Genere e patologie cardiovascolari

Dott.sa Francesca Loparco

UOC Medicina Interna

PO Ostuni

Agenda

- Medicina di genere
- Sex and Gender
- Ormoni sessuali e CVD
- Fattori di rischio CV e differenze di genere
- Patologie cardiometaboliche
- Terapia e differenze di genere
- Take home message

GENERE E PATOLOGIE CARDIOVASCOLARI (1)

EDITORIAL

The Yentl Syndrome

Bernadine Healy, M.D.

Article Figures/Media

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.Two studies published in this issue . . .

N Engl J Med 1991; 325:274-276

«Just like a man.....»

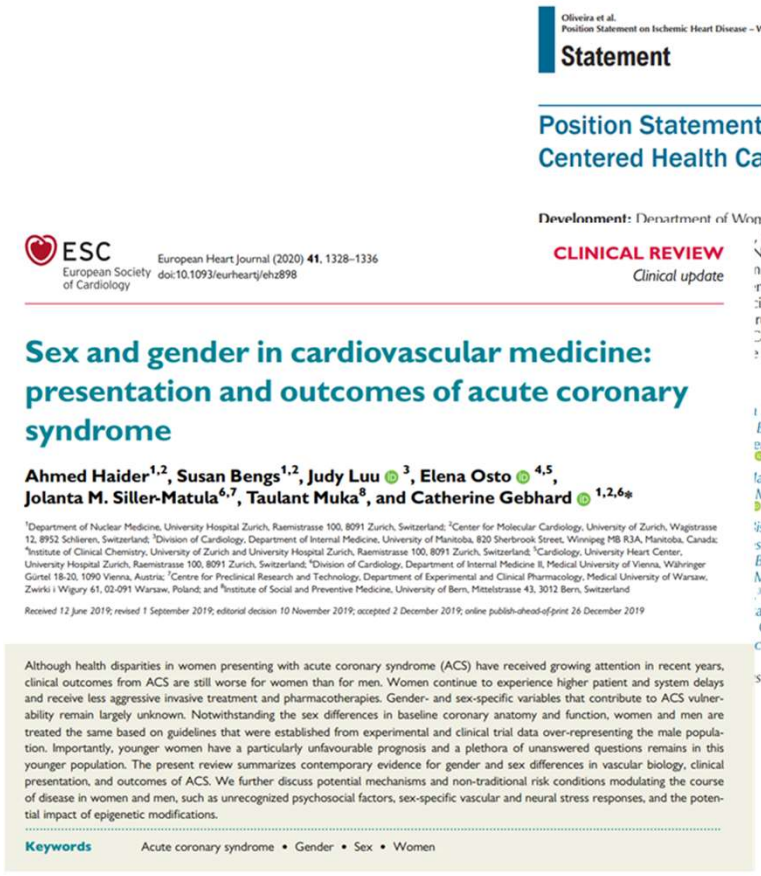
Questione femminile in medicina

GENERE E PATOLOGIE CARDIOVASCOLARI (2)

La **Medicina di Genere** si propone di studiare i meccanismi attraverso i quali le differenze legate al genere agiscono sullo stato di salute e sull'insorgenza e il decorso di molte malattie, nonché sugli outcomes delle terapie rafforzando quindi il concetto di *"personalizzazione delle terapia"* .

Si propone inoltre di incentivare la ricerca clinica ad una maggiore equità di genere con una adeguata rappresentazione delle donne negli studi clinici poiché ad oggi esse risultano essere sotto rappresentate o che almeno i dati vengano più adeguatamente analizzati tenendo conto del genere per vincere la cosiddetta *Gender blindness*.

GENERE E PATOLOGIE CARDIOVASCOLARI (3)



ESC European Society of Cardiology

European Heart Journal (2020) **41**, 1328–1336
doi:10.1093/eurheartj/ehz898

CLINICAL REVIEW
Clinical update

Sex and gender in cardiovascular medicine: presentation and outcomes of acute coronary syndrome

Ahmed Haider[1,2], Susan Bengs[1,2], Judy Luu[3], Elena Osto[4,5], Jolanta M. Siller-Matula[6,7], Taulant Muka[8], and Catherine Gebhard[1,2,6]*

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Although health disparities in women presenting with acute coronary syndrome (ACS) have received growing attention in recent years, clinical outcomes from ACS are still worse for women than for men. Women continue to experience higher patient and system delays and receive less aggressive invasive treatment and pharmacotherapies. Gender- and sex-specific variables that contribute to ACS vulnerability remain largely unknown. Notwithstanding the sex differences in baseline coronary anatomy and function, women and men are treated the same based on guidelines that were established from experimental and clinical trial data over-representing the male population. Importantly, younger women have a particularly unfavourable prognosis and a plethora of unanswered questions remains in this younger population. The present review summarizes contemporary evidence for gender and sex differences in vascular biology, clinical presentation, and outcomes of ACS. We further discuss potential mechanisms and non-traditional risk conditions modulating the course of disease in women and men, such as unrecognized psychosocial factors, sex-specific vascular and neural stress responses, and the potential impact of epigenetic modifications.

Keywords Acute coronary syndrome • Gender • Sex • Women

Statement

Position Statement on Ischemic Heart Disease – Women-Centered Health Care – 2023

Development: Department of Women's Cardiology (Departamento de Cardiologia da Mulher – DCM), , Nuclear Cardiology and Cardiovascular Rehabilitation (Departamento de Nuclear e Reabilitação Cardiovascular – DERC), Department of Cardiovascular n Cardiovascular – DIC), Department of Atherosclerosis (Departamento de nt of Heart Failure (Departamento de Insuficiência Cardíaca – DEIC) of the ciedade Brasileira de Cardiologia – SBC); Brazilian Society of Cardiovascular rurgia Cardiovascular – SBCCV); Brazilian Society of Cardiac Arrhythmias Cardíacas – SOBRAC); Brazilian Society of Hemodynamics and Interventional e Hemodinâmica e Cardiologia Intervencionista – SBHCI)

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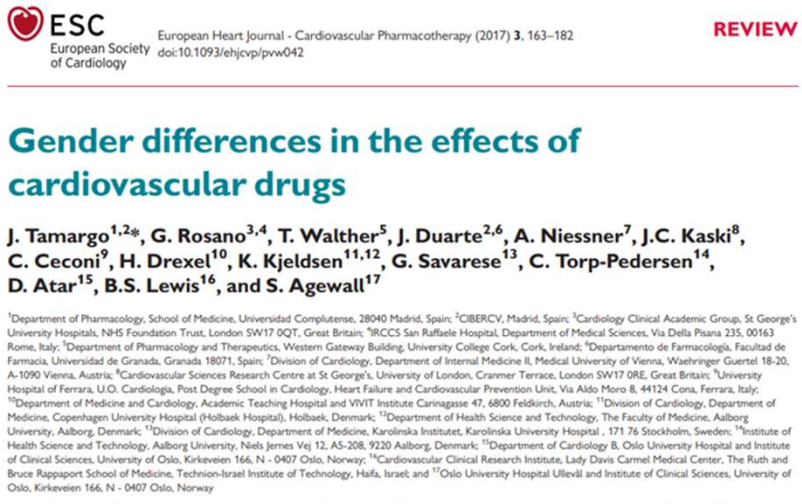

ESC European Society of Cardiology

European Heart Journal - Cardiovascular Pharmacotherapy (2017) **3**, 163–182
doi:10.1093/ehjcvp/pvw042

REVIEW

Gender differences in the effects of cardiovascular drugs

J. Tamargo[1,2]*, G. Rosano[3,4], T. Walther[5], J. Duarte[2,6], A. Niessner[7], J.C. Kaski[8], C. Ceconi[9], H. Drexel[10], K. Kjeldsen[11,12], G. Savarese[13], C. Torp-Pedersen[14], D. Atar[15], B.S. Lewis[16], and S. Agewall[17]

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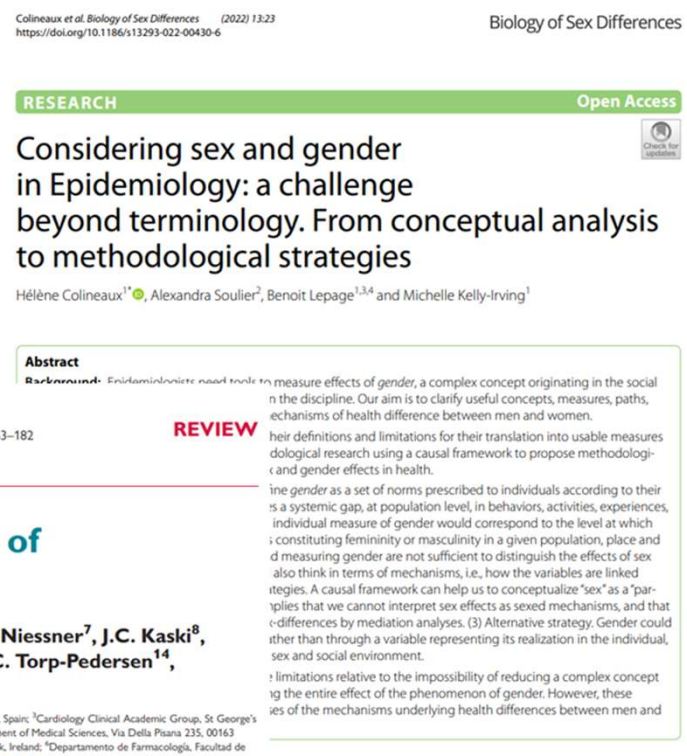

Colineaux *et al. Biology of Sex Differences* (2022) 13:23
https://doi.org/10.1186/s13293-022-00430-6

Biology of Sex Differences

RESEARCH Open Access

Considering sex and gender in Epidemiology: a challenge beyond terminology. From conceptual analysis to methodological strategies

Hélène Colineaux[1*], Alexandra Soulier[2], Benoit Lepage[1,3,4] and Michelle Kelly-Irving[1]

Abstract

Background: Epidemiologists need tools to measure effects of *gender*, a complex concept originating in the social
n the discipline. Our aim is to clarify useful concepts, measures, paths,
echanisms of health difference between men and women.
heir definitions and limitations for their translation into usable measures
dological research using a causal framework to propose methodologi-
and gender effects in health.
ine *gender* as a set of norms prescribed to individuals according to their
s a systemic gap, at population level, in behaviors, activities, experiences,
individual measure of gender would correspond to the level at which
constituting femininity or masculinity in a given population, place and
d measuring gender are not sufficient to distinguish the effects of sex
also think in terms of mechanisms, i.e., how the variables are linked
tegies. A causal framework can help us to conceptualize "sex" as a "par-
plies that we cannot interpret sex effects as sexed mechanisms, and that
-differences by mediation analyses. (3) Alternative strategy. Gender could
ther than through a variable representing its realization in the individual,
sex and social environment.
limitations relative to the impossibility of reducing a complex concept
g the entire effect of the phenomenon of gender. However, these
es of the mechanisms underlying health differences between men and

SEX AND GENDER (1)

- Il **sesso biologico** si riferisce alla conformazione sul piano biologico del corpo per come è definita dai cromosomi sessuali, dagli ormoni, dai genitali esterni e interni, dall'insieme dei caratteri fisici e biologici specifici che, all'interno di una stessa specie, contraddistinguono maschi e femmine, in quanto diversamente preposti alla funzione riproduttiva.
- Il **Genere** è inteso come le differenze tra uomini e donne, che ogni società costituisce sulla base di determinanti sociali, culturali, comportamentali a partire dalla propria concezione delle differenze tra corpo maschile e femminile con i quali le società trasformano i corpi sessuati (maschio/femmina/intersessuale) in identità personali socialmente riconosciute (uomo/donna) e organizzano la divisione dei ruoli e dei compiti tra donne e uomini.

SEX AND GENDER (2)

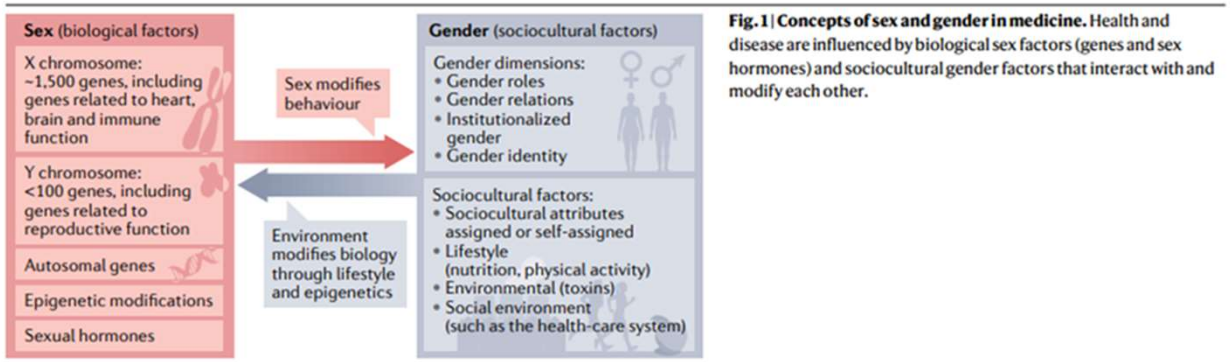

Fig. 1 | Concepts of sex and gender in medicine. Health and disease are influenced by biological sex factors (genes and sex hormones) and sociocultural gender factors that interact with and modify each other.

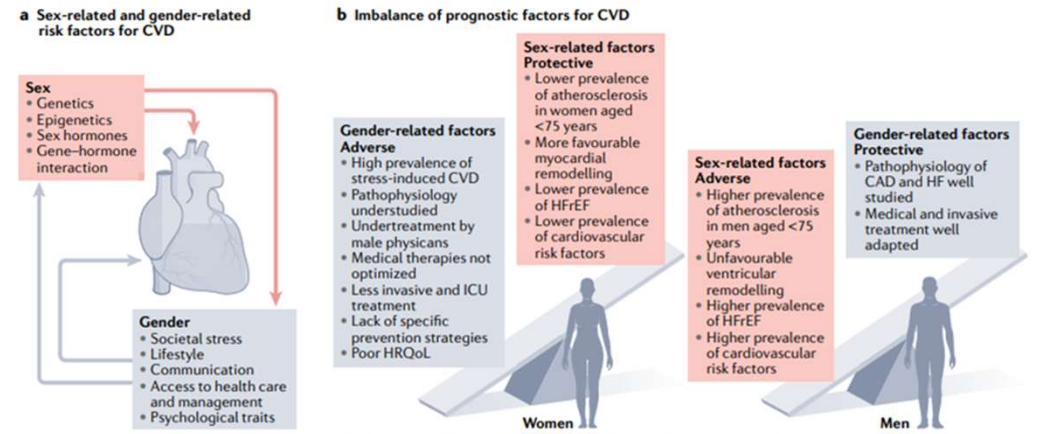

Fig. 4 | Sex-related and gender-related disparities in CVD risk and outcomes. **a**, Factors contributing to sex-related and gender-related modulation of cardiovascular disease (CVD) risk and outcomes in women and men. **b**, Factors associated with positive or negative CVD outcomes in women and men. CAD, coronary artery disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HRQoL, health-related quality of life; ICU, intensive care unit.

Gender: Difficilmente quantificabile

- concetto fortemente legato al sesso ma non sempre coincide con il sesso biologico.

- può significativamente influenzare i comportamenti legati alla salute e interagire con i fattori di rischio CV

Regitz-Zagrosek, Nature 2023

Perche’ parlare di CVD e Differenze di genere?

ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–107
https://doi.org/10.1093/eurheartj/ehad191

ESC GUIDELINES

2023 ESC Guidelines for the management of acute coronary syndromes

Developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC)

THE LANCET COMMISSIONS | VOLUME 397, ISSUE 10292, P2385-2438, JUNE 19, 2021
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The *Lancet* women and cardiovascular disease Commission: reducing the global burden by 2030

Birgit Vogel, MD • Prof Monica Acevedo, MD • Yolande Appelman, MD • Prof C Noel Bairey Merz, MD • Alaide Chieffo, MD • Prof Gemma A Figtree, MD • et al. Show all authors

Published: May 16, 2021 • DOI: https://doi.org/10.1016/S0140-6736(21)00684-X • Check for updates

17. Sex differences

There are currently no data supporting the differential management of ACS based on sex. However, several studies have reported that women presenting with ACS are treated differently than men.[914–918] This includes being less likely than men to receive ICA, timely revascularization, CR, and secondary prevention medications.[914–918]

Healthcare providers and policymakers should be conscious of this potential gender bias in the management of ACS and make a concerted effort to ensure that women with ACS receive evidence-based care.

In order to ensure the generalizability of the findings yielded by RCTs, patient recruitment should be reflective of real-world populations from different socioeconomic backgrounds.[919] Several studies have reported that a disproportionately low proportion of women are recruited to CV trials.[920–922] Alongside historic underrepresentation of other subsets of patients, including older patients and ethnic minorities, this suggests an underlying recruitment bias.[923] Increased representation of female patients in future clinical trials is required to better inform the optimal management of women with ACS.[924]

GENDER RELATED DISPARITIES IN CVD

- Esordio atipico e ritardato
  - FR non tradizionali
- Scarsa rappresentazione delle donne nei trials CV

EPIDEMIOLOGIA DEL PROBLEMA

CVD principale causa di morte nei paesi membri ESC causando
2.2 milioni (45%) morti nelle donne
1.9 milioni (39%) morti negli uomini

>75 anni nelle donne

1)**La cardiopatia ischemica**:
38% delle morti CV nelle donne
44% delle morti CV negli uomini

2)**Stroke**
26% delle morti CV nelle donne
21% negli uomini

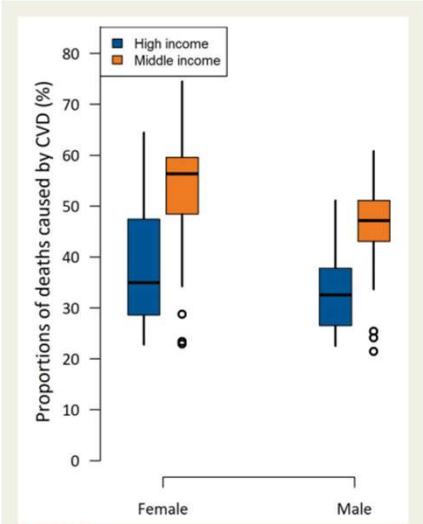


Figure 42 Proportion of deaths caused by cardiovascular disease in European Society of Cardiology member countries, stratified by sex and national income status.

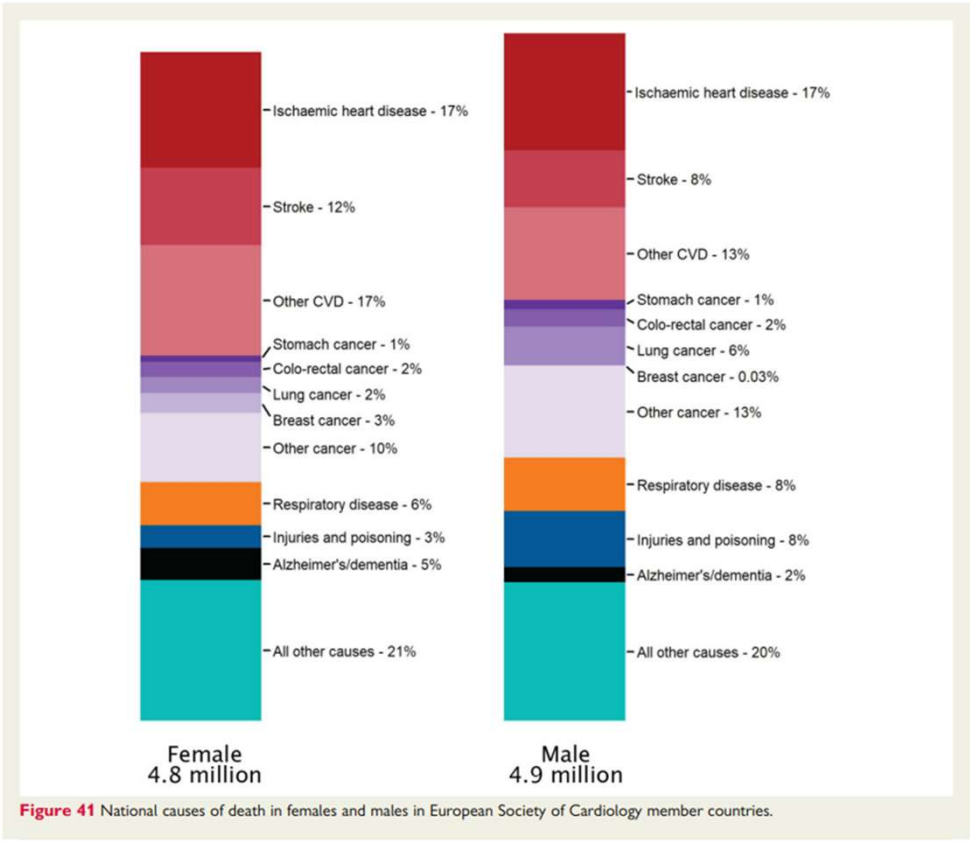
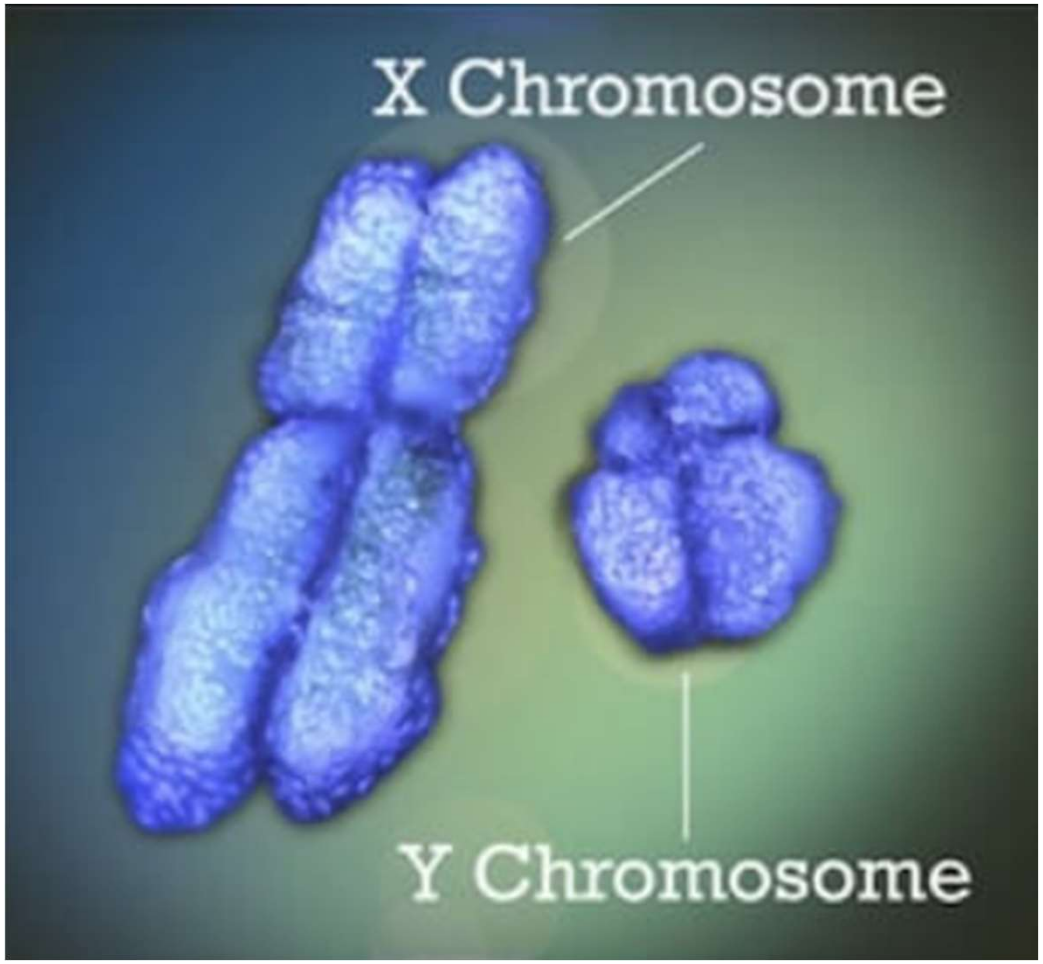


Figure 41 National causes of death in females and males in European Society of Cardiology member countries.

European Heart Journal (2022) 43, 716–799

DIFFERENZE DI GENERE

GENETICO
EPIGENETICO
ORMONALE
ANATOMICO
AMBIENTALE



DIFFERENZE DI GENERE

GENETICO
EPIGENETICO
ORMONALE
ANATOMICO
AMBIENTALE

Sex-Related Differences in the Cardiovascular System

Parameter	Manifestations
Anatomy	• Dimensions that are smaller in women (adjust for age and race): left ventricular mass, ventricular wall thickness, left atrial dimension, left ventricular end-diastolic dimension, and vessel size
Hormonal influences	• Estrogen and progesterone are most influential in women; testosterone is predominant in men • Menstruation can affect hematologic and electrocardiographic indices
Cardiovascular function	• Stoke volume is women is 10% less • Pulse rate in women is 3–5 beats/minute faster • Ejection fraction is higher in women
Physiology	• Women have reduced sympathetic and enhanced parasympathetic activity • Women have lower plasma concentrations of norepinephrine
Cardiovascular adaptations	• In response to stress, women experience an increased pulse rate, resulting in increased cardiac output; men increase vascular resistance, resulting in increased blood pressure • Women are more sensitive to altitude or body positioning changes and experience more orthostatic hypotension and syncope
Hematologic indices	• Women have a lower number of circulating red blood cells per unit volume of plasma (resulting in a lower hematocrit) • Because of a lower hemoglobin, women have a lower oxygen-carrying capacity; this is balanced by women having a lower oxygen consumption
Electrocardiographic and electrophysiologic indices	• Women on average have a longer corrected QT interval and a shorter sinus node recovery time • Drug-induced torsades de pointes is more common in women • Sudden cardiac death and atrial fibrillation are less common in women

Finks S. Cardiovascular Disease in Women. Pharmacotherapy Self Assessment Program Seventh Edition Book 1 Cardiology. 7 ed. American College of Clinical Pharmacy; 2010. 179–201.[350]

Need permission to use Table 1.

Circulation. 2016 March 29; 133(13): 1302–1331.

ORMONI SESSUALI E CVD (1)

Table 1 Sex hormones and their effects on cells of the cardiovascular system

Sex hormone	Cell type	Effect	References
17β-estradiol	Cardiomyocytes	↓ Hypertrophy	[34–37]
		↑ ATP synthesis	[38]
		↓ ROS production	[39]
		↓ Contractility	[40]
		↓ Apoptosis	[41, 42, 55]
	Endothelial cells	↑ Vasorelaxation	[44–49]
		↑ Proliferation	[45, 46, 48, 49]
		↑ Migration	[45, 46, 48, 49]
		↑ Angiogenesis	[50•]
	Vascular smooth muscle cells	↑ Vasorelaxation	[51]
		↓ Proliferation	[37, 52]
		↓ Migration	[37, 52]
		↓ Inflammation	[53]
	Fibroblasts	↓ Fibrosis	[35, 54, 55]
Testosterone	Cardiomyocytes	↑ Hypertrophy	[56–58]
		↑ Contractility	[59]
		↑ ROS production	[61]
		↑ Glucose uptake	[60]
	Endothelial cells	↑ Vasorelaxation	[62–64]
		↑ Proliferation	[73]
	Vascular smooth muscle cells	↑ Vasorelaxation	[65–72]
		↑ / ↓ Inflammation	[74–77]
		↑ Apoptosis	[78]
Progesterone	Cardiomyocytes	↑ β-oxidation	[79]
		↑ Proliferation	[80]
	Endothelial cells	↑ Vasorelaxation	[81–83]
		↓ Atherogenesis	[84]
		↑ ROS production	[85]
	Vascular smooth muscle cells	↑ Vasorelaxation	[81–83]
		↓ Atherogenesis	[84]
		↑ ROS production	[85]

Willemars, Current Heart Failure Reports 2022

In menopausa la perdita degli estrogeni altera la vasodilatazione, disfunzione endoteliale, porta a incremento dei marcatori di infiammazione, altera il profilo lipidico, pressorio e la tolleranza al glucosio con un aumento globale del Rischio Cv.

ORMONI SESSUALI E CVD (2)

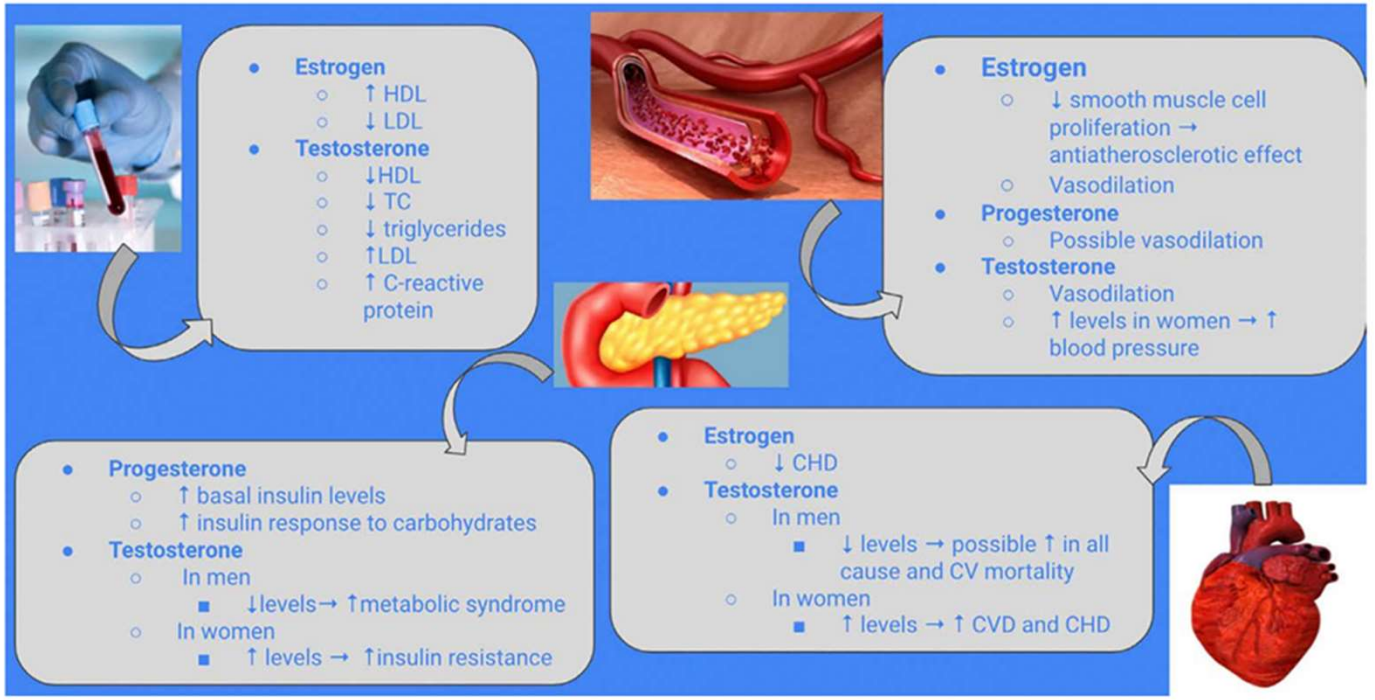


FIGURE 3 Cardiometabolic Effects of Endogenous Sex Hormones. CHD, congenital heart disease; CV, cardiovascular; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol.

FATTORI DI RISCHIO CV E GENERE (1)

UOMINI E DONNE CONIDVIDONO GLI STESSI

FATTORI DI RSCHIO MA….CON DELLE PECULIARITA’

From SEX to GENDER

Connelly, Canadian Journal of Cardiology 2021

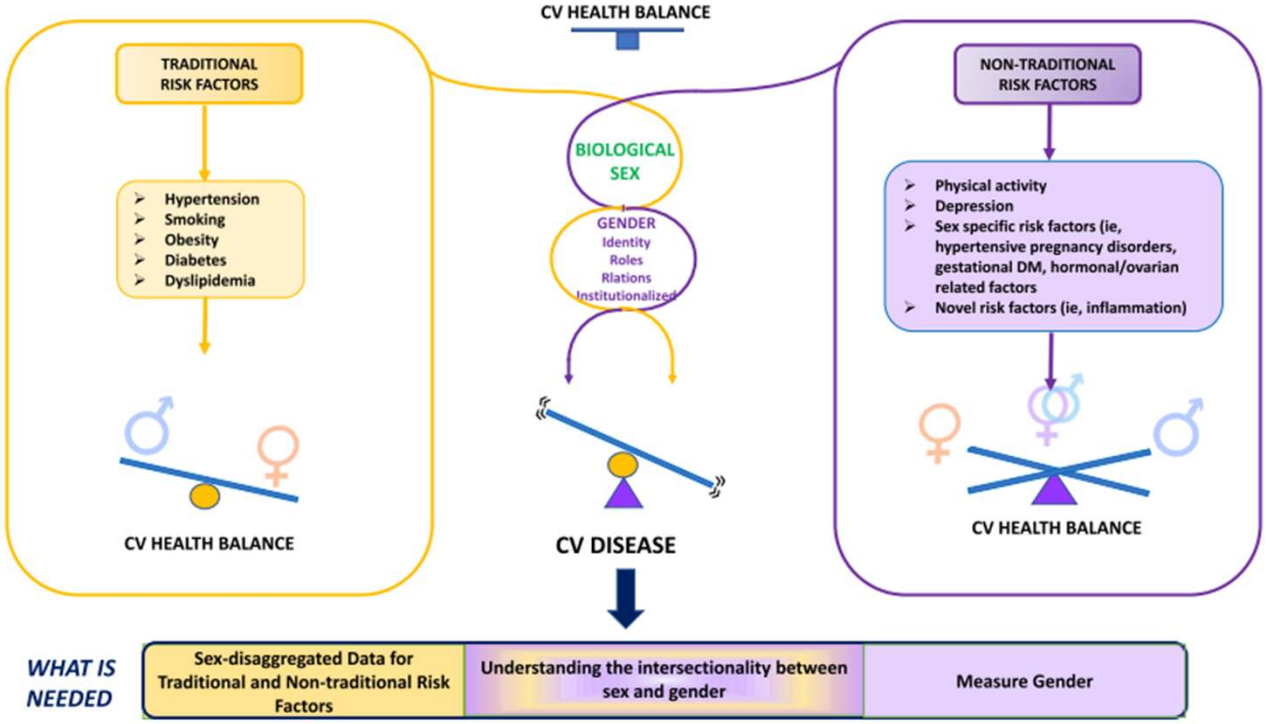
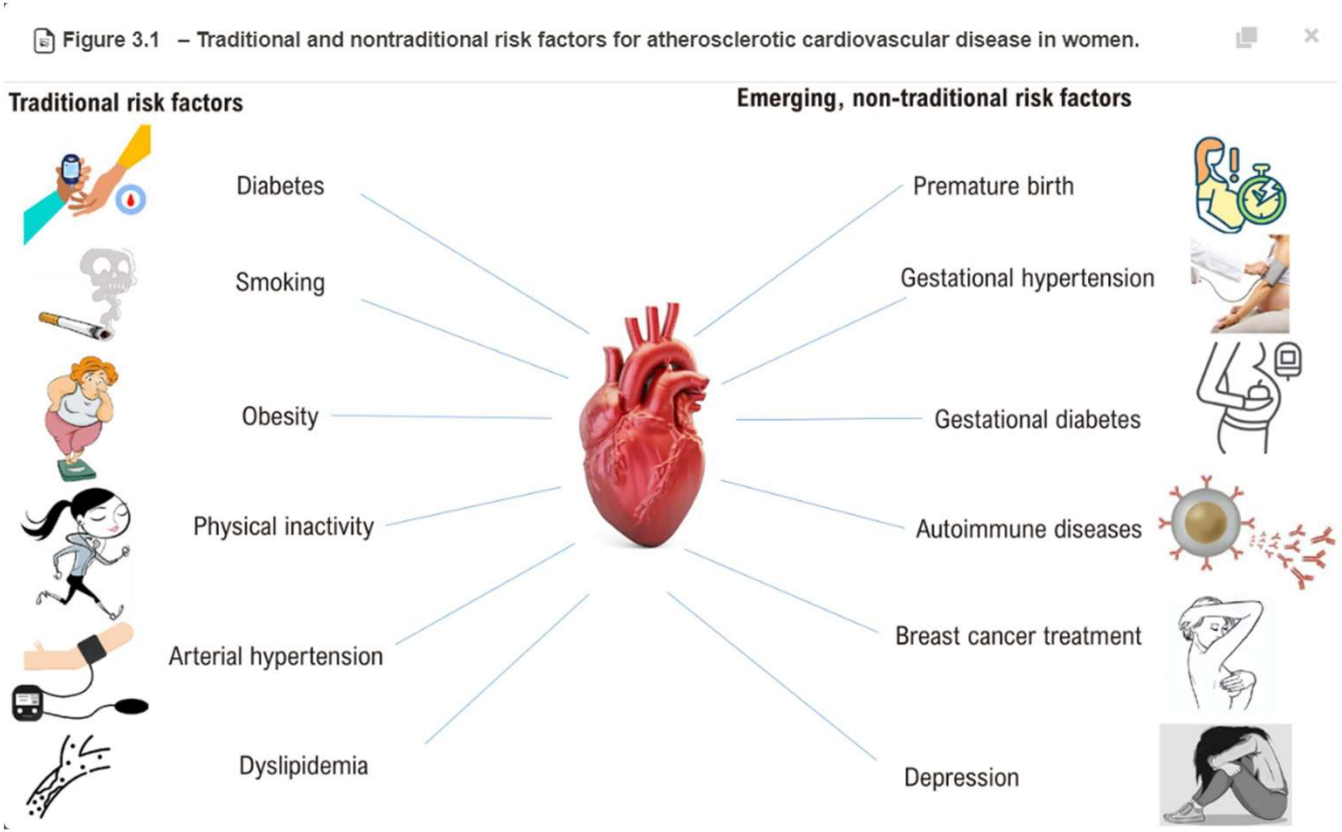


Figure 1. Traditional and nontraditional cardiovascular (CV) risk factors: biological sex, gender, and their interaction as modifiers of CV health. Established (traditional and nontraditional) CV risk factors interact with both sex and gender to influence CV risk and disease. DM, diabetes mellitus.

FATTORI DI RISCHIO CV E GENERE (2)



Oliveira et al, Arq Bras Cardiol. 2023

Come stratificare il rischio CV?

Frahmingam Score
Sistema Core

FATTORI DI RISCHIO CV E GENERE (3)

FATTORI DI RISCHIO TRADIZIONALI

- **FUMO**: Una recente metanalisi di 75 studi di coorte (2.4 milioni di individui) ha dimostrato come il rischio relativo di sviluppare infarto sia maggiore del 25% nelle donne fumatrici rispetto agli uomini.

  Benjamin EJ, Circulation. 2017

- **ETA'** : l'effetto cardioprotettivo degli estrogeni in fase pre menopausale ritarda la comparsa di CAD di circa 8 10 anni; dopo i 55 anni il rischio di CAD aumenta nelle donne cosi come nell'uomo.

  McSweeney JC, Circulation. 2016

European Society of Cardiology

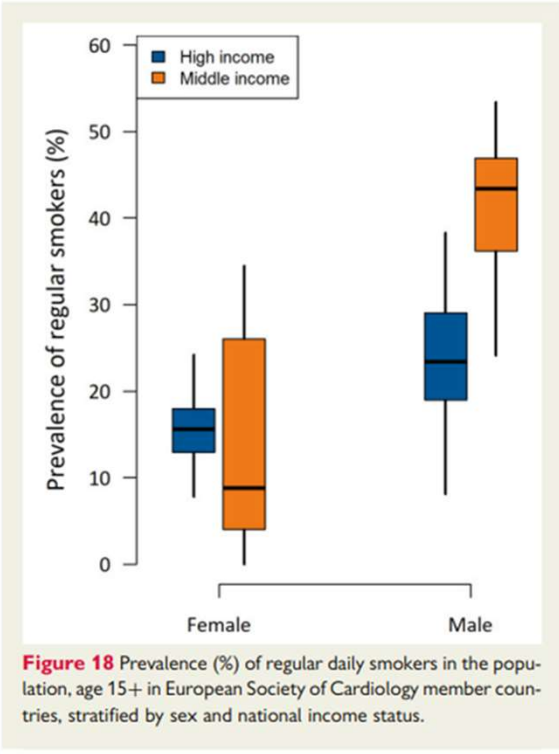


Figure 18 Prevalence (%) of regular daily smokers in the population, age 15+ in European Society of Cardiology member countries, stratified by sex and national income status.

FATTORI DI RISCHIO CV E GENERE (4)

FATTORI DI RISCHIO TRADIZIONALI

- **ATTIVITA' FISICA**: Correla negativamente con la mortalità CV. Le donne risultano però essere meno attive dal punto di vista fisico probabilmente poiché nella loro vita viene data priorità allo svolgimento di attività come il *caregiving* e faccende domestiche.

- **OBESITA':** La prevalenza di obesità nelle donne è in costante aumento nel periodo che va dal 1980 al 2014. Non è stato documentato un ulteriore incremento negli uomini a partire del 2006.

Flegal, JAMA 2016

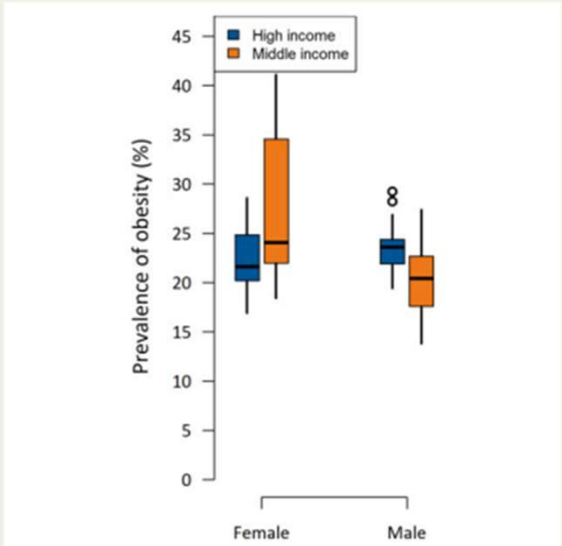


Figure 27 Prevalence of obesity (BMI ≥ 30 kg/m²) among adults, stratified by sex and national income status in European Society of Cardiology member countries.

FATTORI DI RISCHIO CV E GENERE (5)

FATTORI DI RISCHIO TRADIZIONALI

- **IPERTENSIONE**: Il miocardio delle donne si adatta al sovraccarico pressorio sviluppando una **ipertrofia concentrica con una minore cavità interna e una parete più spessa del VS**, mantengono una migliore FE e contrattilità dovuta a un minore rimodellamento rispetto al uomo.

L'ipertrofia del VS dovuta al sovraccarico pressorio regredisce meno efficacemente nelle donne rispetto agli uomini con farmaci che inibiscono il RAS. Regitz-Zagrosek, Physiol Rev 2017

- **DISLPIDEMIA**: Gli uomini se comparati con donne della stessa età hanno un profilo lipidico meno favorevole e più aterogeno.

Dayan, can J Cardiol 2020

TABLE 4. Summary of Sex Differences in the Prevention of, and Predisposition to, Cardiovascular Disease in People With T2DM

Risk factor/risk marker	Sex differences in prevalence and intensity	Sex differences in treatment and interventions
Diabetes control and treatment		T2DM less well controlled in women in many cross-sectional studies Women were underrepresented in many trials of newer antidiabetic drugs
Obesity	Higher prevalence in women with T2DM Higher mean BMI in women than in men, even at the diagnosis of T2DM	No sex difference in the impact of lifestyle intervention on CVD outcomes
Hypertension	More common in women with T2DM after the age of 60-65 y	Less well controlled in women with T2DM in many cross-sectional studies Women less likely than men to receive evidence-based treatments such as angiotensin-converting enzyme inhibitors
Dyslipidemia	More common in women with T2DM after the age of 60 y Higher levels of total and LDL cholesterol in women but also higher levels of HDL cholesterol in women	Worse control of LDL cholesterol in women with T2DM Women less likely than men to receive statin therapy Women were underrepresented in primary prevention trials of statin therapy

Al Salameh, Mayo Clinic Proceedings 2019

FATTORI DI RISCHIO CV E GENERE (5)

FATTORI DI RISCHIO TRADIZIONALI

- **DIABETE MELLITO:** il rischio CV dei pazienti diabetici rispetto ai non diabetici è maggiore nelle donne rispetto agli uomini. Questo aumentato rischio relativo delle donne diabetiche rispetto agli uomini diabetici è imputabile agli emergenti e multipli fattori di rischio che colpiscono le donne, differente prescrizione e aderenza alla farmacoterapia ma anche alla diversa composizione, distribuzione di grasso corporeo, diverse adipochine prodotte. Gerdts, NatureMedicine 2019

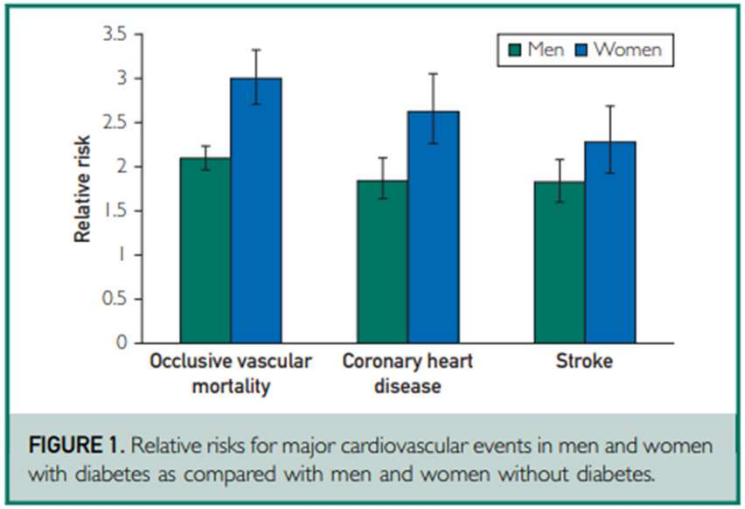


FIGURE 1. Relative risks for major cardiovascular events in men and women with diabetes as compared with men and women without diabetes.

Al Salameh, Mayo Clinic Proceedings 2019

FATTORI DI RISCHIO CV E GENERE (6)

FATTORI DI RISCHIO NON TRADIZIONALI

- **APO: Adverse pregnancy outcome**

Pre-eclampsia: CVD HR 2.2 (1.7-2.7) – IA HR 5.6 (5.1-6-3)

Grandi, Paediatr Perinat Epidemiol 2017

Diabete gestazionale: CVD HR 1.98 (1.57-2.50)

Grandi, Paediatr Perinat Epidemiol 2017

SGA: incremento del rischio CVD nella madre proporzionale alla severità della SGA e al n di parti SGA Ngo, Heart Lung Circ 2015

- **Menarca precoce e tardivo:** mortalità per tutte le cause HR 1.23 (1.10-1-38) – CVD 1.27 (1.22-1.31) Agarwala, Circulation 2021
- **Aborti ripetuti:** n2 HR 1.75 (1.22-2.52) -n>2 HR 3.18 (1.49-6.8) Wagner, Heart 2015
- **Allattamento:** ruolo protettivo

FATTORI DI RISCHIO CV E GENERE (6)

FATTORI DI RISCHIO NON TRADIZIONALI

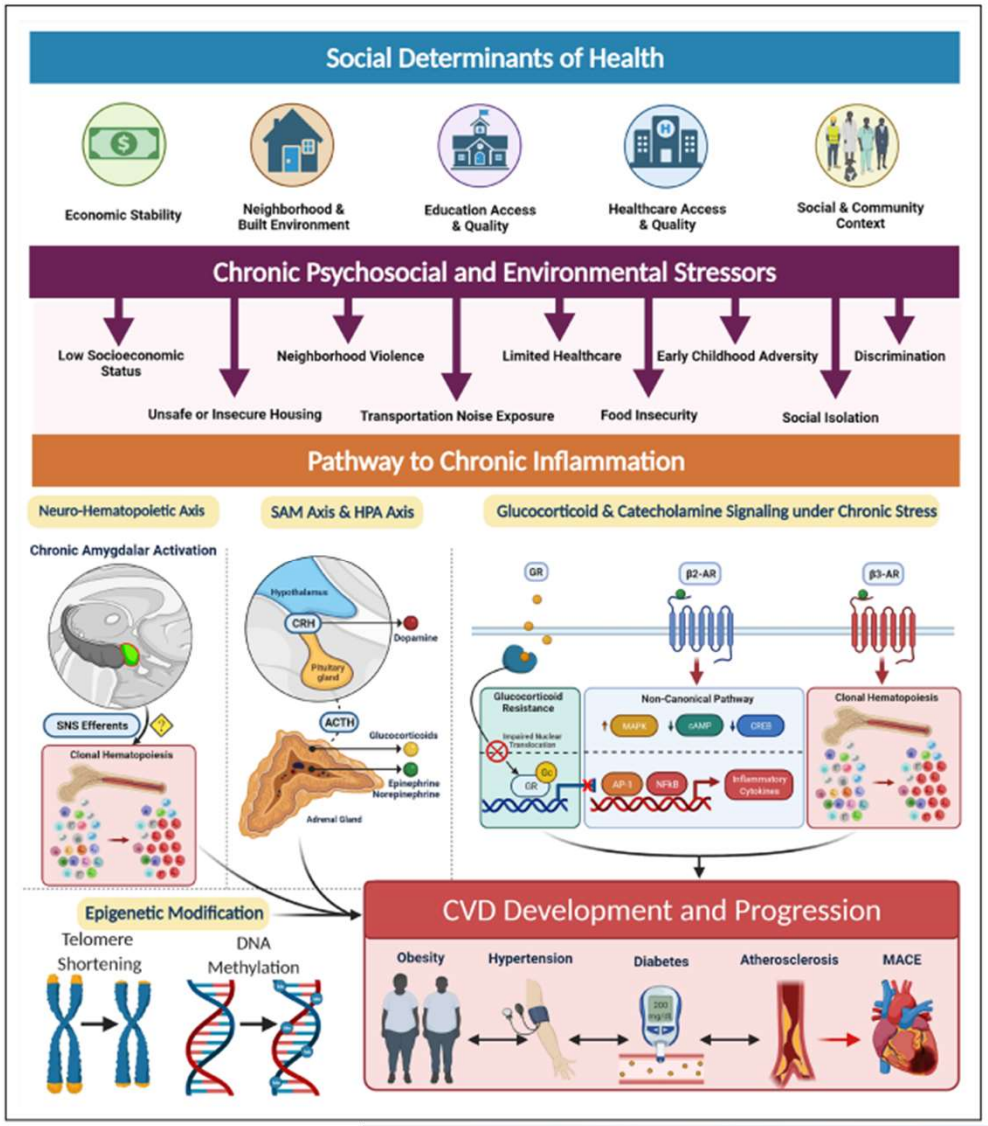
- **PCOS:** Mets, Insulino resistenza, obesità e rischio CV Cho et al, J AM Coll Cardiolo 2021
- **Insufficienza ovarica precoce** CVD HR 1.36, 95% CI:1.19-1-56, p<0.001 Honigberg, JAMA 2019
- **Menopausa**
- **RT e CHT per cr mammario** (antracicline, trastuzumab), condivisione dei fattori di rischio.
- **Patologie autoimmuni:** AR 2-to 3-fold higher risk of MI 5=5 higher risk of stroke Garcia, Circ Res 2016

FATTORI DI RISCHIO CV E DIFFERENZE DI GENERE

DETERMINANTI SOCIALI LO STATO DI SALUTE

Biologia delle avversità

Circulation Research. 2022;130:782–799



Depressione e violenza domestica

EDITORIAL

American Heart Association.

Matters of the Heart and Mind: Interpersonal Violence and Cardiovascular Disease in Women

Rola El-Serag, MD; Rebecca C. Thurston, PhD

Donne con storia di violenza domestica hanno frequentemente :
- Alcolismo
- Dm2
- IA

Violenza domestica si associa a:
31% incremento di rischio per successive **CVD**
51% incremento di rischio di **DM2**
44% incremento di rischio di **morte per tutte le cause**

DEPRESSIONE
Raddoppia il Rischio CV nelle donne
Aumenta il rischio di patologia CV precoce

Cho et al, J Am Coll Cardiol 2020

Uncosciousness: sottostima del rischio

Approximately 56% of women do not know their CVD risk nor appreciate its significance.

This lack of awareness is more profound among women in higher-risk groups, such as racial and ethnic minorities.

Furthermore, healthcare providers continue to utilize traditional approaches to assess and manage CVD in women, which may underestimate CVD risk and miss global factors (such as IPV), likely affecting their entire spectrum of care.

El-Serag, J Am Heart Assoc 2020

PATOLOGIE CARDIOMETABOLICHE (1)

SCOMPENSO CARDIACO

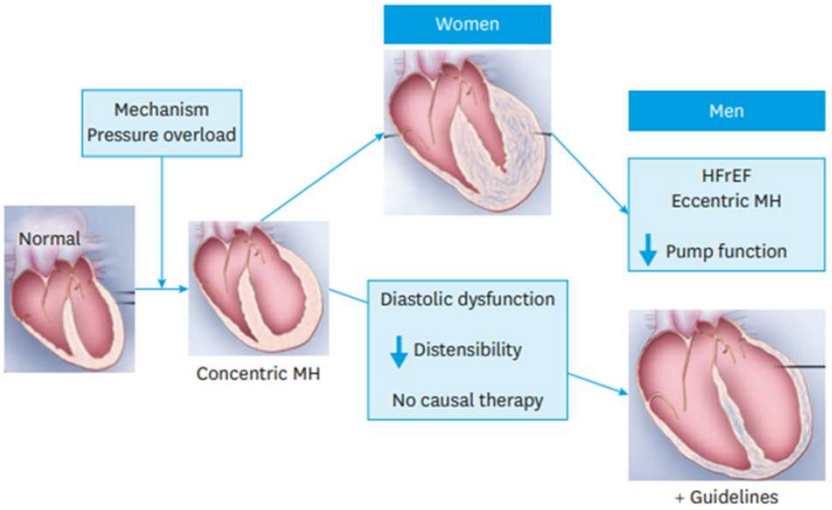


Figure 2. Paradigmatic changes in male and female hearts under pressure overload: both genders respond primarily with concentric MH, but women stay more in concentric MH with maintained diastolic function, whereas men develop more easily eccentric MH. Adapted from Regitz-Zagrosek and Kararigas G.[23]
HFrEF = heart failure reduced ejection fraction; MH = myocardial hypertrophy.

https://doi.org/10.36628/ijhf.2020.0004

Zagrosek, Int J Heart Fail. 2020

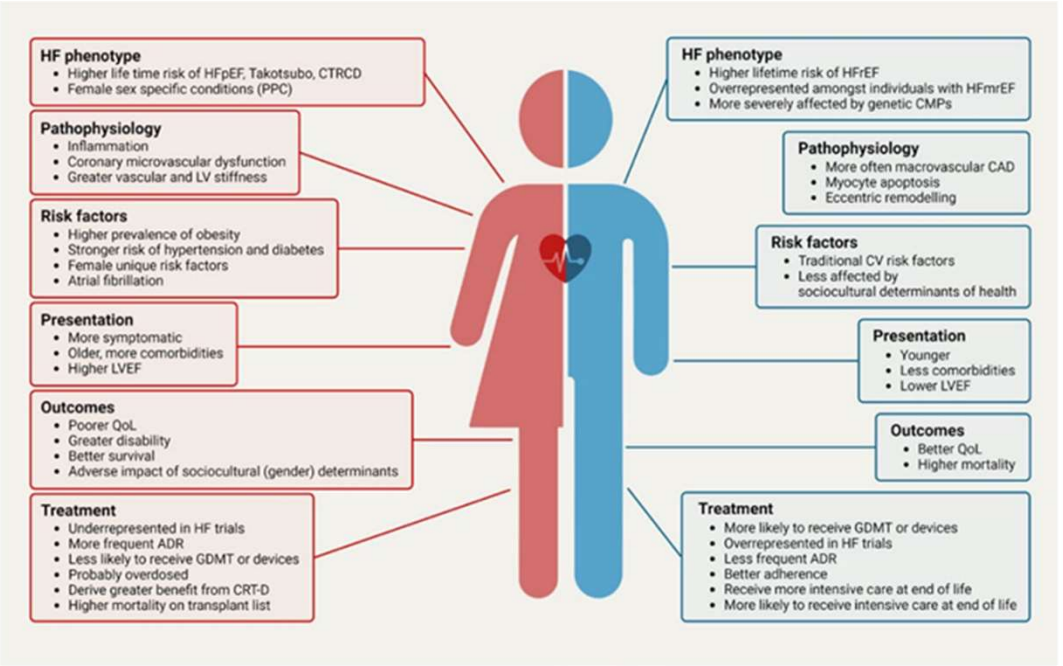


Figure 2: Sex and gender differences in heart failure.
ADR, Adverse drug reactions; CAD, Coronary artery disease; CMP, Cardiomyopathy; CRT-D, Cardiac resynchronisation therapy with defibrillator; CTRCD, Cancer treatment related cardiac dysfunction; CV, Cardiovascular; GDMT, Guideline-directed medical therapy; HF, Heart failure; HFmrEF, Heart failure with mildly reduced ejection fraction; HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; LV, Left ventricular; LVEF, Left ventricular ejection fraction; PPC, Peripartum cardiomyopathy; QoL, quality of life.

Delco, Cardiovasc Med 2023

PATOLOGIE CARDIOMETABOLICHE (1)

SCOMPENSO CARDIACO

Circulation
Volume 115, Issue 24, 19 June 2007; Pages 3111-3120
https://doi.org/10.1161/CIRCULATIONAHA.106.673442

American Heart Association.

HEART FAILURE

Guest Editor for this article was Edgardo Escobar, MD.

Sex Differences in Clinical Characteristics and Prognosis in a Broad Spectrum of Patients With Heart Failure

Results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Program

Among patients with heart failure, women have lower risks of most fatal and nonfatal outcomes. O'Meara et al.

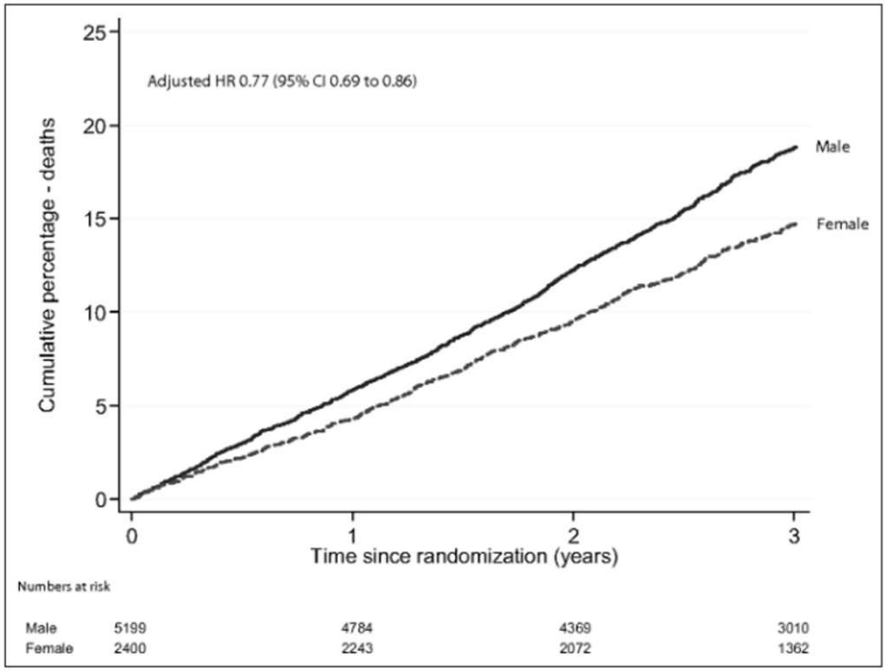


Figure 1. Kaplan-Meier curves for all-cause mortality in CHARM, standardized to median risk and shown by sex.

PATOLOGIE CARDIOMETABOLICHE (1)

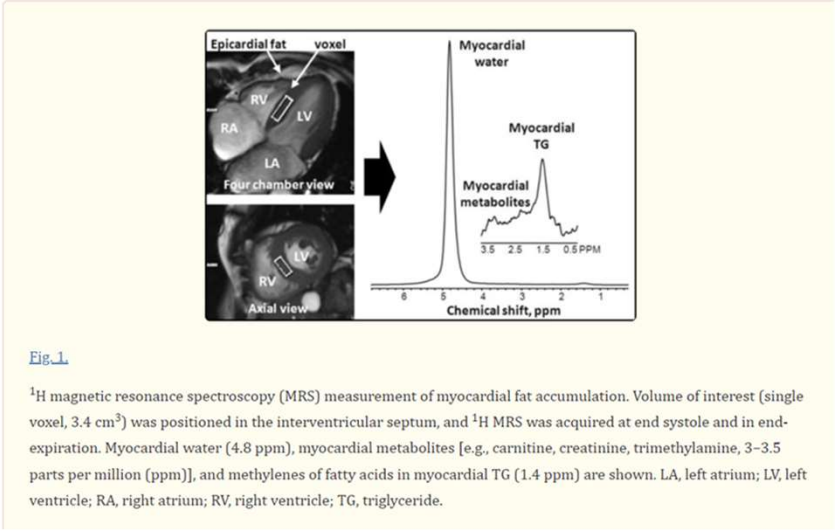


Fig. 1.

^{1}H magnetic resonance spectroscopy (MRS) measurement of myocardial fat accumulation. Volume of interest (single voxel, 3.4 cm^{3}) was positioned in the interventricular septum, and ^{1}H MRS was acquired at end systole and in end-expiration. Myocardial water (4.8 ppm), myocardial metabolites [e.g., carnitine, creatinine, trimethylamine, 3–3.5 parts per million (ppm)], and methylenes of fatty acids in myocardial TG (1.4 ppm) are shown. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; TG, triglyceride.

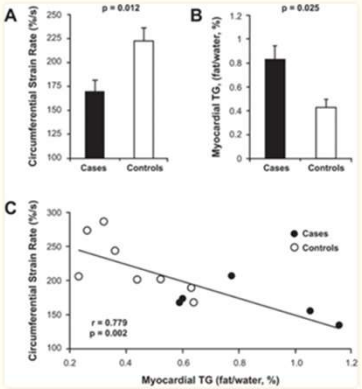


Fig. 2.

Diastolic circumferential strain rate and myocardial TG content. *A*: diastolic circumferential strain rate was significantly higher in reference controls than in cases (217 ± 15 vs. 168 ± 12%/s; $P = 0.012$). *B*: myocardial TG content was significantly higher in cases than in reference controls (0.83 ± 0.12% vs. 0.43 ± 0.06%; $P = 0.025$). *C*: myocardial TG content correlated inversely with diastolic circumferential strain rate ($r = -0.779$; $P = 0.002$), demonstrating that diastolic dysfunction is present in women with coronary microvascular dysfunction.

Wei J,. Am J Physiol Heart Circ Physiol 2016

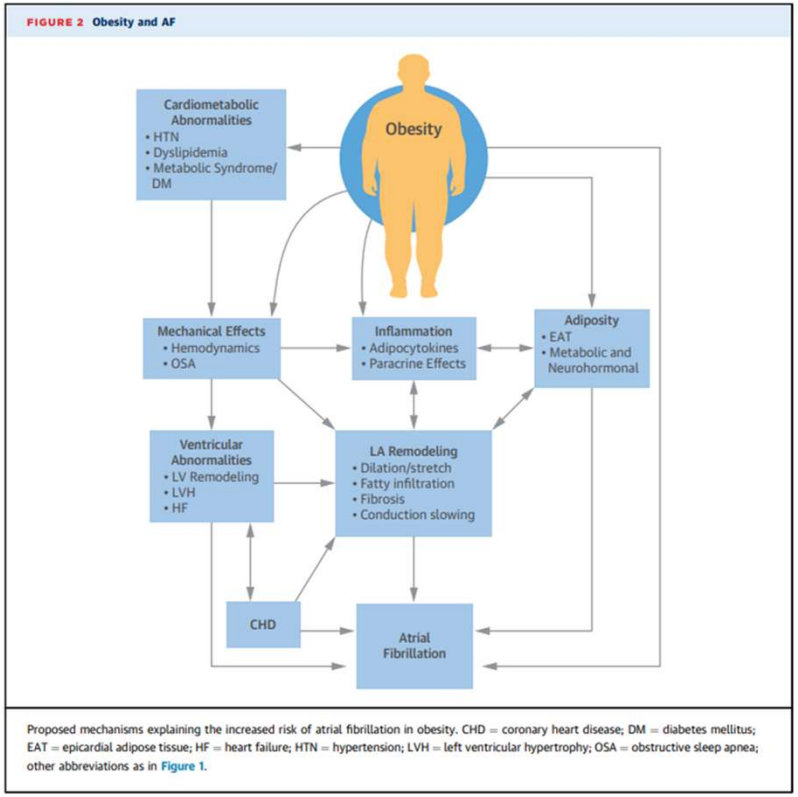
We investigated the prevalence of **myocardial steatosis and diastolic dysfunction in women** with CMD (coronary microvascular dysfunction) and subclinical HFpEF.

We measured myocardial triglyceride content (TG) and diastolic function, by proton magnetic resonance spectroscopy and magnetic resonance tissue tagging, respectively. When compared with reference controls: Women with CMD had **higher myocardial TG content** (0.83 ± 0.12% vs. 0.43 ± 0.06%; P = 0.025) and lower diastolic circumferential strain rate (168 ± 12 vs. 217 ± 15%/s; P = 0.012), with **myocardial TG content correlating inversely with diastolic circumferential strain rate** (r = −0.779; P = 0.002).

Diastolic disfunction vs **CMD and no obstructive CAD**

PATOLOGIE CARDIOMETABOLICHE (1)

FIBRILLAZIONE ATRIALE



Lavie, JAMC 2017

Blum, J AM Heart Assoc 2017

Table 2. Symptom Status According to AF Type and Sex

Characteristic	Paroxysmal			Persistent			Permanent			
	Women	Men	*P* Value*	Women	Men	*P* Value*	Women	Men	*P* Value*	*P* Value†
Any symptoms	247 (89.8)	442 (75.7)	<0.0001	82 (87.2)	198 (72.3)	0.003	57 (67.1)	103 (45.0)	0.0005	<0.0001
Palpitations	210 (76.4)	328 (56.2)	<0.0001	57 (60.6)	105 (38.3)	0.0002	29 (34.1)	50 (21.8)	0.03	<0.0001
Dyspnea	87 (31.6)	111 (19.0)	<0.0001	42 (44.7)	86 (31.4)	0.02	33 (38.8)	40 (17.5)	<0.0001	<0.0001
Fatigue	60 (21.8)	104 (17.8)	0.2	38 (40.4)	70 (25.6)	0.006	17 (20.0)	34 (14.9)	0.3	<0.0001
Dizziness	77 (28.0)	90 (15.4)	<0.0001	23 (24.5)	35 (12.8)	0.007	16 (18.8)	22 (9.6)	0.03	0.009
Effort intolerance	18 (6.6)	84 (14.4)	0.0009	18 (19.2)	56 (20.4)	0.8	4 (4.7)	13 (5.7)	1.0	<0.0001
Chest pain	35 (12.7)	64 (11.0)	0.4	9 (9.6)	16 (5.8)	0.2	8 (9.4)	17 (7.4)	0.6	0.02
Syncope	12 (4.4)	19 (3.3)	0.4	3 (3.2)	6 (2.2)	0.7	2 (2.4)	4 (1.8)	0.7	0.2

Table 3. Symptom Status and Health Perception According to Sex

	Baseline			1-Y Follow-up			2-Y Follow-up			3-Y Follow-up		
	Women	Men	*P* Value*	Women	Men	*P* Value*	Women	Men	*P* Value*	Women	Men	*P* Value*
n	454	1088		409	981		292	708		177	411	
Any symptoms, n (%)	386 (85.0)	743 (68.3)	<0.0001	201 (49.1)	320 (32.6)	<0.0001	140 (48.0)	226 (31.9)	<0.0001	73 (41.2)	128 (31.1)	0.02
Palpitations	296 (65.2)	483 (44.4)	<0.0001	142 (34.7)	203 (20.7)	<0.0001	92 (31.5)	138 (19.5)	<0.0001	49 (27.7)	71 (17.3)	0.004
Dyspnea	162 (35.7)	237 (21.8)	<0.0001	55 (13.4)	87 (8.9)	0.01	41 (14.0)	49 (6.9)	0.0003	20 (11.3)	28 (6.8)	0.07
Fatigue	115 (25.3)	208 (19.1)	0.006	50 (12.2)	71 (7.2)	0.003	18 (6.2)	50 (7.1)	0.6	12 (6.8)	27 (6.6)	0.9
Dizziness	116 (25.6)	147 (13.5)	<0.0001	58 (14.2)	66 (6.7)	<0.0001	31 (10.6)	41 (5.8)	0.007	14 (7.9)	22 (5.4)	0.2
Effort intolerance	40 (8.8)	153 (14.1)	0.005	14 (3.4)	46 (4.7)	0.3	8 (2.7)	29 (4.1)	0.3	4 (2.3)	16 (3.9)	0.3
Chest pain	52 (11.5)	97 (8.9)	0.12	23 (5.6)	29 (3.0)	0.02	17 (5.8)	14 (2.0)	0.001	7 (4.0)	7 (1.7)	0.1
Syncope	17 (3.7)	29 (2.7)	0.26	12 (2.9)	5 (0.5)	0.0002	7 (2.4)	1 (0.1)	0.0003	2 (1.1)	1 (0.2)	0.2
Health perception, 0–100, median (IQR)	70.0 (50.0–80.0)	76.0 (60.0–85.0)	<0.0001	74.0 (60.0–80.0)	80.0 (65.0–90.0)	<0.0001	75.0 (60.0–85.0)	80.0 (65.0–90.0)	0.0004	ns		

IQR indicates interquartile range; ns indicates not surveyed.
*P-values were based on the χ^2 test or Wilcoxon rank sum test, as appropriate.

PATOLOGIE CARDIOMETABOLICHE (1)

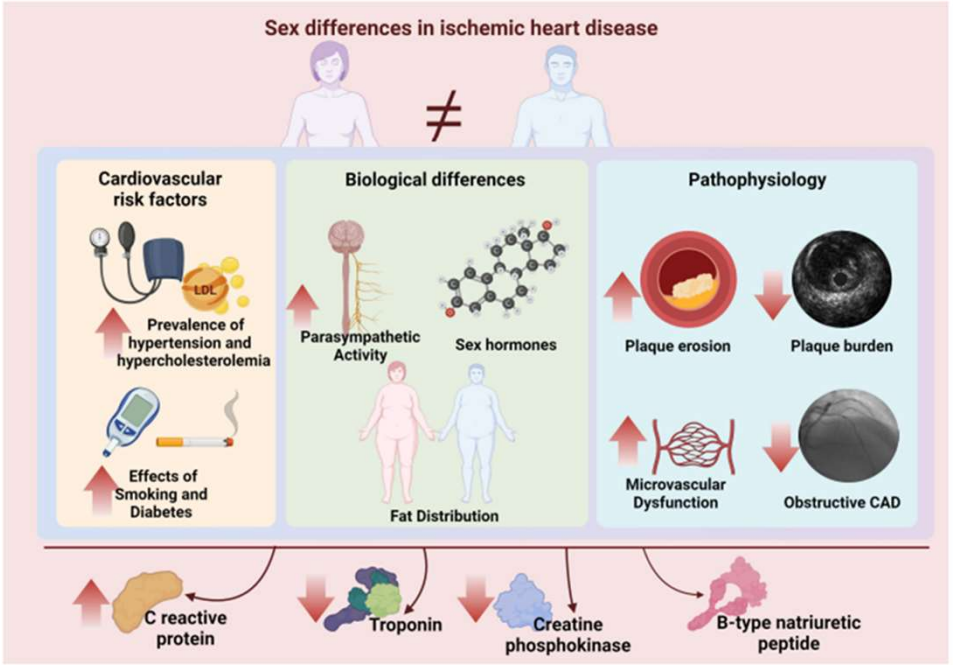
CARDIOPATIA ISCHEMICA

- coronaropatia aterosclerotica
- disfunzione coronarica microvascolare
- anomalie vasomotorie
- dissezione coronarica spontanea (80% donne)
- cardiopatia indotta dallo stress.

DONNE Nstemi e Sindrome coronarica cronica
Maggiore frequenza di complicanze

Cenko, JACC 2019

SINTOMI: asintomatiche, sintomi atipici, angina



Bergami, Rev. Cardiovasc. Med. 2022

PATOLOGIE CARDIOMETABOLICHE (1)

CARDIOPATIA ISCHEMICA

Mortalità a 30 giorni dopo STEMI > donne
OR 1.88; 95%CI, 1.24-3-26 Cenko et al, JAMA 2018

La mortalita a 1 anno correla maggiormente con il genere e non con il sesso biologico.

«help-seeking behavior, access to healthcare, and individual use of the healthcare system»

Marriage: prognosi migliore nell'uomo
maggiore mortalità nelle donne
Mehta, 2015
Kilpi, 2015

Pelletier et al. JACC VOL. 67, NO. 2, 2016

PATOLOGIE CARDIOMETABOLICHE (1)

ANEURISMA AORTA ADDOMINALE

E’ sei volte più comune negli uomini
Nelle donne si sviluppa circa 10 anni dopo con peggiore prognosi. Il sesso femminile è un **fattore predittivo di morte intraospedaliera per rottura** di AAA.

Garcia et al, Circ Res 2017

AOPD

Le donne sono frequentemente asintomatiche o si presentano con sintomi atipici.
Spesso viene **sottodiagnosticata** poiché i sintomi vengono associati ad altre condizioni come artrosi, osteoporosi, mialgie.
Le donne che sviluppano PAD generalmente sono **più anziane** degli uomini e con una **classe Rutherford più avanzata**, e un **coinvolgimento multivascolare**, inoltre il sesso femminile correla con una maggiore probabilita di coinvolgimento **femoro popliteo**. Hanno un **maggior e più rapido declino funzionale** e peggioramento della qualità della vita.

Pabon, Circ res 2022

PATOLOGIE CARDIOMETABOLICHE (1)

ICTUS

Uomini: Maggiore incidenza

FR: IMA, PAD, DM, alcol

Donne: Maggiore prevalenza (4.1milioni di donne che vivono con esiti di stroke vs 3.1 milioni di uomini

FR: FA e ipertensione, contraccettivi, gravidanza

Tipologia: emorragia subaracnoidea, circolo anteriore

Esordio: piu tardive

Maggiore peso della familiarità

Non significative differenze del NIHSS.

Reeves, Lancet Neurol 2008

TERAPIA MEDICA E DIFFERENZE DI GENERE

ESC European Society of Cardiology
European Heart Journal - Cardiovascular Pharmacotherapy (2017) 3, 163–182
doi:10.1093/ehjcvp/pvw042

REVIEW

Gender differences in the effects of cardiovascular drugs

J. Tamargo[1,2]*, G. Rosano[3,4], T. Walther[5], J. Duarte[2,6], A. Niessner[7], J.C. Kaski[8], C. Ceconi[9], H. Drexel[10], K. Kjeldsen[11,12], G. Savarese[13], C. Torp-Pedersen[14], D. Atar[15], B.S. Lewis[16], and S. Agewall[17]

Table 3 Sex differences in drug pharmacodynamics

Drug class	Outcomes
Alcohol	Higher vulnerability of W to acute and chronic complications of alcoholism
Anaesthetics: propofol	W are less sensitive to propofol. W wake up faster and require higher doses than M for the same effect
ACEIs	No mortality benefit in W with asymptomatic LV systolic dysfunction
Antidepressants	W respond better to selective serotonin/noradrenaline uptake inhibitors. M respond better to TCA and MAO inhibitors than W
Antipsychotic drugs	More effective in W. They require lower doses to control symptoms
Aspirin	Higher protective effect against stroke in W and against MI in M. Aspirin is more active in male platelets. Aspirin resistance is more frequent in W
Benzodiazepines	Diazepam impairs psychomotor skills to a greater extent in W. They should be initiated at lower dosages in W
Beta blockers	Greater reduction in blood pressure and heart rate in W treated with metoprolol and propranolol
Digoxin	W with HF have an increased risk of mortality on digoxin therapy. W require lower doses and lower plasma levels (< 0.8 ng/mL)
Glucocortioids	Females are more sensitive to the effects of methylprednisolone
Heparin	W had increased partial thromboplastin time, even after weight-adjusted dosing, suggesting an increased sensitivity

Table 2 Sex-related differences in drug pharmacokinetic parameters

Drug class	Outcomes in females
Anaesthetics: propofol	Plasma propofol levels decline more rapidly in W at the end of infusion
Alcohol	Lower gastric alcohol dehydrogenase activity in W. Higher plasma concentrations in W as compared with M following an equivalent drink
Antidepressants	Higher AUC and C_{max} in W
H1-antihistamines	Slower metabolism and elimination in W
Antipsychotic drugs[a]	Higher plasma levels and Vd and lower Cl in W. Reduce the dosage in W or increase dosage in M. Olanzapine is more rapidly eliminated in M than in W
Aspirin	Bioavailability and plasma levels of aspirin and salicylate are higher in W possibly due to lower activity of aspirin esterase, larger Vd and lower Cl in W than in M. Differences disappear with OCP
Benzodiazepines	Lower initial plasma levels due to larger Vd, and possibly higher Cl, in W. OC reduce their Cl. Higher plasma levels of free diazepam in W
Beta-receptor agonists	W are less sensitive
Beta blockers: metoprolol, propranolol	W have higher plasma levels due to a smaller Vd and slower Cl. Drug exposure to metoprolol increases by OC
	Renal Cl of atenolol and metoprolol increases during P due to enhanced hepatic metabolism
Calcium channel blockers	Faster Cl of verapamil, and nifedipine in W. Increased bioavailability and decreased clearance of oral verapamil in W compared with M
Digoxin	W have higher serum digoxin concentrations due to reduced Vd and lower Cl. Drug Cl increases during P
Glucocorticoids	Oral Cl and Vd of prednisolone are higher in M. Prednisolone clearance was reduced by OC
Heparin	W had higher plasma levels and APTT values than M due to a lower Cl
Iron	Oral absorption of iron is greater in W than in M
Isosorbide mononitrate	W had significantly higher serum plasma concentrations compared with men, probably due to the lower body weights in females
Labetalol	Labetalol concentrations are 80% higher in W
Lidocaine	W has a larger Vd and may require a higher i.v. bolus dose than M. Higher free plasma levels in W receiving OCP, as alpha 1-acid glycoprotein levels are reduced by oestrogens

TERAPIA MEDICA E DIFFERENZE DI GENERE

ZHAO ET AL, J AM HEART ASSOC 2020

Systematic review and meta Analysis

43 studi

2 milioni di partecipanti

➔Minore prescrizione di aspirina, statina e ACE I nelle donne

➔Maggiore prescrizione di diuretico

- Minore consapevolezza del rischio CV

- Scarsa aderenza alla terapia (scarsa percezione di efficacia e maggiore timore di ADR)

TERAPIA MEDICA E DIFFERENZE DI GENERE

STATINE

Inibizione della 3-hydroxy3-methyl-glutaryl-CoA (HMG-CoA)

Effetti pleiotropici (NoS, stress ossidativo e infammazione)

1) Donne displipidemiche raggiungono meno frequentemente i target terapeutici e sperimentano una riduzione meno efficace delle LDL.
2) Donne ad alto rischio ricevono meno frequentemnte dosi adeguate di statine o terapia di combinazione.
3) Diversa risposta nei due sessi: Maggiore volume di distribuzione, metabolismo più rapido (CYP3A4) ad eccezione della pravastatina, effetti degli ormoni sessuali.
4) Polimorfismo di ERalfa (atorvastatina -HDL).
5) ADR: Maggiore tossicità muscolare e DM2.

Cangemi, Pharmacological Research 2017

TERAPIA MEDICA E DIFFERENZE DI GENERE

ASPIRINA in prevenzione primaria

Women's Health Study 2005: low dose aspirin -> riduzione stroke a 10 anni

-> non riduzione del MI

-> donna >65 anni riduzione di stroke e MI

Follow up a 15 anni: vantaggio nelle donne >65 anni

ASCEND

ARRIVE 2018: non riduzione egli eventi CV ma aumento del sanguinamento

ASPREE

Update 2019 needed to treat (sanguinamento) minore del needed to treat per prevenire ASCVD (210 vs 265)

TERAPIA MEDICA E DIFFERENZE DI GENERE

ASPIRINA in prevenzione primaria

4.6. Aspirin Use

Recommendations for Aspirin Use

Referenced studies that support recommendations are summarized in Online Data Supplements 17 and 18.

COR	LOE	Recommendations
IIb	A	1. Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk.[S4.6-1–S4.6-8]
III: Harm	B-R	2. Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age.[S4.6-9]
III: Harm	C-LD	3. Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.[S4.6-10]

Acc/Aha 2019

Recommendations for antithrombotic therapy

Recommendations	Class[a]	Level[b]
Aspirin 75 - 100 mg daily is recommended for secondary prevention of CVD.[619]	I	A
Clopidogrel 75 mg daily is recommended as an alternative to aspirin in secondary prevention in case of aspirin intolerance.[620]	I	B
Clopidogrel 75 mg daily may be considered in preference to aspirin in patients with established ASCVD.[620,621]	IIb	A
Concomitant use of a proton pump inhibitor is recommended in patients receiving antiplatelet therapy who are at high risk of gastrointestinal bleeding.[622,623]	I	A
In patients with DM at high or very high CVD risk, low-dose aspirin may be considered for primary prevention in the absence of clear contraindications.[5,624,625]	IIb	A
Antiplatelet therapy is not recommended in individuals with low/moderate CV risk due to the increased risk of major bleeding.[624,626–630]	III	A

Esc 2021

TAKE HOME MESSAGES

- CVD grande impatto sullo stato di salute delle donne.
- Necessità di nuovi strumenti di stratificazine del rischio CV.
- Necessità di *sex specific care*.
- Aumentare la consapevolezza delle donne.
- Colmare il *Gender Gap.*
- Paziente con disforia di genere e rischio CV.

Grazie