SABATO 14 SETTEMBRE 2019
Teatro "G. MODENA", PALMANOVA (UD)

IL POSSIBILE DIFFERENTE IMPATTO DELLO SCOMPENSO HFrEF TRA UOMINI E DONNE, ANCHE DIFFERENTE TERAPIA?

MARCO MERLO

DIPARTIMENTO DI SCIENZE MEDICHE, CHIRURGICHE E DELLA SALUTE
UNIVERSITÀ DEGLI STUDI DI TRIESTE

REGIONE AUTONOMA FRIULI VENEZIA GIULIA
Azienda Sanitaria Universitaria Integrata di Trieste

HEART FAILURE

HEART FAILURE: DEFINITION

REGIONE AUTONOMA FRIULI VENEZIA GIULIA
Azienda Sanitaria Universitaria Integrata di Trieste

Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.

[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

[b]BNP>35 pg/ml and/or NT-proBNP>125 pg/mL.

ESC-HF guidelines. Ponikowski P. Eur Heart J 2016

HFrEF: PROGNOSIS

- Negli ultimi 30 anni, **i miglioramenti terapeutici hanno aumentato la sopravvivenza e ridotto le ospedalizzazioni** per i pazienti con HFrEF, ma i risultati spesso permangono insoddisfacenti.
- I dati europei più recenti (studio pilota ESC-HF) dimostrano che i tassi di **mortalità** per tutte le cause a 12 mesi dei **pazienti ospedalizzati e ambulatoriali** sono rispettivamente del **17% e del 7%**, mentre i tassi di ospedalizzazione a 12 mesi sono rispettivamente del 44% e 32%.

La maggior parte dei decessi è dovuta a cause cardiovascolari, soprattutto morte improvvisa e peggioramento dell'HF.

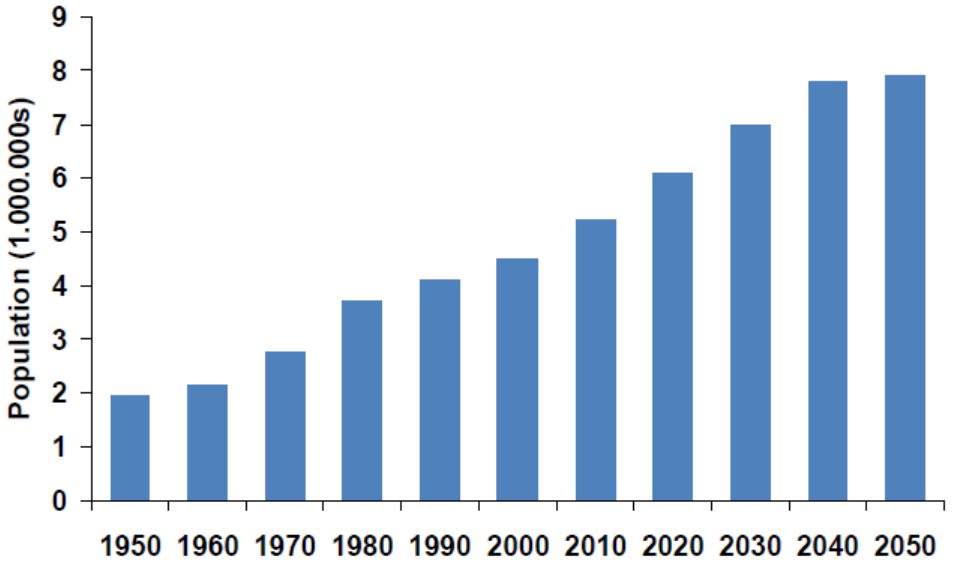
7-17%
a 12 mesi

32-44%
a 12 mesi

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *EHJ (2016) 37 (27):2129-2200*

HEART FAILURE: PROJECTION

Effetto dell'invecchiamento della popolazione in prevalenza di insufficienza cardiaca in USA



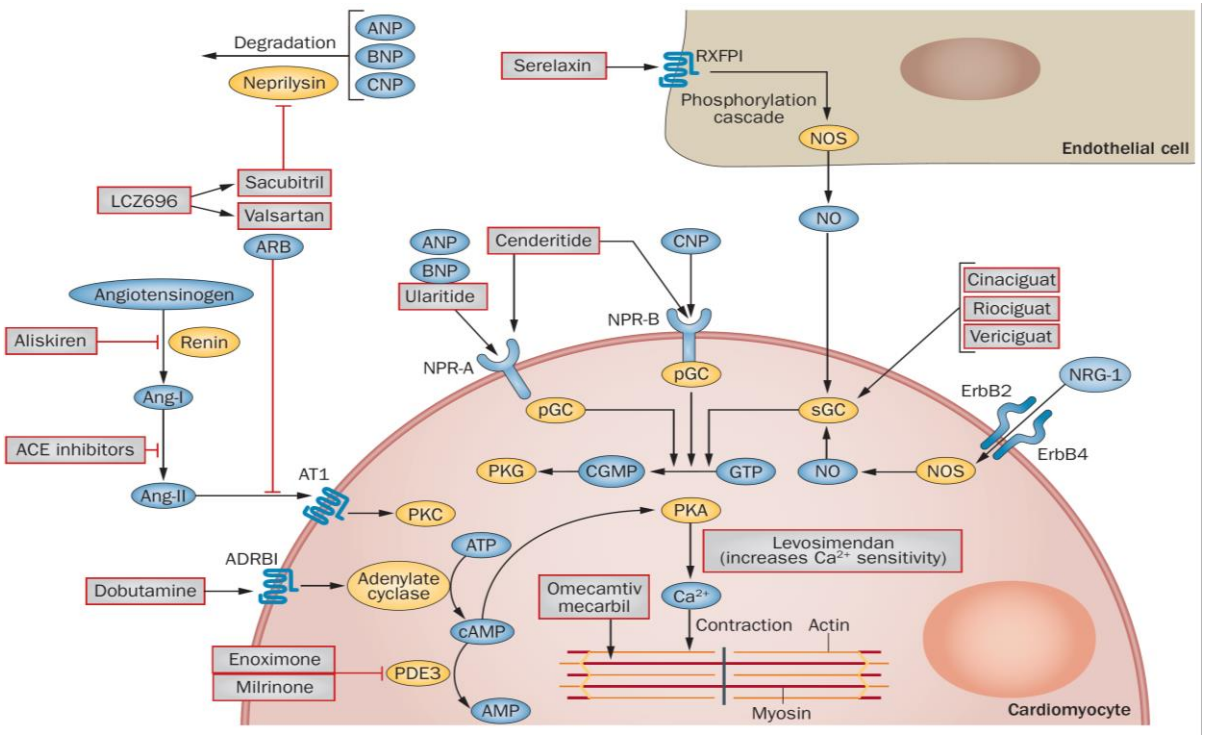
data from U.S. Bureau of the Census Data and Projections in Bristow MR Management of heart failure Edt

HFrEF: THERAPY PERSPECTIVES

REVIEWS

New medical therapies for heart failure

Thomas G. von Lueder and Henry Krum

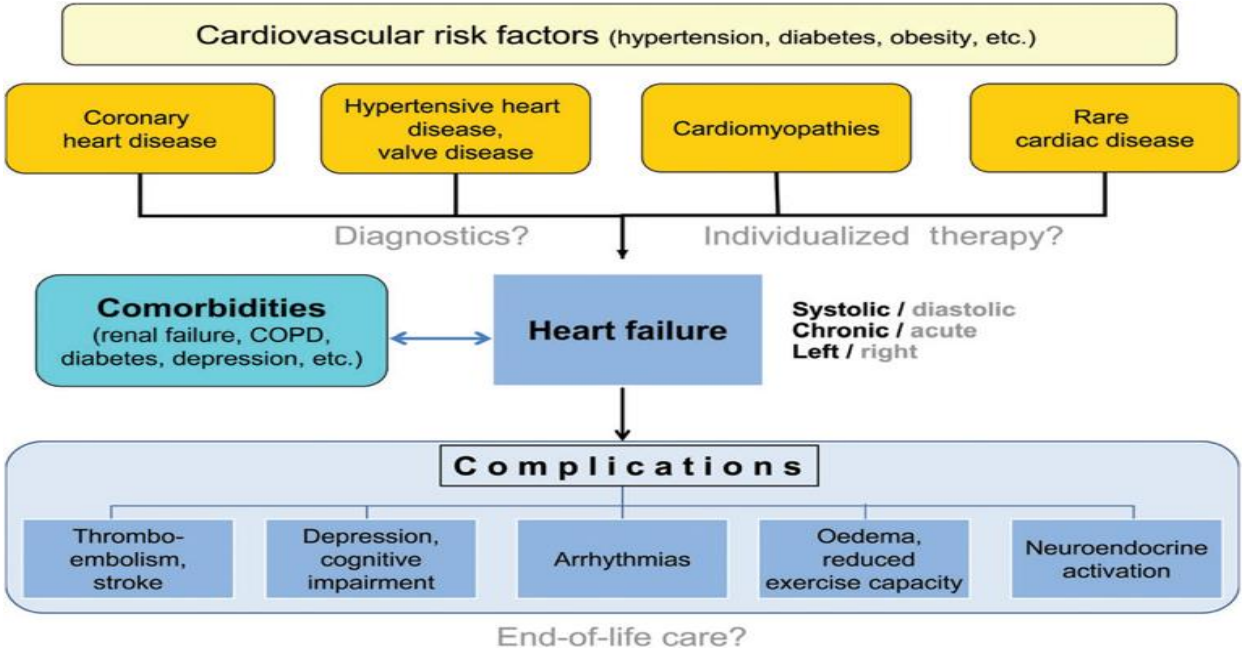


HEART FAILURE: NEW CLASSIFICATION?

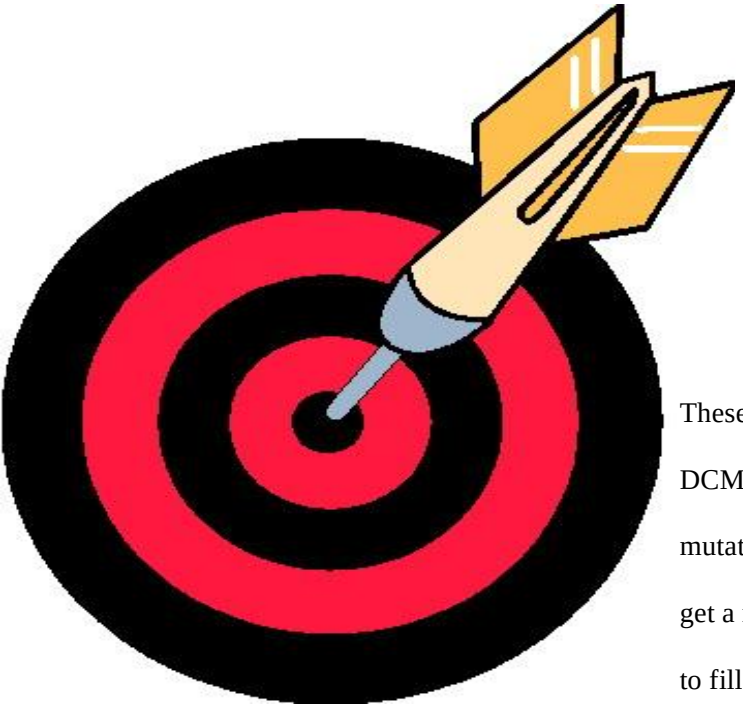
The Year in Cardiology

The Year in Cardiology 2013: heart failure

Georg Ertl[1]* and Frank Ruschitzka[2]



HFrEF: PRECISION MEDICINE



Editorial

Lamin A/C Cardiomyopathy
Cutting Edge to Personalized Medicine

Gianfranco Sinagra, MD; Matteo Dal Ferro, MD; Marco Merlo, MD

These observations, as a whole, indicate the correct way to follow in personalizing risk stratification in DCM: the independent variable should be the specific mutation, rather than any clustering attempt (i.e. mutation type, mutation position, gene or gene clusters). These clusters, in fact, may help the clinician get a rough orientation, but do not allow a truly personalized medicine. Multicenter studies are needed to fill the gap in knowledge of the multiple and heterogeneous genotype-phenotype correlations promoting the onset of DCM in mutation carriers, and Lamin A/C might represent, once again, the starting point.

(*Circ Cardiovasc Genet*. 2017;10:e002004.
DOI: 10.1161/CIRCGENETICS.117.002004.)

HFrEF: GENDER MEDICINE

1. Physiological bases

2. Epidemiology

3. Heart Failure - Clinical features and Treatment

4. Outcome

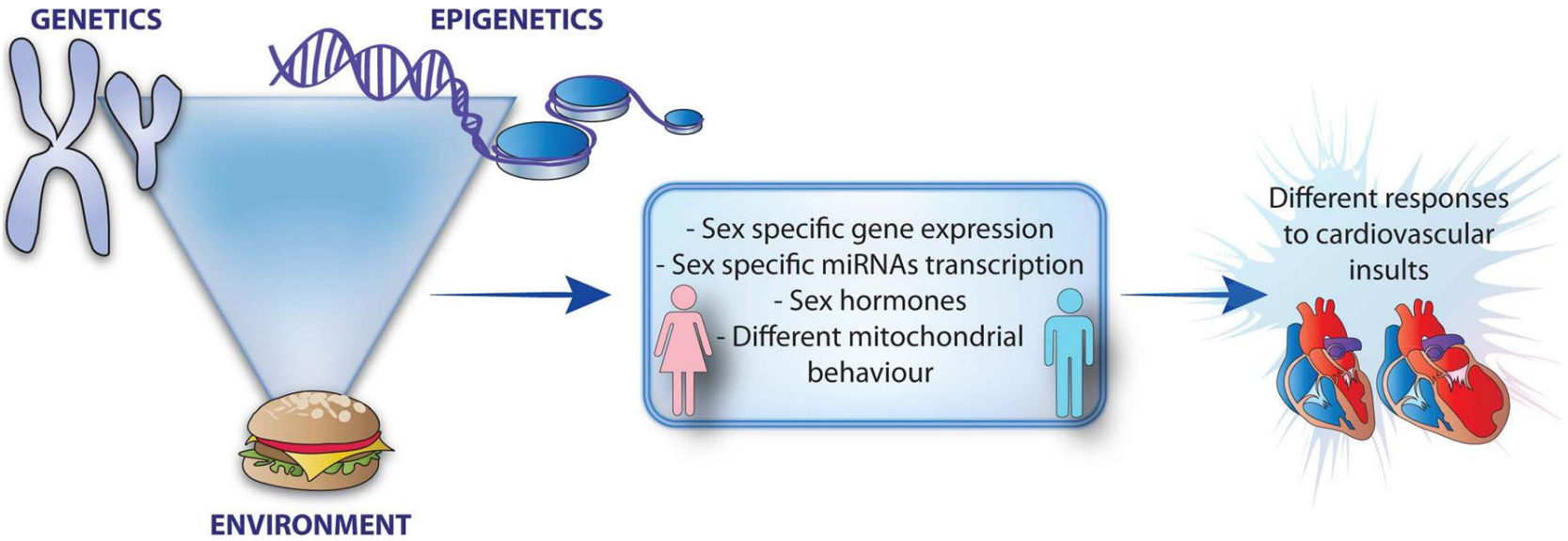
5. Sex-related prognostic predictors

PHYSIOLOGICAL BASES

Heart Failure Reviews
https//doi.org/10.1007/s10741-019-09824-y

Gender-related differences in heart failure: beyond the “one-size-fits-all” paradigm

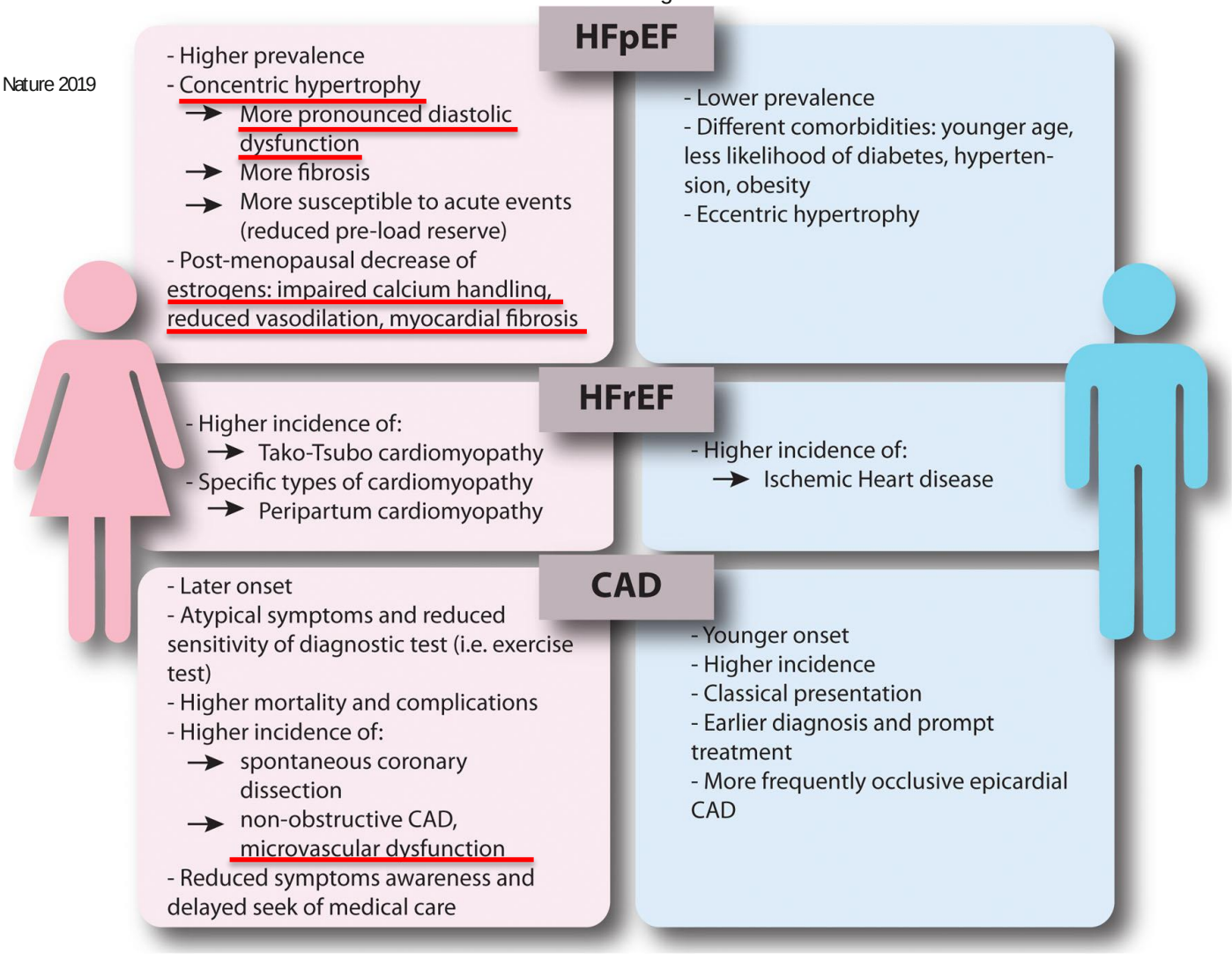
Annamaria De Bellis[1] &Giulia De Angelis[1] &Enrico Fabris[1] &Antonio Cannatà[1] &Marco Merlo[1] &Gianfranco Sinagra[1]



Heart Failure Reviews
https://doi.org/10.1007/s10741-019-09824-y

Gender-related differences in heart failure: beyond the "one-size-fits-all" paradigm

Annamaria De Bellis[1] &Giulia De Angelis[1] &Enrico Fabris[1] &Antonio Cannatà[1] &Marco Merlo[1] &Gianfranco Sinagra[1]



1. *Physiological bases*

2. ***Epidemiology***

3. *Heart Failure - Clinical features and Treatment*

4. *Outcome*

5. *Sex-related prognostic predictors*

EPIDEMIOLOGY

Differential Impact of Heart Failure With Reduced Ejection Fraction on Men and Women

Pooja Dewan, MBChB,[a] Rasmus Rørth, MD,[a,b] Pardeep S. Jhund, MBChB, PhD,[a] Li Shen, MBChB, PhD,[a] Valeria Raparelli, MD, PhD,[c,d] Mark C. Petrie, MBChB,[a] William T. Abraham, MD,[e] Akshay S. Desai, MD,[f] Kenneth Dickstein, MD, PhD,[g] Lars Køber, MD, DMSc,[b] Ulrik M. Mogensen, MD, PhD,[a,b] Milton Packer, MD,[h] Jean L. Rouleau, MD,[i] Scott D. Solomon, MD,[f] Karl Swedberg, MD, PhD,[j,k] Michael R. Zile, MD,[l] John J.V. McMurray, MD[a]

- N. 15,415 (3,357 women, **21,8%**) from *PARADIGM* and *ATMOSPHERE* trials
- Outcome: first HF hospitalization or CV death
- Follow-up duration: 26.6 months

Sex-Based Differences in Heart Failure Across the Ejection Fraction Spectrum

Phenotyping, and Prognostic and Therapeutic Implications

Davide Stolfo, MD,[a,b] Alicia Uijl, MSc,[a,c] Ola Vedin, MD, PhD,[d] Anna Strömberg, PhD,[e] Ulrika Ljung Faxén, MD, PhD,[a,f] Giuseppe M.C. Rosano, MD, PhD,[g] Gianfranco Sinagra, MD,[b] Ulf Dahlström, MD, PhD,[e] Gianluigi Savarese, MD, PhD[a]

- N. 42,987 patients (**37%** females) from Swedish Heart Failure Registry
- Outcome: all-cause death/HF hospitalization

1. Physiological bases

2. Epidemiology

3. Heart Failure - Clinical features and Treatment

4. Outcome

5. Sex-related prognostic predictors

CLINICAL FEATURES

- ***Age*** (w > m)
- ***Cardiovascular risk factors***:
  - Obesity (w > m)
  - Arterial hypertension (w > m)
  - Diabetes (m > w)
  - Active/previous smoke (m > w)
  - Alcohol consumption (m > w)
- ***CV diseases***:
  - Valve disease (w > m)
  - Peripheral arterial disease (m > w)
  - CAD (m > w)
  - Prior PCI/CABG (m > w)
  - Atrial fibrillation (m > w)
- ***Comorbidities***:
  - CKD (w > m)

AGEING HEART

CLINICAL FEATURES

- ***NYHA Class*** (worse in women)
- ***Biomarkers (NT-proBNP)*** (higher in women)
- ***Quality of life*** (worse in women)

- ***ECG findings***:
  - Heart rate (higher in women)
  - AF (w > m)
  - LBBB (w > m)

- ***Echo findings:***
  - Ejection Fraction (higher in women)

PHARMACOLOGICAL TREATMENT

- Different drug bioavailability?
- Sex-specific amount and distribution of body fat?
- Different cytochrome-mediated metabolism and renal clearance?

E.g. higher plasma concentration of beta-blockers has been demonstrated in women, as well as a greater digital or angiotensin-converting-enzyme inhibitors toxicity or a greater susceptibility to malignant arrhythmias secondary to the intake of antiarrhythmic QT-prolonging drugs.

WOMEN AND CLINICAL TRIALS

- ***Under-representation of women in RCTs (30%):***

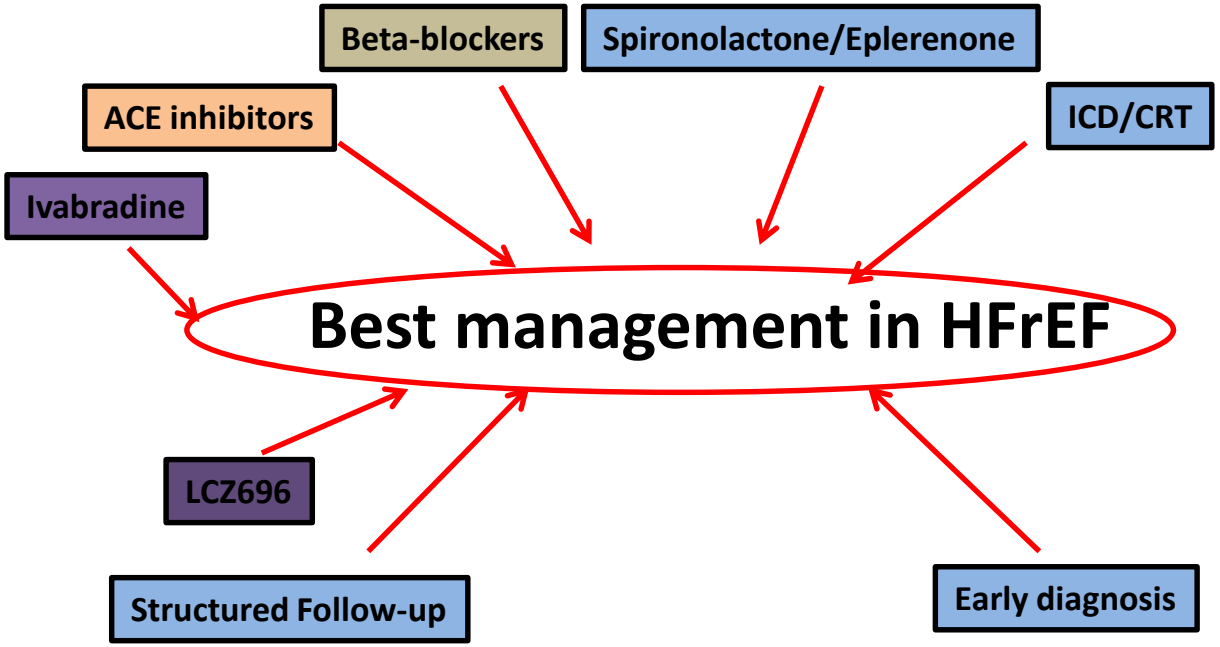
- Inclusion/exclusion criterias (age, eGFR)
- Burden of comorbidities
- Social factors

Representation of women in heart failure with reduced ejection fraction clinical trials

Medical Therapy for HFrEF	Name	Trial (% Women, Number Women)
Beta blockers	Carvedilol	COPERNICUS[22] (20%, 469)
		US Carvedilol Study[21] (23%, 256)
	Metoprolol succinate	MERIT-HF[24] (23%, 898)
	Bisoprolol	CIBIS II[23] (19%, 515)
ACEI	Captopril, enalapril, ramipril, trandolapril, zofenopril	Meta-analysis[17] (19%, 2373)
	Captopril, enalapril, lisinopril, quinapril, ramipril	Meta-analysis[16] (23%, 1587)
ARB	Valsartan	Val-HeFT[19] (20%, 1003)
	Losartan	ELITE II[42] (31%, 966)
	Candesartan	CHARM—low EF[18] (26%, 1188)
Aldosterone antagonist or MRA	Eplerenone	EPHESUS[27] (29%, 1918)
		EMPHASIS-HF[26] (22%, 610)
	Spironolactone	RALES[25] (27%, 446)
Hydralazine or isosorbide dinitrate		V-HeFT I[28] (0%, 0)
		V-HeFT II[29] (0%, 0)
		A-HeFT[30] (40%, 420)
Digoxin		DIG[33] (22%, 1520)
Angiotensin receptor-neprilysin inhibitor	Sacubitril-valsartan	PARADIGM-HF[34] (22%, 1832)
Ivabradine		SHIFT[35] (23%, 1535)

Heart Fail Clin. 2019 January ; 15(1): 19–27.

HFrEF: THERAPY AND MANAGEMENT

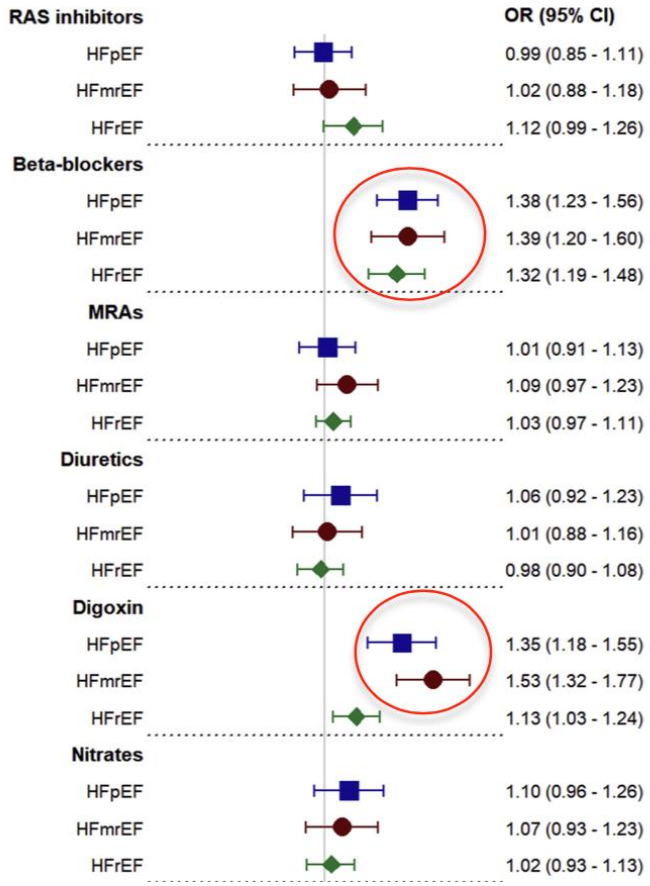


PHARMACOLOGICAL TREATMENTS

- ACEi/ARBs (ARBs > ACEi in women: cough?)
- MRAs (w = m)
- Beta-blockers* (controversial)
- Digoxin (w > m)
- Diuretics* (relative underuse in women?)
- VKA/DOACs (w < m)

	Women (n = 3,357)	Men (n = 12,058)	p Value
Digitalis	1,089 (32.4)	3,692 (30.6)	0.048
Beta-blocker	3,075 (91.6)	11,168 (92.6)	0.049
MRA	1,555 (46.3)	5,718 (47.4)	0.2599
ACE inhibitor	2,842 (84.7)	10,697 (88.7)	<0.0001
ARB	551 (16.4)	1,434 (11.9)	<0.0001
CCB§	330 (9.8)	1,035 (8.6)	0.0245
Statins	1,598 (47.6)	6,787 (56.3)	<0.0001
Aspirin	1,557 (46.4)	6,393 (53.0)	<0.0001
Anticoagulants	897 (26.7)	3,906 (32.4)	<0.0001
In patients with atrial fibrillation on ECG	67.1	71.2	0.029
In patients with atrial fibrillation history	60.6	66.6	<0.001
CHA_2DS_2-VASc score ≥2	67.1	71.5	0.019
Diuretic	2,698 (80.4)	9,638 (79.9)	0.574

Dewan, P. et al. J Am Coll Cardiol. 2019;73(1):29-40.



Stolfo, D. et al. J Am Coll Cardiol HF. 2019;7(6):505-15.

NON-PHARMACOLOGICAL TREATMENT

Sex Differences in the Use of Implantable Cardioverter-Defibrillators for Primary and Secondary Prevention of Sudden Cardiac Death

JAMA. 2007;298(13):1517-1524

Table 2. Cumulative Rates of Implantable Cardioverter-Defibrillator (ICD) Use by Year of Cohort Entry

Sex and Year of Cohort Entry	No. of ICDs by December 31, 2005	Cumulative Rate of ICD Use[a] Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Primary Prevention Cohort								
Men								
1999 (n = 9449)	276	7.6	10.8	13.8	19.1	23.2	27.7	31.0
2000 (n = 9364)	266	7.8	12.5	17.6	21.9	26.9	30.7	
2001 (n = 9288)	276	11.0	15.7	20.9	26.6	33.3		
2002 (n = 9411)	313	13.1	20.2	30.2	36.1			
2003 (n = 9756)	315	13.1	20.2	30.2				
2004 (n = 9568)	299	25.6	36.2					
2005 (n = 9081)	242	32.3						
Women								
1999 (n = 10071)	56	1.8	2.5	2.9	3.8	4.4	5.0	6.0
2000 (n = 10130)	73	2.3	3.1	3.7	5.1	6.8	7.6	
2001 (n = 9995)	93	3.2	4.7	6.1	7.9	10.6		
2002 (n = 10248)	80	4.2	6.8	7.2	10.1			
2003 (n = 10300)	104	5.1	6.7	10.9				
2004 (n = 10238)	75	6.3	8.2					
2005 (n = 9522)	65	8.6						
Secondary Prevention Cohort								
Men								
1999 (n = 7124)	494	51.0	54.3	56.3	60.1	63.9	66.7	70.1
2000 (n = 7185)	551	57.7	61.5	65.4	69.3	74.6	79.1	
2001 (n = 7117)	645	74.2	78.2	83.0	89.2	92.8		
2002 (n = 7592)	838	95.7	101.5	107.1	113.0			
2003 (n = 7917)	868	96.1	102.2	107.1				
2004 (n = 7770)	864	107.4	116.0					
2005 (n = 7547)	721	102.2						
Women								
1999 (n = 6855)	156	16.9	17.8	19.3	20.2	21.3	22.1	23.4
2000 (n = 6747)	146	18.1	19.2	19.6	20.7	21.3	22.5	
2001 (n = 6617)	160	20.0	22.0	23.4	24.1	24.3		
2002 (n = 6780)	241	31.5	34.4	34.9	36.3			
2003 (n = 6806)	251	33.6	36.9	37.5				
2004 (n = 6843)	246	34.4	37.2					
2005 (n = 6763)	240	38.4						

[a]Values shown are per 1000 Medicare beneficiaries. Values in outermost diagonal indicate the cumulative incidence of ICD use in each cohort by the end of the study period.

32,3 ‰

8,6 ‰

102,2 ‰

38,4 ‰

Results In the 2005 primary prevention cohort, 32.3 per 1000 men and 8.6 per 1000 women received ICD therapy within 1 year of cohort entry. In multivariate analyses, men were more likely than women to receive ICD therapy (hazard ratio [HR], 3.15; 95% confidence interval [CI], 2.86-3.47). Among men and women alive at 180 days after cohort entry, the hazard of mortality in the subsequent year was not significantly lower among those who received ICD therapy (HR, 1.01; 95% CI, 0.82-1.23). In the 2005 secondary prevention cohort, 102.2 per 1000 men and 38.4 per 1000 women received ICD therapy. Controlling for demographic variables and comorbid conditions, men were more likely than women to receive ICD therapy (HR, 2.44; 95% CI, 2.30-2.59). Among men and women alive at 30 days after cohort entry, the hazard of mortality in the subsequent year was significantly lower among those who received ICD therapy (HR, 0.65; 95% CI, 0.60-0.71).

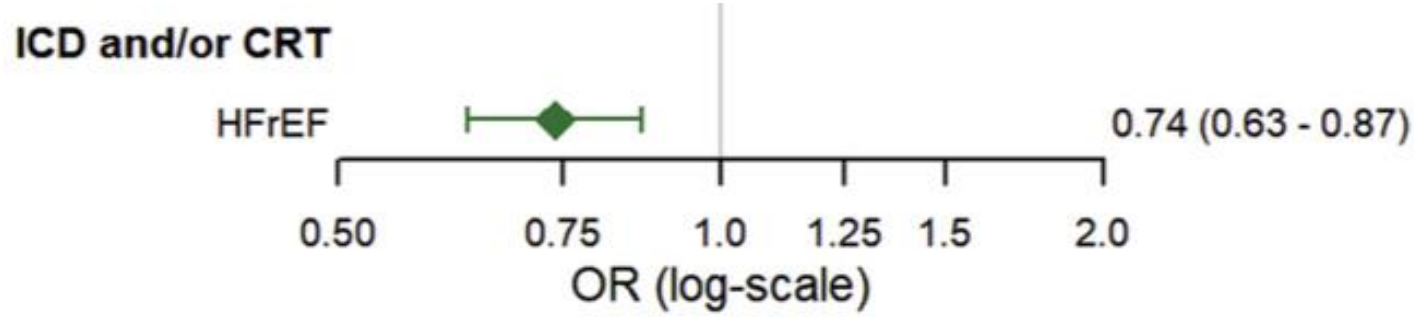
Conclusion In the Medicare population, women are significantly less likely than men to receive ICD therapy for primary or secondary prevention of sudden cardiac death.

NON-PHARMACOLOGICAL TREATMENT

Pacemaker	310 (9.2)	1,490 (12.4)	<0.0001
ICD (including CRT-D)	290 (8.6)	2,001 (16.6)	<0.0001
ICD only	196 (5.8)	1,371 (11.4)	<0.0001
CRT-P or CRT-D	137 (4.1)	830 (6.9)	<0.0001

Dewan, P. et al. J Am Coll Cardiol. 2019;73(1):29-40.

Concomitant medications						
RAS inhibitors	3,311 (74)	3,749 (70)‡	4,744 (85)	2,904 (81)‡	15,333 (91)	6,037 (89)‡
MRA	1,139 (25)	1,461 (27)	1,259 (23)	909 (25)‡	5,543 (33)	2,210 (32)
Digoxin	678 (15)	1,117 (21)‡	761 (14)	724 (20)‡	2,967 (18)	1,220 (18)
Diuretic	3,699 (82)	47,16 (87)‡	3,950 (71)	2,892 (80)‡	13,311 (79)	5,588 (82)‡
Nitrate	769 (17)	1,037 (19)‡	876 (16)	647 (18)‡	2,596 (15)	1,151 (17)‡
Beta-blocker	3,451 (77)	4,302 (80)‡	4,735 (85)	3,132 (87)‡		
ICD and/or CRT	58 (1.3)	46 (0.9)‡	151 (2.7)	49 (1.4)‡	1,218 (7.3)	245 (3.6)‡



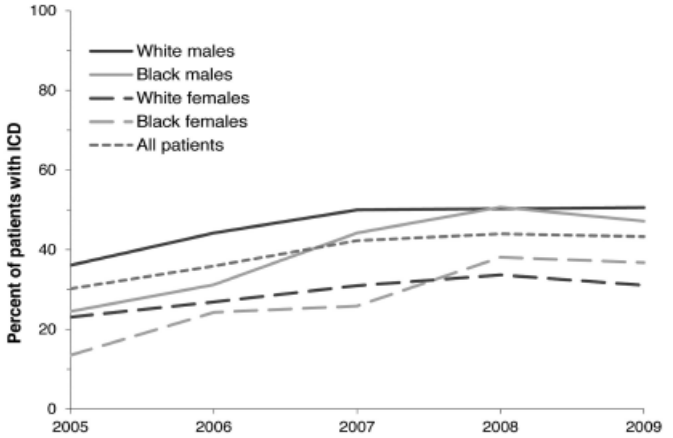
Stolfo, D. et al. J Am Coll Cardiol HF. 2019;7(6):505-15.

NON-PHARMACOLOGICAL TREATMENT

Trends in Use of Implantable Cardioverter-Defibrillator Therapy Among Patients Hospitalized for Heart Failure
Have the Previously Observed Sex and Racial Disparities Changed Over Time?

(*Circulation*. 2012;125:1094-1101.)

In an analysis of the Medicare Claims database:
women were 3 times less likely than men to receive an ICD for primary prevention
and 2,5 times less likely tha men to receive an ICD for secondary prevention !!!



Number of patients					Total
White males	856	1304	1189	1403	1268	6020
Black males	106	157	197	223	195	878
White females	480	699	606	744	647	3176
Black females	89	144	170	181	155	739
All patients	1671	2499	2368	2822	2520	11880

Table 3. Results of Multivariable Analyses Examining Sex and Race Effects Separately by Comparing Men With Women, Adjusted for Race, and by Comparing Whites With Blacks, Adjusted for Sex

	Adjusted OR (95% CI) Per Year	*P* for Time Trend	*P* for Differer in Time Trend
Whites	1.24 (1.07–1.45)	0.005	0.06
Blacks	1.61 (1.30–2.00)	<0.001	
Men	1.26 (1.08–1.47)	0.003	0.510
Women	1.37 (1.14–1.64)	0.001	

OR indicates odds ratio; CI, confidence interval.

No longer racial disparities… sex differences persisted

Conclusions—In the GWTG-HF quality improvement program, a significant increase in ICD therapy use was observed over time in all sex and race groups. The previously described racial disparities in ICD use were no longer present by the end of the study period; however, sex differences persisted. (*Circulation*. 2012;125:1094-1101.)

1. Physiological bases

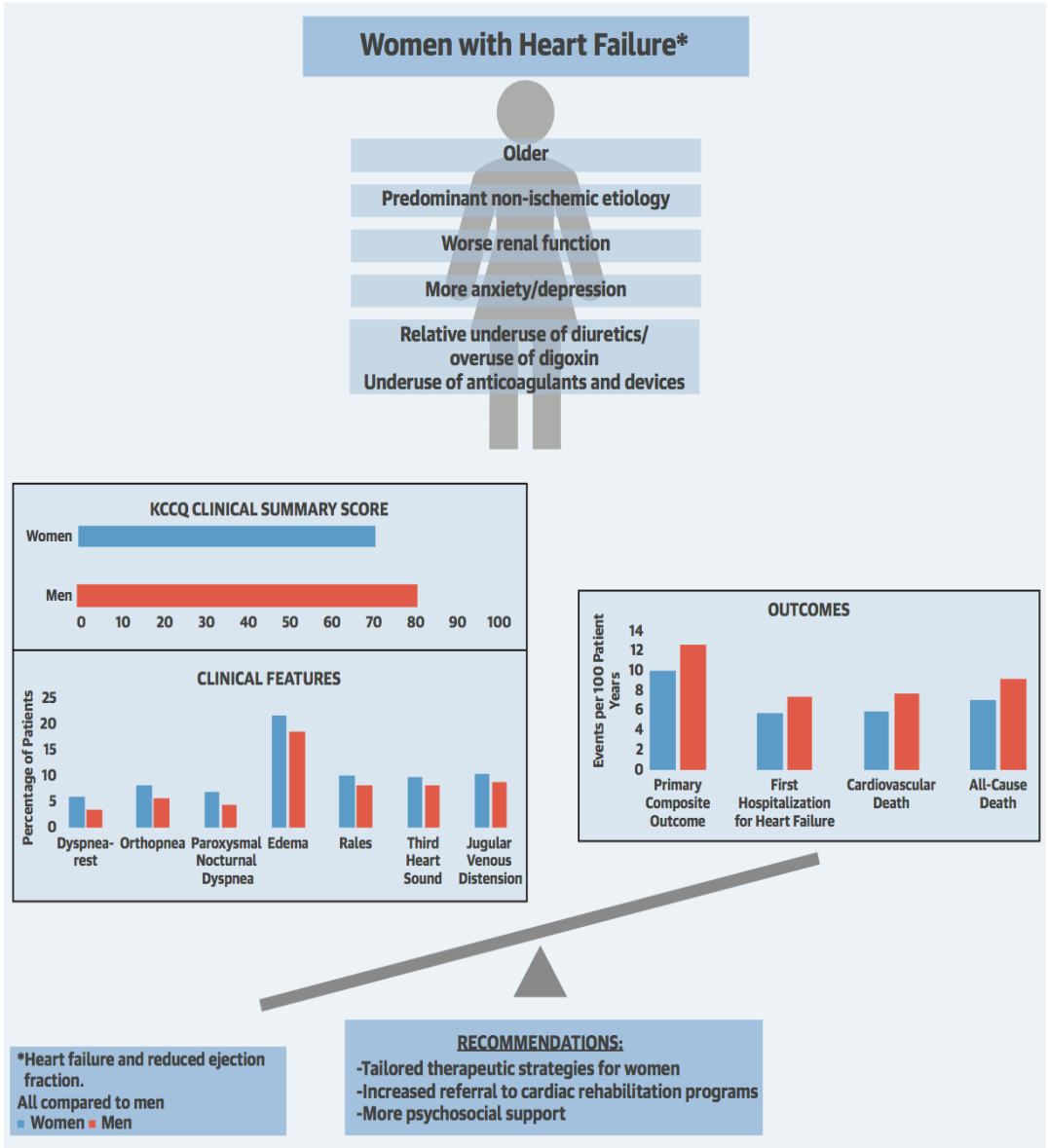
2. Epidemiology

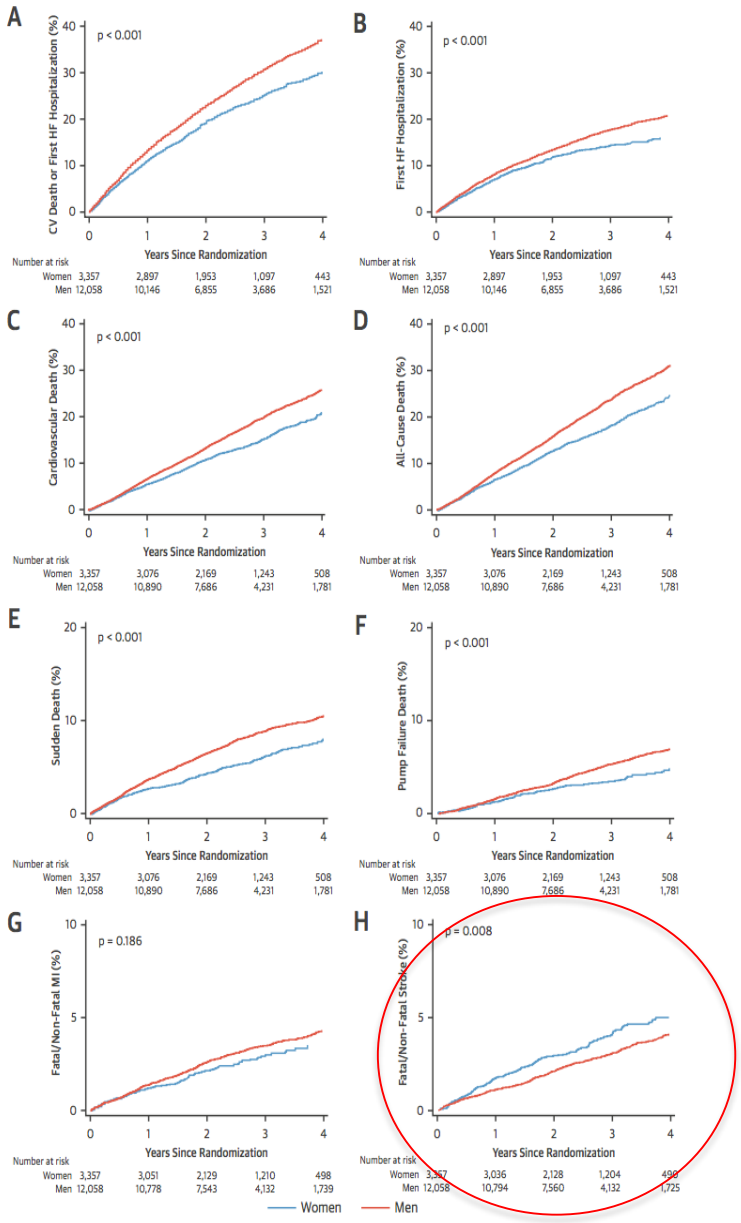
3. Heart Failure - Clinical features and Treatment

4. Outcome

5. Sex-related prognostic predictors

Outcome: sex-related paradox?





Dewan, P. et al. J Am Coll Cardiol. 2019;73(1):29-40.

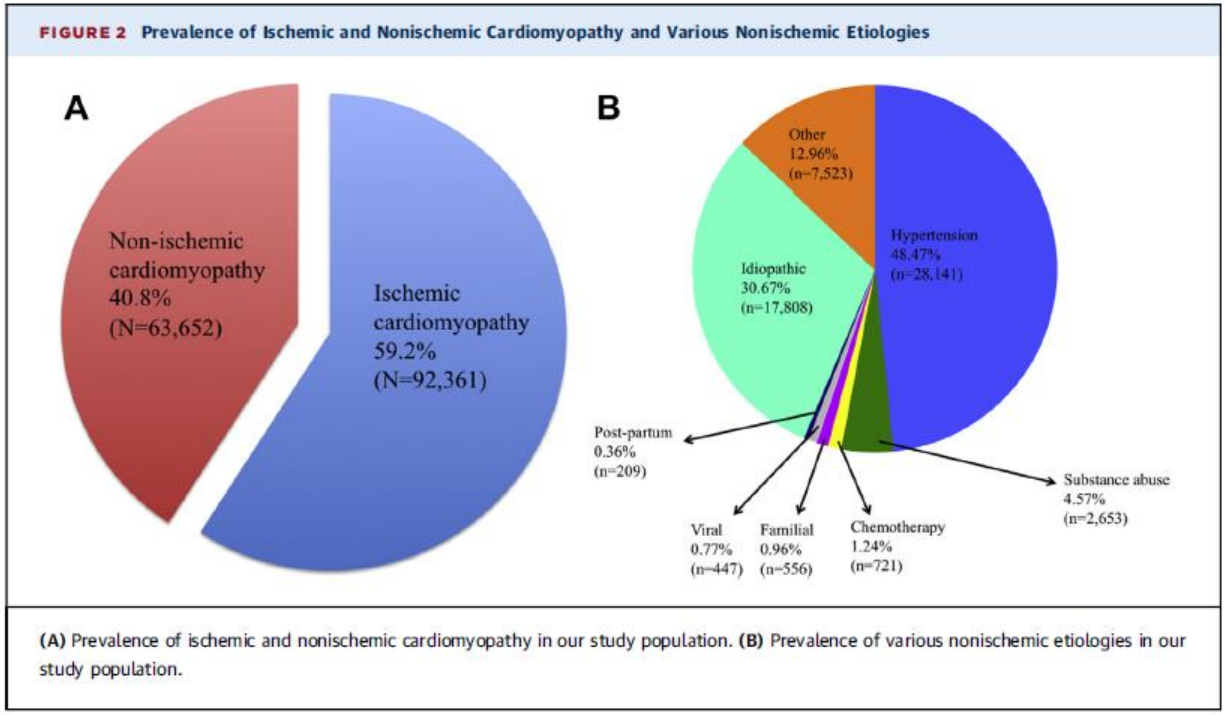
Outcome: sex-related paradox?

	Males		Females			
	Event Rate (%)	Event Rate (per 100 patient-yrs)	Event Rate (%)	Event Rate (per 100 patient-yrs)	HR (95% CI) Unadjusted Females vs. Males	HR (95% CI) Adjusted Females vs. Males
All-cause death/HF hospitalization						
HFpEF	1,929 (42.7)	20.45 (19.56-21.39)	2,545 (46.8)	23.79 (22.88-24.73)	1.14 (1.07-1.21)†	0.93 (0.88-0.99)†
HFmrEF	2,258 (40.4)	17.45 (16.74-18.18)	1,601 (44.1)	20.67 (19.68-21.71)	1.16 (1.08-1.23)†	0.91 (0.85-0.97)†
HFrEF	8,546 (50.4)	25.09 (24.57-25.63)	3,302 (48.2)	23.89 (23.09-24.72)	0.95 (0.92-0.99)†	0.80 (0.77-0.84)†
All-cause death						
HFpEF	1,888 (41.8)	16.27 (15.54-17.02)	2,373 (43.6)	17.54 (16.85-18.26)	1.07 (1.01-1.14)*	0.81 (0.76-0.87)
HFmrEF	2,009 (35.9)	12.73 (12.18-13.30)	1,459 (40.2)	15.27 (14.50-16.07)	1.19 (1.11-1.27)*	0.82 (0.77-0.89)
HFrEF	6,433 (38.0)	13.64 (13.32-13.98)	2,701 (39.4)	14.55 (14.01-15.11)	1.06 (1.02-1.11)*	0.80 (0.74-0.84)
Cardiovascular death						
HFpEF	1,102 (24.4)	9.49 (8.95-10.07)	1,506 (27.7)	11.13 (10.58-11.71)	1.17 (1.08-1.26)*	0.82 (0.76-0.89)
HFmrEF	1,231 (22.0)	7.80 (7.38-8.25)	917 (25.3)	9.58 (8.98-10.22)	1.22 (1.12-1.32)*	0.78 (0.72-0.86)
HFrEF	4,441 (26.2)	9.42 (9.15-9.70)	1844 (26.9)	9.94 (9.49-10.40)	1.05 (0.99-1.11)*	0.75 (0.70-0.79)
Noncardiovascular death						
HFpEF	786 (17.4)	6.77 (6.31-7.26)	867 (15.9)	6.41 (6.00-6.85)	0.94 (0.85-1.04)*	0.80 (0.73-0.89)
HFmrEF	778 (13.9)	4.93 (4.59-5.29)	542 (15.0)	5.69 (5.23-6.19)	1.15 (1.03-1.28)*	0.90 (0.80-1.01)
HFrEF	1,992 (11.8)	4.23 (4.04-4.41)	857 (12.5)	4.62 (4.32-4.94)	1.09 (1.01-1.18)*	0.89 (0.82-0.97)
HF hospitalization						
HFpEF	1,398 (31.0)	14.82 (14.07-15.62)	1,799 (33.1)	16.82 (16.06-17.61)	1.11 (1.03-1.19)†	0.98 (0.91-1.05)†
HFmrEF	1,665 (29.8)	12.87 (12.26-13.50)	1,124 (31.0)	14.51 (13.69-15.39)	1.10 (1.02-1.18)†	0.94 (0.86-1.02)†
HFrEF	6,686 (39.5)	19.63 (19.17-20.11)	2,439 (35.6)	17.65 (16.96-18.36)	0.90 (0.86-0.94)†	0.81 (0.77-0.86)†
Cardiovascular hospitalization						
HFpEF	2,498 (55.3)	36.57 (35.17-38.04)	3,050 (56.1)	38.84 (37.49-40.24)	1.04 (0.99-1.10)†	0.97 (0.92-1.03)*
HFmrEF	2,985 (53.3)	31.11 (30.01-32.24)	1,940 (53.5)	33.21 (31.77-34.73)	1.04 (0.98-1.10)†	0.95 (0.90-1.01)*
HFrEF	9,759 (57.6)	37.21 (36.48-37.96)	3,728 (54.4)	34.54 (33.45-35.66)	0.94 (0.90-0.97)†	0.90 (0.86-0.93)*
Noncardiovascular hospitalization						
HFpEF	2,778 (61.5)	43.62 (42.02-45.27)	3,399 (62.5)	48.23 (46.64-49.88)	1.07 (1.02-1.13)	0.99 (0.94-1.04)
HFmrEF	3176 (56.8)	33.37 (32.23-34.55)	2,116 (58.3)	38.73 (37.12-40.42)	1.12 (1.06-1.19)	0.99 (0.94-1.05)
HFrEF	8,678 (51.2)	29.26 (28.65-29.88)	3,587 (52.3)	32.06 (31.02-33.12)	1.08 (1.04-1.12)	1.00 (0.96-1.04)

*Significant interaction ($p < 0.05$) in the sex ejection fraction category. †Significant interaction ($p < 0.01$) in the sex ejection fraction category.
HR = hazard ratio; CI = confidence interval; CV = cardiovascular.

Stolfo, D. et al. J Am Coll Cardiol HF. 2019;7(6):505-15.

HFrEF: ETIOLOGICAL CLASSIFICATION



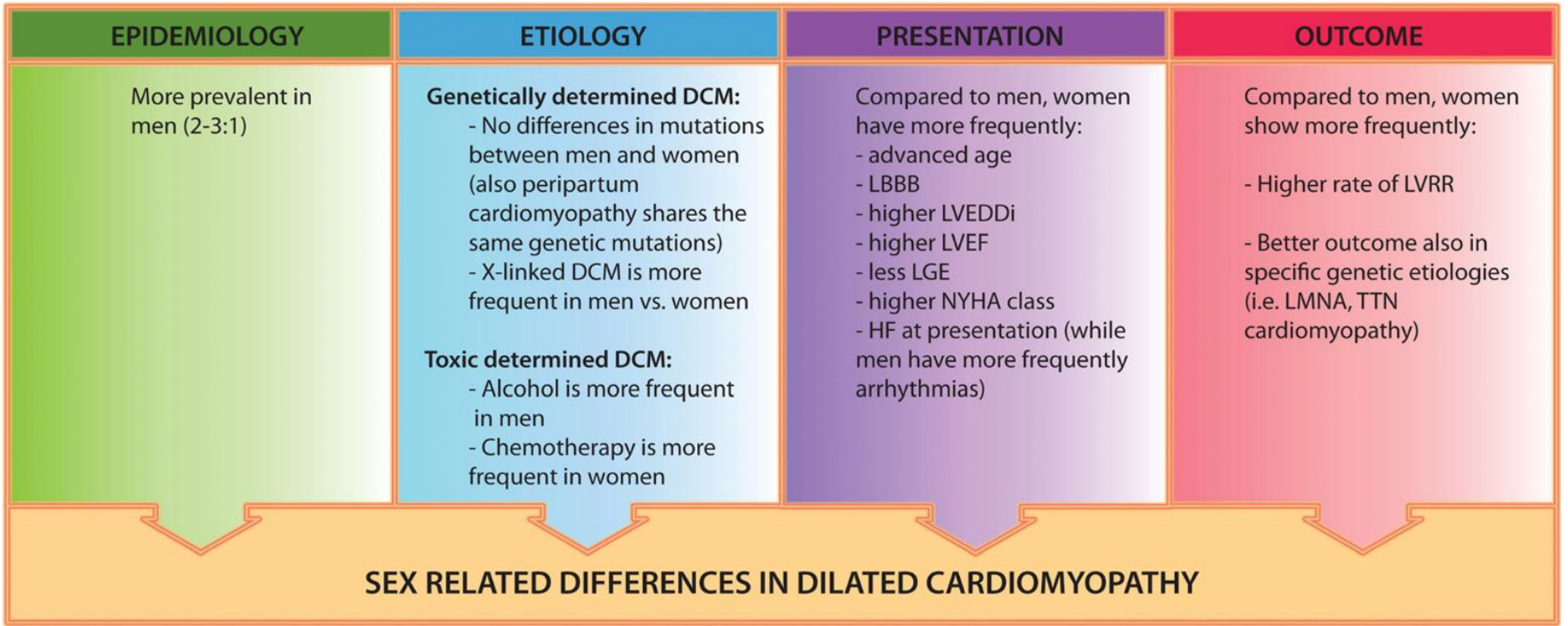
Shore S et al. JACC HF, 2015

DILATED CARDIOMYOPATHY

Heart Failure Reviews
https://doi.org/10.1007/s10741-019-09824-y

Gender-related differences in heart failure: beyond the "one-size-fits-all" paradigm

Annamaria De Bellis[1] &Giulia De Angelis[1] &Enrico Fabris[1] &Antonio Cannatà[1] &Marco Merlo[1] &Gianfranco Sinagra[1]



ESC European Society of Cardiology

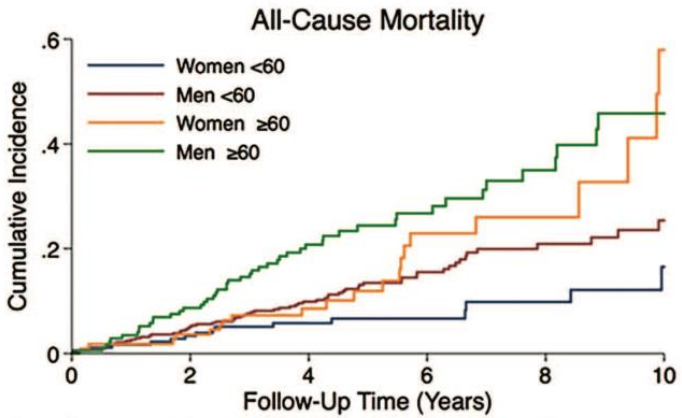
European Journal of Heart Failure (2018) **20**, 1392–1400
doi:10.1002/ejhf.1216

RESEARCH ARTICLE

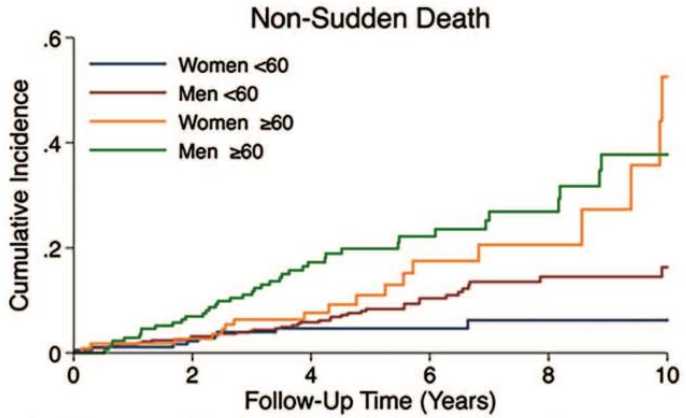
Sex- and age-based differences in the natural history and outcome of dilated cardiomyopathy

Brian P. Halliday[1,2], Ankur Gulati[1], Aamir Ali[1,2], Simon Newsome[3], Amrit Lota[1,2], Upasana Tayal[1,2], Vassilios S. Vassiliou[1,4], Monika Arzanauskaite[1], Cemil Izgi[1], Kaushiga Krishnathasan[1], Arvind Singhal[1], Kayla Chiew[2], John Gregson[3], Michael P. Frenneaux[4], Stuart A. Cook[1,2,5], Dudley J. Pennell[1,2], Peter Collins[1,2], John G.F. Cleland[1,2,6], and Sanjay K. Prasad[1,2]*

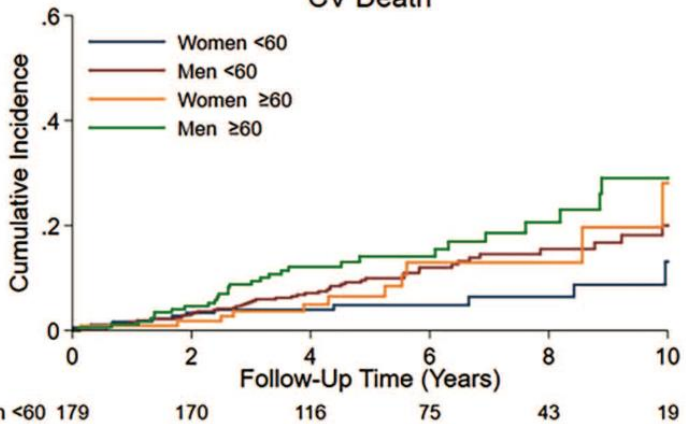
- N. 881 patients with DCM (n. 290 women, 32,9%)
- **Median follow-up: 59 months**
- Endpoint:
  - Primary endpoint: all-cause mortality
  - Secondary endpoints: CV, non-sudden and sudden cardiac death



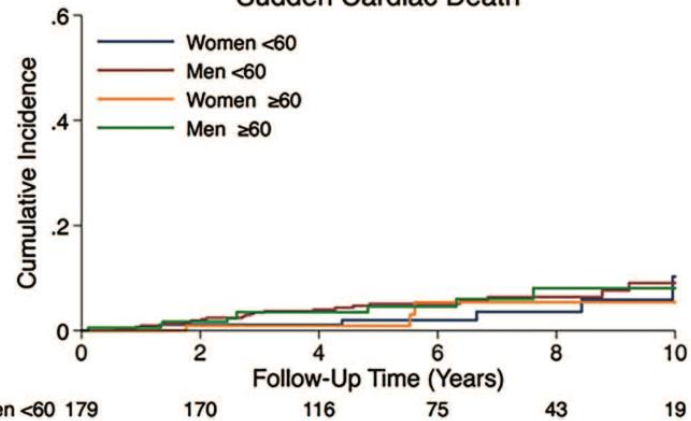
Women <60	179	170	116	75	43	19
Men <60	418	385	287	154	78	39
Women ≥60	111	106	70	29	13	5
Men ≥60	173	157	104	53	30	13



Women <60	179	170	116	75	43	19
Men <60	418	385	287	154	78	39
Women ≥60	111	106	70	29	13	5
Men ≥60	173	157	104	53	30	13



Women <60	179	170	116	75	43	19
Men <60	418	385	287	154	78	39
Women ≥60	111	106	70	29	13	5
Men ≥60	173	157	104	53	30	13



Women <60	179	170	116	75	43	19
Men <60	418	385	287	154	78	39
Women ≥60	111	106	70	29	13	5
Men ≥60	173	157	104	53	30	13

Accepted Manuscript

Sex differences in the long-term prognosis of dilated cardiomyopathy

Antonio Cannatà, MD, Enrico Fabris, MD, Marco Merlo, MD, Jessica Artico, MD, Piero Gentile, MD, Carola Pio Loco, MD, Andrea Ballaben, MD, Federica Ramani, PhD, Giulia Barbati, PhD, Gianfranco Sinagra, MD, FESC

PII: S0828-282X(19)30377-0

DOI: https://doi.org/10.1016/j.cjca.2019.05.031

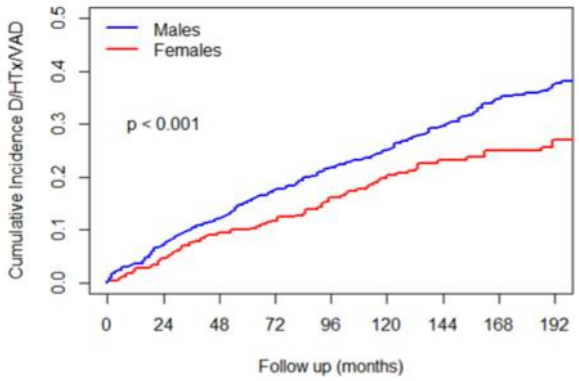
- N. 1 113 patients with DCM (n. 333 women, 30%)
- **Median follow-up 126 months**
- Outcome:
  - All-cause mortality/HTx/VAD
  - CV death/HTx/VAD
  - SCD/MVA

- ***BASELINE FEATURES***:
  - Women older than men
  - Sinus rhythm (w > m)
  - Similar NYHA class, LVEF, Restrictive Filling Pattern, moderate-to-severe RM, OMT
  - LBBB (w > m)
  - Moderate-to-severe LV dilation (w > m)

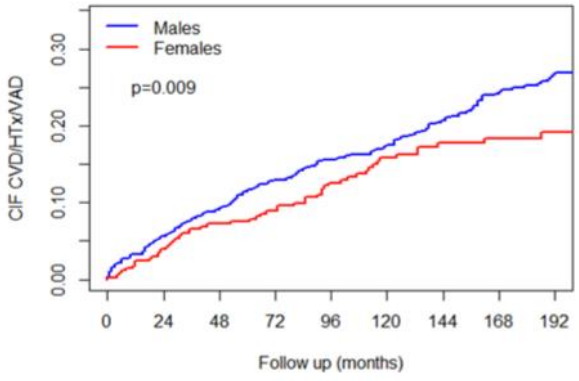
Total Cohort

1113 DCM patients

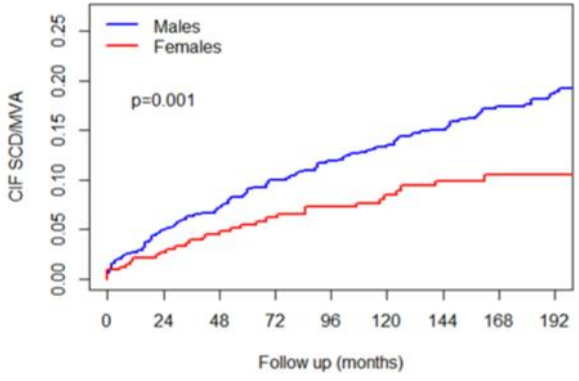
A



C



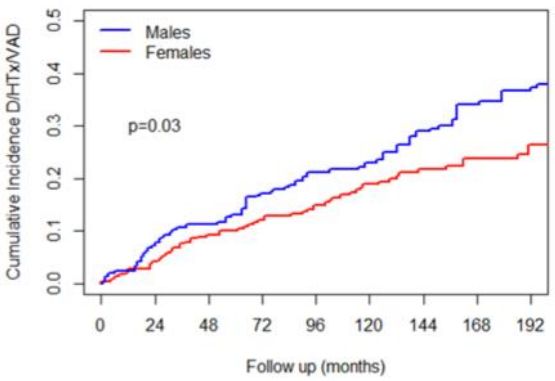
E



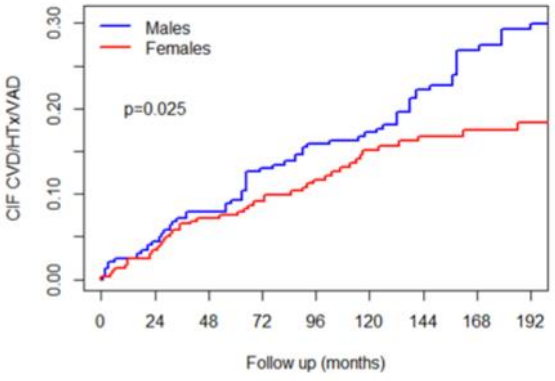
Matched Cohort

586 DCM patients

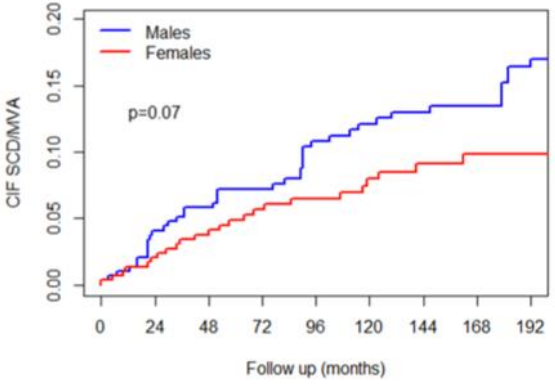
B



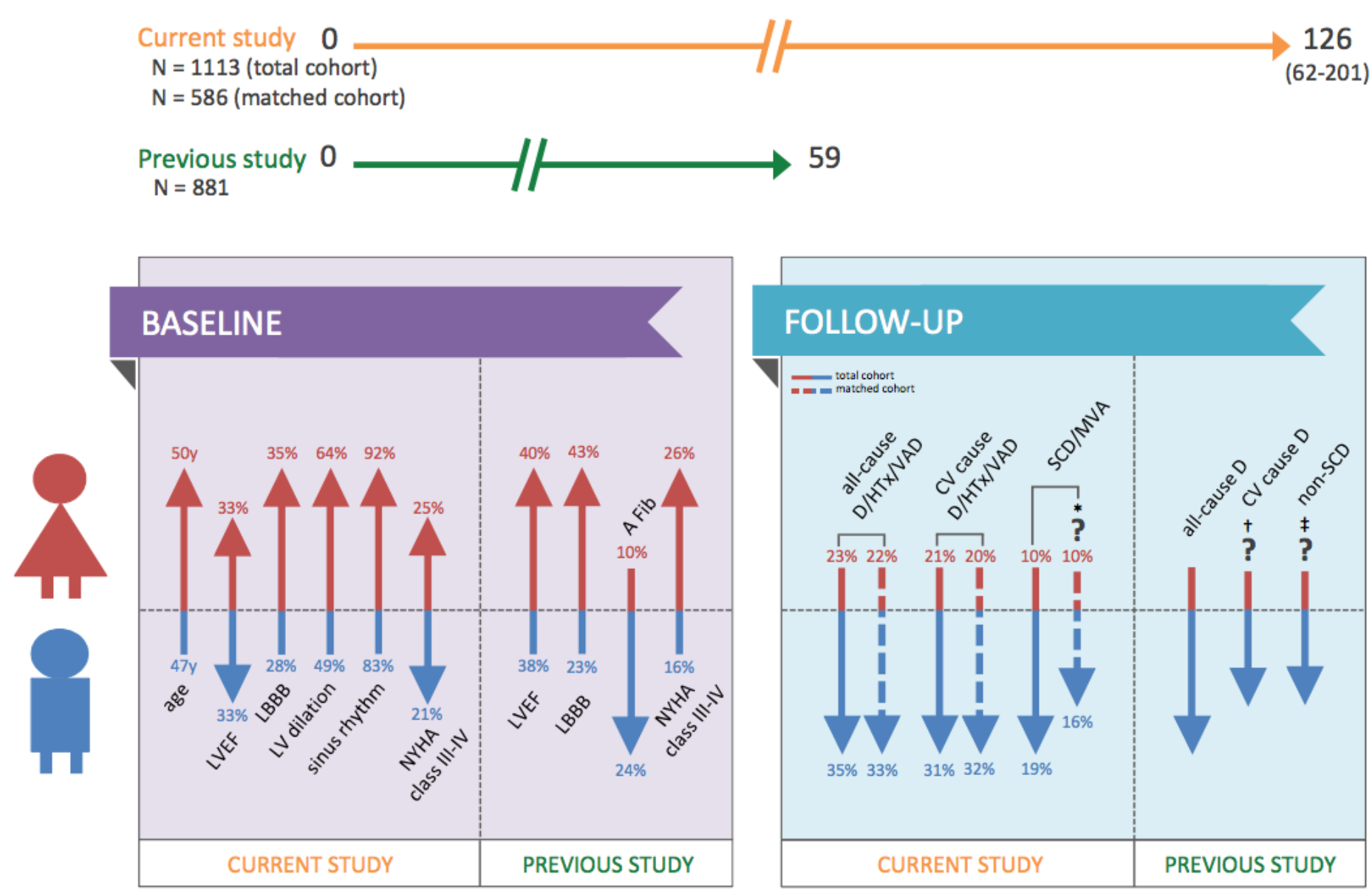
D



F



Cannatà A. et al.
Canadian Journal of Cardiology (2019)



REGIONE AUTONOMA FRIULI VENEZIA GIULIA
Azienda Sanitaria Universitaria Integrata di Trieste

Yogasundaram H, et al. Battle of the Sexes: Differential Prognosis by Sex in Dilated Cardiomyopathy, Canadian Journal of Cardiology (2019)

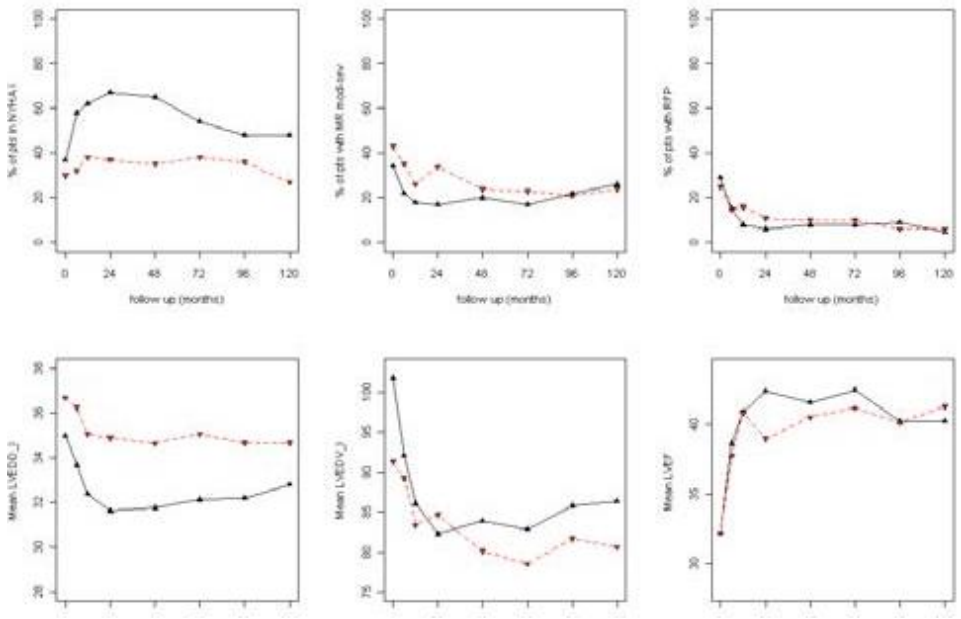
REVERSE REMODELING

ORIGINAL ARTICLES Epidemiology Biostatistics and Public Health - 2017, Volume 14, Number 3

Conflicting gender-related differences in the natural history of patients with Idiopathic Dilated Cardiomyopathy

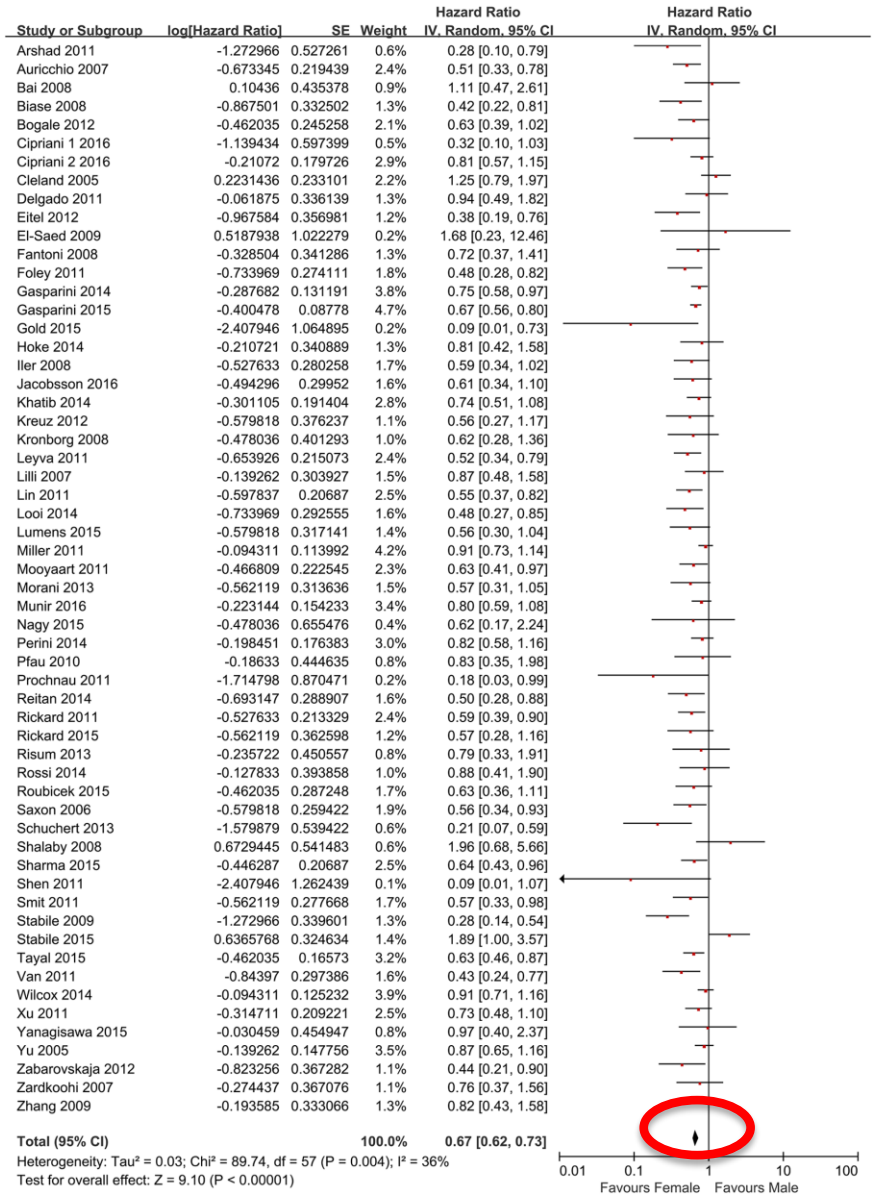
Vitali-Serdoz Laura [1], Lutman Cristina [1], Cadamuro Elena [1], Barbati Giulia [1], Zecchin Massimo [1], Merlo Marco [1], Puggia Ilaria [1], Pinamonti Bruno [1], Di Lenarda Andrea [2], Sinagra Gianfranco [1]

(1) Cardiovascular Department, Ospedali Riuniti and University of Trieste, Italy
(2) Cardiovascular Center, Azienda per i Servizi Sanitari n° 1 of Trieste, Italy



REVERSE REMODELING AFTER CRT

REGIONE AUTONOMA FRIULI VENEZIA GIULIA
Azienda Sanitaria Universitaria Integrata di Trieste



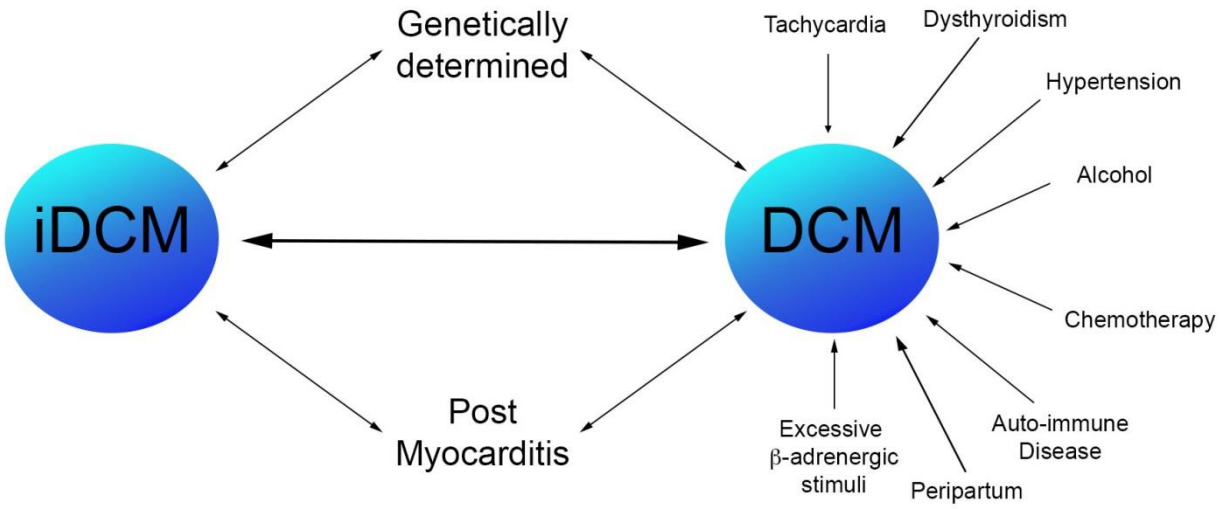
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Arshad 2011	-1.272966	0.527261	0.6%	0.28 [0.10, 0.79]
Auricchio 2007	-0.673345	0.219439	2.4%	0.51 [0.33, 0.78]
Bai 2008	0.10436	0.435378	0.9%	1.11 [0.47, 2.61]
Biase 2008	-0.867501	0.332502	1.3%	0.42 [0.22, 0.81]
Bogale 2012	-0.462035	0.245258	2.1%	0.63 [0.39, 1.02]
Cipriani 1 2016	-1.139434	0.597399	0.5%	0.32 [0.10, 1.03]
Cipriani 2 2016	-0.21072	0.179726	2.9%	0.81 [0.57, 1.15]
Cleland 2005	0.2231436	0.233101	2.2%	1.25 [0.79, 1.97]
Delgado 2011	-0.061875	0.336139	1.3%	0.94 [0.49, 1.82]
Eitel 2012	-0.967584	0.356981	1.2%	0.38 [0.19, 0.76]
El-Saed 2009	0.5187938	1.022279	0.2%	1.68 [0.23, 12.46]
Fantoni 2008	-0.328504	0.341286	1.3%	0.72 [0.37, 1.41]
Foley 2011	-0.733969	0.274111	1.8%	0.48 [0.28, 0.82]
Gasparini 2014	-0.287682	0.131191	3.8%	0.75 [0.58, 0.97]
Gasparini 2015	-0.400478	0.08778	4.7%	0.67 [0.56, 0.80]
Gold 2015	-2.407946	1.064895	0.2%	0.09 [0.01, 0.73]
Hoke 2014	-0.210721	0.340889	1.3%	0.81 [0.42, 1.58]
Iler 2008	-0.527633	0.280258	1.7%	0.59 [0.34, 1.02]
Jacobsson 2016	-0.494296	0.29952	1.6%	0.61 [0.34, 1.10]
Khatib 2014	-0.301105	0.191404	2.8%	0.74 [0.51, 1.08]
Kreuz 2012	-0.579818	0.376237	1.1%	0.56 [0.27, 1.17]
Kronborg 2008	-0.478036	0.401293	1.0%	0.62 [0.28, 1.36]
Leyva 2011	-0.653926	0.215073	2.4%	0.52 [0.34, 0.79]
Lilli 2007	-0.139262	0.303927	1.5%	0.87 [0.48, 1.58]
Lin 2011	-0.597837	0.20687	2.5%	0.55 [0.37, 0.82]
Looi 2014	-0.733969	0.292555	1.6%	0.48 [0.27, 0.85]
Lumens 2015	-0.579818	0.317141	1.4%	0.56 [0.30, 1.04]
Miller 2011	-0.094311	0.113992	4.2%	0.91 [0.73, 1.14]
Mooyaart 2011	-0.466809	0.222545	2.3%	0.63 [0.41, 0.97]
Morani 2013	-0.562119	0.313636	1.5%	0.57 [0.31, 1.05]
Munir 2016	-0.223144	0.154233	3.4%	0.80 [0.59, 1.08]
Nagy 2015	-0.478036	0.655476	0.4%	0.62 [0.17, 2.24]
Perini 2014	-0.198451	0.176383	3.0%	0.82 [0.58, 1.16]
Pfau 2010	-0.18633	0.444635	0.8%	0.83 [0.35, 1.98]
Prochnau 2011	-1.714798	0.870471	0.2%	0.18 [0.03, 0.99]
Reitan 2014	-0.693147	0.288907	1.6%	0.50 [0.28, 0.88]
Rickard 2011	-0.527633	0.213329	2.4%	0.59 [0.39, 0.90]
Rickard 2015	-0.562119	0.362598	1.2%	0.57 [0.28, 1.16]
Risum 2013	-0.235722	0.450557	0.8%	0.79 [0.33, 1.91]
Rossi 2014	-0.127833	0.393858	1.0%	0.88 [0.41, 1.90]
Roubicek 2015	-0.462035	0.287248	1.7%	0.63 [0.36, 1.11]
Saxon 2006	-0.579818	0.259422	1.9%	0.56 [0.34, 0.93]
Schuchert 2013	-1.579879	0.539422	0.6%	0.21 [0.07, 0.59]
Shalaby 2008	0.6729445	0.541483	0.6%	1.96 [0.68, 5.66]
Sharma 2015	-0.446287	0.20687	2.5%	0.64 [0.43, 0.96]
Shen 2011	-2.407946	1.262439	0.1%	0.09 [0.01, 1.07]
Smit 2011	-0.562119	0.277668	1.7%	0.57 [0.33, 0.98]
Stabile 2009	-1.272966	0.339601	1.3%	0.28 [0.14, 0.54]
Stabile 2015	0.6365768	0.324634	1.4%	1.89 [1.00, 3.57]
Tayal 2015	-0.462035	0.16573	3.2%	0.63 [0.46, 0.87]
Van 2011	-0.84397	0.297386	1.6%	0.43 [0.24, 0.77]
Wilcox 2014	-0.094311	0.125232	3.9%	0.91 [0.71, 1.16]
Xu 2011	-0.314711	0.209221	2.5%	0.73 [0.48, 1.10]
Yanagisawa 2015	-0.030459	0.454947	0.8%	0.97 [0.40, 2.37]
Yu 2005	-0.139262	0.147756	3.5%	0.87 [0.65, 1.16]
Zabarovskaja 2012	-0.823256	0.367282	1.1%	0.44 [0.21, 0.90]
Zardkoohi 2007	-0.274437	0.367076	1.1%	0.76 [0.37, 1.56]
Zhang 2009	-0.193585	0.333066	1.3%	0.82 [0.43, 1.58]
Total (95% CI)			**100.0%**	**0.67 [0.62, 0.73]**

Heterogeneity: Tau² = 0.03; Chi² = 89.74, df = 57 (P = 0.004); I² = 36%
Test for overall effect: Z = 9.10 (P < 0.00001)

Fig 2. Forest plot for sex-specific differences in all-cause mortality of patients who received CRT.

Han et al. Plos One 2017

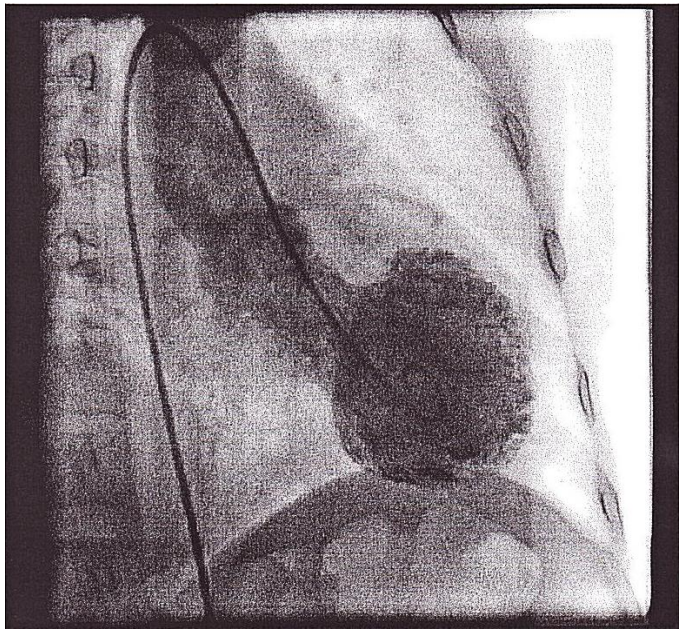
DCM: ETIOLOGICAL CLASSIFICATION



Merlo M et al. Eur J Heart Fail. 2018

STRESS-INDUCED CARDIOMYOPATHY

- Reported by Japanese in 1990
- “Broken heart”, apical ballooning, stress CM
- Octopus trap appearance
- Up to 90% women, age > 60
- 70% with Severe emotional stress
- Troponin moderately elevated
- Echo resolution within ~ 30 days



Rivera et al. Med Sci Monit, 2011;17(6):RA135-147

PERIPARTUM CARDIOMYOPATHY

- 1/4000 live US births
- 1 month pre or 5 months post-partum
- Increased maternal age, multiparity, multiple gestations, preeclampsia/HTN
- 2.9x more likely in AA women
- ?viral, immune, stress, prolactin, tocolysis, hereditary
- Usual HF therapy, until resolved
- 4% need transplant
- Future pregnancies NOT recommended

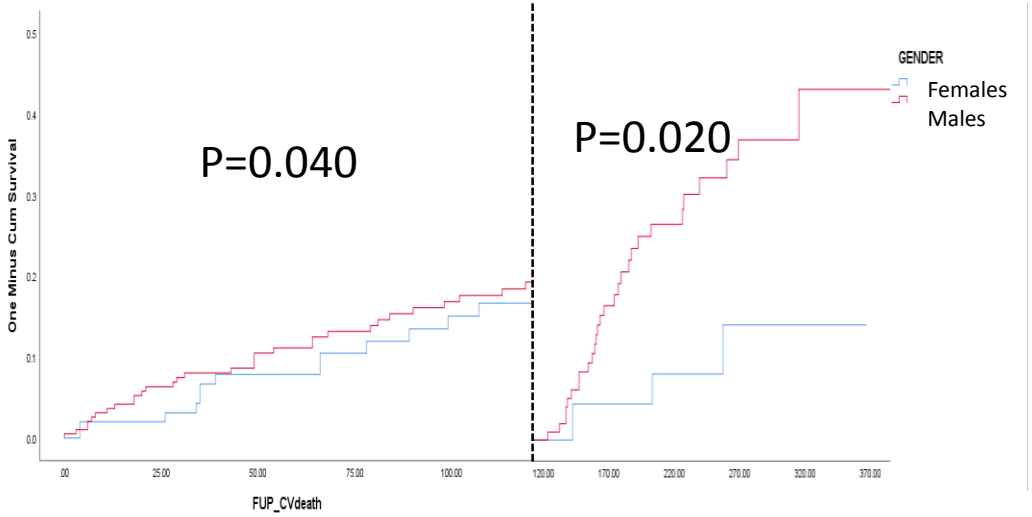
CHEMOTHERAPY-INDUCED CARDIOMYOPATHY

- **Breast cancer most common malignancy**
- Adriamycin
  - Dose dependent cardiotoxicity (>450 mg/m2)
  - Clinical HF in 2-7% of pts; increases over time
- Herceptin
  - Reduces recurrence rate up to 50%
  - CHF in 2-4%; up to 3-27% after combination
  - Esp in pts with elevated troponin/BNP
- Cyclophosphamide, XRT

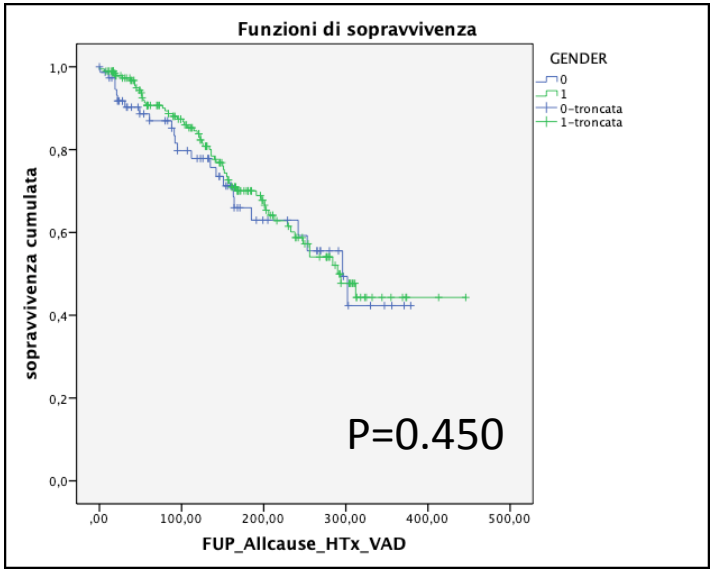
GENETIC DCM

Truly idiopathic DCM

Landmark Analysis at 120 months of Follow-up



Genetic DCM

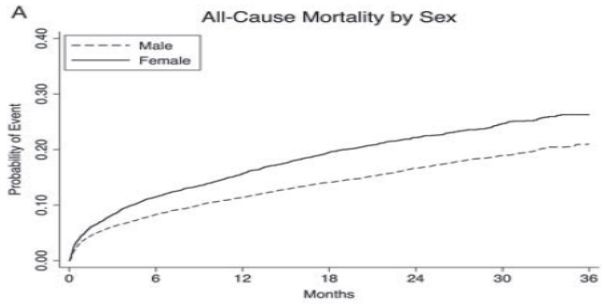


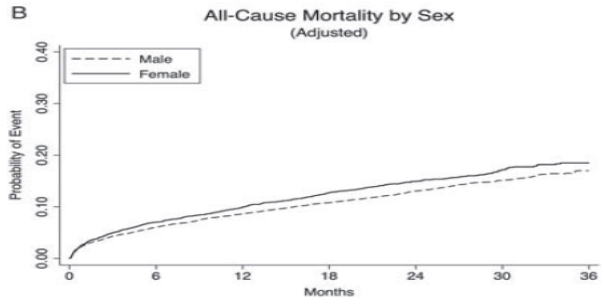
Cannatà A, Merlo M, Mestroni L, Sinagra G et al. Preliminary data

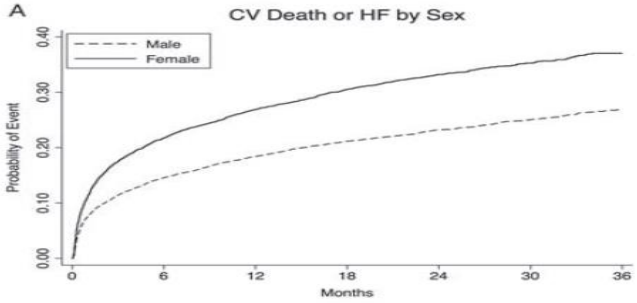
ISCHEMIC HEART DISEASE

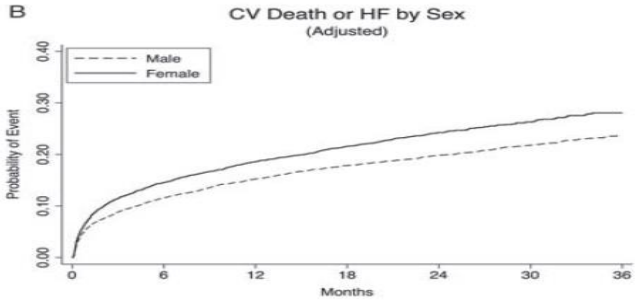
Sex differences in clinical characteristics and outcomes after myocardial infarction: insights from the Valsartan in Acute Myocardial Infarction Trial (VALIANT)

European Journal of Heart Failure







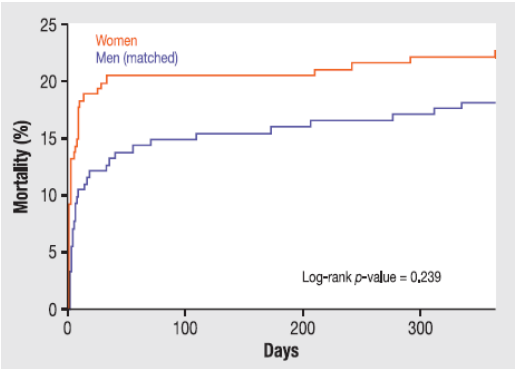


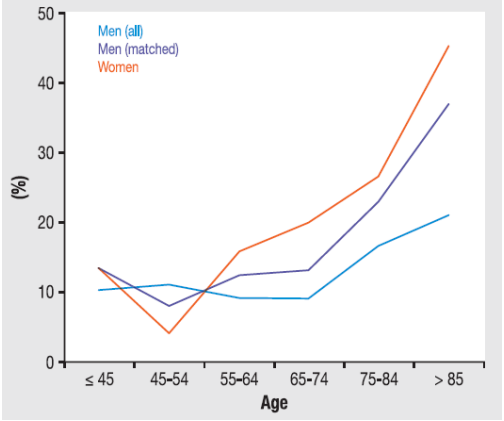
Conclusions In VALIANT, the risk of HF following MI was higher in women than men after adjusting for age and comorbidities, although the risk of other fatal and non-fatal outcomes were similar. The higher long-term risk of HF in women appears to be independent of the extent of left ventricular systolic dysfunction or remodelling compared with men.

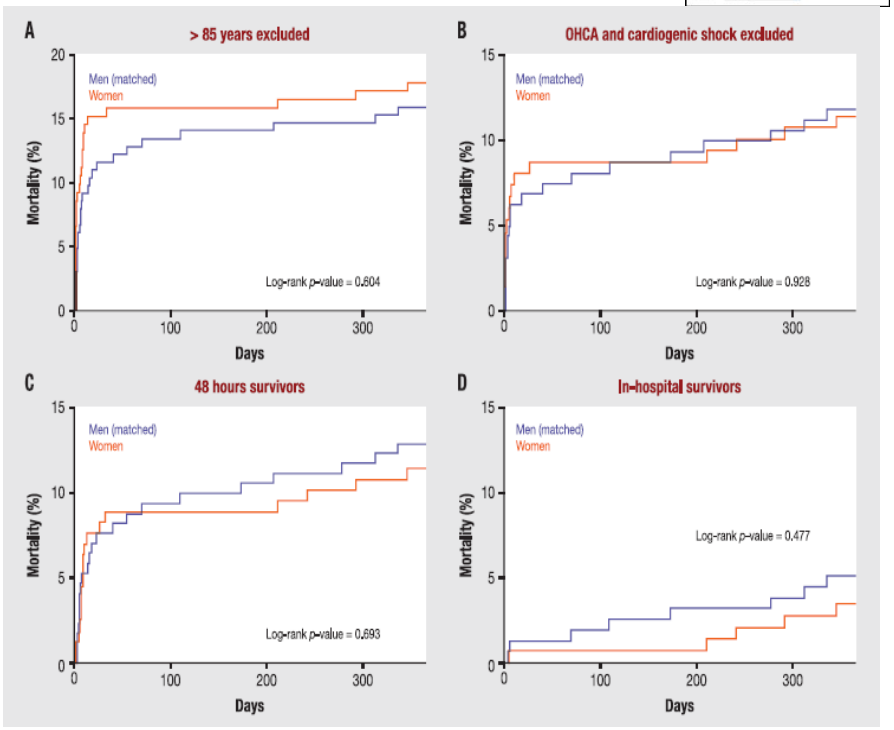
European Journal of Heart Failure (2015) **17**, 301–312

Sex-related differences after contemporary primary percutaneous coronary intervention for ST-segment elevation myocardial infarction

Total 775 patients 593 men + 182 women







Archives of Cardiovascular Disease (2015)

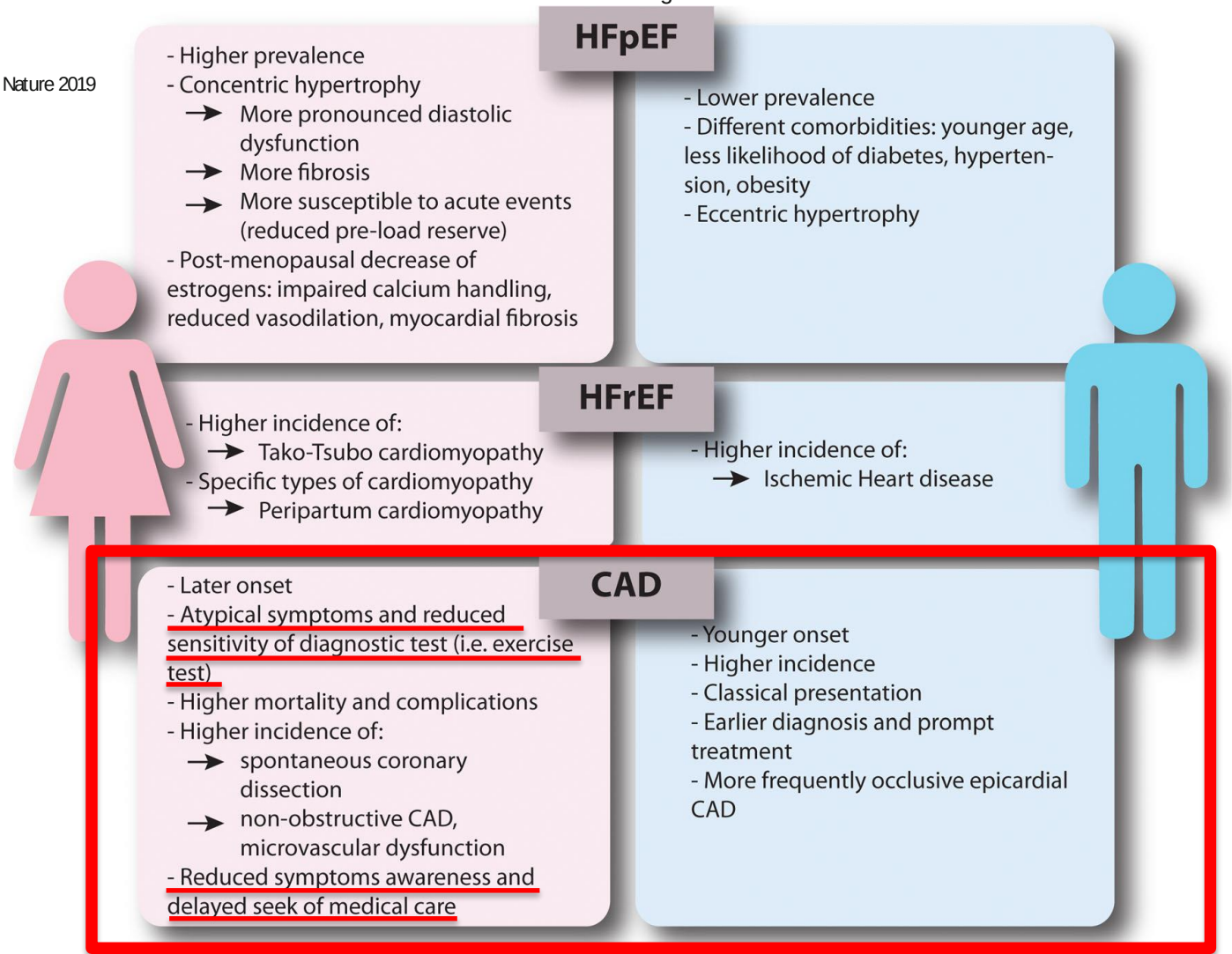
HFrEF: GENDER MEDICINE

Heart Failure Reviews
https://doi.org/10.1007/s10741-019-09824-y

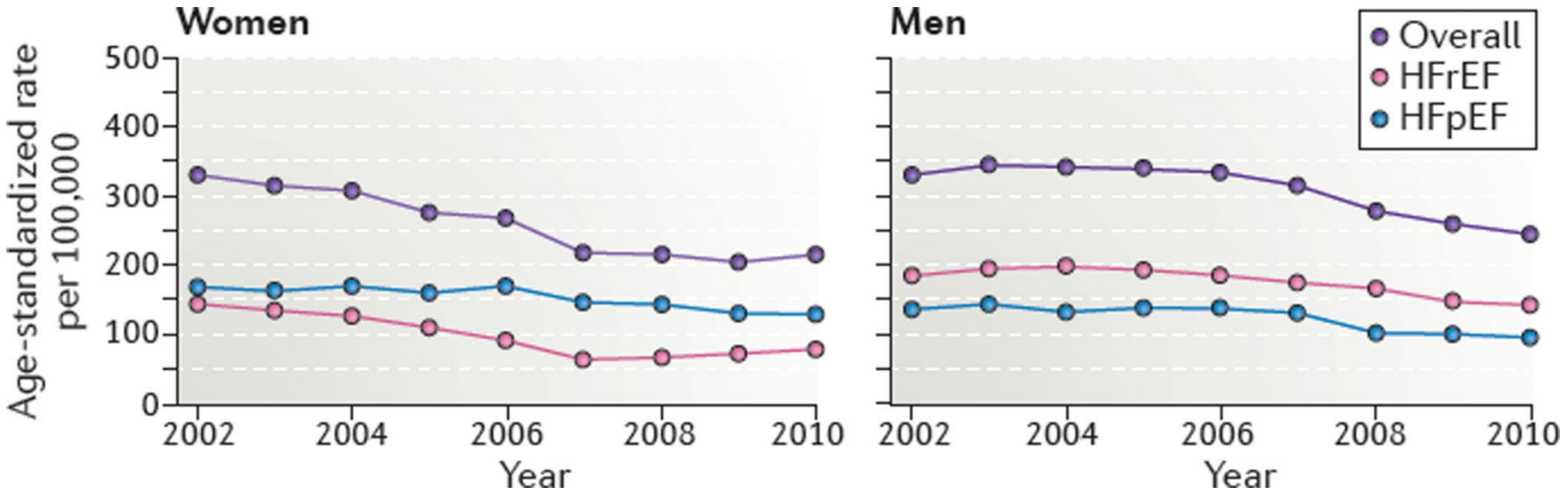
Check for updates

Gender-related differences in heart failure: beyond the "one-size-fits-all" paradigm

Annamaria De Bellis[1] &Giulia De Angelis[1] &Enrico Fabris[1] &Antonio Cannatà[1] &Marco Merlo[1] &Gianfranco Sinagra[1]



HFpEF



Ziaeian and Fonarow, Nat Cardiol Rev. 2016

HFpEF

Characteristic	Women (n=2491)	Men (n=1637)	*P* Value
Age, y	72±7	71±7	<0.001
Obesity*, %	46	35	<0.001
Heart failure cause, % ischemic	19	34	<0.001
Hypertension, %	91	85	<0.001
Atrial fibrillation, %	27	33	<0.001
Diabetes mellitus, %	28	27	0.74
Chronic obstructive pulmonary disease, %	8	13	<0.001
Smoking, %	9	32	<0.001
NYHA class II/III/IV, %	20/77/2	22/75/3	0.006
Hospitalization in the last 6 mo, %	44	45	0.49
Ejection fraction, %	61±9	58±9	<0.001
Minnesota living with heart failure score	45±21	39±21	<0.001
Median (Q1–Q3) NT-pro-BNP, pg/mL	301 (126–897)	413 (155–1051)	<0.001
Hemoglobin, g/dL	13.5±1.8	14.5±1.9	<0.001
Anemia†, %	11	16	<0.001
Chronic kidney disease‡, %	34	26	<0.001
Medications			
Loop diuretic, %	51	53	0.08
Thiazide diuretic, %	41	34	<0.001
Spironolactone, %	15	17	0.08
Angiotensin-converting enzyme inhibitor, %	23	29	<0.001
Digoxin, %	12	16	0.006
β-Blocker, %	59	59	0.93
Antiarrythmic, %	8	11	0.003
Calcium channel blocker, %	42	37	<0.001
Nitrate, %	25	30	<0.001
Oral anticoagulant, %	55	64	<0.001
Aspirin, %	52	59	<0.001
Lipid lowering, %	28	35	<0.001

Lam C et al.
Circulation Heart Fail 2012

HFpEF

Outcome	Event Rate Per 100 Patient-Years		Multivariable Analysis*	
	Women	Men	HR (95% CI), Women vs Men	*P* Value
All-cause death	4.32	6.72	0.70 (0.59–0.83)	<0.001
All-cause hospitalization or death	19.42	25.05	0.80 (0.72–0.89)	<0.001
Cardiovascular hospitalization or death	11.76	15.97	0.81 (0.72–0.92)	0.001
Noncardiovascular hospitalization or death	9.89	12.40	0.78 (0.69–0.90)	<0.001
Heart failure hospitalization or death	4.43	5.02	0.94 (0.77–1.14)	0.51
First all-cause hospitalization	18.43	23.14	0.77 (0.66–0.89)	<0.001

Lam C et al. Circulation Heart Fail 2012

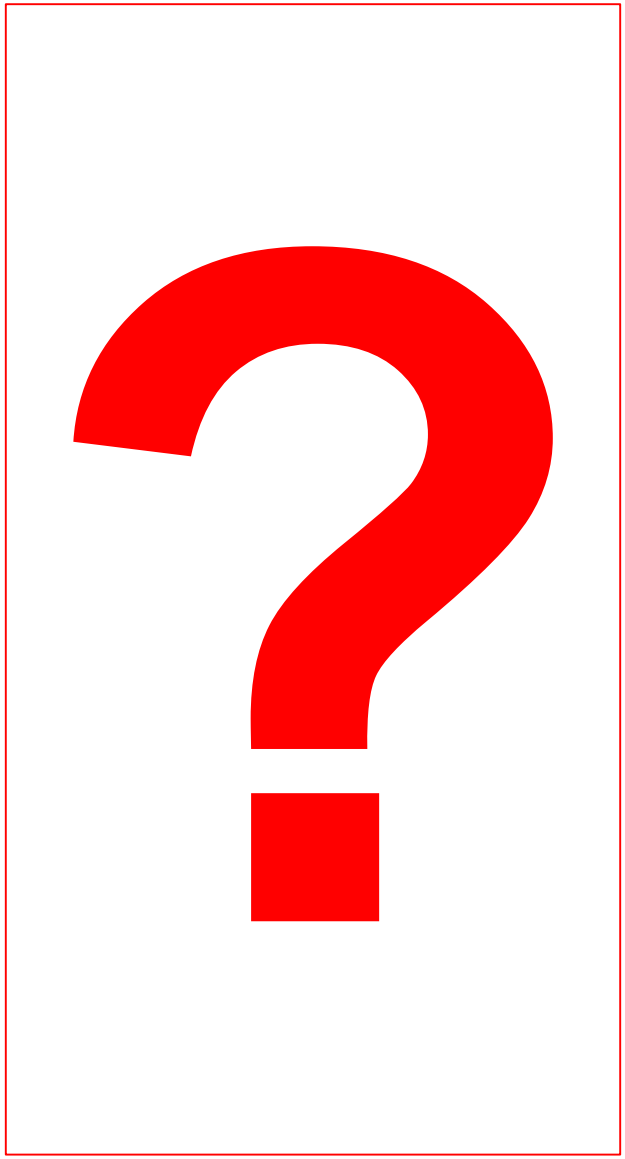
1. Physiological bases

2. Epidemiology

3. Heart Failure - Clinical features and Treatment

4. Outcome

5. Sex-related prognostic predictors



CONCLUSIONS

- Male sex is a negative predictive factor for both HFrEF and DCM (also after adjustment for baseline features). Women present poorer outcome only post-MI HFrEF
- Additional years of life are of poorer quality in women
- Hurdles and challenges
  - *awareness of CV disease, aspecific symptoms, differences in access to healthcare, less caregiver support or living alone, socio-economic and educational factors*
  - *underrepresentention in RCTs*
  - *undertreatment with implantable devices*
  - *Sex-specific prognostic tools for different management*
- **No different therapy but need of different approach towards personalized medicine**

GRAZIE