 (1.3)	67 (1.6)	1.2 (0.8–1.8)	0.25
Death for all causes	125 (3.6)	157 (3.8)	1.0 (0.8–1.3)	0.7

TIA = transient ischemic attack.

Poli et al., Thrombosis Res 2013;131:12-16

Gender Differences in Efficacy and Safety of DOACs

A. Risk for stroke and SE. **B.** Risk for major bleeding in women vs men.



Raccah BH et al. Ann Pharmacother 2018:1-8

Le donne sono meno rappresentate nei trial

Percent of women in AF trials

- Trial con warfarin 35%
- RE-LY 36%
- ROCKET AF 39%
- ARISTOTLE 35%
- ENGAGE AF 38%

Increasing Participation of Women in Cardiovascular Trials

JACC Council Perspectives

Leslie Cho, MD,[a] Amanda R. Vest, MBBS, MPH,[b] Michelle L. O'Donoghue, MD, MPH,[c] Modele O. Ogunniyi, MD,[d] Amy A. Sarma, MD,[e] Kara J. Denby, MD,[a] Emily S. Lau, MD,[e] Jeanne E. Poole, MD,[f] Kathryn J. Lindley, MD,[g] Roxana Mehran, MD,[h] for the Cardiovascular Disease in Women Committee Leadership Council

ESC European Society of Cardiology

European Heart Journal (2021) **00**, 1–5
doi:10.1093/eurheartj/ehab457

VIEWPOINT
Clinical trials

The importance of achieving sex- and gender-based equity in clinical trials: a call to action

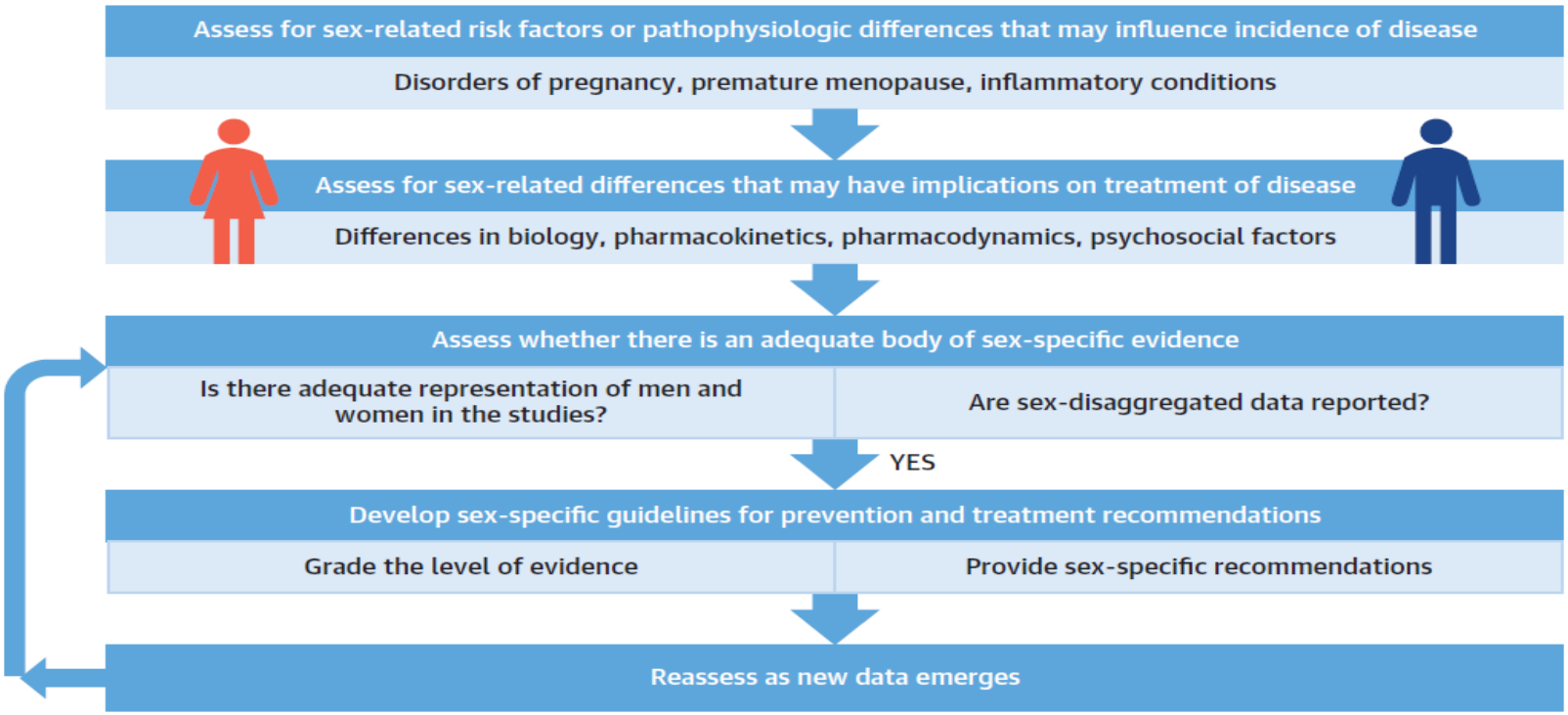
Jeske van Diemen [1]*, Petra Verdonk [2], Alaide Chieffo [3], Evelyn Regar [4], Fina Mauri[5], Vijay Kunadian [6], Garima Sharma [7], Roxanne Mehran[8], and Yolande Appelman [9]

August 2021

Is it Time for Sex-Specific Guidelines for Cardiovascular Disease?

Ersilia M. DeFilippis, MD,[a] Harriette G.C. Van Spall, MD, MPH[b,c,d]

FIGURE 1 An Algorithm for the Development of Sex-Specific Guidelines



J Am Coll Cardiol 2021;78:189-192

Nella donna
i farmaci possono avere effetti diversi

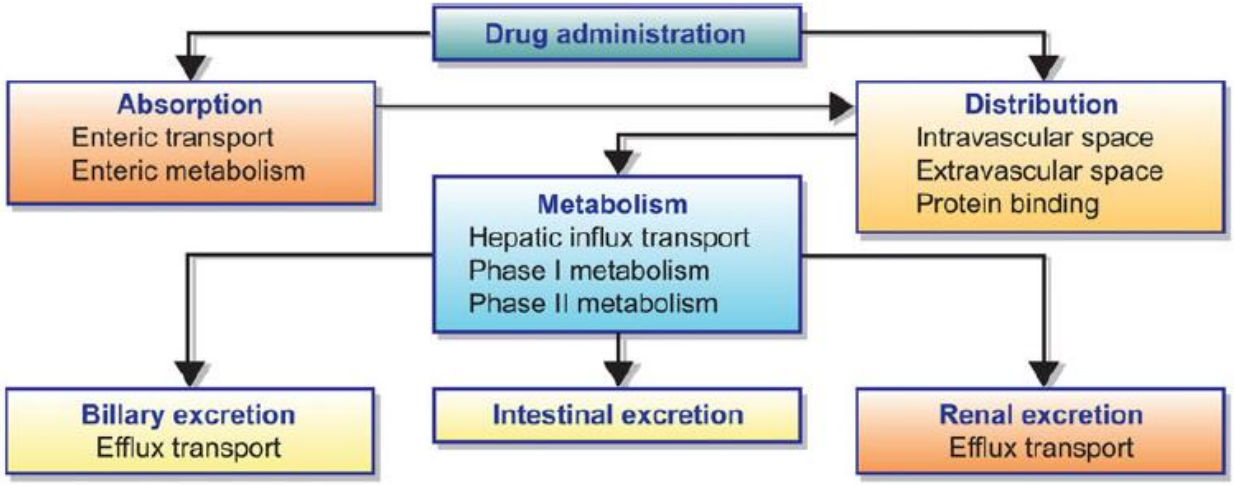
European Heart Journal (2015) **36**, 2677–2680
doi:10.1093/eurheartj/ehv161

CURRENT OPINION

Gender differences in the effect of cardiovascular drugs: a position document of the Working Group on Pharmacology and Drug Therapy of the ESC

Giuseppe M.C. Rosano[1,2]*, Basil Lewis[3], Stefan Agewall[4], Sven Wassmann[5], Cristiana Vitale[1], Harald Schmidt[6], Heinz Drexel[7], Atul Patak[8], Christian Torp-Pedersen[9], Keld Per Kjeldsen[10], and Juan Tamargo[11]

Differenze di genere nell'assorbimento e metabolismo dei farmaci



Absorption:
- Slower GI motility and transit time
- Lower gastric acid secretion
- Less drug enzymes and transporters
- Lower absorption rates

Body composition:
- Lower BW, organ size and blood flow

Distribution:
- Greater body fat and lower body water content (Higher Vd for lipophilic drugs, Lower Vd for water-soluble drugs)
- Less α1-acid glycoprotein
- Lower cardiac output

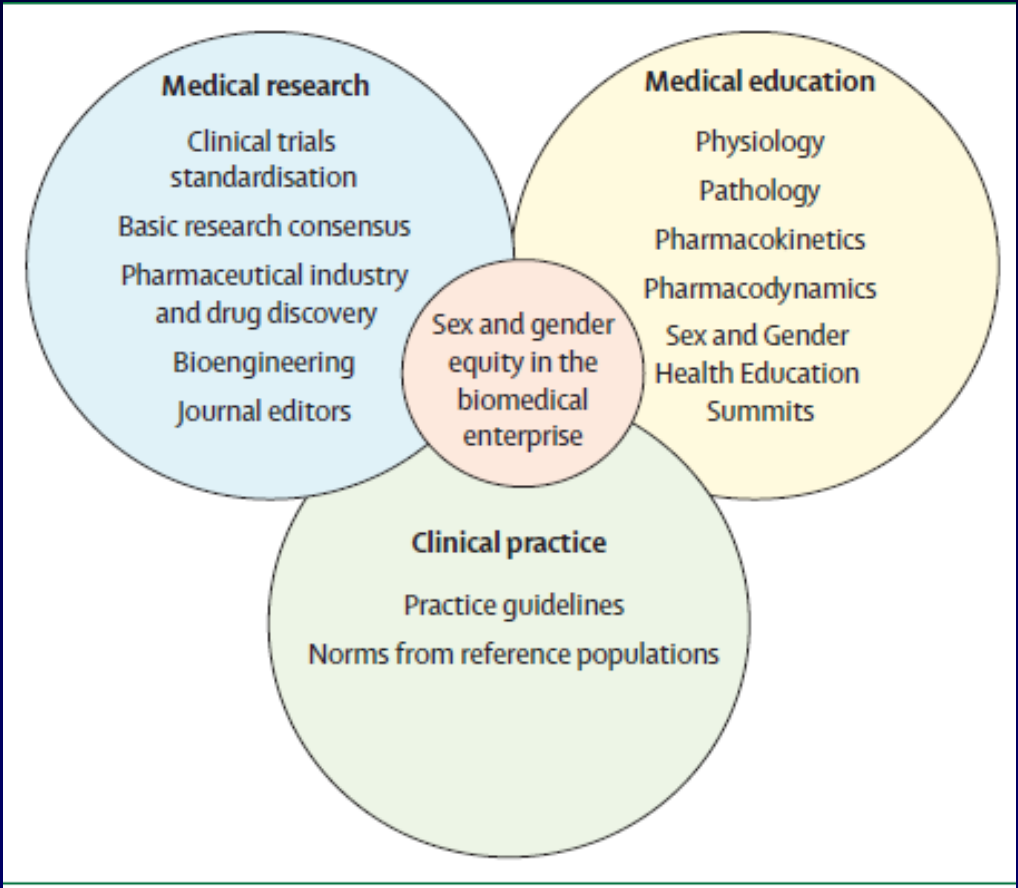
Excretion:
- Lower renal blood flow, glomerular filtration rate (GFR), tubular secretion and reabsorption
- Slower clearance of renally excreted drugs
- Longer elimination half-life

Other Factors:
- Differences in BW, cardiac output, plasma volume and regional blood flow

CYP Enzyme	Enzyme Activity
1A2	M > W
2A6	W > M
2B6	W > M
2C9	M = W
2C19	M = W
2D6	Mostly W > M
3A4	Mostly W > M
UDP-glucuronosyltransferases (UGTs)	M > W
Sulfotransferases	M > W
N-acetyltransferases	M < W
Methyltransferases	M > W

Rosano et al, Eur Heart J 2015: 36, 2677-2680

How to promote sex and gender equity in the biomedical interprise



Mauvais-Jarvis et al. Lancet 2020