Meeting Nazionale ITACARE-P 2025

La Cardiologia Riabilitativa e Preventiva come snodo fondamentale della cura della persona con cardiopatia

La terapia farmacologica: quello che già sappiamo e (spesso) non facciamo

Drs. Fabiana Isabella Gambarin
Cardiologia Riabilitativa
ICS Maugeri Veruno

CENTRO CONGRESSI FRENTANI
Roma, 21-22 novembre 2025

COME SIAMO MESSI

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

2024 ESC Guidelines for the management of chronic coronary syndromes

Table 8 Evidence-based doses of disease-modifying drugs in key randomized trials in patients with heart failure with reduced ejection fraction

	Starting dose	Target dose
ACE-I		
Captopril[a]	6.25 mg *t.i.d.*	50 mg *t.i.d.*
Enalapril	2.5 mg *b.i.d.*	10–20 mg *b.i.d.*
Lisinopril[b]	2.5–5 mg *o.d.*	20–35 mg *o.d.*
Ramipril	2.5 mg *b.i.d.*	5 mg *b.i.d.*
Trandolapril[a]	0.5 mg *o.d.*	4 mg *o.d.*
ARNI		
Sacubitril/valsartan	49/51 mg *b.i.d.*[c]	97/103 mg *b.i.d.*
Beta-blockers		
Bisoprolol	1.25 mg *o.d.*	10 mg *o.d.*
Carvedilol	3.125 mg *b.i.d.*	25 mg *b.i.d.*[e]
Metoprolol succinate (CR/XL)	12.5–25 mg *o.d.*	200 mg *o.d.*
Nebivolol[d]	1.25 mg *o.d.*	10 mg *o.d.*
MRA		
Eplerenone	25 mg *o.d.*	50 mg *o.d.*
Spironolactone	25 mg *o.d.*[f]	50 mg *o.d.*
SGLT2 inhibitor		
Dapagliflozin	10 mg *o.d.*	10 mg *o.d.*
Empagliflozin	10 mg *o.d.*	10 mg *o.d.*

Class	Examples	Initial dose (typical)	Target dose (trial-based)
ACE inhibitors	Ramipril, Perindopril, Trandolapril	Ramipril 2.5 mg od Perindopril 2–4 mg od	Ramipril 10 mg (HOPE) Perindopril 8 mg (EURO
ARBs	Valsartan, Candesartan Losartan	Valsartan 40–80 mg bid	Max tolerated dose
Beta-blockers	Metoprolol, Bisoprolol, Atenolol	Metoprolol 25–50 mg/d Bisoprolol 1.25–2.5 mg/	Metoprolol ≥100 mg/d Bisoprolol 5–10 mg/d

European Heart Journal (2024) **45**, 3415–3537
The Lancet, Volume 362, Issue 9386, 782 - 788
(J Clin Hypertens. 2005;7:188–193)
Eur J Clin Invest. 2024;54:e14309.

Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study

Lancet 2019; 394: 1254–63

These findings suggest that **women with HFrEF** may experience **similar benefits** as men and **fewer adverse effects** at **lower doses** of ACE inhibitors or ARBs and β-blockers. The data support sex-specific studies to analyze optimal drug doses.

Karol E. Watson, MD, PhD, FACC - Editor-in-Chief - NEJM Journal Watch Cardiology

...up-titration of these drugs to maxim...
...ommended in current heart failure guidelines (table...
The main finding of the present study suggests, howeve...
that these doses may not be appropriate in women. Ou...
...ultinational observational study findings showed s...
...ses in the optimal dose of ACE inhibitors...

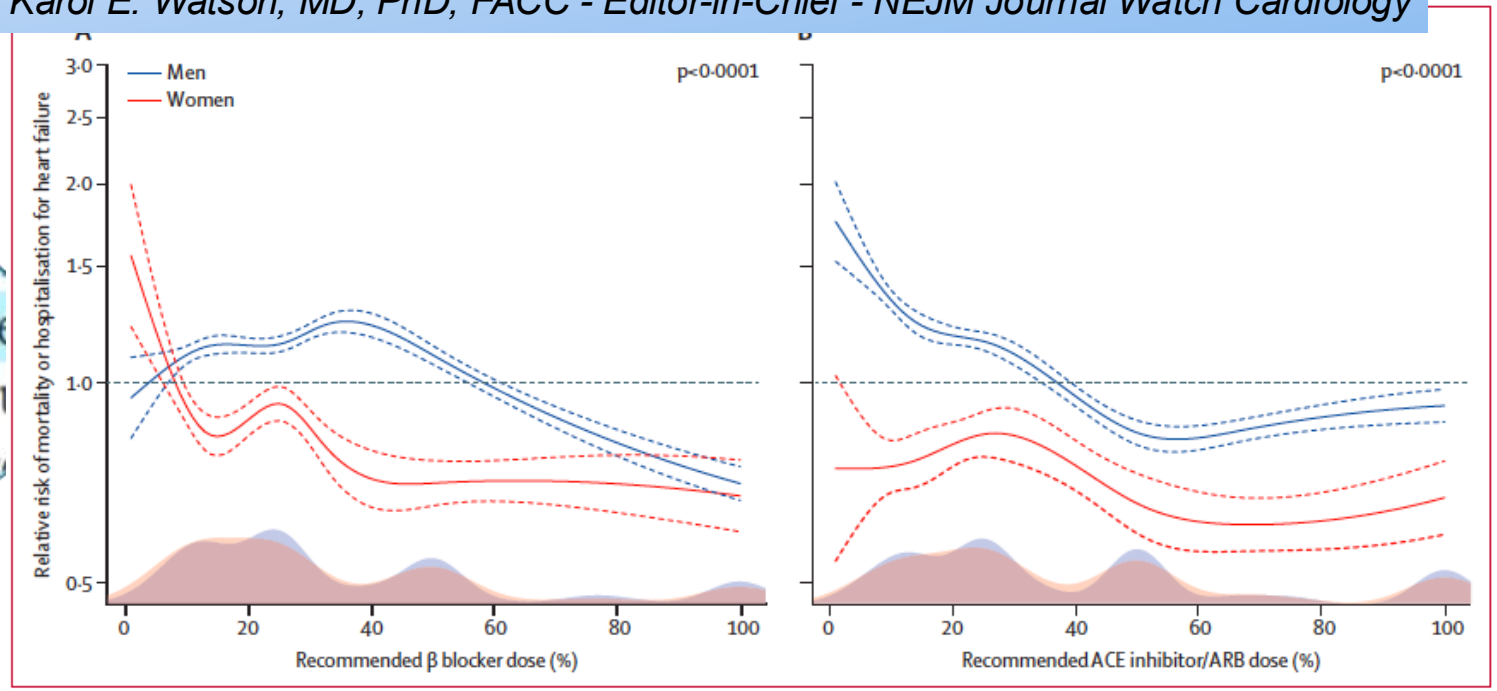


Figure 2: Validation of optimal β blocker (A) and ACE inhibitor or ARB dose (B)

POFFARBACCO!!!

Position paper ANMCO: Differenze di genere nell'approccio farmacologico cardiovascolare

↑ 2,5 Concentrazioni plasmatiche massime di diversi ACEI, ARB e β-bloccanti nelle donne, a parità di dose somministrata

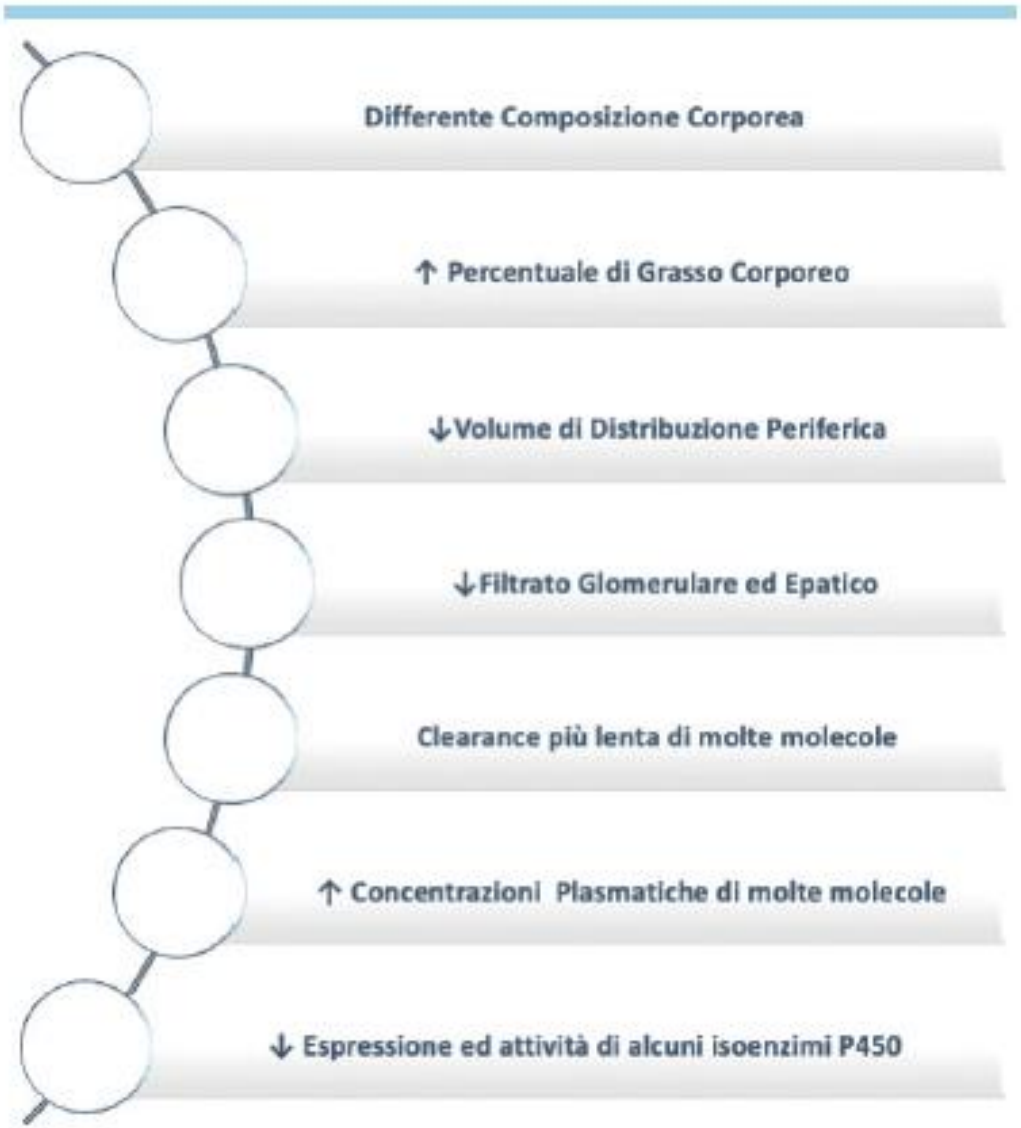
- 50–60% della dose target di β-bloccanti
- -40–60% della dose target di ACEI/ARB

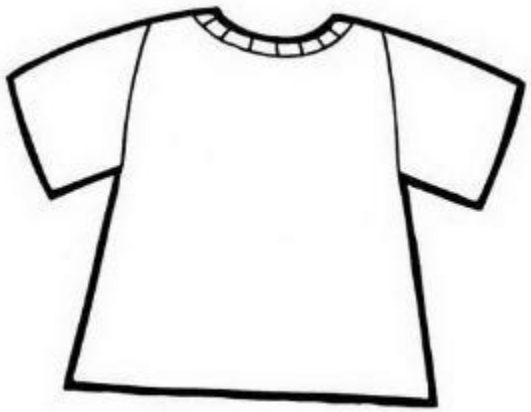
→ ↓30% rischio di mortalità per tutte le cause e ospedalizzazioni per scompenso cardiaco

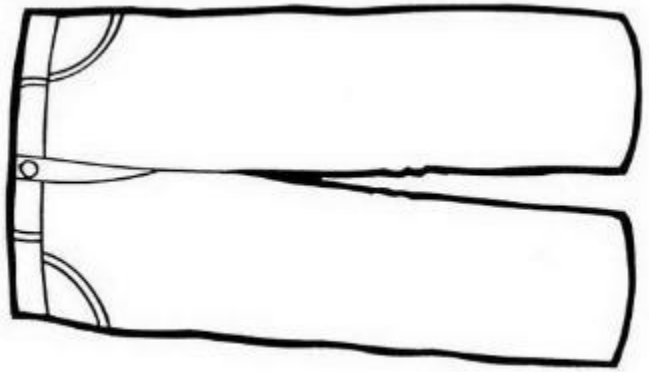
Aumentando la dose di β-bloccanti, ACEI e ARB nelle donne con HFrEF non si ottengono ulteriori benefici

→ ↑Tasso di eventi avversi da farmaci

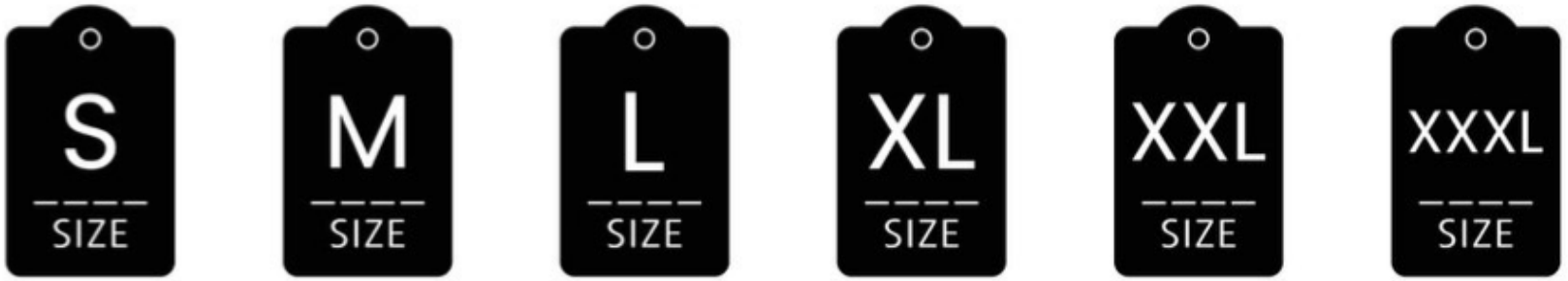
→ Necessità di definire dosaggi basati sul sesso





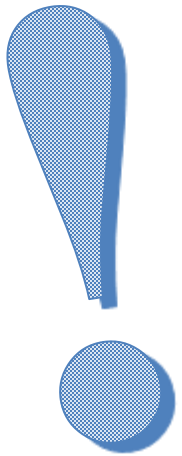


www.disegnidacolorareGratis.it



NEI TRIAL FARMACOLOGICI

LE DONNE COMPAIONO POCO



Nei grandi trial degli anni ’90–2000 sulle terapie cardiovascolari farmacologiche (ACE-I, ARB, β-blockers), la proporzione di donne nell’arruolamento spesso oscillava tra **~15% e 27%**

Clinical Trial > Lancet. 1999 Jun 12;353(9169):2001-7.

Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)

Clinical Trial > Lancet. 1999 Jan 2;353(9146):9-13.

The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial

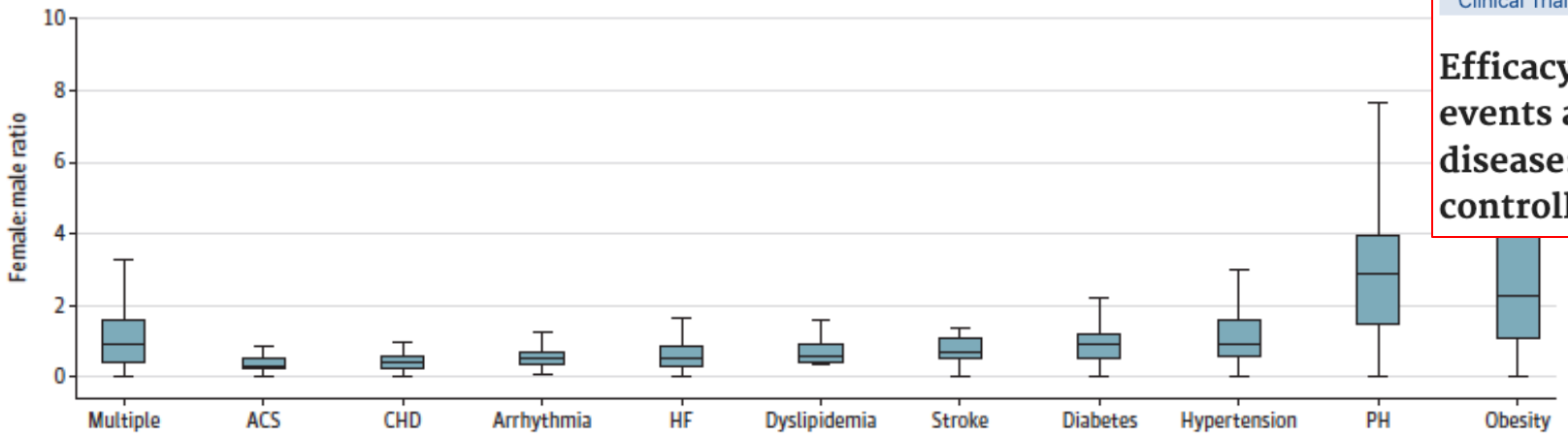
EFFECTS OF AN ANGIOTENSIN-CONVERTING–ENZYME INHIBITOR, RAMIPRIL, ON CARDIOVASCULAR EVENTS IN HIGH-RISK PATIENTS

THE HEART OUTCOMES PREVENTION EVALUATION STUDY INVESTIGATORS*

Angiotensin-Converting–Enzyme Inhibition in Stable Coronary Artery Disease

The PEACE Trial Investigators*

JAMA Network Open. 2025;8(8):e2529104.

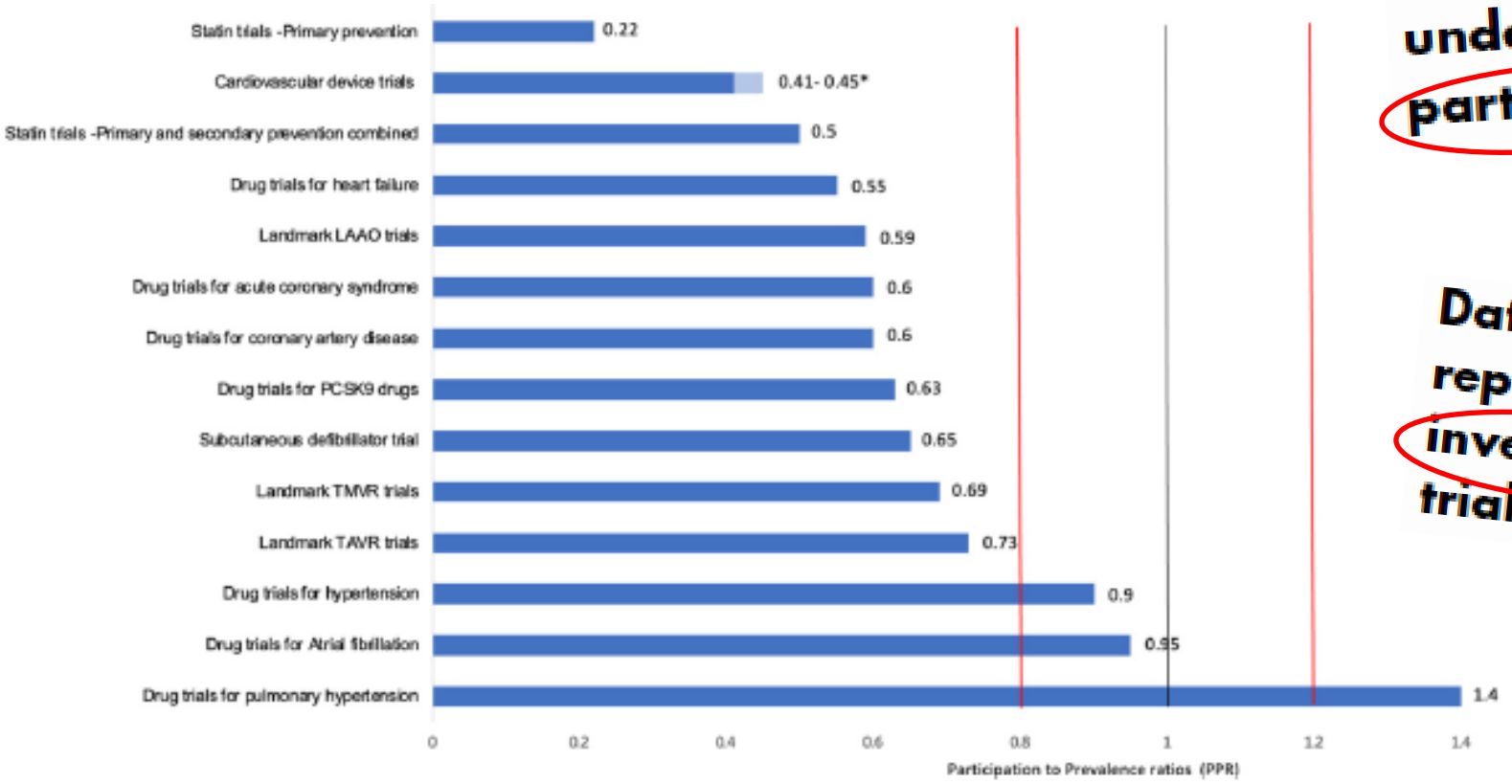


Clinical Trial > Lancet. 2003 Sep 6;362(9386):782-8. doi: 10.1016/s0140-6736(03)14286-9.

Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study)

The under-representation of women in cardiovascular clinical trials: State-of-the-art review and ethical considerations

Sonya Burgess, PhD, MBChB[1,2], Sarah Zaman, PhD, MBChB[1,3,4], Cindy Towns, PhD, MBChB[5], Megan Covlewright, MD[6], and F. Aavsha Cader, MBBS, MSc[7]



Data demonstrating under-representation of women as participants in clinical trials

Data demonstrating under representation of women as investigators and authors in clinical trials

(Am Heart J 2025;282:81–92.)

Prima del 2019:

Reporting on sex-based analysis in clinical trials of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker efficacy

DM Rabi MD MSc[1], N Khan MD MSc[4], M Vallee MD PhD[5], MA Hladunewich MD MSc[6], SW Tobe MD[6], L Pilote MD PhD[7]

Sex specific data was only available for 43% of the studies, with only six ACEI studies and three ARB studies reporting sex-specific outcomes (Rabi et al., 2008).

TABLE 1
Summary of the effects of sex steroid hormones on the renin-angiotensin system

Testosterone	
	Increased angiotensinogen messenger RNA
	Increased plasma renin activity
Estrogen	
	Increased angiotensinogen
	Decreased plasma renin activity
	Decreased angiotensin-converting enzyme expression
	Decreased angiotensin 1 receptor expression

Gender Differences in Cardiovascular Pharmacotherapy—the Example of Hypertension: A Mini Review

Jacklean Kalibala [1], Antoinette Pechère-Bertschi [2] and Jules Desmeules [1,3*]*

CONCLUSION

Regarding the treatment of hypertension, an increasing number of studies show interactions between gender and PK as well as pharmacogenetics, that could influence BP control and prevention of CV events. On the whole women seem to be more prone to ADR in all antihypertensive drug groups. Although gender differences in drug toxicity are often attributed to differences in body weight and composition, several studies reviewed here show persistent gender dimorphism even after adjustment for these factors.

TABLE 1 | Sex differences in hepatic metabolism and transporters (P-Gp).

	Sex difference	Hormonal influence
CYP 1A2	Female > Male	Inhibited by oral contraceptives
CYP2A1	Female < Male	
CYP 2A6	Female > Male	Induced by estrogens and oral contraceptives
CYP 2B6	Female > Male	Induced by estrogens and oral contraceptives
CYP 2E1	Female < Male	
CYP2D6	Conflicting data	
CYP 2C9	Female = Male	
CYP 2C19	No consistent data	Inhibited by oral contraceptives
CYP 3A4	Female > Male	Induced by testosterone and progesterone.
UGTs	Female < Male	Induced by oral contraceptives
NATs	Female = Male	
TPMT	Female < Male	
P-Gp	Female < Male	Induced by estrogens Inhibited by testosterone

CYP, cytochrome P450; NATs, arylamine N-acetyltransferase; UGTs, Uridine 5'-diphospho-glucuronosyltransferases; TPMT, Thiopurine methyl transferase; P-Gp, glycoprotein P.

MINI REVIEW
published: 06 May 2020
doi: 10.3389/fphar.2020.00564

European Heart Journal - Quality of Care and Clinical Outcomes (2025) **00**, 1–20
https://doi.org/10.1093/ehjqcco/qcaf113

Age- and sex-related differences in heart failure characteristics and treatment patterns across the ejection fraction spectrum: first data from the BRING-UP 3 Heart Failure study

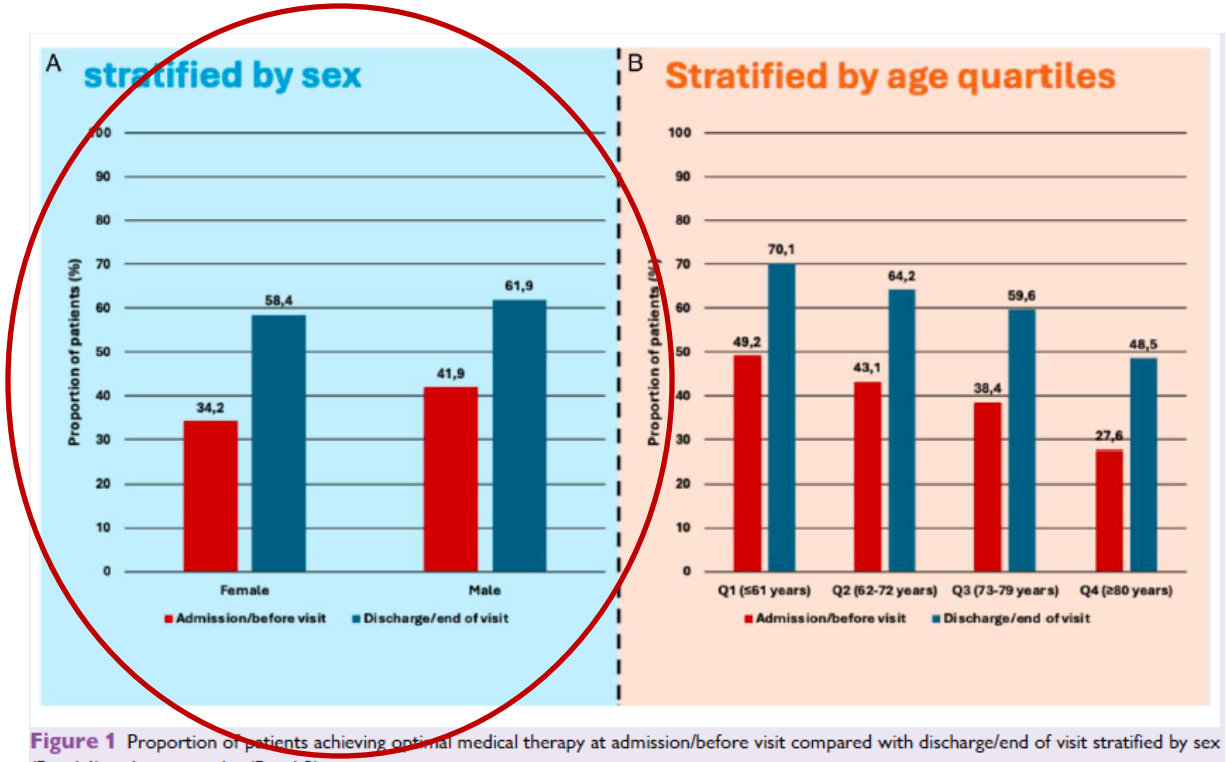


Figure 1 Proportion of patients achieving optimal medical therapy at admission/before visit compared with discharge/end of visit stratified by sex (Panel *A*) and age quartiles (Panel *B*).

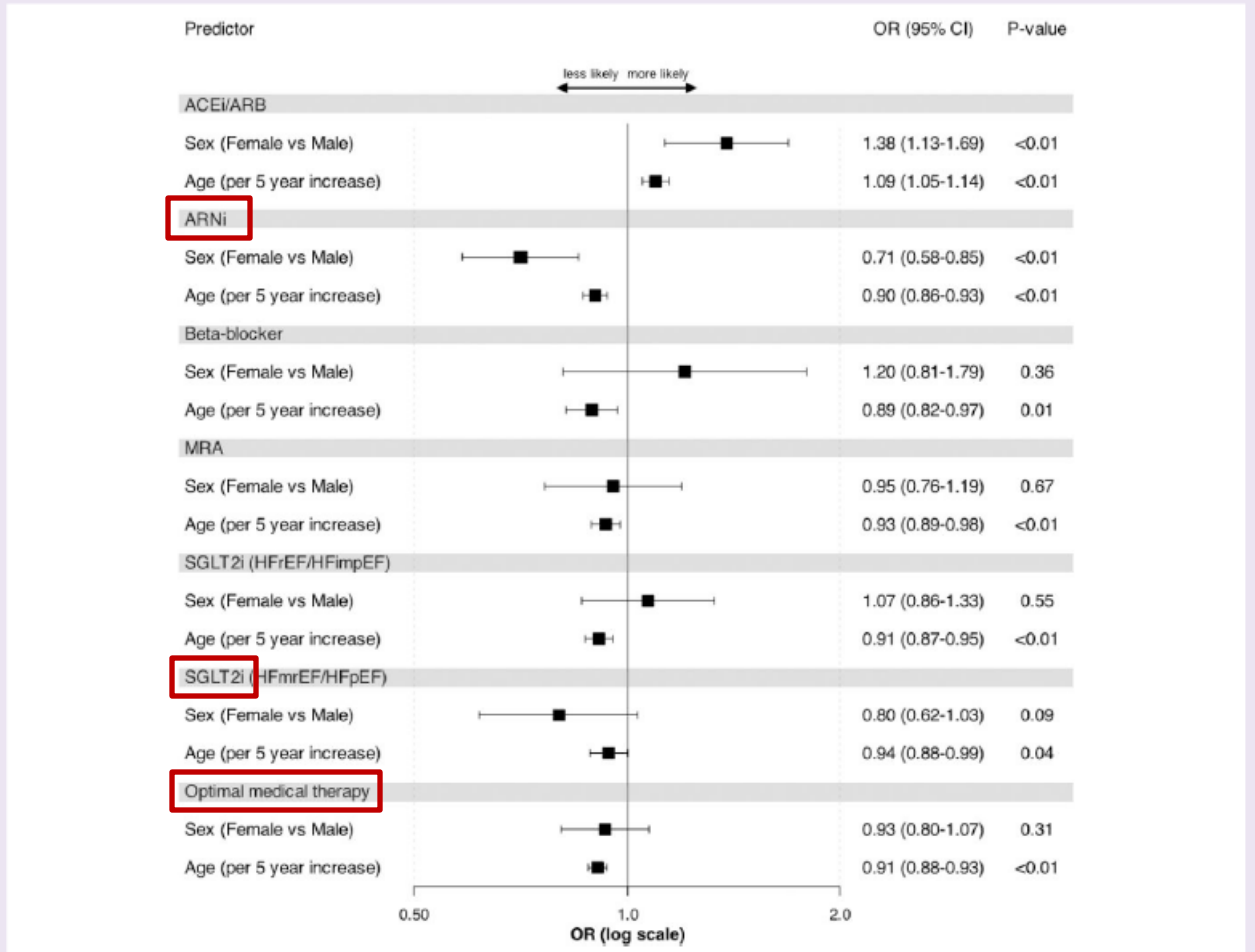
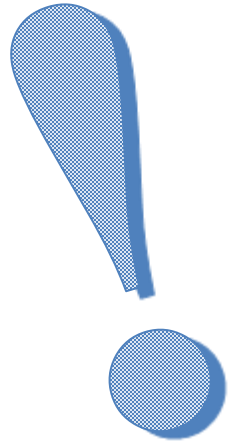


Figure 5 Sex and age association with medical therapy prescription at discharge/end of visit and optimal medical therapy in fully adjusted prediction models. ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor/neprilysin inhibitor; CI, confidence interval; MRA, mineralocorticoid receptor antagonist; OR, odds ratio; SGLT2i, sodium-glucose co-transporter type II inhibitor.

LA CONSAPEVOLEZZA DEL PROPRIO RISCHIO CARDIOVASCOLARE

È BASSA TRA LE DONNE



S. Maffei et al, J Clin Med 2022; 11, 1695

Journal of Clinical Medicine

MDPI

Article

Cardiovascular Risk Perception and Knowledge among Italian Women: Lessons from IGENDA Protocol

Quale consapevolezza del rischio cardiovascolare nelle donne?

Questionario anonimo – 4454 donne (44±14 aa):

- **> 60%** ritiene che la patologia CV sia una condizione quasi esclusiva del sesso maschile
- **< 10%** si ritiene ad elevato rischio CV

- **1 donna su 30** muore per cancro al seno
- **1 donna su 3** muore per cardiopatia ischemica
- **2 donne su 3** *con diabete* muoiono per cardiopatia ischemica

Le donne sono più esposte al rischio di RITARDO DIAGNOSTICO / TERAPEUTICO

- Attribuzione dei sintomi a condizioni croniche
- Bassa percezione di rischio di malattie cardiovascolari (infarto miocardico)
- Più elevati livelli di imbarazzo connessi ai falsi allarmi.

JR Finnegan et al , Preventive Medicine 2000

Asghari et al. BMC Cardiovascular Disorders (2022) 22:508

Cardiovascular risk factor distribution and subjective risk estimation in urban women – The BEFRI Study: a randomized cross-sectional study

Sabine Oertelt-Prigione[1,2*], Ute Seeland[1,2], Friederike Kendel[3], Mirjam Rücke[1], Agnes Flöel[4], Wolfgang Gaissmaier[5], Christine Heim[3], Renate Schnabel[6], Verena Stangl[2,7] and Vera Regitz-Zagrosek[1,2,8]

Table 3 Multiple regression analysis of predictors for subjective under- and overestimation of cardiovascular risk: underestimation

	OR	95% CI	*P*
Age >50 years	3.5	2.6–4.8	<0.0001
Joblessness	1.9	1.4 –2.6	<0.0001
Social risk factors (3 or more)	1.5	1.1–2.1	0.009
Positive subjective health rating	1.7	1.2–2.3	0.003

Goodness-of-fit (Wald) n.s.; Hosmer-Lemeshow n.s.; ROC for prediction 0.71.

Conclusions

The present study is the first evaluation of women's subjective risk estimation demonstrating how the most vulnerable individuals, the elderly, and the socially disadvantaged bear the greatest risk of subjective underestimation

Oertelt-Prigione *et al. BMC Medicine* (2015) 13:52

PER MIGLIORARE LA FARMACOTERAPIA NELLE DONNE

QUALI POSSIBILI SOLUZIONI

(Am Heart J 2025;282:81–92.)

8 Action Items To increase the representation of women as participants in clinical trials

1. Apply the evidence

Increase women in trial leadership and women investigators

-Women trial leads & authors increase the enrolment of women in trials

-Women trial leads & authors increase the enrolment of traditionally under-represented ethnic groups

-Seek appropriate representation at all levels: PIs, manus

-Ensure disparity of authorship is addressed where it is m

2. Invest in diverse research teams

-Establish high quality mentorship and sponsorship progra

capacity for diverse trial leadership

3. Acknowledge the importance of trust

-Trust is critical to successful enrolment of women- it is

with physician patient concordance of sex and ethnicity

-Prioritise time to communicate

-Communication should be patient centred

4. Address study protocols

-Delay trial closure until adequate enrolment of women is achieved

-Use prospective power calculations to calcula

-Avoid inappropriate inclusion/exclusion criteri

-Allow women of childbearing age to participat

-Be ready to discuss co

-Ensure women have b

5. Remove barriers to enrolment

-Consider telehealth follow up where possible,

-Arrange transportation without financial penalty

-Arrange on-site care for dependants during study visits or compensation for alternative care costs

6. Ethically incentivise sites

-Reward/Acknowledge sites achieving higher recruitment of women

-Reward/Acknowledge sites with high representation of women as investigators

-Reward/Acknowledge sites ensuring the involvement of women consumers/patients in study design

7. Alter expectations- From medical journals, industry stakeholders, funding bodies and peer review

-Routinely request reporting of sex-based representation/differences and well powered outcome analysis

-Prioritise RCTs where RCT data gaps exist: SCAD, MINOCA and diseases predominantly affecting women

8. Meaningfully address cardiology's workforce diversity and culture issues

-Recognise the clear link between the under-representation of women in cardiology workforces and the under-representation of women and diverse populations in cardiovascular clinical trials.

-Recognise implicit bias & adopt zero tolerance for overt or covert workplace harassment

...cominciamo a PENSARCI!

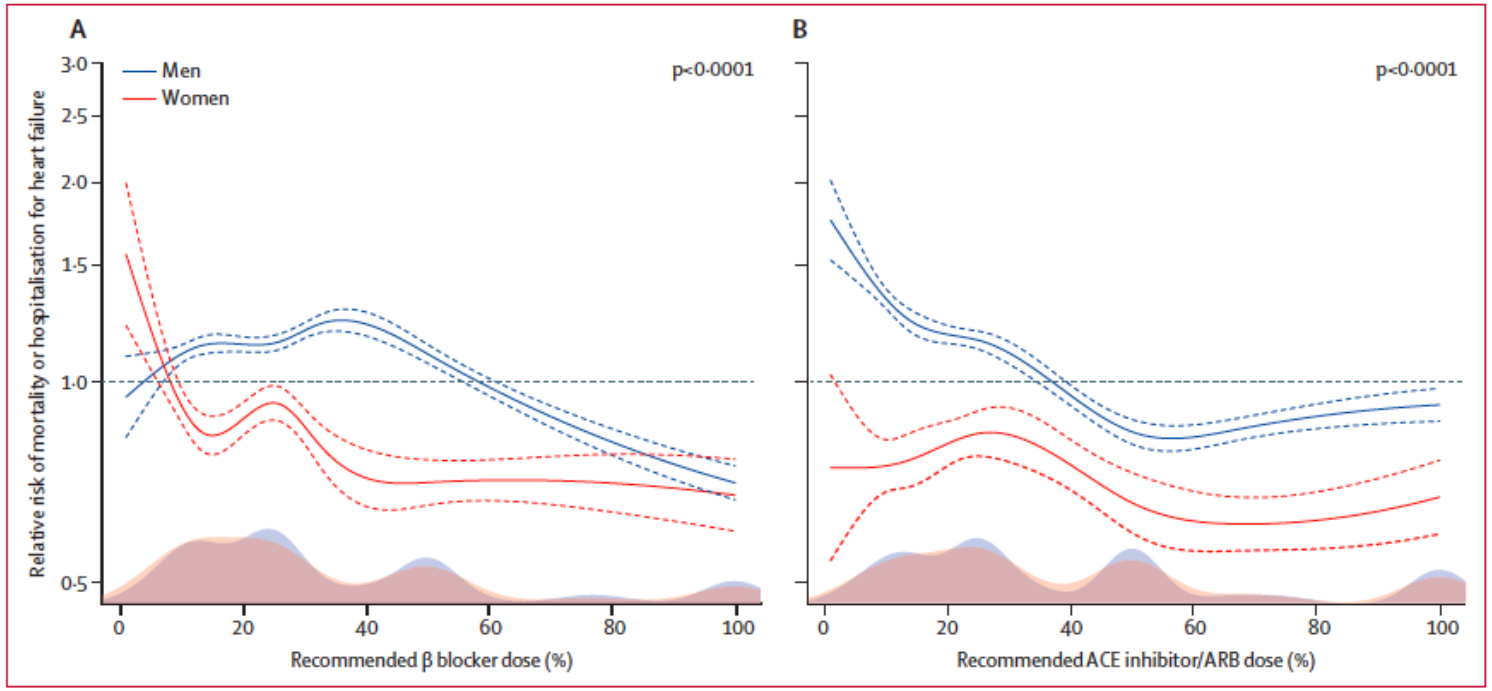


Figure 2: Validation of optimal β blocker (A) and ACE inhibitor or ARB dose (B)

LA TERAPIA FARMACOLOGICA

NON È L'UNICA MENO RAPPRESENTATA

L'ESERCIZIO FISICO è TERAPIA*!*

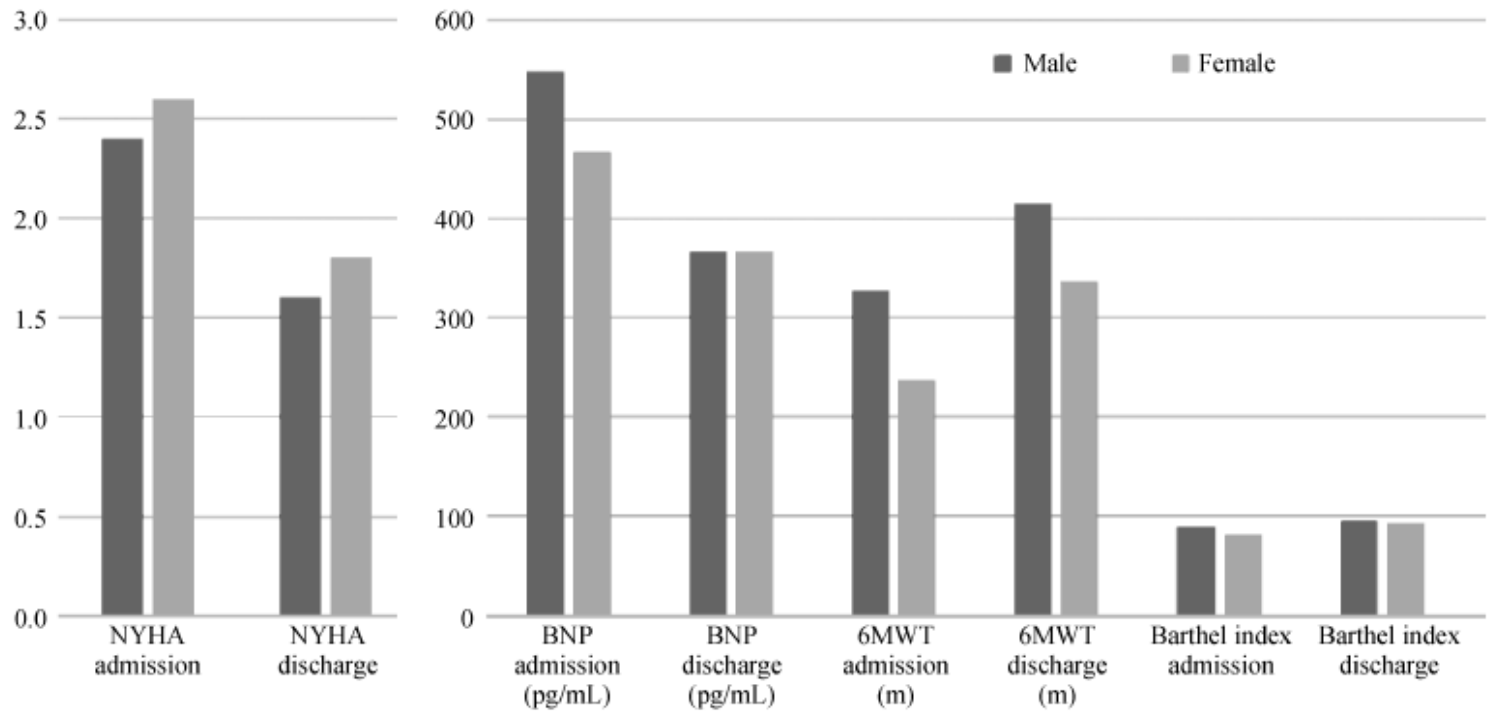


Figure 1. Gender differences in the efficacy of cardiovascular rehabilitation. BNP: brain natriuretic peptide; NYHA: New York Heart Association; 6MWT: six minute walking test;

Women are much less likely than men to complete cardiac rehabilitation with only ≈15% to 20% of eligible women participating in comparison with 22% to 30% of eligible men.

Grazie per l'Attenzione!