IL CUORE INSUFFICIENTE NEI GENERI: DIFFERENTI FENOTIPI?

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The European Journal of Heart Failure

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Gender related differences in patients presenting with acute heart failure. Results from EuroHeart Failure Survey II

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Gender Differences in In-Hospital Management and Outcomes in Patients With Decompensated Heart Failure: Analysis From the Acute Decompensated Heart Failure National Registry (ADHERE)

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CATHERINE GALVIN, MSN, ANP-C,[5] JALAL K. GHALI, MD,[6] AND ROBERT M. MOSKOWITZ, MD,[7]
ON BEHALF OF THE ADHERE SCIENTIFIC ADVISORY COMMITTEE, INVESTIGATORS,
COORDINATORS, AND STUDY GROUP

Bronx, New York; New York, New York; San Francisco, California; Los Angeles, California; White Plains, New York; Shreveport, Louisiana; Fairfield, Connecticut

Age- and Gender-Related Differences in Quality of Care and Outcomes of Patients Hospitalized With Heart Failure (from OPTIMIZE-HF)

Gregg C. Fonarow, MD[a,*], William T. Abraham, MD[b], Nancy M. Albert, PhD, RN[c],
Wendy Gattis Stough, PharmD[d], Mihai Gheorghiade, MD[e], Barry H. Greenberg, MD[f],
Christopher M. O'Connor, MD[g], Jie Lena Sun, MS[h], Clyde Yancy, MD[i], and James B. Young, MD[j];
for the OPTIMIZE-HF Investigators and Hospitals

Baseline characheristic by gender: from "EURO HEART FAILURE SURVEY II"

	Male (n = 2.196)	Female (n= 1.384)	P value or OR (95% CI)
Age	67.8	73.1	< 0.0001
Coronary artery disease (%)	59.6 %	44.1 %	0.54 (0.47–0.61)
Dilated cardiomyopathy	22.3%	14.5 %	0.59 (0.49–0.70)
Hypertension (%)	59.4%	67.4%	1.41 (1.23–1.63)
Diabetes mellitus	31.4%	35.0%	1.18 (1.02–1.36)
COPD	22.1%	15.0%	0.62 (0.52–0.74)
Thyroid disease	4.4%	11.1%	2.69 (2.07–3.50)

Nieminen et al. European Journal of Heart Failure. 2008;10:140-148

Clinical characteristics by Sex: from ADHERE REGISTRY (N= 105.388)

	Male (n = 50.713)	Female (n= 54.674)	P value
Age , years	70.1 ± 14	74.1 ± 14	< .0001
LVEF % (mean)	32.9 ± 15.8	42.2 ± 17.3	< .0001
EF > 40%	28 %	51 %	< .0001
Ischemic etiology	32 %	19 %	< .0001
Coronary artery disease	64 %	51%	< .0001
Hypertension	70 %	76%	< .0001
Thyroid disease	11%	24%	< .0001
Diabetes mellitus	44%	44%	.170
Atrial fibrillation	31%	30%	.0009

Galvao M, et al. J Card Fail. 2006;12:100-7

The ADHERE database provides information on both diastolic and systolic dysfunction

HF with 'preserved' EF (LVEF > 40%) n = 25,256

Women were *older*

(75.4 ys vs 71.8 ys; P < .0001)

had a higher mean LVEF

(56.9% vs 54.1%;

P < .0001)

HF with LV systolic dysfunction n = 45,607

Also in this cohort *women were older* than men

(72.4 ys vs 68.9 ys, p < .0001)

The mean LVEF was higher in women than in men

(27.0% versus 24.7%; P < .0001)

Galvao M, et al. J Card Fail. 2006;12:100-7

One of the most notable sex-related differences in HF is that most women have HF with preserved ejection fraction (HFpEF), whereas men have HF with reduced ejection fraction (HFrEF).

Why are women more likely than men to have higher EF?

Sex-Related Differences in Myocardial Function and Remodeling

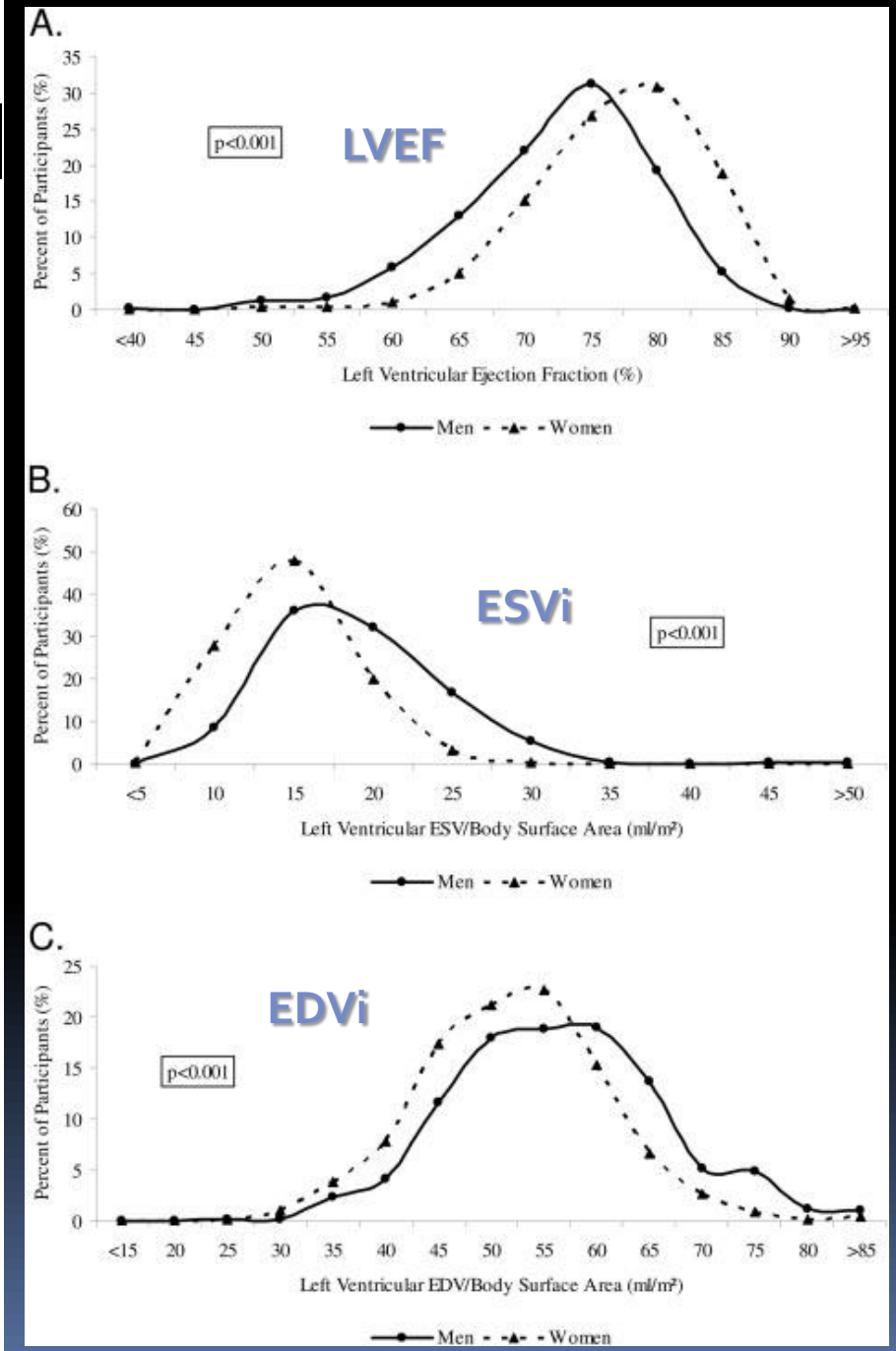
Women Have Higher Left Ventricular Ejection Fractions Than Men Independent of Differences in Left Ventricular Volume

The Dallas Heart Study

Anne K. Chung, BS; Sandeep R. Das, MD, MPH; David Leonard, PhD; Ronald M. Peshock, MD; Farhana Kazi, MD; Shuaib M. Abdullah, MD; Russell M. Canham, MD; Benjamin D. Levine, MD; Mark H. Drazner, MD, MSc

Using cardiac magnetic resonance imaging in a probability-based sample of Dallas County residents aged 30 to 65 years (1435 women and 1183 men), they compared LVEF in women and men

Circulation. 2006;113:1597-1604



The median (25th, 75th percentile) LVEF was 75% in women versus 70% in men (*P < .001)*

The corresponding partition values defining 'abnormal ejection fraction' (defined as below the 2.5th percentile of a healthy subset of the DHS) in women are therefore correspondingly higher (<61% in women vs. <55% in men)

These data suggests that many women with ejection fraction 50–60% may in fact have *systolic dysfunction.*

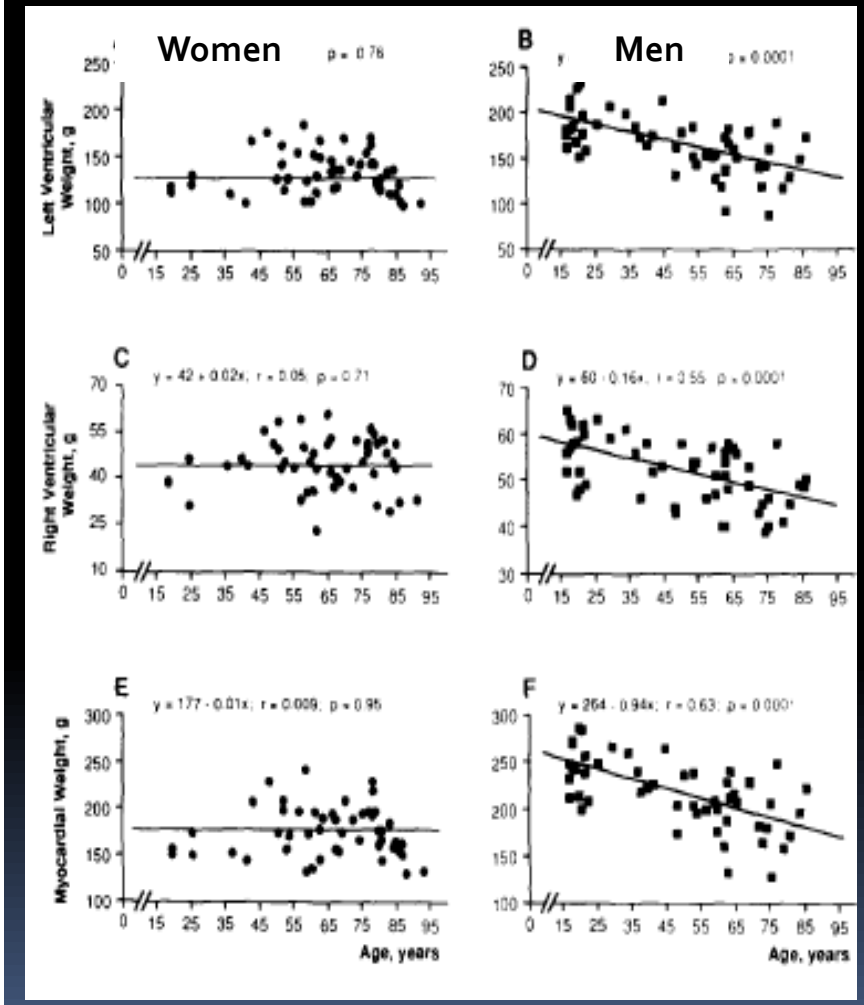
Circulation. 2006;113:1597-1604

Aging Cardiomyopathy

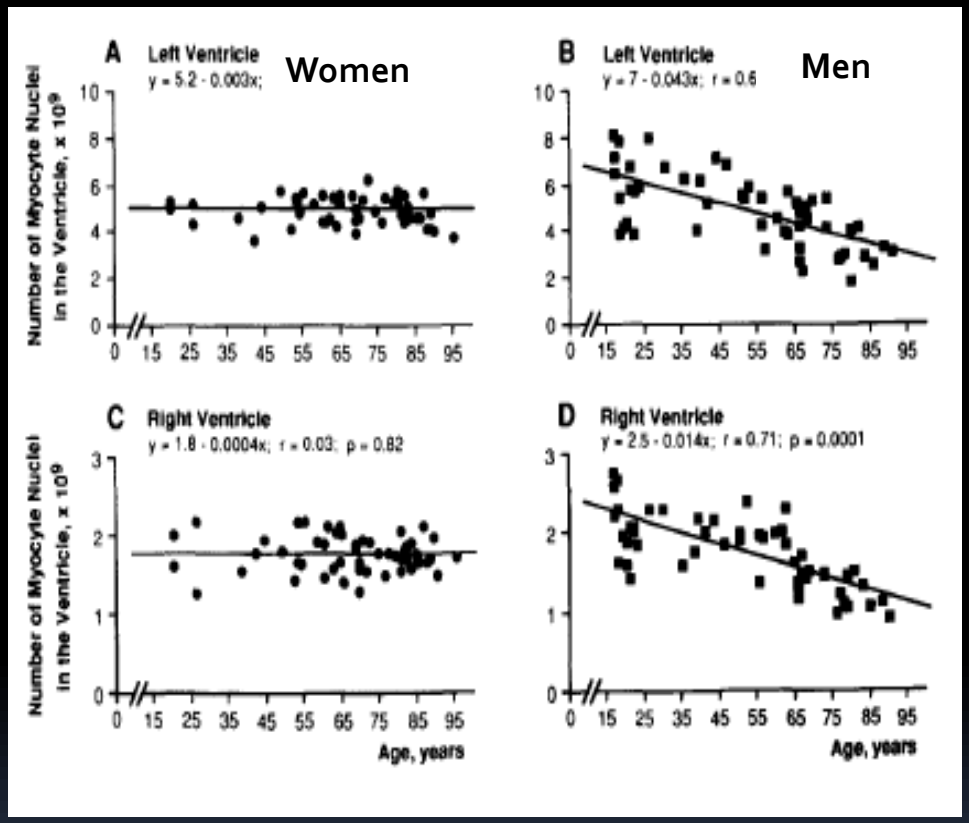
Women	Men
Preservation of cardiac weight	Reduction in cardiac weight (1g/year)
Preservation in myocyte number	Reduction in myocyte number (64 million/year)
Preservation in myocyte volume	Increase in myocyte volume
Low apoptotic index	Apoptotic index 3-fold higher than women

Aging Cardiomyopathy

Men experience loss of myocardium at the rate of 1 g per year across the lifespan, whereas left ventricular mass is preserved in women



Effects of aging on cardiac weight in women and men



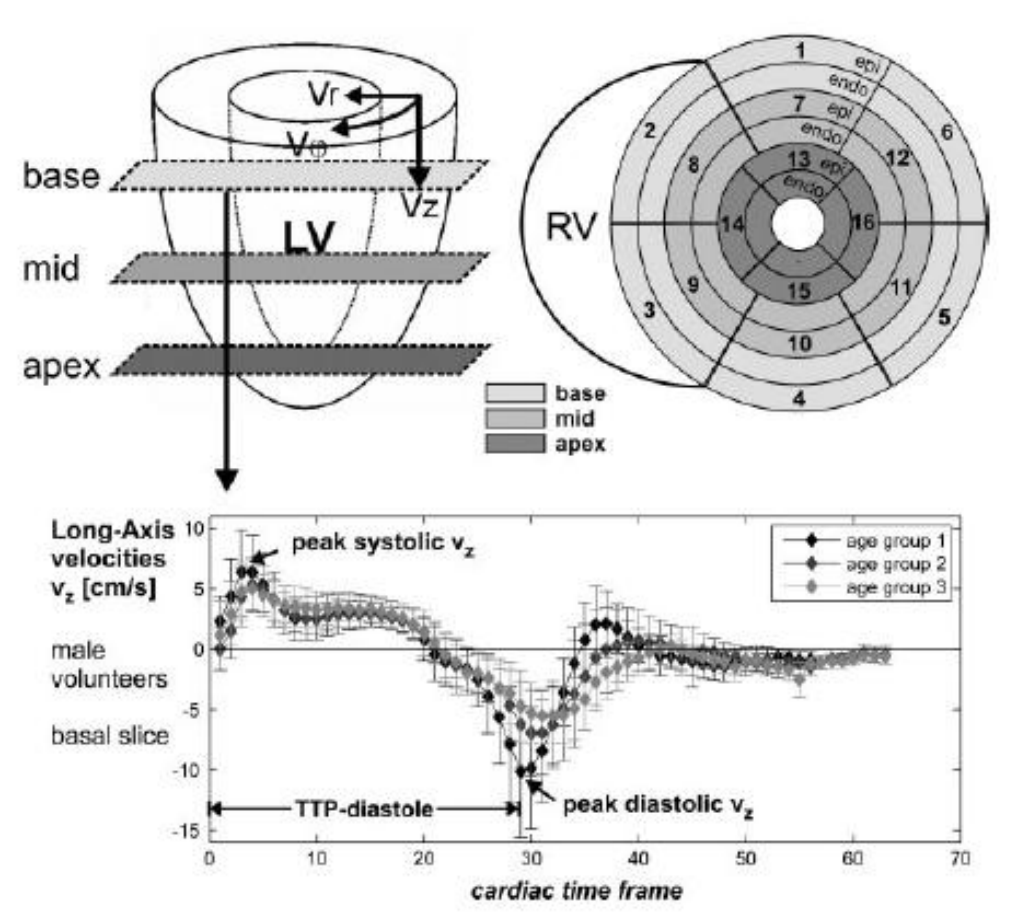
Effects of aging on the total number of ventricular myocyte nuclei in women and men.

Olivetti G, Giordano G et al. JACC 1995 (26) 1068-1079

Magnetic Resonance Tissue Phase Mapping of Myocardial Motion

New Insight in Age and Gender

Daniela Föll, MD; Bernd Jung, PhD; Elfriede Schilli, MD; Felix Staehle, PhD; Annette Geibel, MD; Jürgen Hennig, PhD; Christoph Bode, MD; Michael Markl, PhD



Magnetic resonance phase-contrast imaging (tissue phase mapping) enabling the analysis of segmental, 3-directional myocardial velocities with high temporal resolution was used to assess left ventricular motion.

Radial, long-axis, and rotational myocardial velocities were acquired in 58 healthy volunteers (3 age groups, 29 women) in left ventricular basal, midventricular, and apical short-axis locations

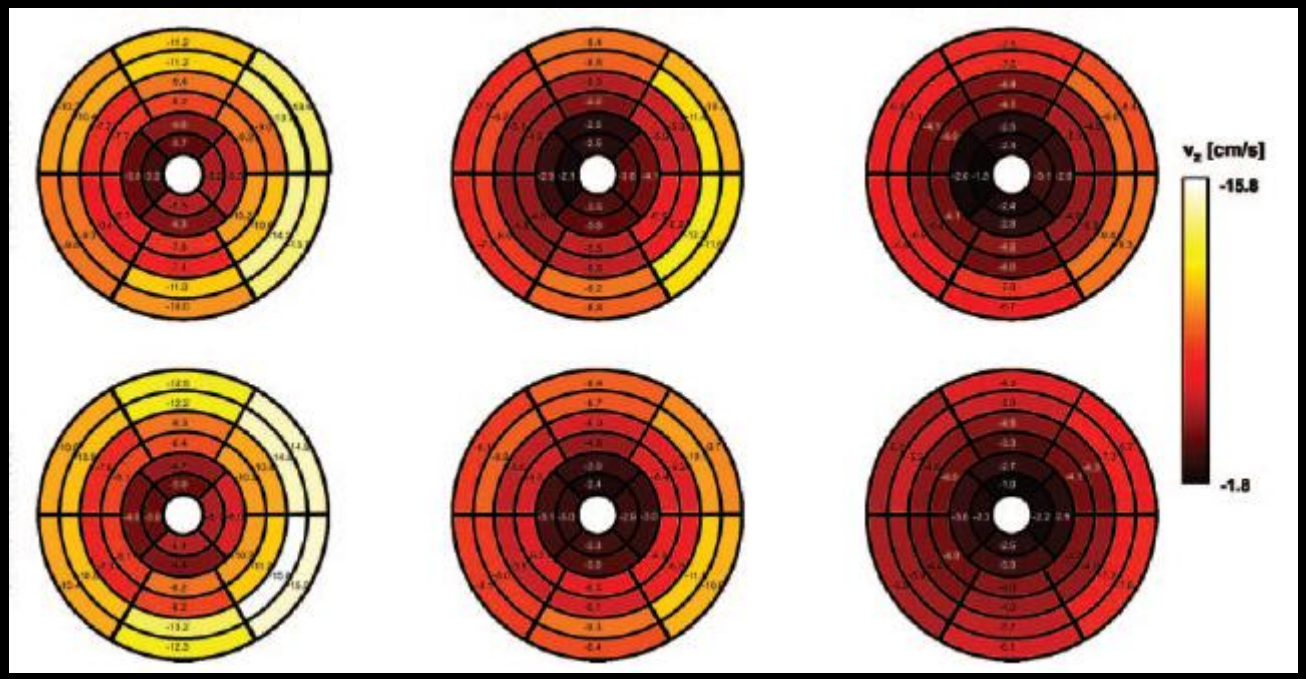
Circ Cardiovasc Imaging. 2010;3:54-64

long-axis peak diastolic velocities

Age group 20-40 | Age group 40-60 | Age group > 60

Male

Female

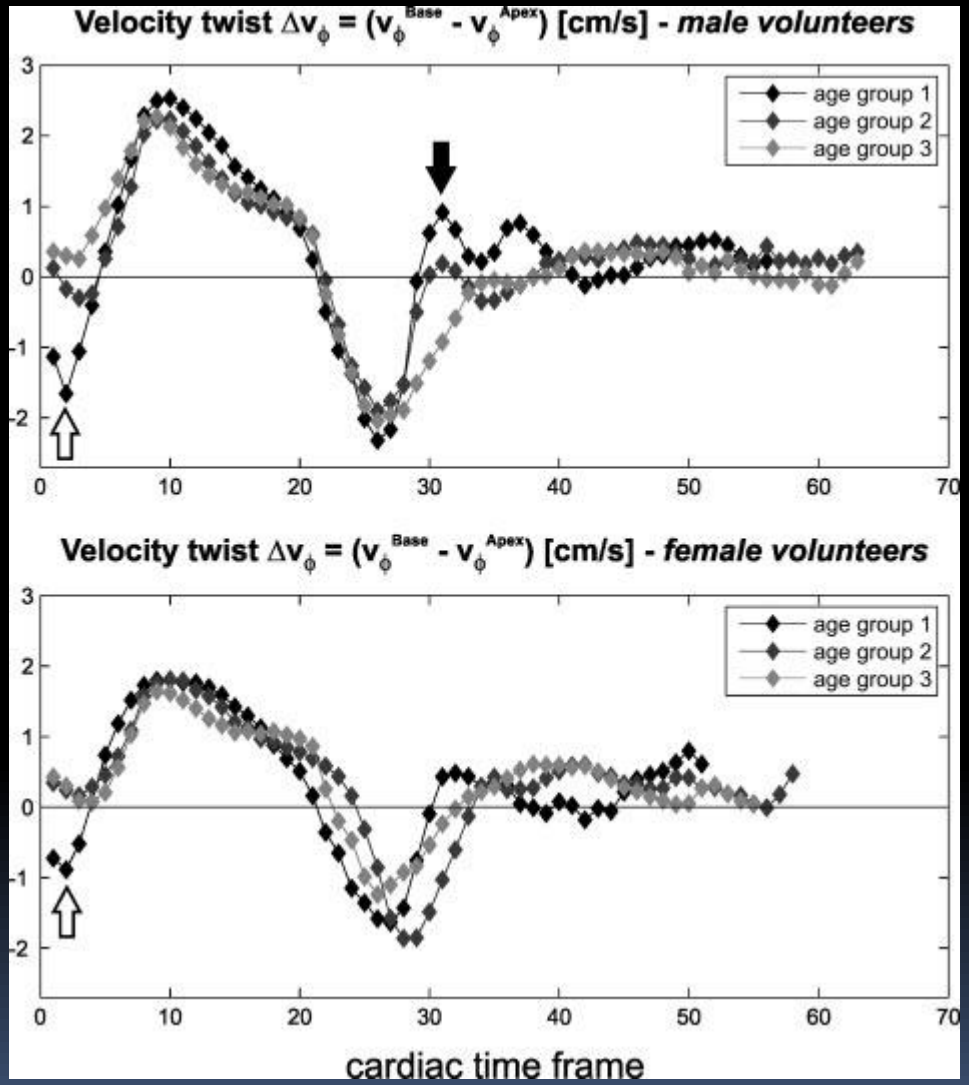


The authors noted that younger women (20–40 years) display enhanced diastolic function compared with young men, however, in the older cohorts, the sex disparities became inverted.

Above the age of 60 years, women displayed substantially greater loss in long-axis diastolic lengthening velocities compared with men (20% lower)

Circ Cardiovasc Imaging. 2010;3:54-64

Apical Rotation and Velocity Twist



Systolic twist was considerably lower in women (2.05 cm/s) compared with men (2.46 cm/s, *p =0.009)*

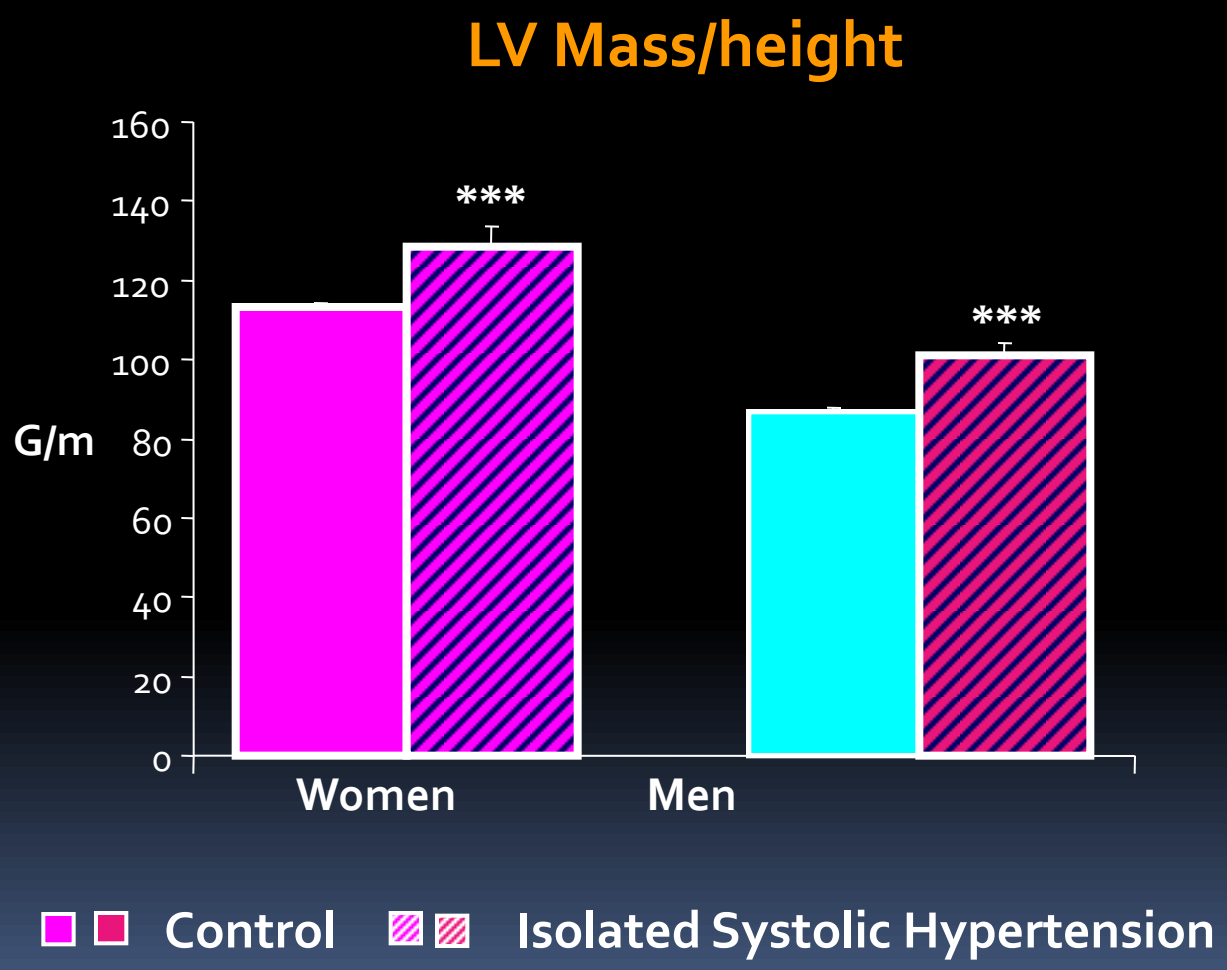
Systolic apical rotation demonstrated an age-related decrease and significant delay (p *<0.05) regarding peak velocities during* systole for both genders, whereas twist was only reduced in women with increased age (*P =0.02, group 1 versus group 3).*

Circ Cardiovasc Imaging. 2010;3:54-64

Myocardial response to pressure/volume overload

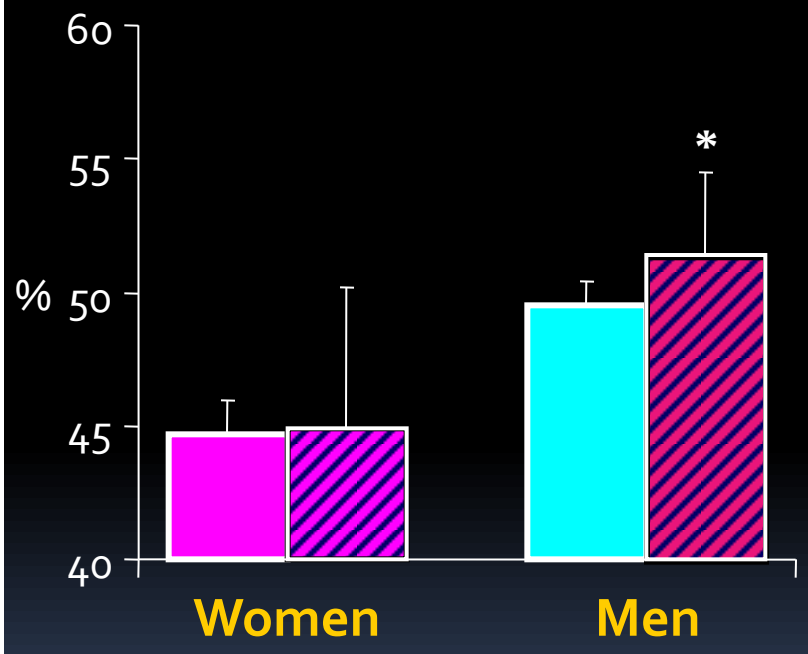
Women	Men
Smaller end-diastolic and -systolic volumes	Larger end-diastolic and -systolic volumes
Greater LV mass/volume ratio	Lower LV mass/volume ratio
Concentric hypertrophy	Significant ventricular dilation
Preserved LV function	Impaired LV function
Later onset of impaired systolic pump performance	*Earlier onset of impaired systolic pump performance*
Greater degree of LVH	Lower degree of LVH

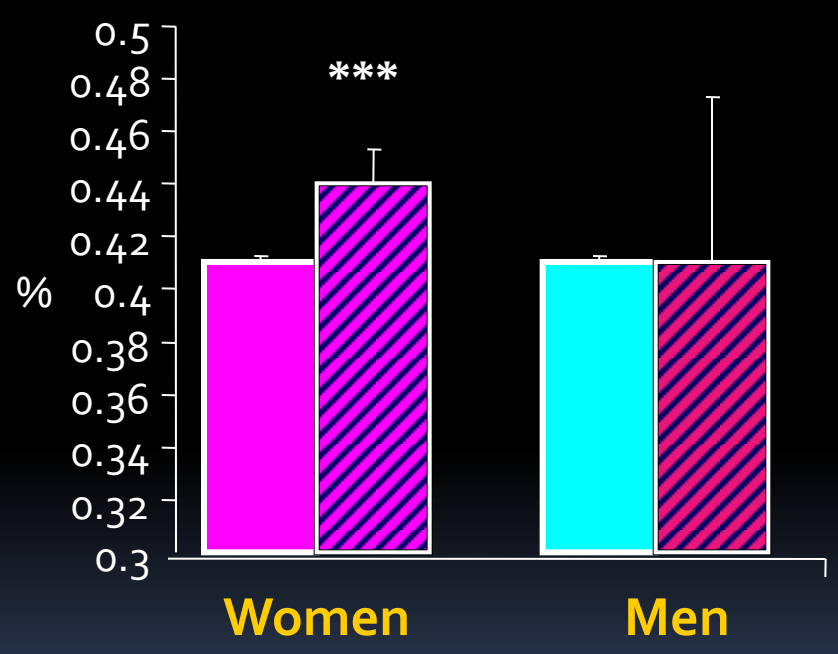
Sex Differences in Cardiac Adaptation to Isolated Systolic Hypertension



Krumholz et al., Am J Cardiol 1993; 72:310

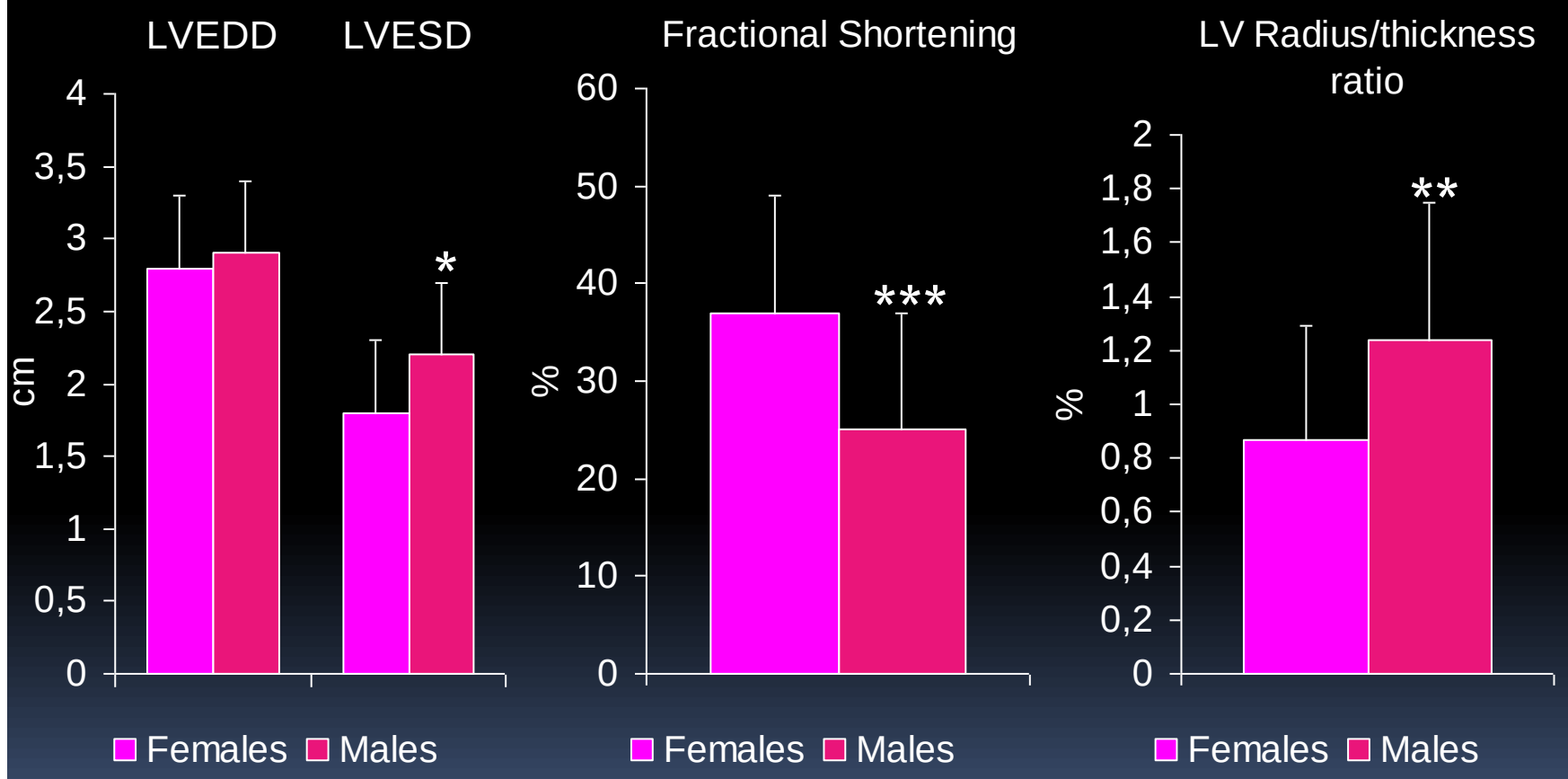
Sex Differences in Cardiac Adaptation to Isolated Systolic Hypertension





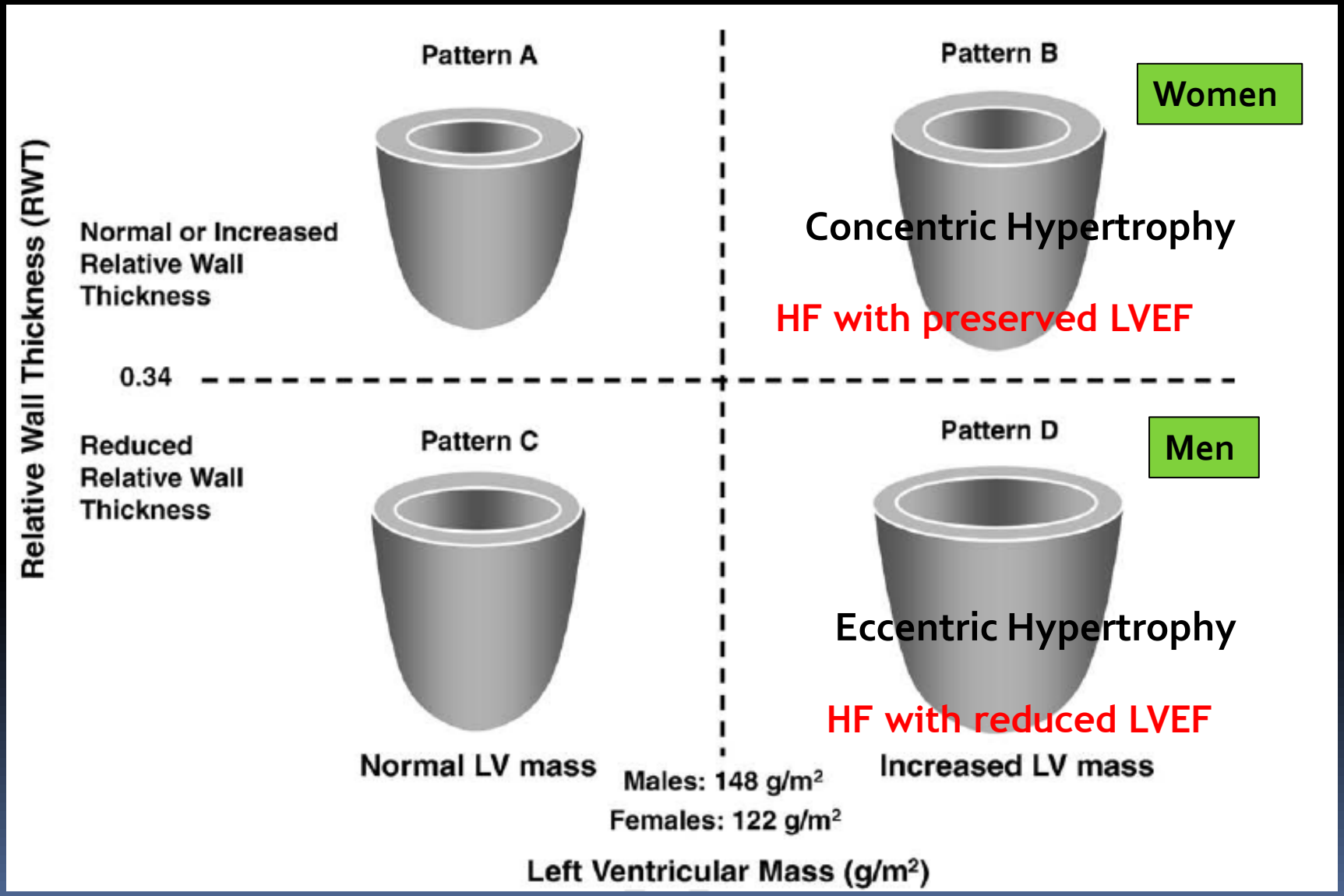
Krumholz et al., Am J Cardiol 1993; 72:310

Sex-associated Differences in LV function in Aortic Stenosis of the Elderly

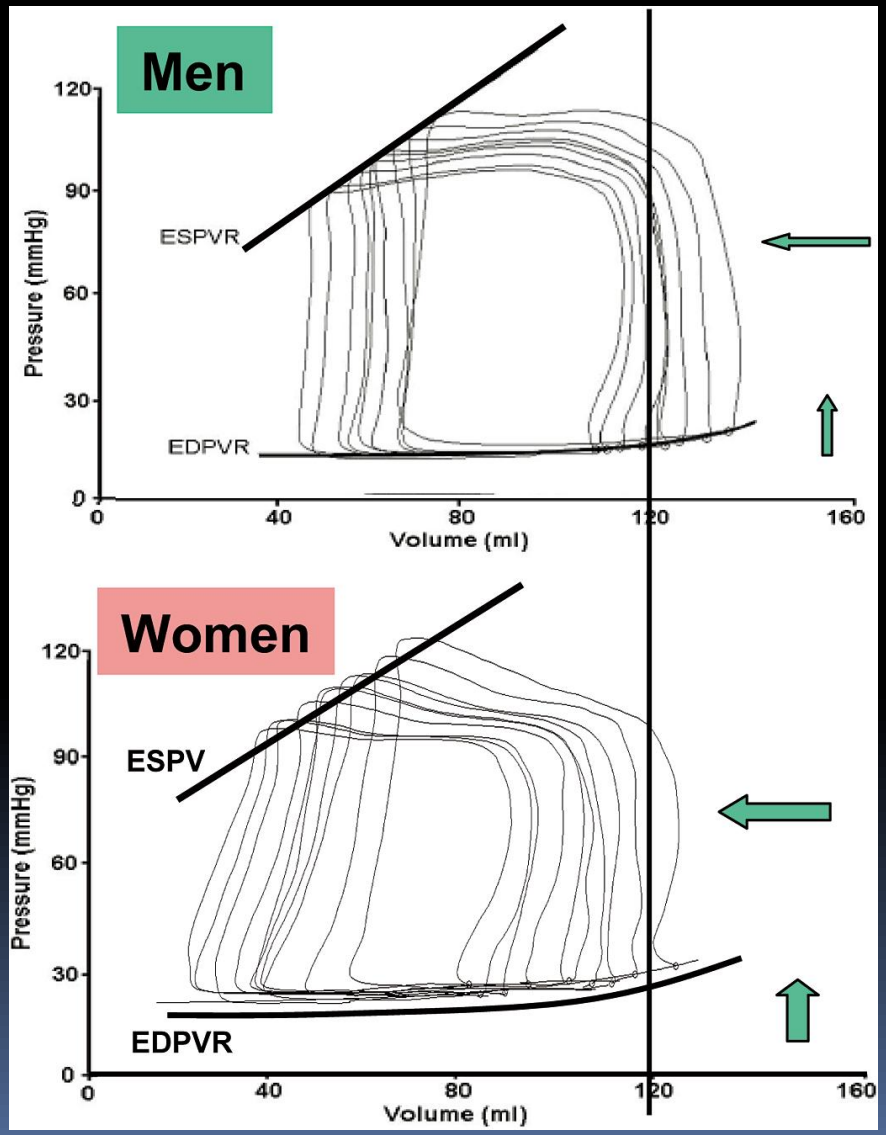


Carroll J, et al. Circulation 1992; 86:1099

Sex-Related Differences in Myocardial Remodeling



Sex-Related Differences in Myocardial Remodeling



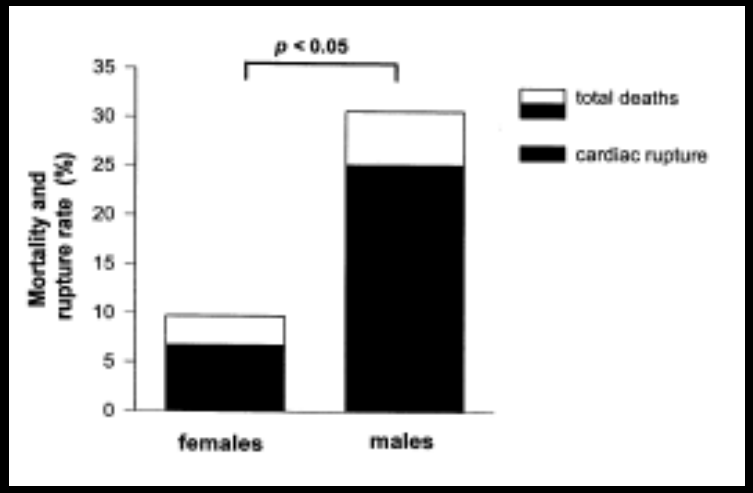
Concentric chamber remodeling with pressure-overload normalizes left ventricular wall stress according to the law of Laplace, but this occurs at the cost of *impairing diastolic chamber compliance and relaxation*

Myocardial response to Acute Myocardial Ischemia

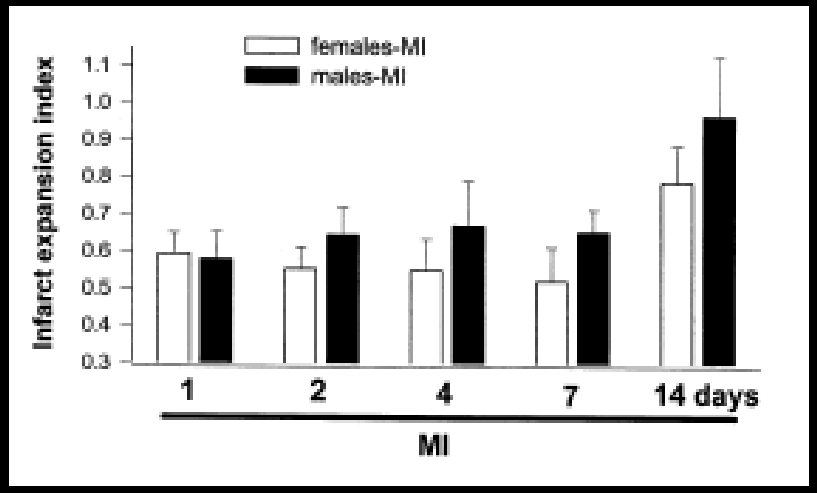
Women	Men
Lower apoptotic rate in peri-infarct region	10-fold higher apoptotic rate in peri-infarct region
Lower bax expression in peri-infarct region	Greater bax expression in peri-infarct region
Earlier myocardial healingd Lower infarct expansion index Better cardiac function Better remodeling	Higher infarct expansion index Greater incidence in cardiac rupture Worse cardiac function Maladaptive remodeling

Myocardial Remodeling in CAD

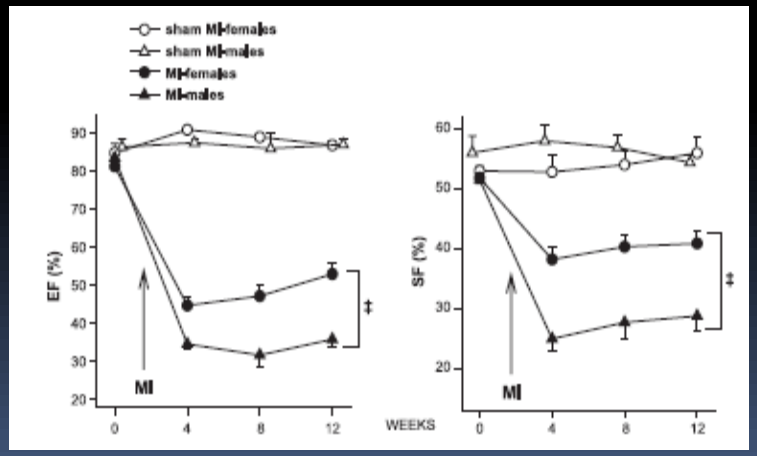
Differences in mortality, infarct expansion index and LV diameters and function between male and female mice after AMI



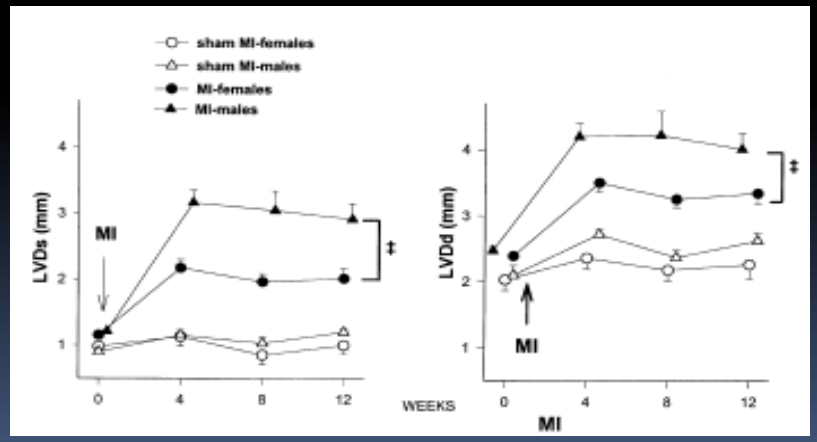
Mortality and rupture rate in acute phase



Infarct expansion index during the first 2 weeks post MI



EF and SF in mice with and without MI



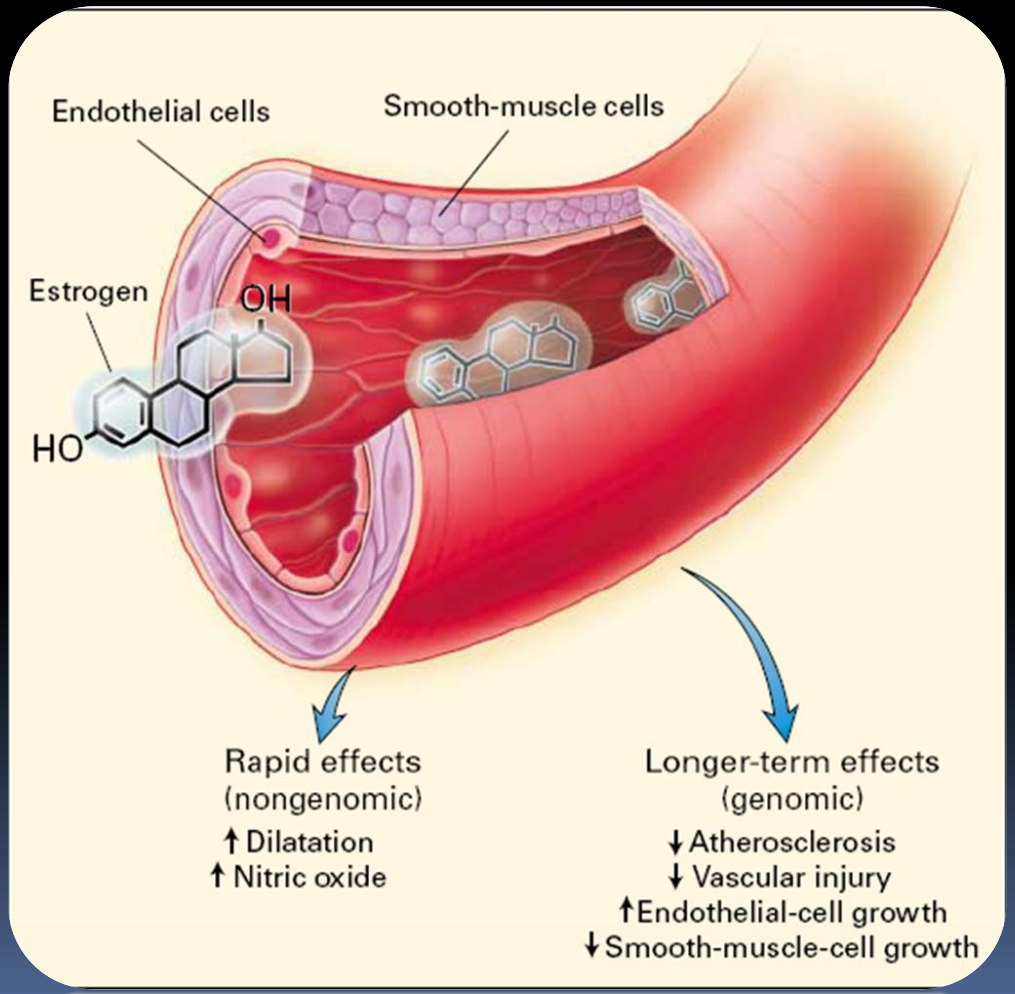
LVESD and LVEDD in mice with and without MI

Cavasin MA et al- *Life Sci* 2004;75: 2181-92

Sex-Related Differences in Myocardial Function and Remodeling:

Is there a role of different hormonal profile?

Cardiovascular effects of estrogen



Vascular endothelial and smooth-muscle cells express the two known ERs: ERs-alpha and ERs-beta.

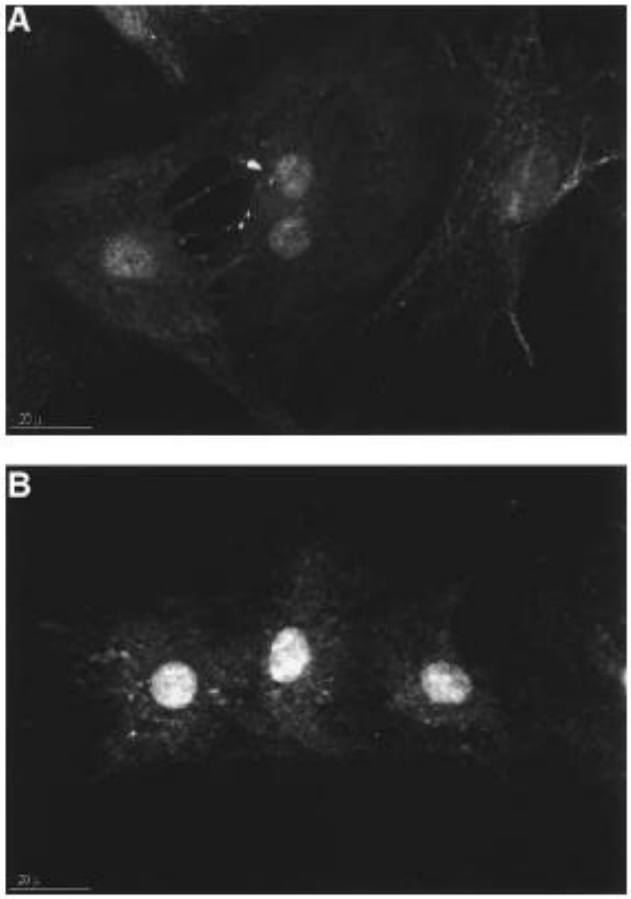
Estrogen have both rapid vasodilatory effects and longer-term actions that inhibit the response to vascular injury and prevent atherosclerosis

Cardiac myocytes and fibroblasts contain functional estrogen receptors

Christian Grohé[a,*], Stefan Kahlert[a], Kerstin Löbbert[a], Michael Stimpel[a], Richard H. Karas[c], Hans Vetter[a], Ludwig Neyses[b]

[a] *Medizinische Univ.-Poliklinik, University of Bonn, Wilhelmstr. 35–37, 53111 Bonn, Germany*
[b] *Department of Medicine, University of Würzburg, Würzburg, Germany*
[c] *Molecular Cardiology Research Center, New England Medical Center, Tufts University School of Medicine, Boston, MA 02111, USA*

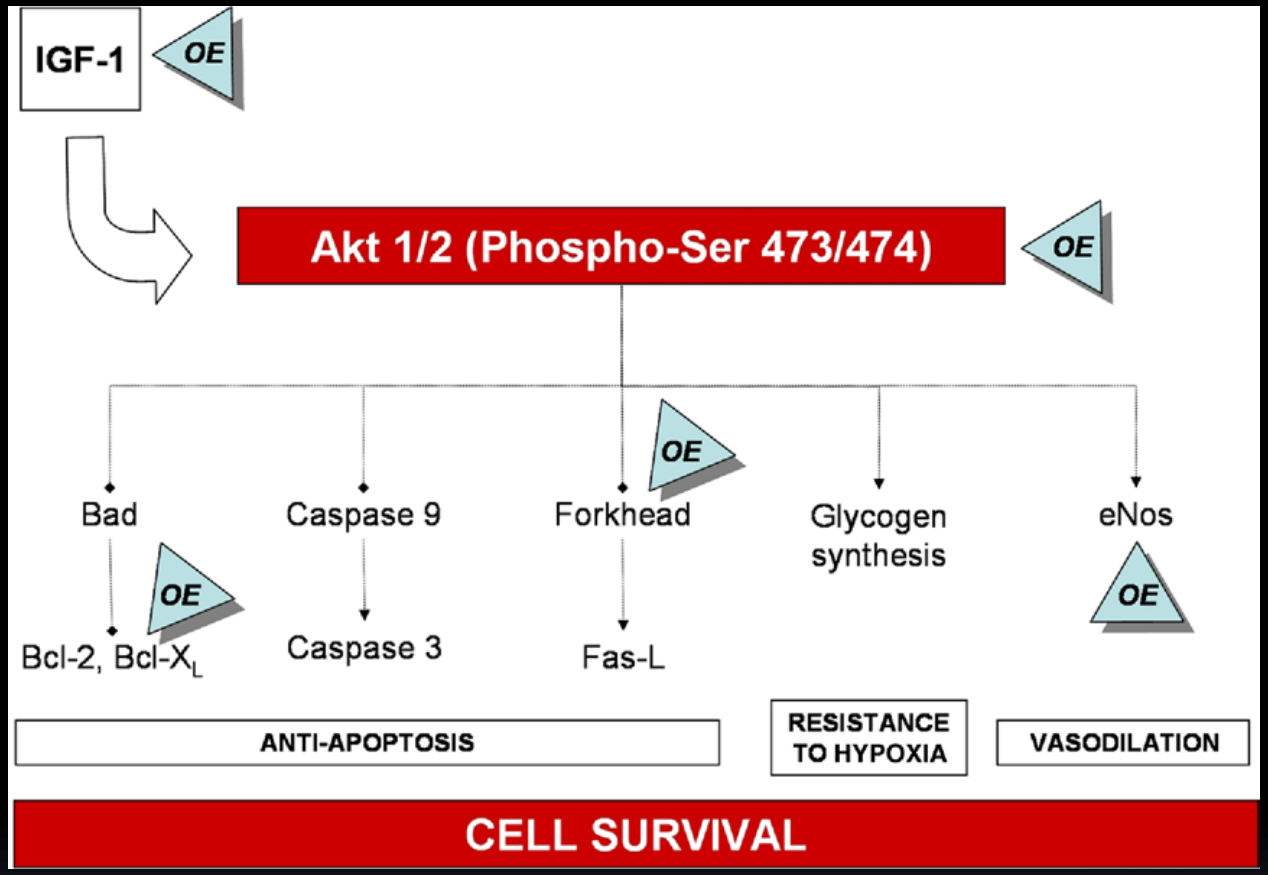
Received 25 August 1997



Cardiac myocytes and cardiac fibroblasts also express functional ERs-α and ERs-β , and this activation downstream targets genes that play a key role in:

- Myocyte survival and apoptosis
- Left ventrticular Hypertrophy

Estrogens and apoptosis



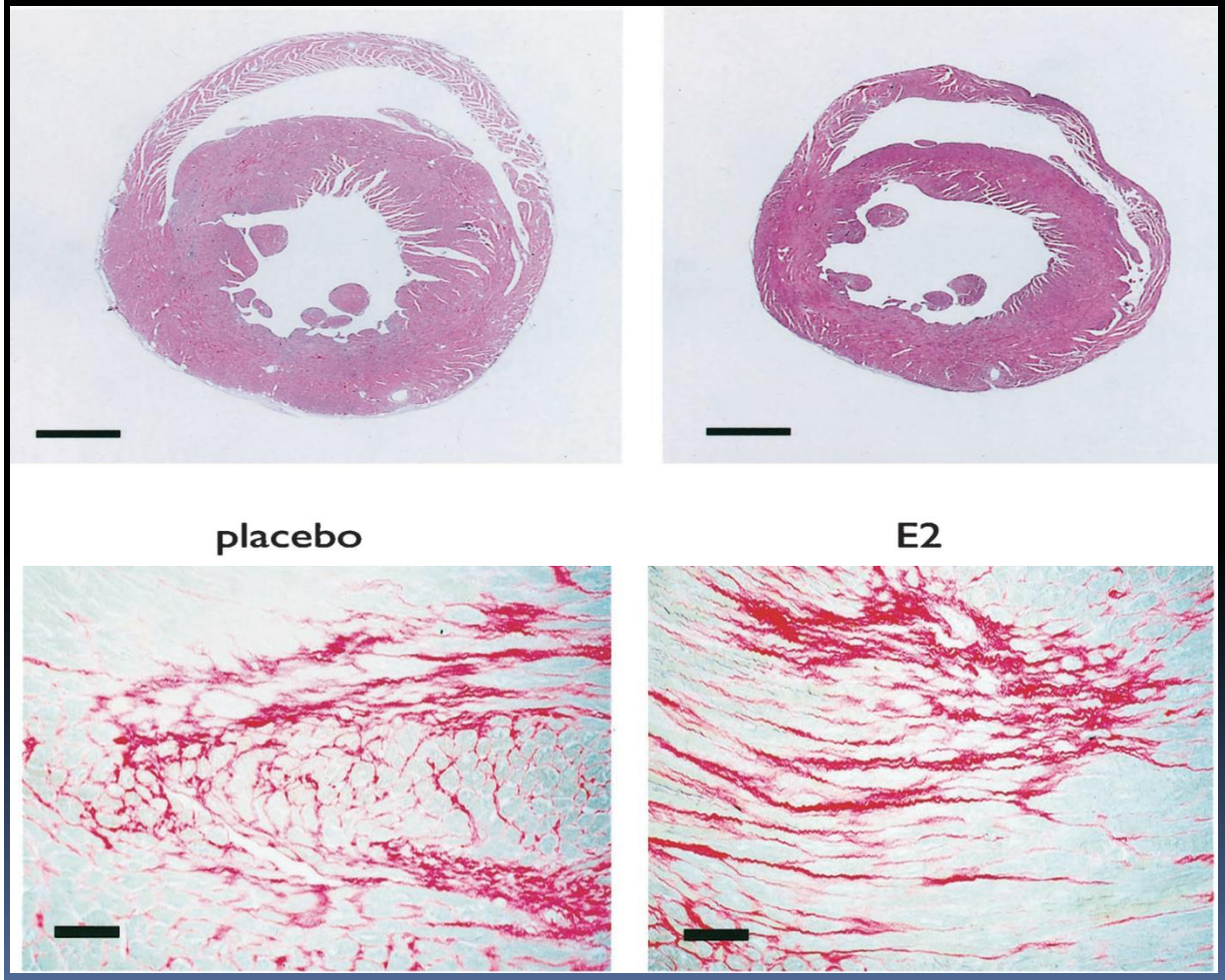
Akt (also known as protein kinasi B) prevents initiation of the mitochondrial pathway of apoptosis

Akt1/2 is overexpressed in the nuclei of the cardiac myocytes of adult pre-menopausal women.

Estrogen may improve cell survival directly enhancing the phosphorilation of insulin-like growth factor-1 receptors (IGF-1R) (a proven stimulus for Akt activation) and indirectly enhancing the expression of antiapoptotic gene products, such as Bcl-2 and Bcl-X, and decreasing the induction of proapoptotic proteins, such as Bax.

17β-Estradiol Attenuates the Development of Pressure-Overload Hypertrophy

Martin van Eickels, MD; Christian Grohé, MD; Jack P.M. Cleutjens, PhD; Ben J. Janssen, PhD; Hein J.J. Wellens, MD; Pieter A. Doevendans, MD



Estrogens and hypertrophy

They demonstrated that greater LVH developed in female ovariectomized mice in a model of pressure overload than ovariectomized mice with replacement of physiological levels of 17-estradiol.

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SI

Hanno un impatto sull’outcome?

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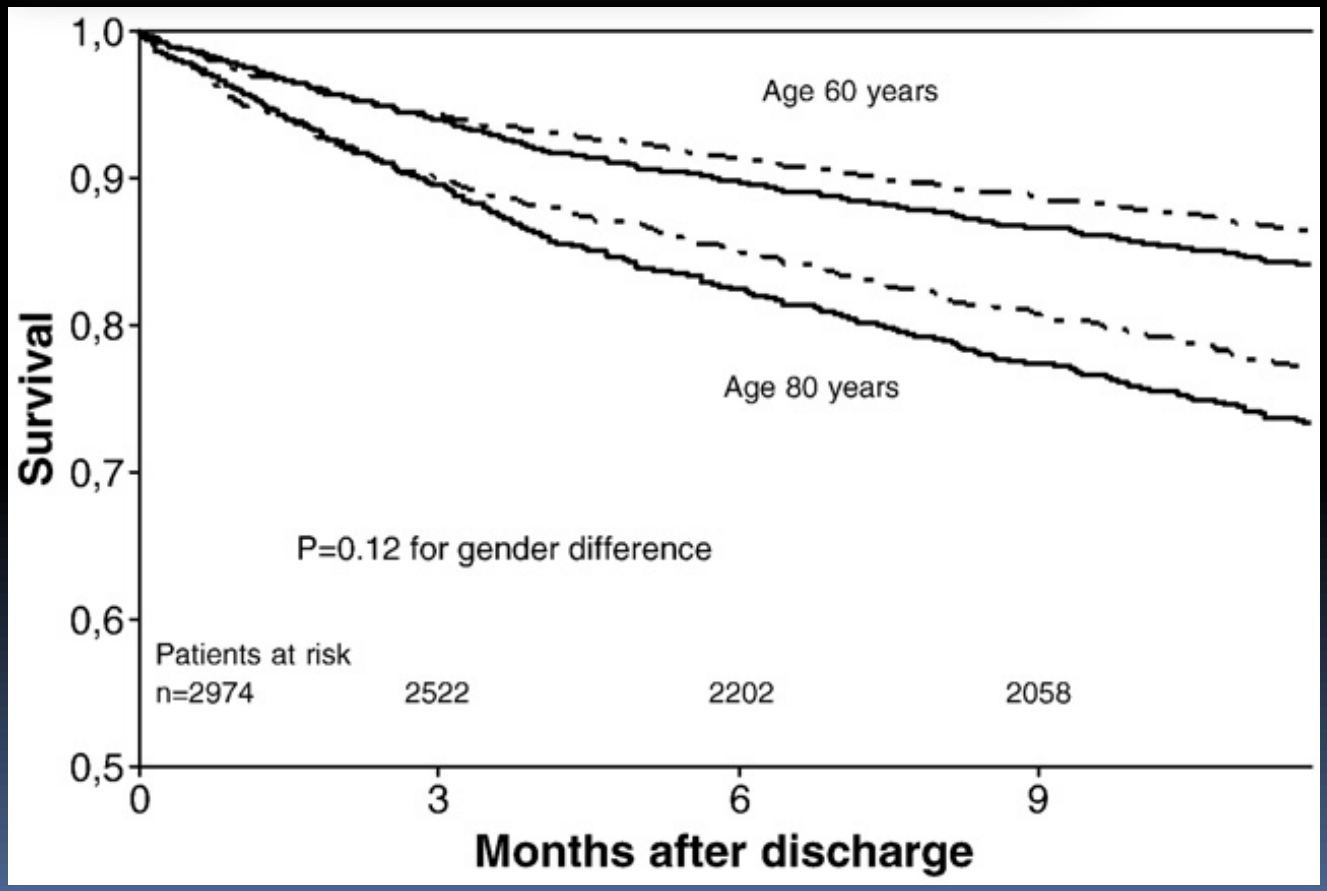
Gender related differences in patients presenting with acute heart failure. Results from EuroHeart Failure Survey II

Markku S. Nieminen [a,*], Veli-Pekka Harjola [a], Matthias Hochadel [f], Helmut Drexler [d], Michel Komajda [g], Dirk Brutsaert [b], Kenneth Dickstein [c], Piotr Ponikowski [i], Luigi Tavazzi [j], Ferenc Follath [e], Jose Luis Lopez-Sendon [h]

Expected survival curves for 60 and 80 year old men and women hospitalized for acute heart failure.



Despite the older age of the female patients, there were no gender differences in the in mortality rates

Nieminen et al. European Journal of Heart Failure. 2008;10:140-148

Gender Differences in In-Hospital Management and Outcomes in Patients With Decompensated Heart Failure: Analysis From the Acute Decompensated Heart Failure National Registry (ADHERE)

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Bronx, New York; New York, New York; San Francisco, California; Los Angeles, California; White Plains, New York; Shreveport, Louisiana; Fairfield, Connecticut

Mortality Odds Ratio* Female vs Males

	OR (95% CI)	p value
ADHERE population	0.974 (0.910–1.042)	.4390
Diastolic dysfunction	1.008 (0.869–1.169)	.9177
Systolic dysfunction	0.992 (0.894–1.100)	.8756

* All values were adjusted for covariates: age, blood urea nitrogen, systolic blood pressure, diastolic blood pressure, sodium, pulse, dyspnea at rest, and creatinine.

Approccio diagnostico e terapeutico

Investigations and procedures performed during hospitalisation	Total (%)	Female (%)	Male (%)	OR (95%-CI)
Echocardiography	79.8	78.4	80.8	0.97 (0.82–1.15)[b]
Exercise testing	4.4	2.6	5.6	0.54 (0.37–0.80)[b]
Holter monitoring	12.5	10.7	13.6	0.82 (0.66–1.02)[b]
Arterial line	8.1	7.3	8.7	0.85 (0.66–1.10)[b]
Pulmonary artery catheter	5.3	4.6	5.7	0.98 (0.72–1.35)[b]
IABP	2.2	1.6	2.6	0.80 (0.47–1.35)[c]
Thrombolysis	3.4	2.5	3.9	0.74 (0.48–1.15)[c]
Coronary angiography	36.5	31.0	39.9	0.78 (0.67–0.91)[c]
PCI	8.4	7.3	9.2	0.72 (0.46–1.11)[c]
CABG	1.8	1.4	2.1	0.69 (0.39–1.19)[c]
Heart transplantation [a]	2.0	1.3	2.4	0.77 (0.44–1.34)[b]
Blood transfusion	5.9	7.2	5.0	1.32 (0.99–1.76)[b]
– Because of bleeding	27.1	19.0	34.5	
BNP/NT-proBNP tested	16.3	15.3	16.9	1.09 (0.91–1.32)[b]

Nieminen et al. Gender related differences in patients presenting with acute heart failure. Results from EuroHeart Failure Survey II. European Journal of Heart Failure. 2008;10:140-148

Management of patients with heart failure in clinical practice: differences between men and women (Euro Heart Survey)

			Gender differences		
			Unadjusted OR* (95% CI)	OR* adjusted for age (95% CI)	Adjusted OR* (95% CI)†
Total population (n = 8914)	*Men (n = 4748) (%)*	*Women (n = 4166) (%)*			
ACE-inhibitors	69	60	0.67 (0.62 to 0.74)	0.77 (0.70 to 0.84)	0.70 (0.64 to 0.77)
β-Blockers	41	32	0.70 (0.65 to 0.77)	0.86 (0.79 to 0.94)	0.90 (0.83 to 0.99)
Spironolactone	26	19	0.67 (0.61 to 0.75)	0.76 (0.69 to 0.85)	0.77 (0.69 to 0.85)
Diuretics	85	88	1.25 (1.11 to 1.42)	1.07 (0.94 to 1.22)	1.05 (0.92 to 1.19)
Cardiac glycosides	38	40	1.12 (1.03 to 1.22)	1.09 (1.00 to 1.19)	1.06 (0.97 to 1.17)
Antithrombotic agents	82	75	0.65 (0.58 to 0.71)	0.67 (0.60 to 0.74)	0.71 (0.63 to 0.79)
Patients with LVSD (n = 3584)	*Men (n = 2490) (%)*	*Women (n = 1094) (%)*			
ACE-inhibitors	80	74	0.71 (0.60 to 0.84)	0.77 (0.65 to 0.91)	0.72 (0.61 to 0.86)
β-Blockers	49	39	0.66 (0.57 to 0.77)	0.76 (0.66 to 0.88)	0.76 (0.65 to 0.89)
Spironolactone	32	25	0.69 (0.59 to 0.81)	0.77 (0.65 to 0.91)	0.75 (0.64 to 0.89)
Diuretics	88	89	1.18 (0.94 to 1.47)	1.06 (0.84 to 1.34)	1.04 (0.82 to 1.32)
Cardiac glycosides	41	45	1.16 (1.05 to 1.28)	1.15 (1.04 to 1.28)	1.27 (1.13 to 1.42)
Antithrombotic agents	87	83	0.66 (0.59 to 0.75)	0.65 (0.57 to 0.74)	0.76 (0.66 to 0.87)
Patients with PLVF (n = 2396)	*Men (n = 4082) (%)*	*Women (n = 2904) (%)*			
ACE-inhibitors	60	58	0.91 (0.77 to 1.07)	0.93 (0.79 to 1.10)	0.86 (0.72 to 1.02)
β-Blockers	40	36	0.85 (0.72 to 1.00)	0.95 (0.80 to 1.12)	0.98 (0.82 to 1.18)
Spironolactone	17	20	1.22 (0.99 to 1.50)	1.24 (1.00 to 1.54)	1.22 (0.98 to 1.52)
Diuretics	78	88	2.03 (1.63 to 2.53)	1.74 (1.39 to 2.18)	1.64 (1.30 to 2.07)
Cardiac glycosides	28	37	1.45 (1.22 to 1.73)	1.37 (1.14 to 1.63)	1.30 (1.06 to 1.58)
Antithrombotic agents	83	77	0.72 (0.59 to 0.88)	0.71 (0.58 to 0.88)	0.76 (0.61 to 0.94)

LVSD, left ventricular systolic dysfunction; PLVF, preserved left ventricular function.
*OR >1 correlates with a higher prevalence in women.
†Adjusted for age, hypertension, diabetes, stroke or transient ischaemic attack (TIA), renal failure, respiratory disease, coronary artery disease, cardiomyopathy, and atrial fibrillation.

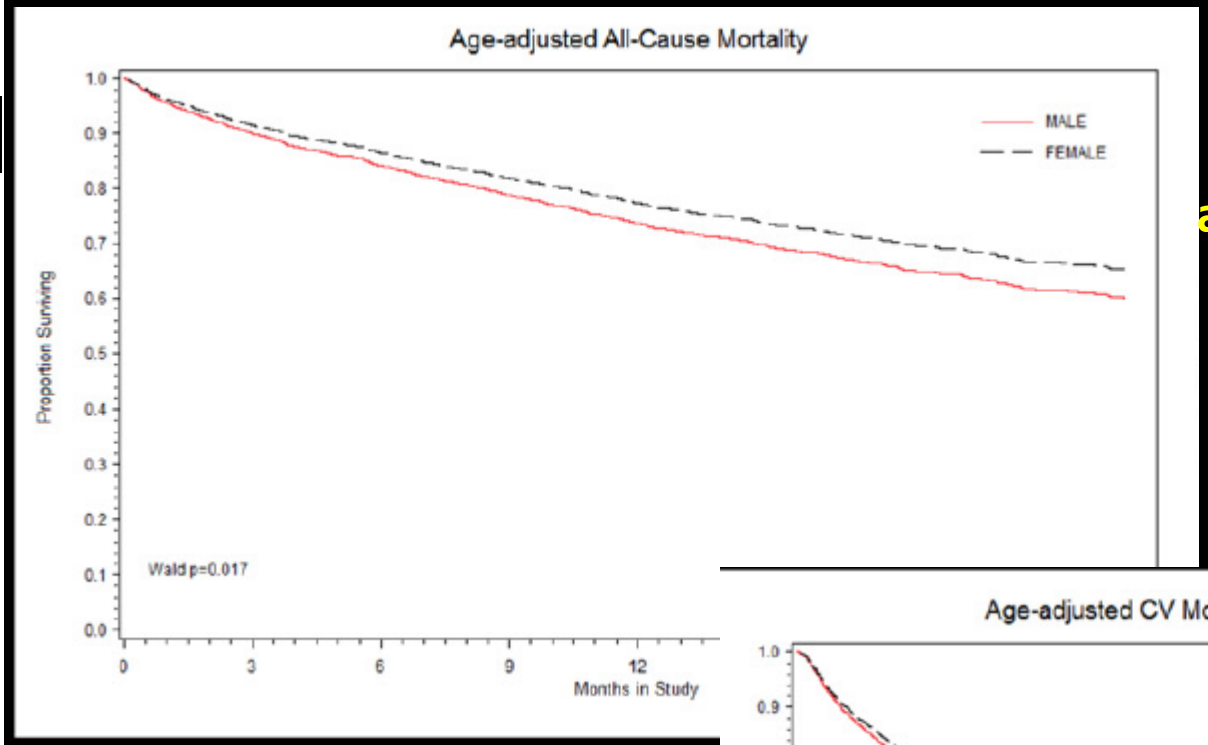
Lenzen JM, 2008;94;10-; Heart

Gender Does Not Affect Postdischarge Outcomes in Patients Hospitalized for Worsening Heart Failure With Reduced Ejection Fraction (from the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan [EVEREST] Trial)

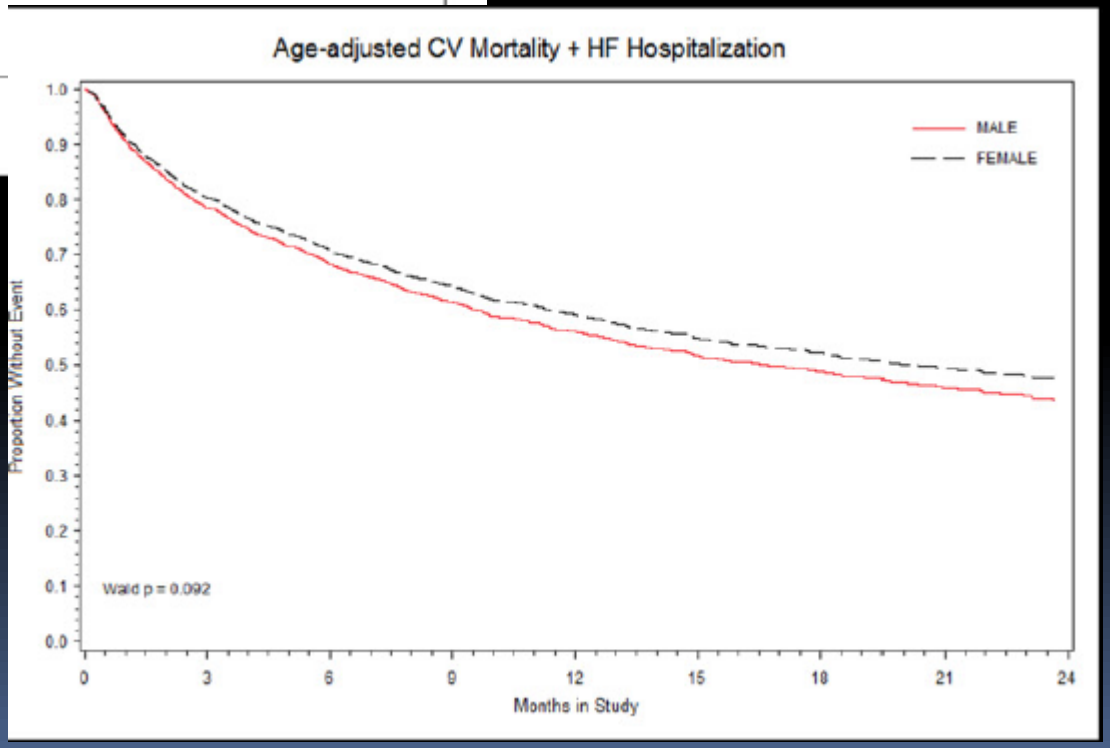
Ami N. Shah, MD[a], Robert J. Mentz, MD[b], Mihai Gheorghiade, MD[a], Mary J. Kwasny, ScD[a], Angela J. Fought, MS[a], Faiez Zannad, MD[c], Karl Swedberg, MD[d], Aldo P. Maggioni, MD[e], and Marvin A. Konstam, MD[f,*]

	Male (n = 3.075)	Female (n= 1.058)	P value
Age , years	64.9 ± 11.9	68.2 ± 11.4	< .0001
LVEF % (mean)	27.0 ± 8.0	28.8 ± 8.2	< .0001
Coronary artery disease	72 %	67 %	.002
Hypertension	68 %	80 %	< .0001
Hypercolesterolemia	50%	45%	.01
Diabetes mellitus	38%	42%	.01
Atrial fibrillation	29%	28%	.70

Ami N. Shah et al. Am J Cardiol 2012;110:1803–1808



Kaplan-Meier analyses of all-cause mortality and CVM and HHF in male versus female patients.



After adjustment for age and other demographic, clinical, and laboratory values, no difference was seen in ACM or CVM HHF between women and men.

Ami N. Shah et al. Am J Cardiol 2012;110:1803–1808

Gender Differences in Advanced Heart Fa

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Table 5. M

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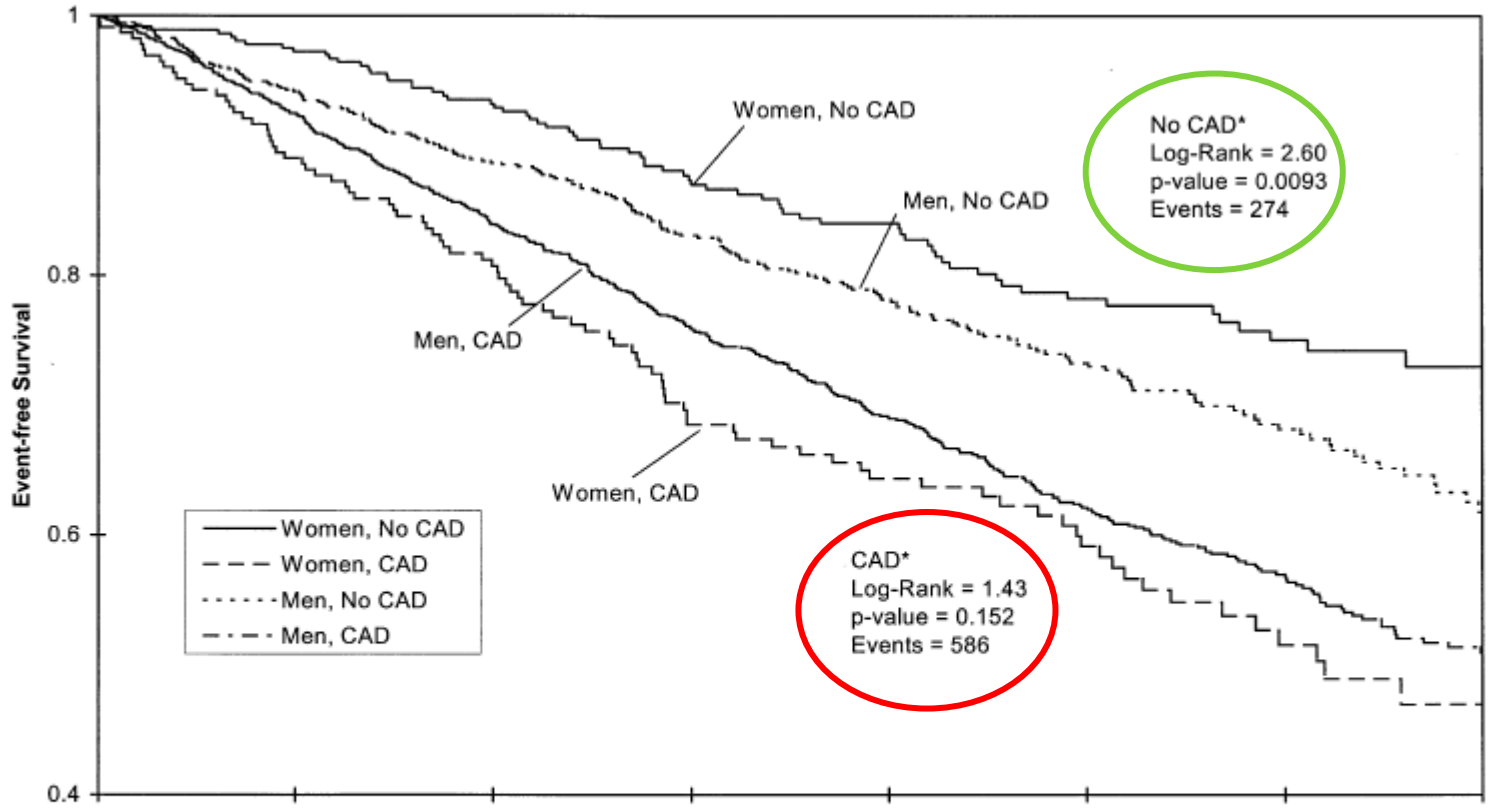


No. at Risk	0	6	12	18	24	30	36	42
No CAD								
Women	365	354	308	241	208	150	101	39
Men	756	712	615	502	406	295	179	76
CAD								
Women	228	203	166	121	102	74	45	14
Men	1359	1257	1015	813	652	454	273	120

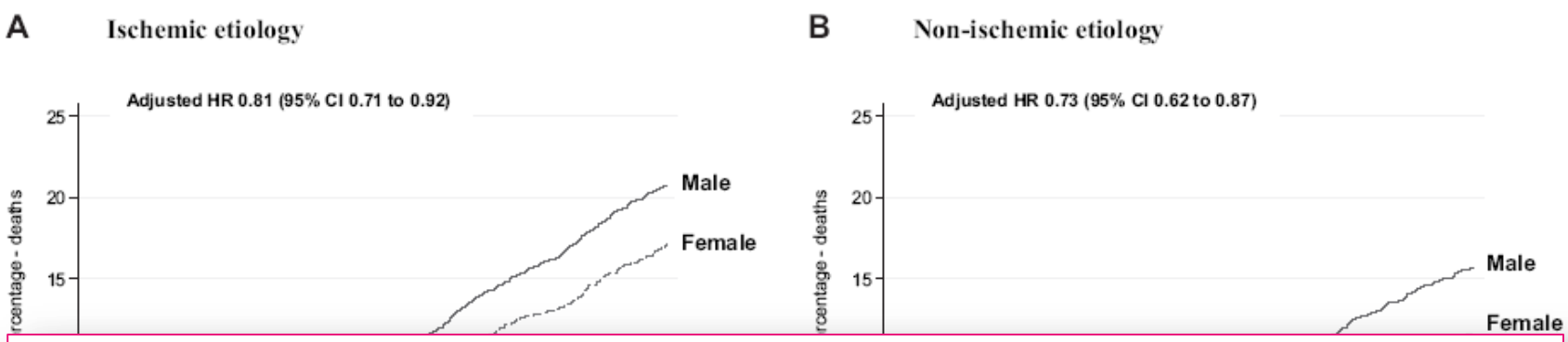
Survival curves by gender within ischemia status.

J Am Coll Cardiol 2003;42:2128 –2134.

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

Kaplan-Meier curves by sex for all-cause mortality in CHARM, for patients with an ischemic cause of HF (A) and a nonischemic cause (B).



Ejection fraction, mean (SE), %	36.9 (0.2)	43.3 (0.3)	6.4 (5.7 to 7.1)	<0.001
Ejection fraction <25%, n (%)	799 (15)	214 (9)	1	. . .
Ejection fraction 25% to <50%, n (%)	3213 (62)	1240 (52)	1.44 (1.22 to 1.70)	<0.001
Ejection fraction ≥50%, n (%)	1187 (23)	946 (39)	2.98 (2.50 to 3.54)	<0.001

Numbers at risk

Male	3465	3170	2855	1934	1734	1614	1514	1076
Female	1216	1120	1017	677	1184	1123	1055	695

O'Meara et al. Circulation. 2007;115:3111-3120

Sex Differences in Clinical Characteristics and Outcomes in Elderly Patients With Heart Failure and Preserved Ejection Fraction

The Irbesartan in Heart Failure With Preserved Ejection Fraction (I-PRESERVE) Trial

Carolyn S.P. Lam, MBBS, MRCP, MS; Peter E. Carson, MD;
Inder S. Anand, MD, FRCP, DPhil (Oxon.); Thomas S. Rector, PhD; Michael Kuskowski, PhD;
Michel Komajda, MD; Robert S. McKelvie, MD, PhD, FRCPC; John J. McMurray, MD;
Michael R. Zile, MD; Barry M. Massie, MD; Dalane W. Kitzman, MD

The Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial is the largest HFPEF trial to date and included 4128 patients, aged ≥ 60ys with signs and symptoms of HF and LVEF ≥ 45%

Lam et al. 2012;5:571-578; Circ Heart Fail.

Baseline clinical characteristics by sex

	Female (n = 2.491)	Male (n= 1.637)	P value
Age	72 ± 7	71 ± 7	< .001
Ischemic cause of HF (%)	19%	34%	<.001
Obesity	46%	35%	<.001
Hypertension (%)	91%	85%	<.001
Atrial Fibrillation	27	33	<.001
NYHA class II/III/IV	20/77/2	22/75/3	.006
Diabetes mellitus	28%	27%	<.74
COPD	8%	13%	<.001
LV Ejection fraction , %	61 ± 9	58 ± 9	<.001

Lam et al. 2012;5:571-578; Circ Heart Fail.

Association between sex and time to first outcomes

Outcome	No. of Events			Event Rate Per 100 Patient-Years		Univariable Analysis		Multivariable Analysis*	
	All Patients	Women	Men	Women	Men	HR (95% CI), Women vs Men	*P* Value	HR (95% CI), Women vs Men	*P* Value
All-cause death	881	447	434	4.32	6.72	0.64 (0.56–0.73)	<0.001	0.70 (0.59–0.83)	<0.001
All-cause hospitalization or death	2430	1382	1049	19.42	25.05	0.79 (0.73–0.86)	<0.001	0.80 (0.72–0.89)	<0.001
Cardiovascular hospitalization or death	1754	970	784	11.76	15.97	0.75 (0.68–0.83)	<0.001	0.81 (0.72–0.92)	0.001
Noncardiovascular hospitalization or death	1483	846	638	9.89	12.40	0.81 (0.72–0.89)	<0.001	0.78 (0.69–0.90)	<0.001
Heart failure hospitalization or death	716	420	296	4.43	5.02	0.89 (0.77–1.04)	0.140	0.94 (0.77–1.14)	0.51
First all-cause hospitalization	2278	1314	964	18.43	23.14	0.82 (0.75–0.88)	<0.001	0.77 (0.66–0.89)	<0.001

HR indicates hazards ratio; HF, heart failure; PCI/CABG, percutaneous coronary intervention/coronary artery bypass surgery; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide.

*Adjusted for age, obesity, New York Heart Association status, HF cause, HF hospitalization within 6 mo, comorbidities/risk factors (history of hypertension, stable angina, myocardial infarction, PCI/CABG, atrial fibrillation, diabetes, stroke/TIA, COPD/asthma, valve disease, smoking), ejection fraction capped at 60%, heart rate, systolic blood pressure, hemoglobin, ln-NT-pro-BNP, natural log-neutrophil count, glomerular filtration rate capped at 90 mL/min per 1.73 m^2, and all medications.

†Death from any cause or hospitalization for protocol-specified cardiovascular cause (HF, myocardial infarction, arrhythmia, or stroke).

Even accounting for baseline differences, women with HFPEF were ≈20% less likely than men to experience death or hospitalization of any cause during follow-up.

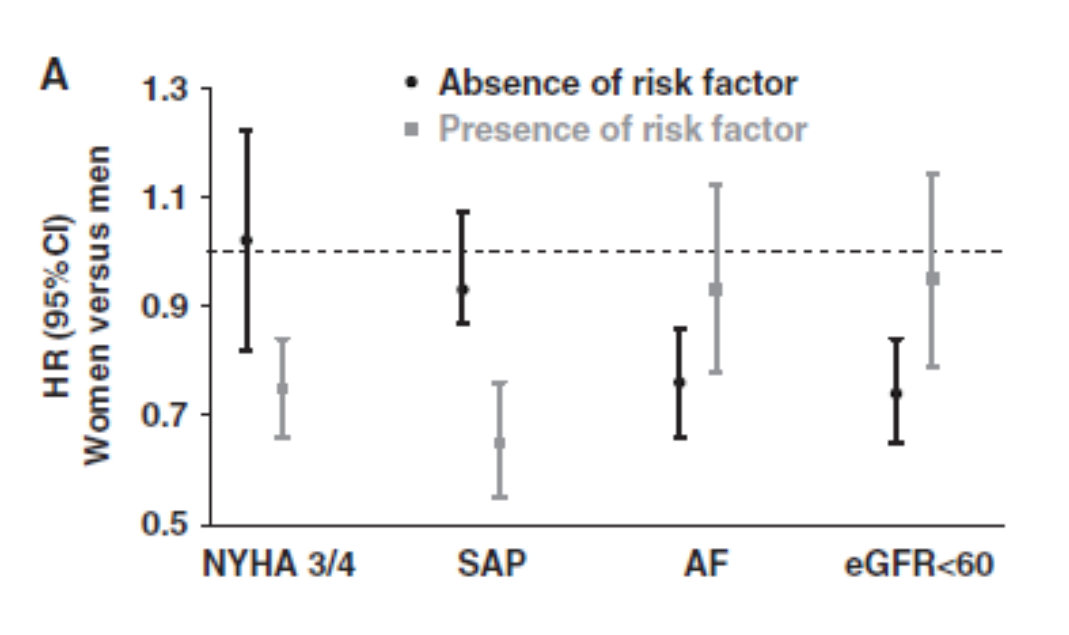
This lower relative risk for women could not be explained by adjustment for differences in baseline characteristics.

Lam et al. 2012;5:571-578; Circ Heart Fail.

To gain further insights into the hazards ratio for all-cause events in women relative to men, they tested for interactions between sex and baseline variables.

Variable	*P* Value Interaction
Age	0.45
Obesity	0.52
NYHA (class III/IV vs I/II)	0.006
HF cause (ischemic vs nonischemic)	0.054
Hypertension	0.41
Stable angina pectoris	0.007
Myocardial infarction	0.13
PCI/CABG	0.96
Atrial fibrillation	0.005
Diabetes mellitus	0.49
Smoking	0.58
Chronic obstructive lung disease	0.59
Valve disease	0.47
Heart rate (per 1 bpm)	0.97
SBP (per 1 mm Hg)	0.90
Hemoglobin (per 1 g/dL)	0.95
NT-pro-BNP (per 1 log unit)	0.44
Hospitalization in 6 mo	0.049
Neutrophil count (per 1 log unit)	0.048
Ejection fraction	0.70
eGFR (per 1 mL/min per 1.73 m^2)	0.01
Antiarrythmic	0.004

Effect of interactions on association between sex and all-cause events



Sex-related difference in risk of all-cause events was modified in the presence or absence of atrial fibrillation, renal dysfunction, stable angina pectoris, or advanced New York Heart Association class symptoms.

Lam et al. 2012;5:571-578; Circ Heart Fail.

Differenti fenotipi hanno un impatto sull'outcome?

Non abbiamo dati univoci, ma sembra che il fenotipo " HFpEF" presenti una prognosi migliore nelle femmine rispetto ai maschi

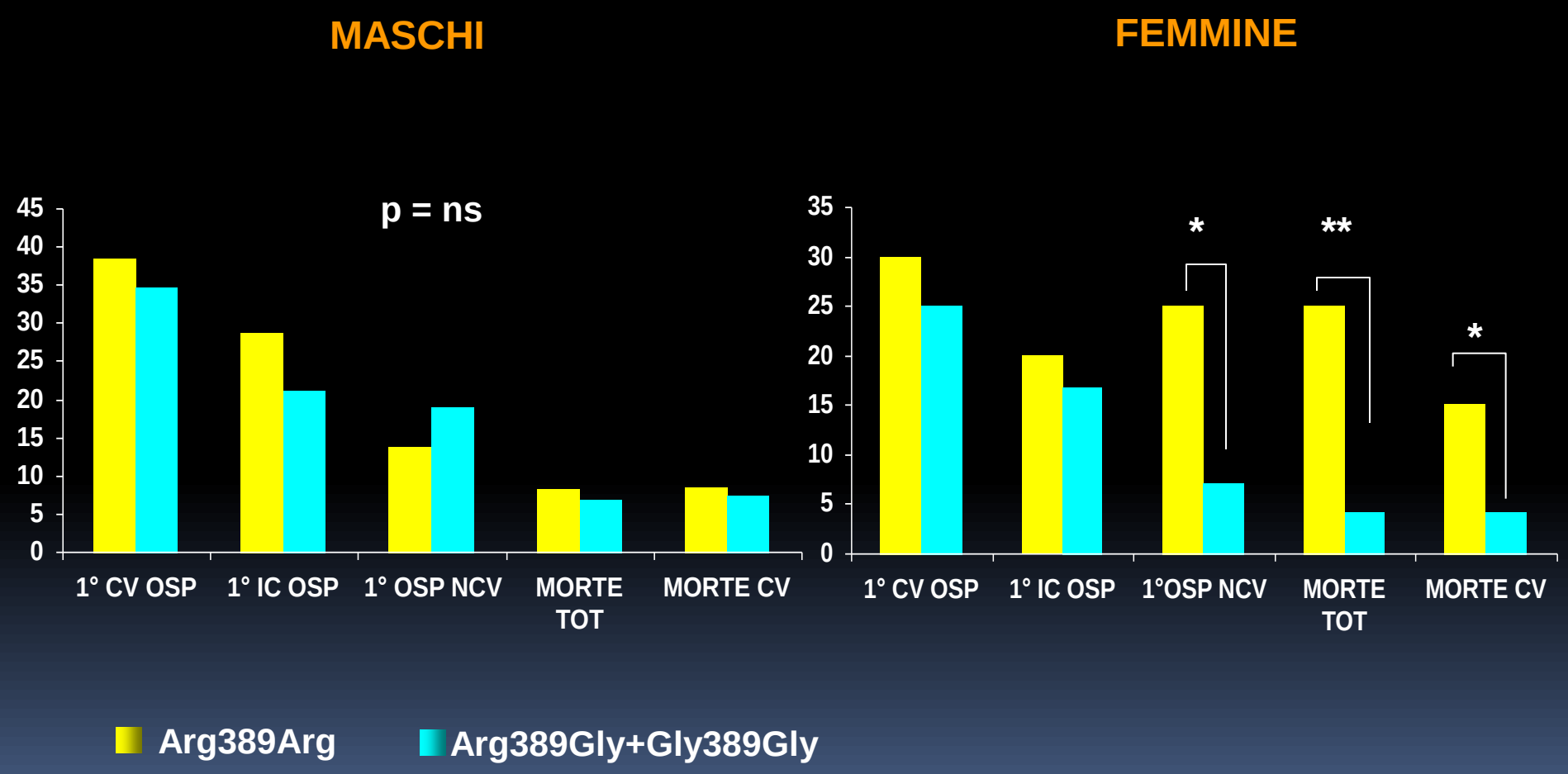
Considerazioni finali

- Esistono differenze di genere e differenti fenotipi
- Esistono molte lacune nelle nostre conoscenze fisiopatologiche e terapeutiche

Caratteristiche in relazione al sesso e al polimorfismo del recettore beta1 adrenergico Arg389Arg vs Arg389Gly+Gly389Gly

	Arg389Arg		Arg389Gly+Gly389Gly		
	M	F	M	F	
	(n=168)	(n=35)	(n=199)	(n=40)	
Età (anni)	64,17±10,20	67,46±11,74	61,52±12,25	63,88±13,49	
CAD (n, %)	95 (56,55%)	15 (0,43)	104 (52,26%)	16 (0,40)	
Diabete mellito (n, %)	36 (21,43%)	6 (0,17)	43 (21,61%)	11 (0,28)	
Ipertensione (n, %)	76 (45,24%)	17 (0,49)	90 (45,23%)	21 (0,53)	
Classe NYHA	2,32±0,81	2,49±0,56	2,30±0,79	2,20±0,52	p = 0,02
FC (bpm/min)	68,05±13,18	70,54±9,77	68,17±12,83	69,45±11,74	
PAS (mmHg)	122,92±18,64	124,29±14,36	123,87±17,50	128,13±21,05	
PAD (mmHg)	77,59 ±10,44	77,86±7,50	78,62±9,66	77,63±9,34	
Creatinina (mg/dl)	1,23±0,43	1,18±0,54	1,58±3,78	1,07±0,43	p = ns
FE (%)	31,65±10,89	35,60±9,98	32,77±10,51	37,55±11,04	p = ns
VO2 di picco (%)	57,49±17,49	55,92±10,35	55,07±15,67	56,27±14,30	

Eventi cardiovascolari in relazione al sesso e al polimorfismo del Arg389Arg vs Arg389Gly+Gly389Gly



Risposta al trattamento farmacologico: cosa sappiamo?

Trial (ref no.)	Year	No. of Pts	No. (%) Women	Average Age (yr)
Captopril-Digoxin (1)	1988	300	51 (17%)	57
SOLVD (prevention) (2)	1992	4,228	486 (11.5%)	59
SOLVD (symptomatic) (3)	1991	2,569	594 (23%)	61
CONSENSUS-I (4)	1987	253	75 (30%)	70
MDC (5)	1993	383	105 (27%)	49
PROMISE (6)	1991	1,088	235 (22%)	64
Vesnarinone (7)	1993	477	63 (13%)	58
RADIANCE (8)	1993	178	42 (24%)	60
DIG (9)	1997	6,800	1,520 (22.4%)	64
Carvedilol (10)	1996	1,094	256 (23%)	48
Total		17,370	3,427 (19.7%)	62

CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; DIG = Digitalis Investigation Group; MDC = Metoprolol in Dilated Cardiomyopathy; Pts = patients; RADIANCE = Randomized Assessment of Diogoxin on Inhibitors of the Angiotensin-Converting Enzyme; ref = reference; SOLVD = Studies of Left Ventricular Dysfunction.

Lindenfeld J, et al. Where are all the women with heart failure? *J Am Coll Cardiol* 1997;30:1417-9.

Factors Distinguishing HF in the Elderly from HF at Middle Age

	Male	Female
Prevalence	<1%	≈10%
Sex	Men > women	Women > men
Etiology	CAD	Hypertension
Clinical features	Typical	Atypical
LVEF	Reduced	Normal
Comorbidities	Few	Multiple
Physician	Cardiologist	Primary care
RCTs	Many	Few
Therapy	Evidence-based	Empiric

Rich MW, Am J Med 2005; 118:342


Grazie per l’attenzione