

# Donna e Scompenso Cardiaco



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FTGM



*Il continuum cardiovascolare nel genere femminile: tappe di  
vita, malattia e cura*

*Massa, 8 marzo 2018*



## Aspettativa di vita - dati ISTAT Italia 2010

Un cuore XY si contrae per 79 anni (FC media 72 bpm)

Un cuore XY batte 2,989,612,800 volte

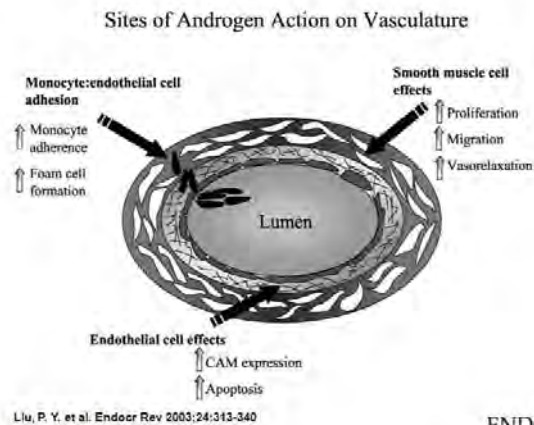
Un cuore XX si contrae per 84 anni (FC media 76 bpm)

Un cuore XX batte 3,355,430,400 volte

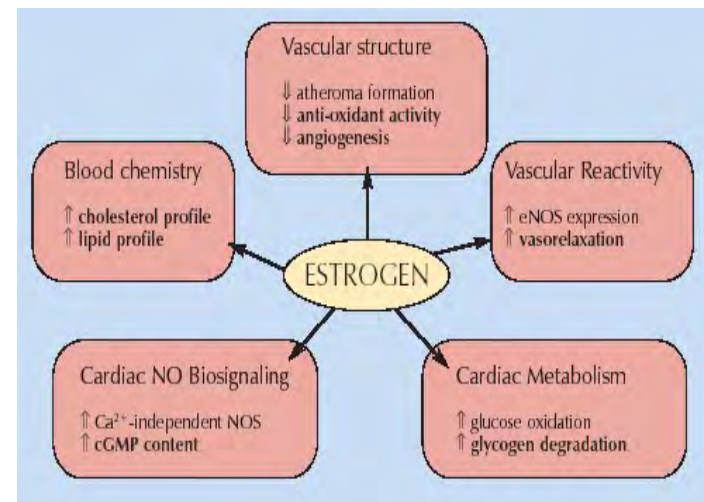
# Cuori XX vs XY sono caratterizzati da un differente *milieu interieur*



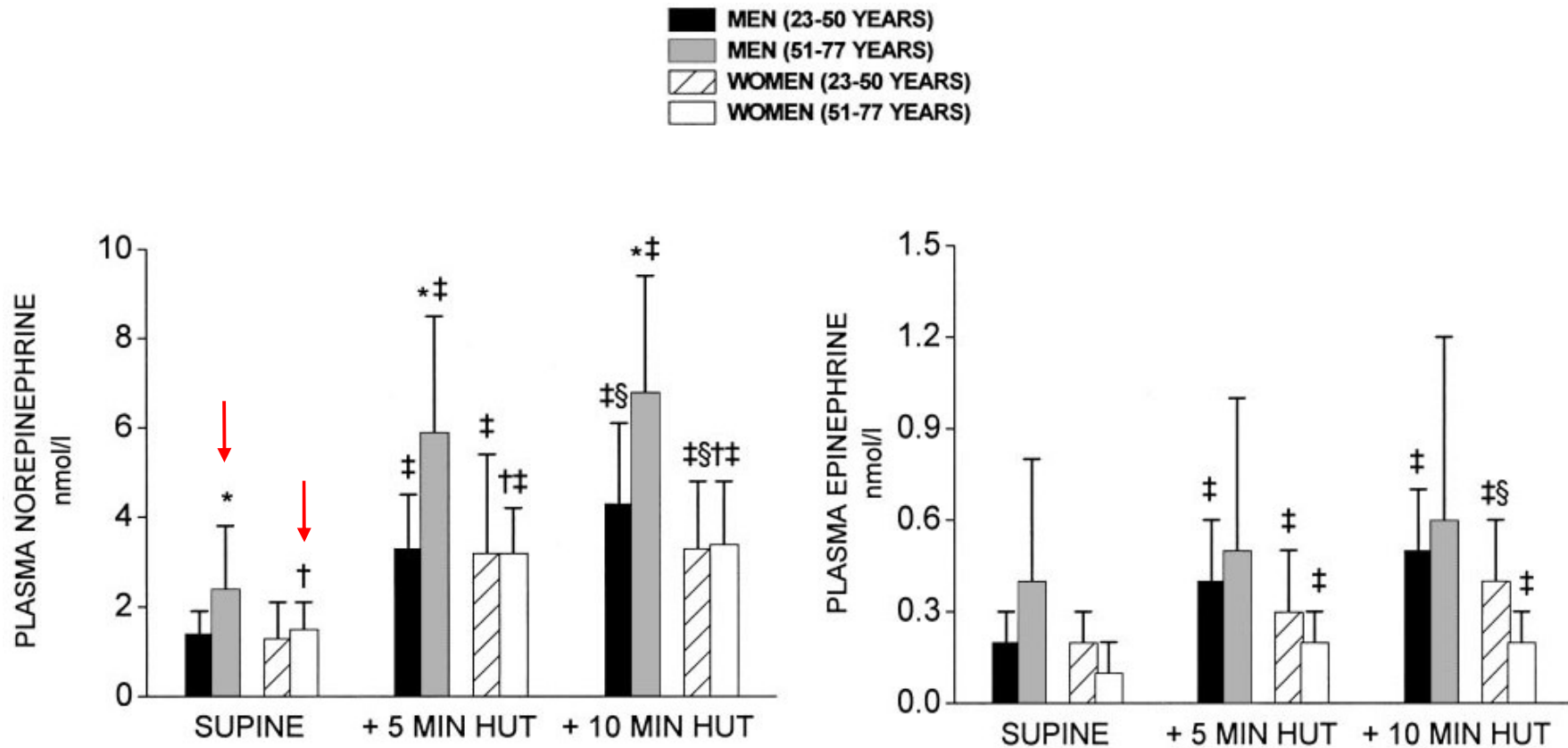
	Men	Premenopausal women	Postmenopausal women
Estrogen	+	10+	+
Testosterone	10+	+	+
ER $\alpha$	+	+	+
ER $\beta$	++	+	+



ENDOCRINE  
REVIEWS

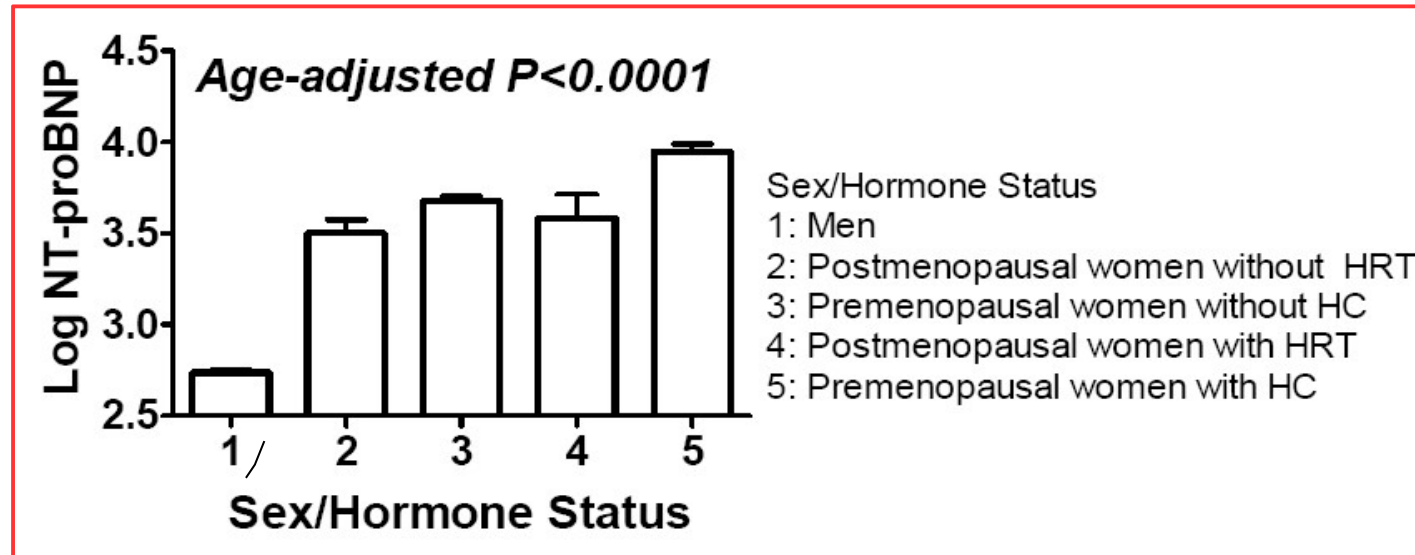


## XX vs XY: una differente regolazione neuro-ormonale



Attivazione adrenergica:  
inferiore livello di noradrenalina in donne giovani vs uomini

**XX vs XY: una differente regolazione neuro-ormonale**  
*Funzione endocrina cardiaca*



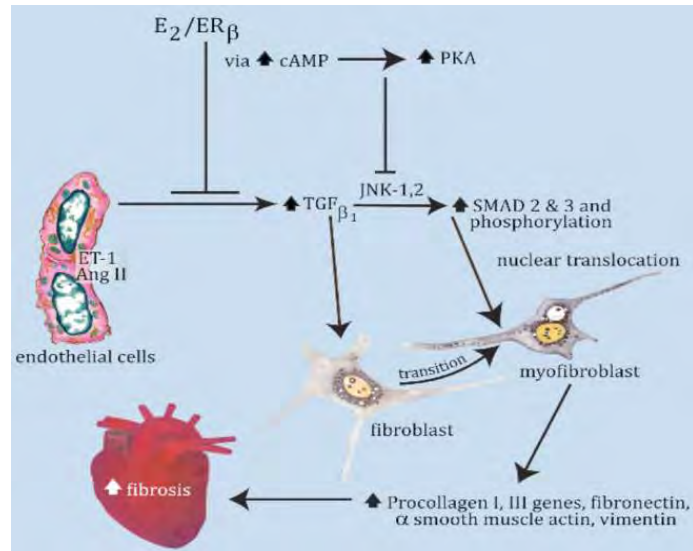
*“Il livello plasmatico di NT-proBNP è correlato al genere ed alla terapia ormonale esogena eseguita in uomini e donne della popolazione generale.”*

Framingham cohort - Lam CSP et al. JACC, 2011

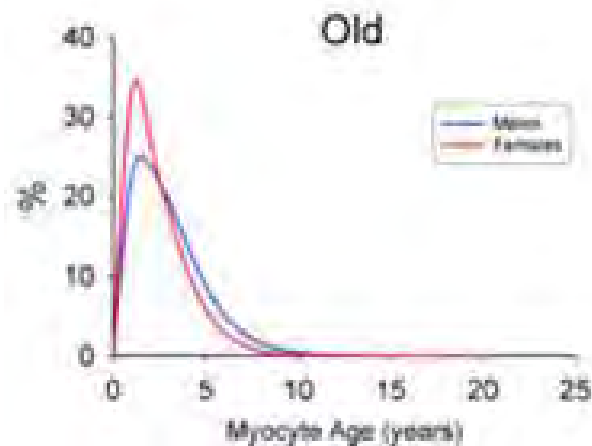
*“I dati della letteratura suggeriscono un effetto antagonista sulla funzione endocrina cardiaca tra gli androgeni (**inibizione**) e gli estrogeni (**eccitazione**).”*

Clerico A, Passino C, Emdin M. JACC, 2011

# XX cuore ed età



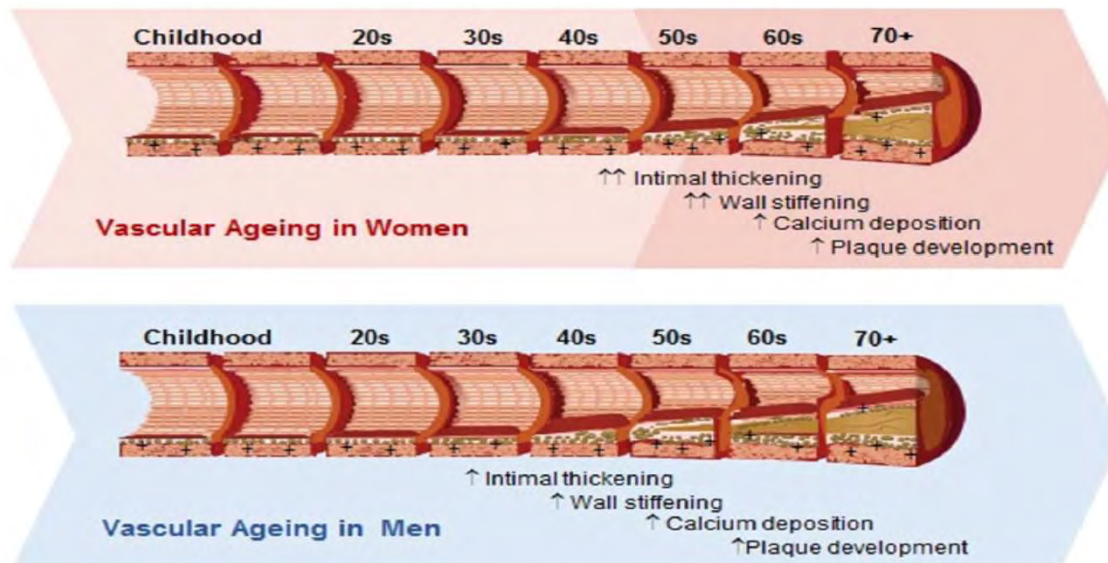
Estradiolo previene la fibrosi cardiaca indotta dalla AngII ed endotelina-1 e protegge dall'ipertrofia ventricolare sinistra



Il cuore femminile presenta una più grande riserva di cellule cardiache staminali e miociti più giovani rispetto al miocardio del cuore maschile

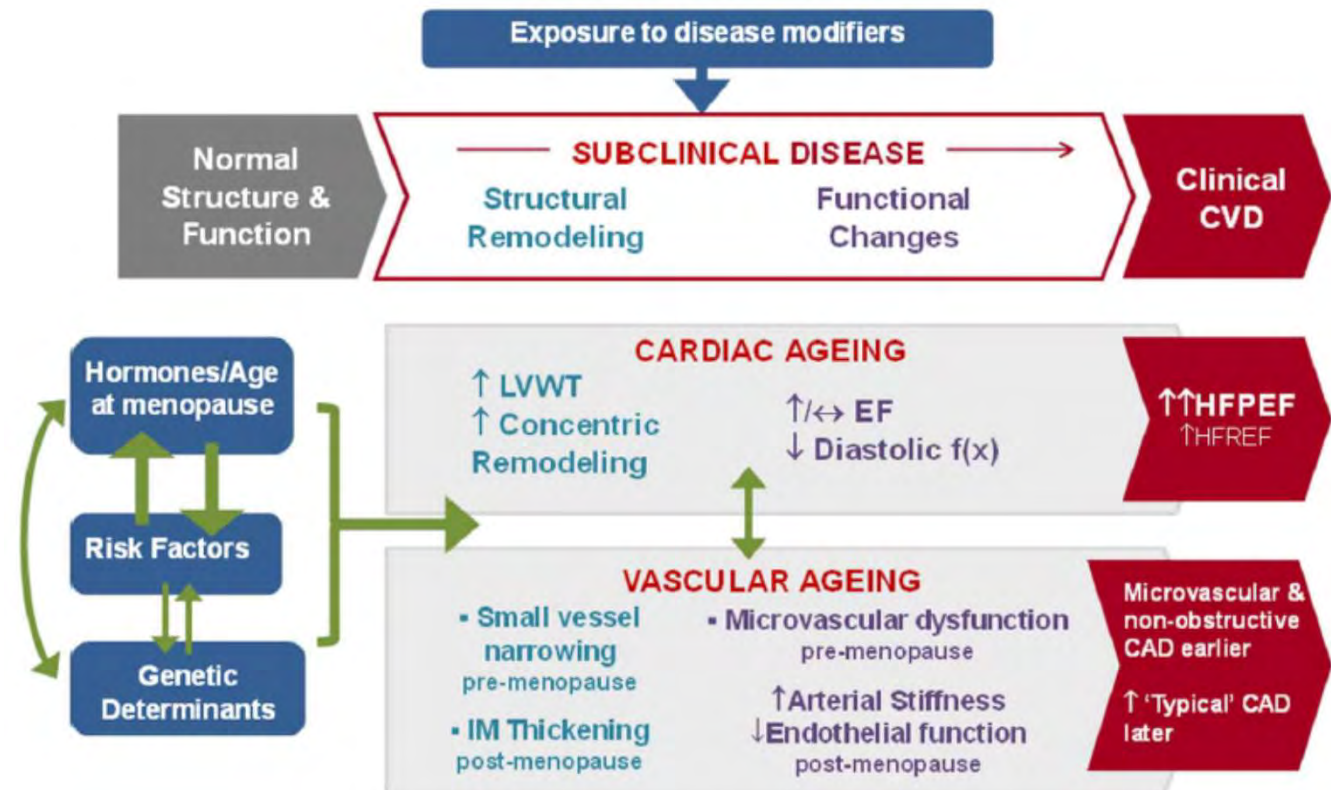
*Pedram, 2010*  
*Babiker, 2006*  
*Kajstura, 2010*



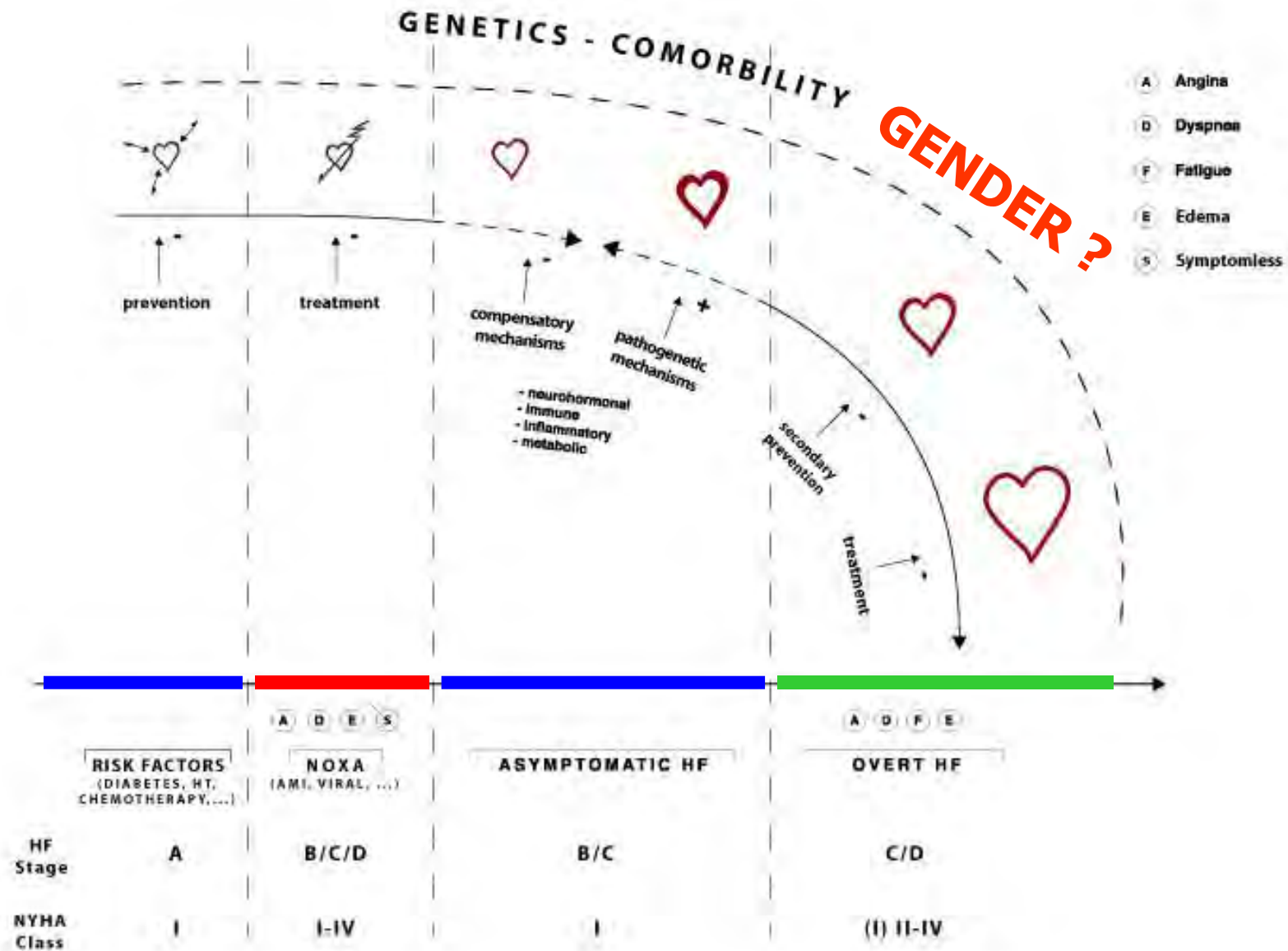


Aging in men vs women

Mertz, Cheng. Heart  
2016



*From risky conditions, through acute damage and ventricular silent dysfunction, up to overt heart failure*





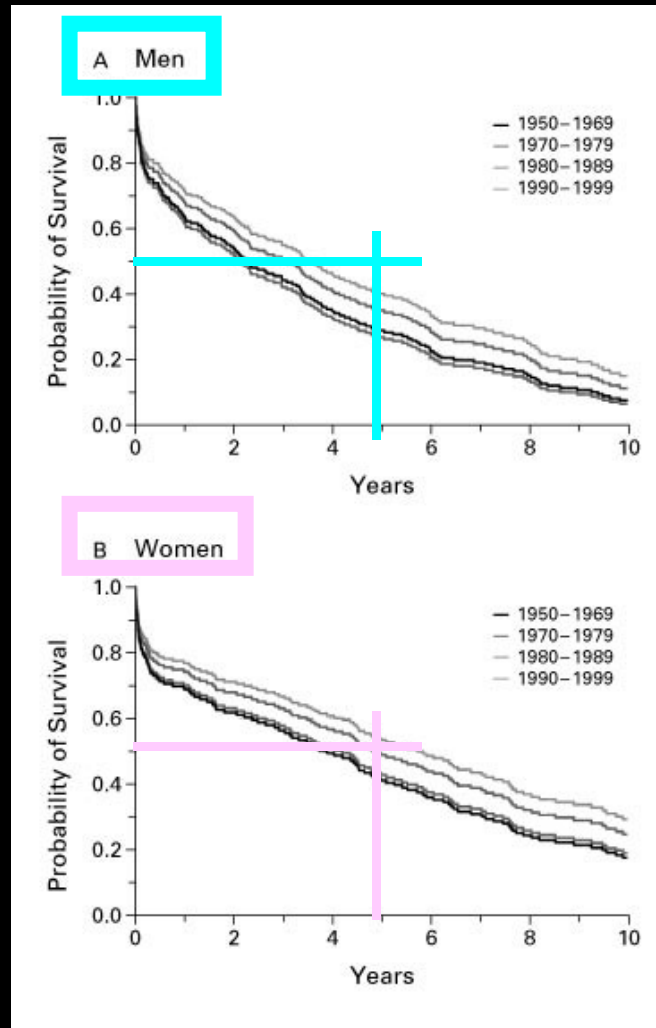
- Congestive heart failure has an extremely poor prognosis



- The incidence of heart failure (HF) in women has dropped by one-third from the 1950s through the 1990s but has remained unchanged in men over the same time period (Framingham Heart Study trends over a 50-year period)

*Levy D, Kenchiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med. 2002;347:1397–1402*

## Temporal Trends in Age-Adjusted Survival after the Onset of Heart Failure among Men (Panel A) and Women (Panel B)



Levy, D. et al. N Engl J Med 2002;347:1397-1402



The NEW ENGLAND  
JOURNAL of MEDICINE

# HF prevalence in women

- Information about HF in women can be acquired from registries, from large group data (insurers/health plans), from statistical data of large organizations, or from clinical trials.



- If we look only to **review clinical trials**, the number of women would appear to barely reach **one-third of all HF patients**.

Study	Number of Patients	Number of Women in	Percentage of Women in
V-HeFT-I (7)	0	0	0
V-HeFT-II (8)	0	0	0
CONSENSUS-I (9)	253	75	30
SOLVD-T (10)	2,569	504	23
SOLVD-P (11)	4,228	476	31
ELITE-I (12)	722	240	31
ELITE-II (13)	3,152	966	30
MERIT-HF (14)	3,991	451	23
CIBIS II (15)	2,647	515	20
COPERNICUS (16)	2,287	465	28
Val-HEFT (17)	5,010	1,002	20
RALES (18)	1,663	446	27
SAVE (19)	2,231	390	22
TRACE (20)	1,749	501	28
CHARM (21)	7,599	243	22
SCD HeFT (22)	2,521	580	23
DIG (23)	6,800	1,520	22.4
Total	47,422	10,907	23



CHARM = Candesartan in Heart Failure-Assessment of Reduction in mortality and morbidity; CIBIS II = Cardiac Insufficiency Bisoprolol Study II; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; DIG = Digitalis Investigation Group; ELITE = Evaluation of Losartan in the Elderly; MERIT-HF = Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure; RALES = Randomized Aldactone Evaluation Study; SAVE = Survival and Ventricular Enlargement; SCD HeFT = Sudden Cardiac Death Heart Failure Trial; SOLVD-P = Studies of Left Ventricular Dysfunction Prevention trial; SOLVD-T = Studies of Left Ventricular Dysfunction Treatment trial; TRACE = Trandolapril Cardiac Evaluation; Val-HEFT = Valsartan Heart Failure Trial; V-HeFT = Vasodilator Heart Failure Trial I and II.

# The major epidemiological surveys of heart failure



- show that the overall prevalence rate of heart failure is similar in men and women.
- Women tend to develop HF at more advanced age
- Overall, within the population, there appear to be more women than men with heart failure.
- Hospitalization rate are similar, but with longer hospital stay for women



# HF and Women: Prognosis



- In a sub analysis of **CIBIS II** female sex was independent predictor of reduce all-cause and CV mortality
- Reduced mortality for HF progression
- In **CHARM trial**, women had significant lower risk of all cause death, CV death and hospitalization
- Lower risk irrespective of HF etiology

**Etiology: Risk factors for heart failure appear to differ markedly between the sexes.**

- **Hypertension**

The risk of heart failure due to hypertension is greater for women than for men (Framingham).

- **Coronary Artery Disease**

The SOLVD trials reported that coronary heart disease is less frequently identified as an etiological factor in women than in men with heart failure

- **Diabetes Mellitus**

Diabetes seems to be a stronger risk factor for heart failure in women than in men, especially in younger women.



**Etiology: Risk factors for heart failure appear to differ markedly between the sexes.**



- **Valvular Heart Disease**

The SOLVD, Framingham, and hospital-based studies report a predominance of women with valvular heart disease.

However, data from the 30-year follow-up of the Framingham study suggest a declining frequency of heart failure secondary to valvular disease in both sexes

## **Etiology: Risk factors for heart failure appear to differ markedly between the sexes.**

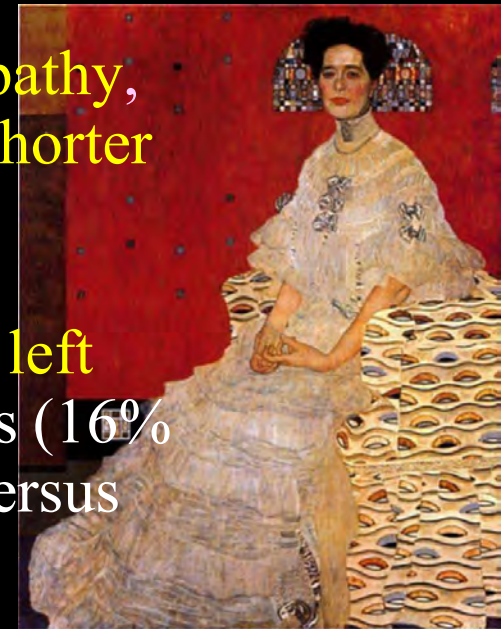
### **Idiopathic Dilated Cardiomyopathy**

- Women are reported to have a markedly lower prevalence of idiopathic dilated cardiomyopathy in many studies (male-to-female ratio, 2–4:1),

- male population has a greater prevalence of covert alcohol abuse or asymptomatic coronary artery disease.

- Women who develop idiopathic dilated cardiomyopathy, however, have greater ventricular dimensions and shorter exercise duration.

- More women than men had an "unknown" cause of left ventricular systolic dysfunction in the SOLVD trials (16% versus 9% in men in the prevention arm and 26% versus 16% in the treatment arm,  $P<0.001$ ).



**Etiology: Risk factors for heart failure appear to differ markedly between the sexes.**

- **Alcoholic Cardiomyopathy**

The evidence of a sex influence on susceptibility to alcohol-induced heart failure is inconclusive. **Women have been found to suffer from alcoholic cardiomyopathy at a similar rate.**

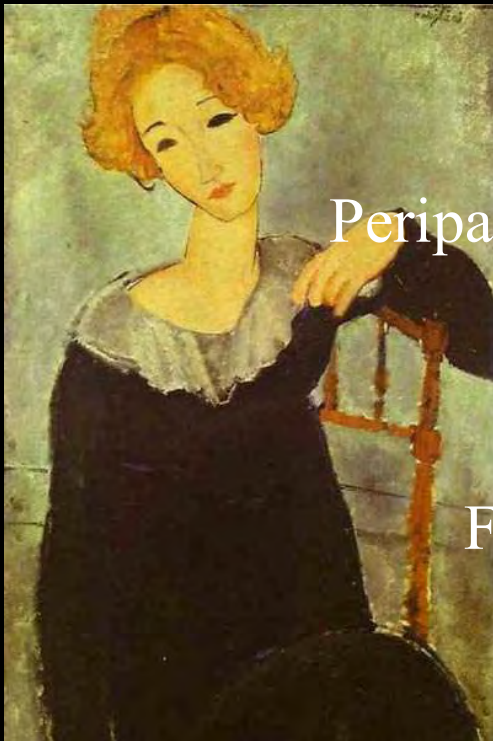
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- **Peripartum Cardiomyopathy**

Peripartum cardiomyopathy is a rare but important disorder that has been reviewed elsewhere.

- **X-Linked Cardiomyopathy**

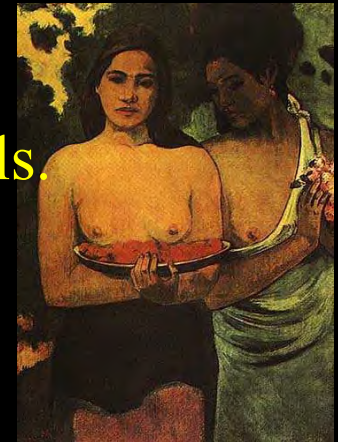
Families with patterns of inheritance suggesting an X-linked cardiomyopathy have been described.





## Diagnosis: is there a sex bias?

- Inaccurate diagnosis (clinical/instrumental)
- Sex bias in referring patients with heart failure to hospitals.
- Women with heart failure are less likely to be referred to hospital than men and more likely to be treated by their general practitioners.



# HF presentation in women

Women with HF present at an older age have a lower prevalence of ischemic heart disease and previous myocardial infarction than men and are more likely to have systemic hypertension and diabetes



More incidence of HFpEF

When controlling for ischemic disease, women are less likely to have undergone coronary bypass surgery. When suffering a myocardial infarction, women are more likely than men to develop HF.

Women with heart failure are also at greater risk of pulmonary embolism than men ( $P=0.01$ ).

# HF presentation in women

- On presentation, women with HF are more symptomatic than men with a greater degree of edema, a third heart sound, murmurs, and more noticeable jugular venous distension.
- In addition, health-related quality of life is low in women who are admitted with HF when compared with men and has a smaller improvement over the hospitalization.
- When controlling for New York Heart Association functional class, women have a greater impairment in daily living activities, which usually require low level effort and, therefore, are less functional than men.



# HF presentation in women



- In the U.S., hospitalization rates for HF have increased from 377,000 in 1979 to 962,000 in 1999.
- In U.S. HF affects 3.1 million men and 2.6 women
- When hospitalized for HF, women have a longer length of stay, leading to higher costs, less involvement by cardiology specialists, and a higher in-patient mortality.
- In the Studies Of Left Ventricular Dysfunction (SOLVD) trials, female gender was one of the factors associated with hospitalization for HF and one-year mortality.



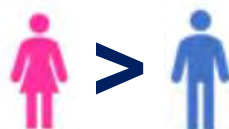
# Diagnosi: Differenze nei peptidi natriuretici




- Peptidi natriuretici cardiaci (PNC) nello SC:

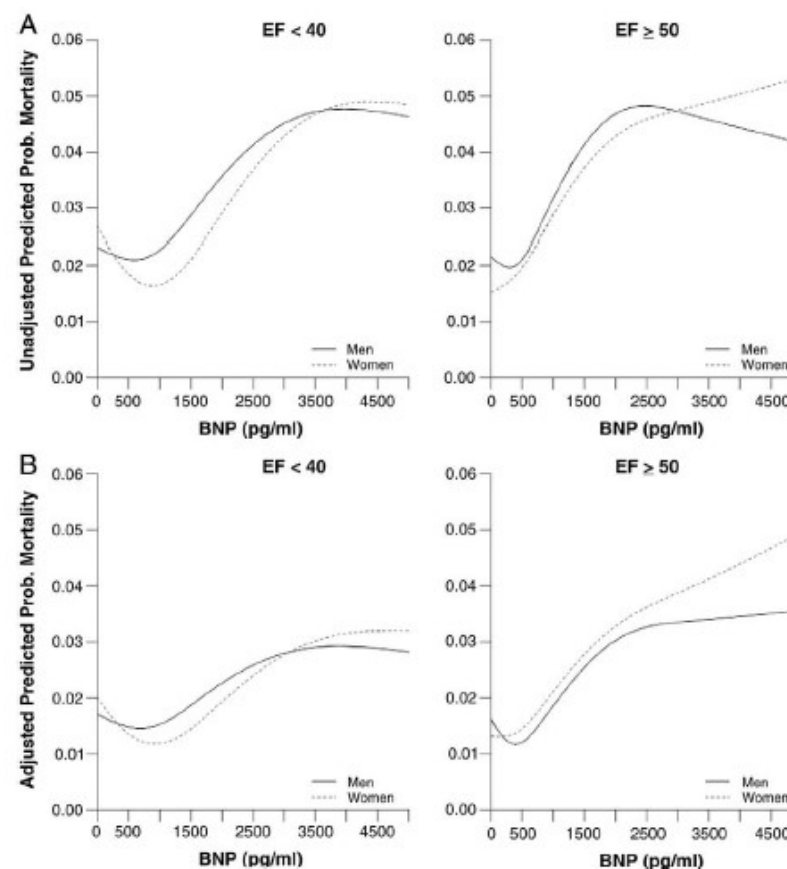


**TUTTAVIA**



in pz stratificati per FE

-  : ↑ SC con frazione di eiezione (FE) preservata (*heart failure with preserved ejection fraction, HFpEF*)
- **HFpEF**: incremento meno marcato dei PNC







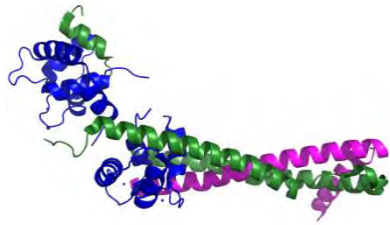
# Peptidi natriuretici cardiaci

## Scompenso cardiaco



- **PNC: accuratezza diagnostica simile** in  e  con dispnea  
insorta di recente  
(Maisel *et al.*, *Am Heart J*, 2004)
- **PNC: stratificazione prognostica simile** in  e  con SC acuto  
(Hsich *et al.*, *Am Heart J*, 2013)

**Non necessari *cut-off* genere-specifici**

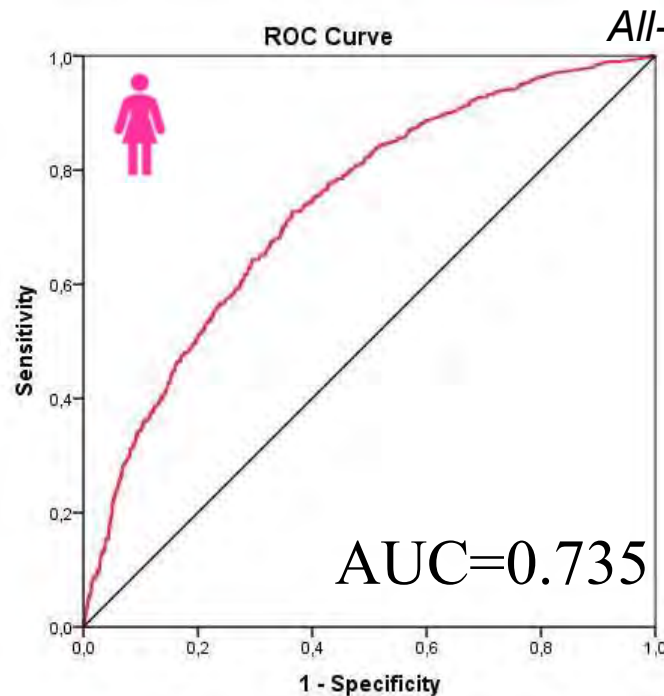


# Troponine

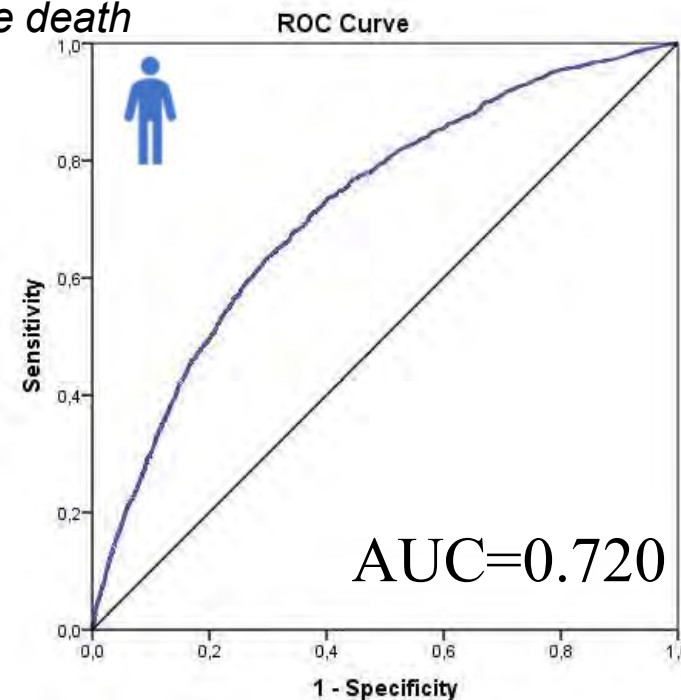
## Scompenso cardiaco



13 ng/L (6-29) vs. 16 ng/L (8-30),  $p < 0.001$



*Cut-off ottimale: 17 ng/L*



*Cut-off ottimale: 23 ng/L*

***Cut-off* ottimale per morte totale e cv calcolato su popolazione totale (18 ng/L)  
predittore indipendente di prognosi in entrambi i sessi**

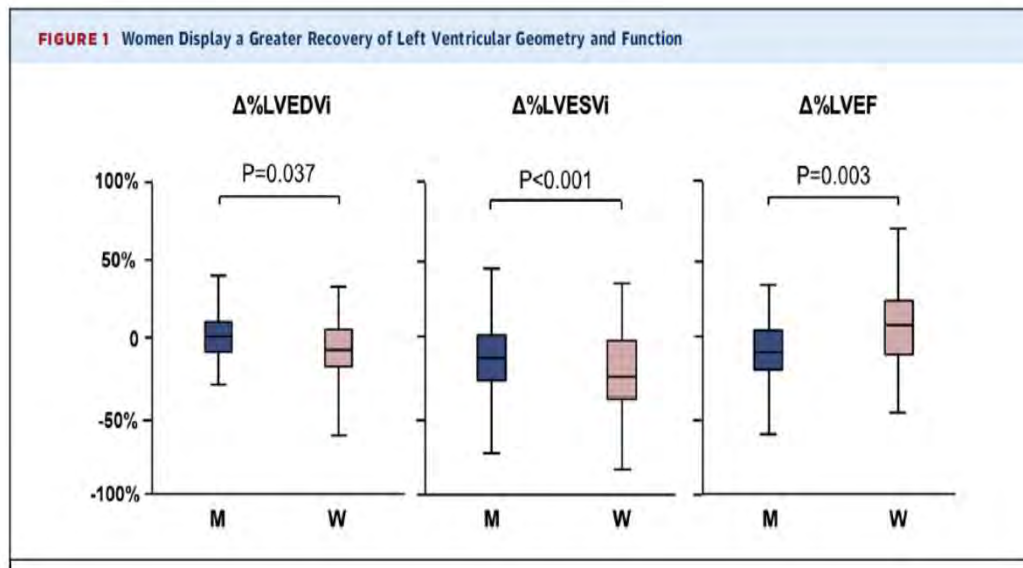
# HF therapy differences: men vs women (1)

Therapy	Drug	Study name, year <sup>ref.</sup>	N pz	% W	Study design	Primary endpoint	Outcome	W vs. M: difference
BBs	Bisoprolol	CIBIS II, 1999 [20]	2647	24	Double blind, placebo controlled	All cause mortality	↓ All cause mortality ↓ CV mortality ↓ Hospital admissions ↓ Treatment withdrawal	36% ↓ all-cause mortality 39% ↓ CV risk of death 70% ↓ risk of death for CHF progression compared to M
	Carvedilol	COPERNICUS, 2002 [33]	2289	20%	Randomized, placebo controlled	All cause mortality	↓ CV death and hospitalization ↓ HF death and hospitalization ↓ All-cause hospital stay ↓ HF hospital stay	No significant differences
	Metoprolol	MERIT-HF, 2002 [35]	3991	29	Randomized, placebo controlled	All cause death or hospitalization	↓ all cause death, ↓ all cause hospitalizations, ↓ CV hospitalization, ↓ HF hospitalization	21% ↓ all-cause death or hospitalization (18% reduction in M), 42% ↓ risk of hospitalization for CHF (10% ↓ in men), Not significant reduction of all-cause mortality (significant in M) No significant sex differences.
	Bisoprolol + carvedilol + metoprolol	MERIT-HF [35] CIBIS II [20] COPERNICUS [33]						
ACE-I	Enalapril	SOLVD, 1992 [36]	4228	12	Randomized, double-blind placebo-controlled	All cause mortality	↓ All cause mortality ↓ CV mortality	Not significant ↓ of CHF-related death or hospitalization (significant in M) Not significant ↓ of all-cause mortality (significant in M). Not significant ↓ of CHF-related death or hospitalization (significant in M)
	ACE-I (overall)	Meta-analysis of 30 trials [37]						
ARBs	Valsartan	Val-HeFT, 2001 [38]	5010	20	Randomized, double-blind placebo-controlled	Mortality and morbidity combined	No differences in mortality ↓ Combined mortality and morbidity	Significant ↓ of morbidity and mortality in both W and M. Not significant ↓ of all-cause mortality in both W and M
	Candesartan	CHARM, 2004 [21]	4576	26	Randomized, placebo-controlled	CV mortality and CHF hospitalization	↓ CV deaths and hospitalizations ↓ All cause mortality ↓ CV mortality ↓ CHF hospitalization	Greater ↓ of all-cause mortality, death or hospitalization for CHF, CV mortality hospitalization for CHF compared to M Significant ↓ of CV death or HF hospitalization in both W and M Significant ↓ of CV death in M, but not in W
ARNI	Sacubitril/valsartan	PARADIGM-HF, 2014 [39]	8399	22	Randomized, double-blind placebo-controlled	Composite of death from any cause and first CHF hospitalization	↓ CV mortality ↓ CHF hospitalization	No sex differences in prognosis
MRAs		RALES, 1999 [42]	1663	27	Double-blind placebo controlled	Death from any cause	↓ All cause mortality ↓ CV mortality	

# HF therapy differences: men vs women (2)

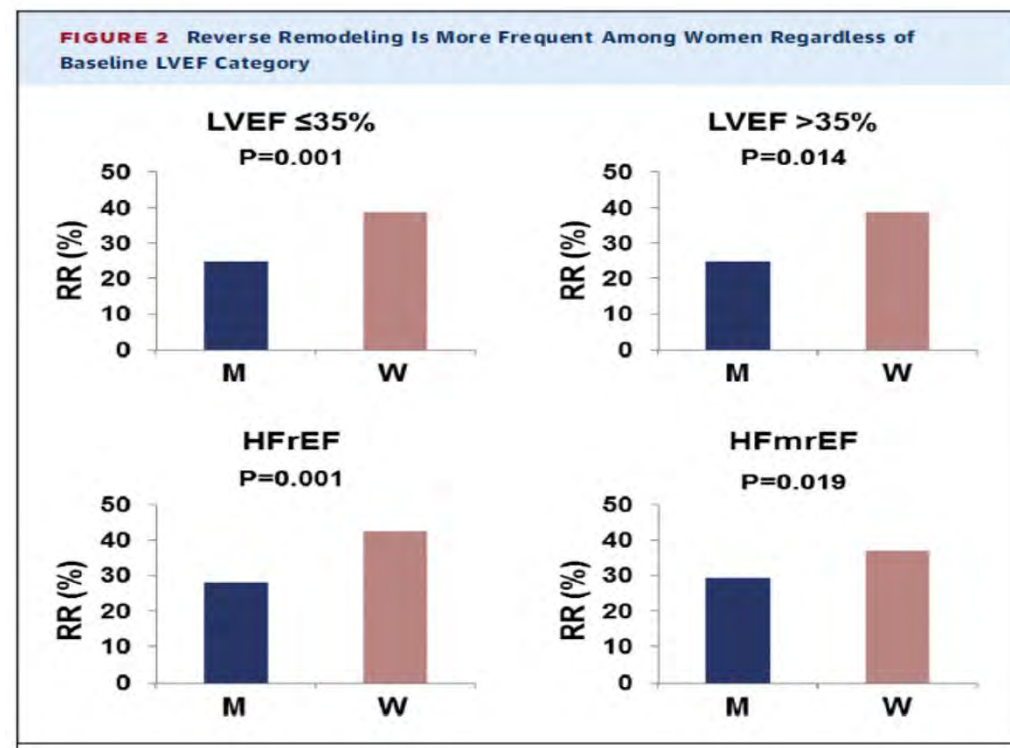
Therapy	Drug	Study name, year <sup>ref.</sup>	N pz	% W	Study design	Primary endpoint	Outcome	W vs. M: difference
Digoxin		DIG, 1997 [45,46]	6800	22	Randomized, double-blind placebo-controlled	Mortality	No change in mortality ↓ all cause hospitalizations ↓ CHF hospitalization	In W, ↑ all-cause mortality than in the placebo arm (not significantly ↑ in M) At multivariate analysis, significantly ↑ risk of death in W (not significantly ↑ in M) Plasma levels 0.5–0.9 mg/mL: ↓ of risk of all-cause mortality, death and hospitalization for CHF in W, compared to placebo. Plasma levels ≥1.2 mg/mL: significantly ↑ mortality in W. No sex differences in prognosis (plasma levels not considered)
ICD		Klein et al., 2011 [48]	99,841	50	Prospective registry	Quality of care Length of stay In-hospital death	= quality of care = length of stay = in hospital mortality	Likelihood of implantation: 40% ↓ in W.
		Russo et al., 2015 [49]	38,912	25	Retrospective registry	Gender differences in outcomes		Significantly ↑ risk of peri-procedural complications, all-cause death, all-cause and CHF re-hospitalization in the first 6 months, compared with M.
		Masoudi et al., 2015 [50]	2954	26	Prospective	Age and sex differences in: Time to death from any cause Time to hospitalization from any cause Device-related complications within the first 90 days.		↑ risk of peri-procedural complications ↓ risk of death and CHF hospitalization.
CRT		Alaeddini et al., 2008 [50]	121,174	40	Retrospective registry	Gender differences in: CHF hospitalizations CRT implantations.		1:3 W:M ratio in implantation.
		MADIT-CRT, 2009 [51]	1820	25	3:2 randomization to CRT + ICD or ICD alone	Death from any cause and non-fatal CHF hospitalization	↓ mortality ↓ CHF hospitalizations ↓ LV volumes ↑ LVEF	↑ propensity to reverse remodeling.
VAD		Hsieh et al., 2012 [58]	1926	21	Prospective	Mortality, infections, bleeding, device malfunction		= risk of death, infection, bleeding, device malfunctioning between W and M.
Heart transplantation		Morris et al., 2015 [59]	110	31	Retrospective	Time to first stroke		↑ risk of stroke (W:M 3:1)
		ISHLT data, 2015 [61]						Less often performed in W Similar survival rates





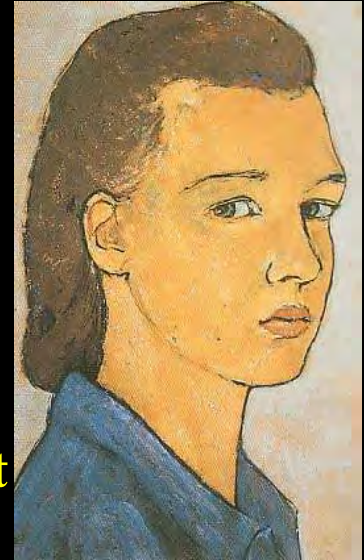
Aimo et al. JACC HF 2017

Reverse remodeling is more frequent among women, regardless of cause and severity of LV dysfunction  
 Female sex is an independent predictor of RR in LV systolic dysfunction





# HF therapy in women



- **Underprescription of ACE Inhibitors in Women With Heart Failure and Left Ventricular Dysfunction**

Women receive ACE inhibitors less often than men as treatment for heart failure, even in the absence of contraindications.

- The cause of ACE inhibitor underprescription for both sexes, and particularly the sex disparity, is unclear.
- Perhaps physicians recognize women to be at greater risk of adverse effects than men, although this should not necessarily preclude treatment.
- **Adherence to Prescribed Therapy**  
In 1 study, women were significantly more adherent to prescribed digoxin treatment than men

# An overview

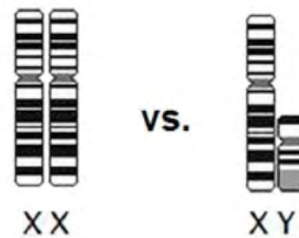
## Epidemiology and clinical presentation

- ↑ **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

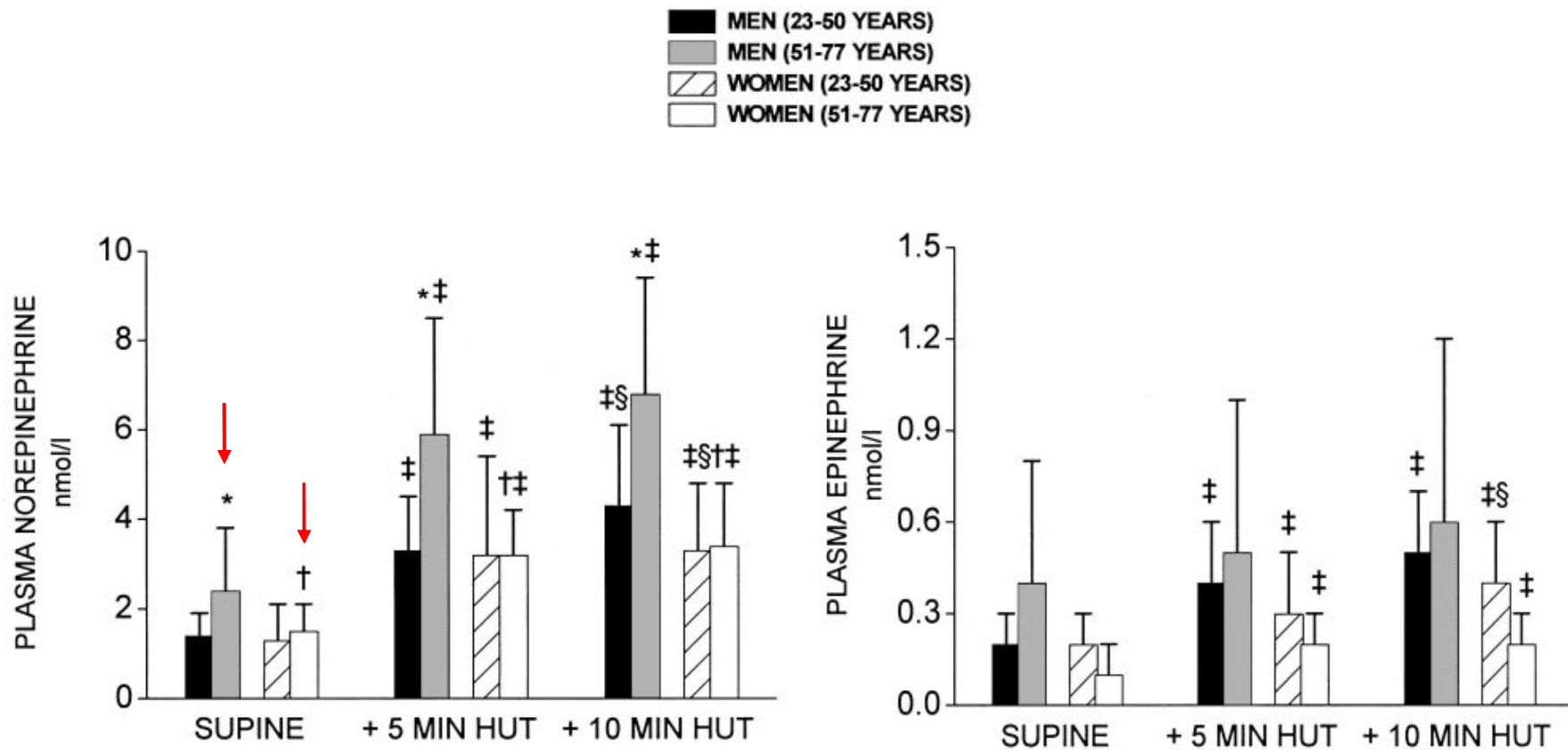
- ↑ prognostic benefit from ARBs
- ↑ response to CRT
- ↓ rates of ICD and HT



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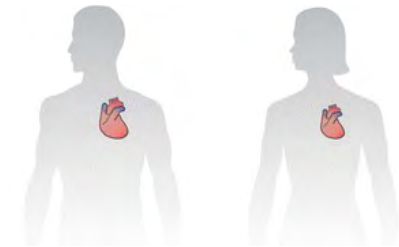


## XX vs XY: una differente regolazione neuro-ormonale



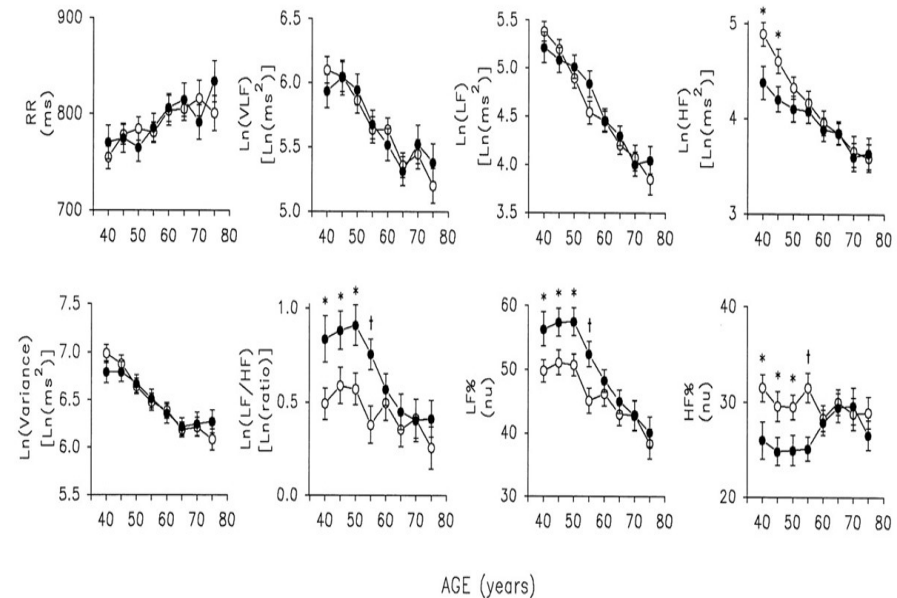
Attivazione adrenergica:  
inferiore livello di noradrenalina in donne giovani vs uomini

# Differenze di genere nella regolazione autonoma



↑ Tono parasimpatico

*"Donne di mezza-età ed uomini hanno una predominante regolazione parasimpatica e simpatica della frequenza cardiaca, rispettivamente. La differenza su descritta viene a mancare dopo la soglia dei 50 anni, mentre nell'uomo si riscontra una tardiva riduzione della predominante regolazione simpatica."*



Kuo TB, et al. Effect of aging on gender differences in neural control of heart rate. Am J Physiol 1999; 277: H2233-H2239.