Disfunzione diastolica e comorbilità cardiovascolare

8 marzo 2018

Rosa Poddighe

Ospedale Versilia

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

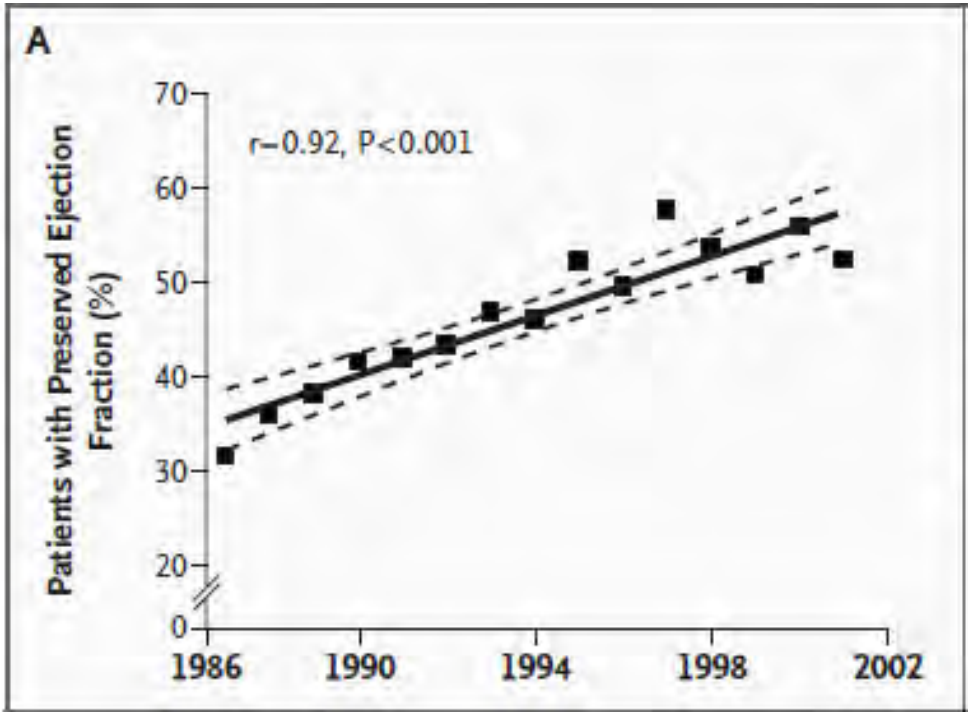
Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

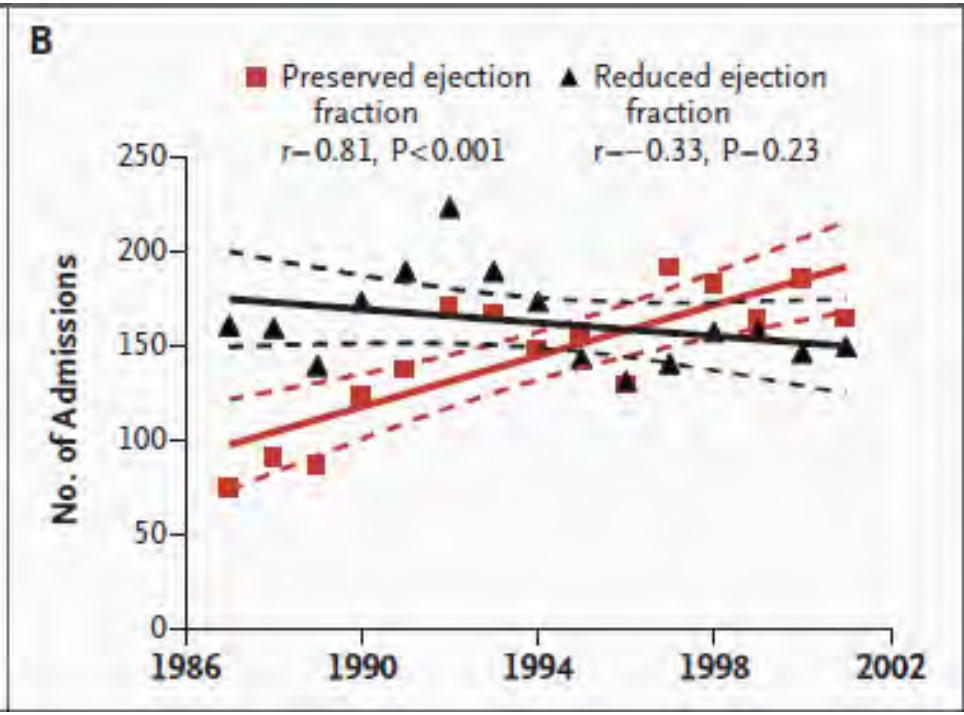
Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction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

Mayo Clinic -Olmsted County Minnesota

6076 pts ospedalizzati per HF dal 1987 al 2001

53% HFrEF e 47% HFpEF

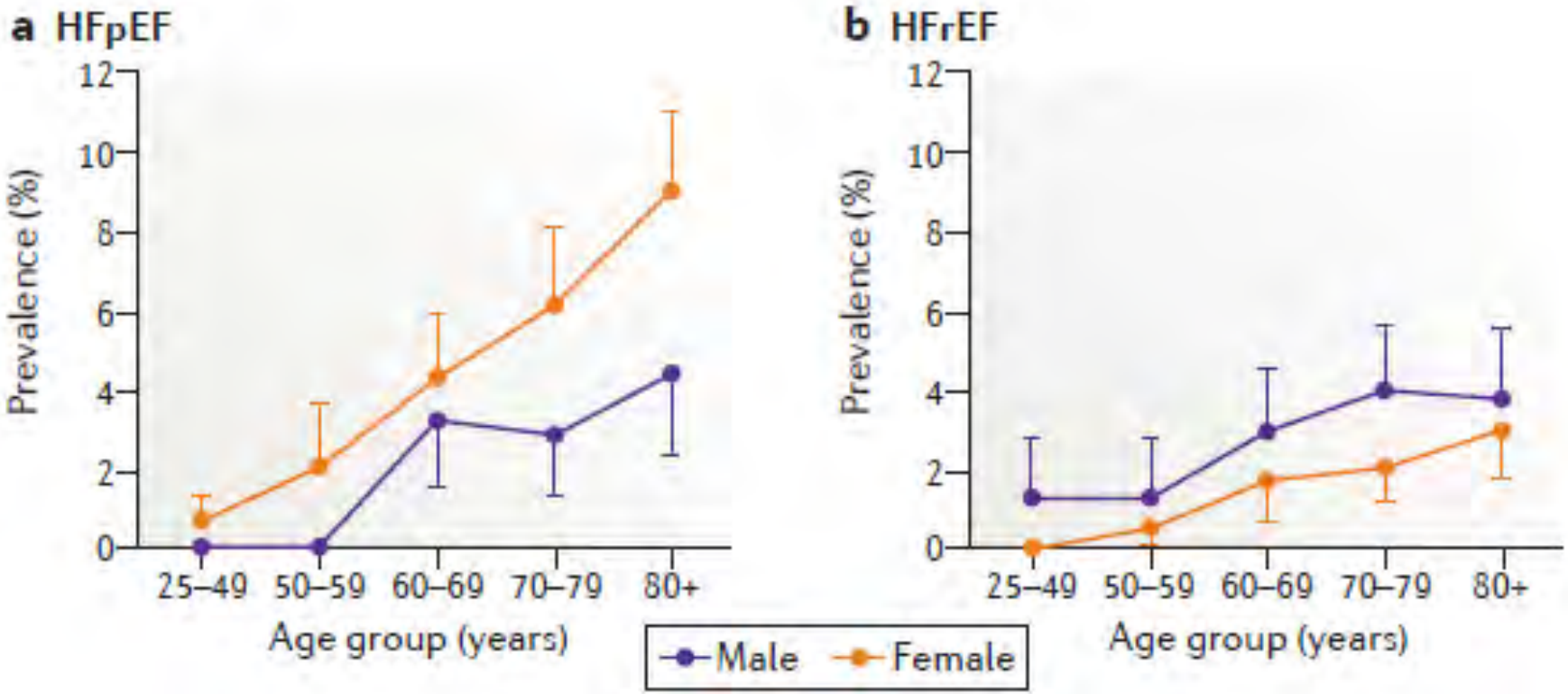




Owan T.E. et al N Engl J Med 2006

EPICA Study- Portugal

age and sex specific HF prevalence



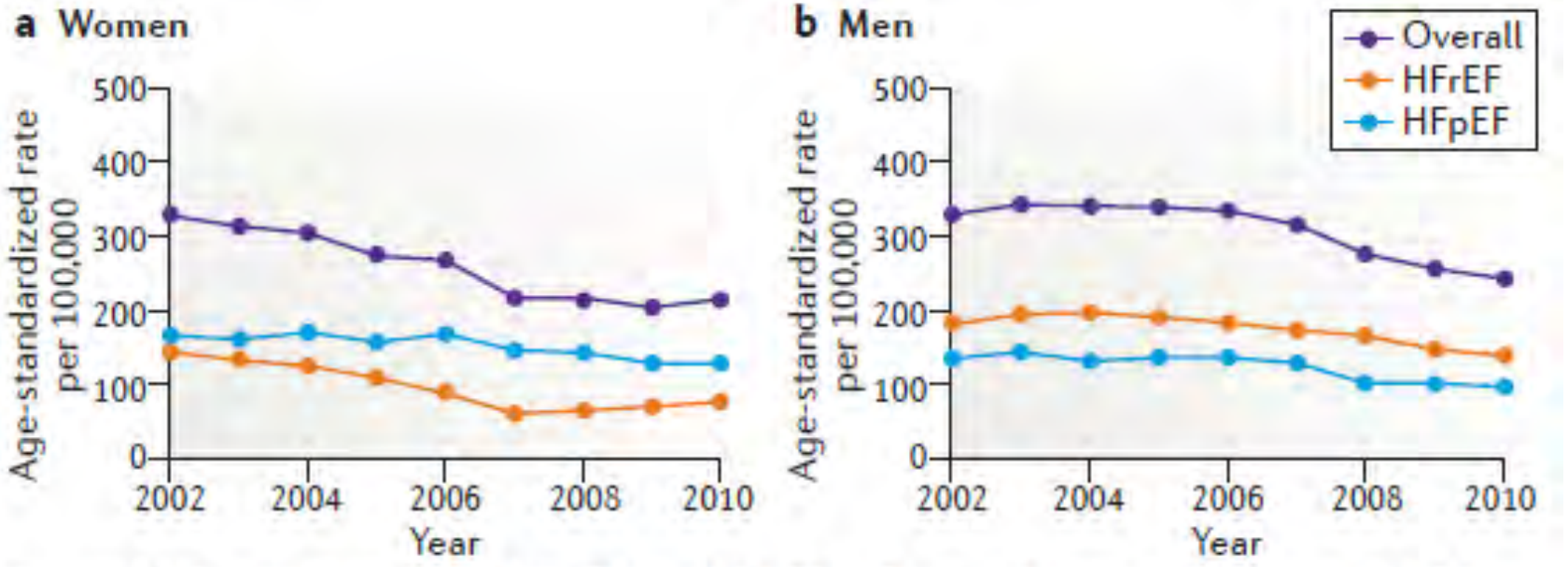
Ceia, F. *et al.* EPICA study. *Eur. J. Heart Fail 2002*

Olmsted County Minnesota

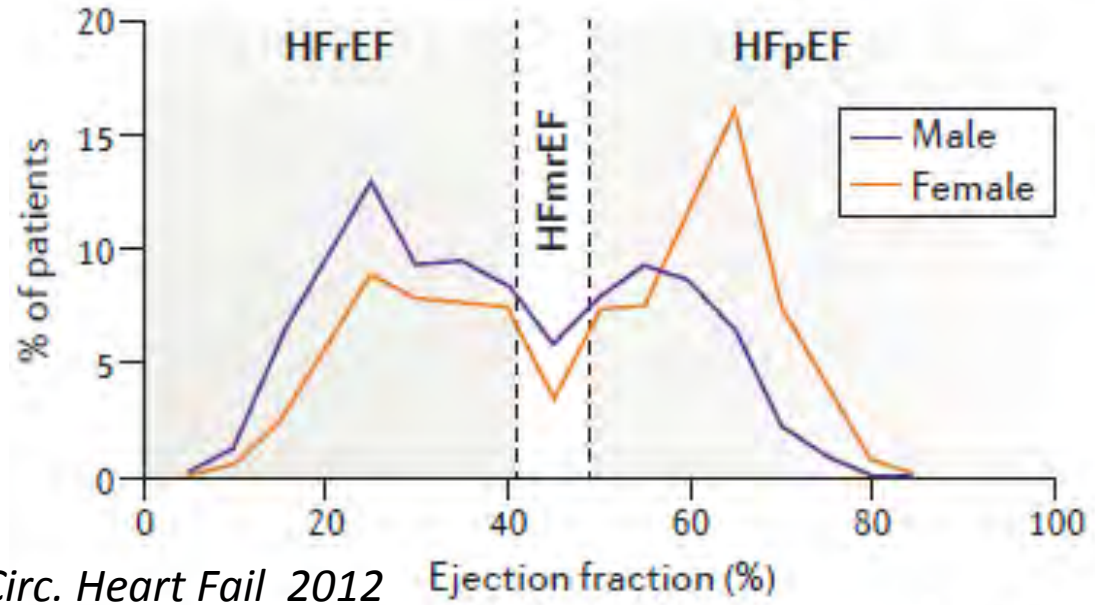
sex specific HF incidence 2000-2010

HF – 37,5%

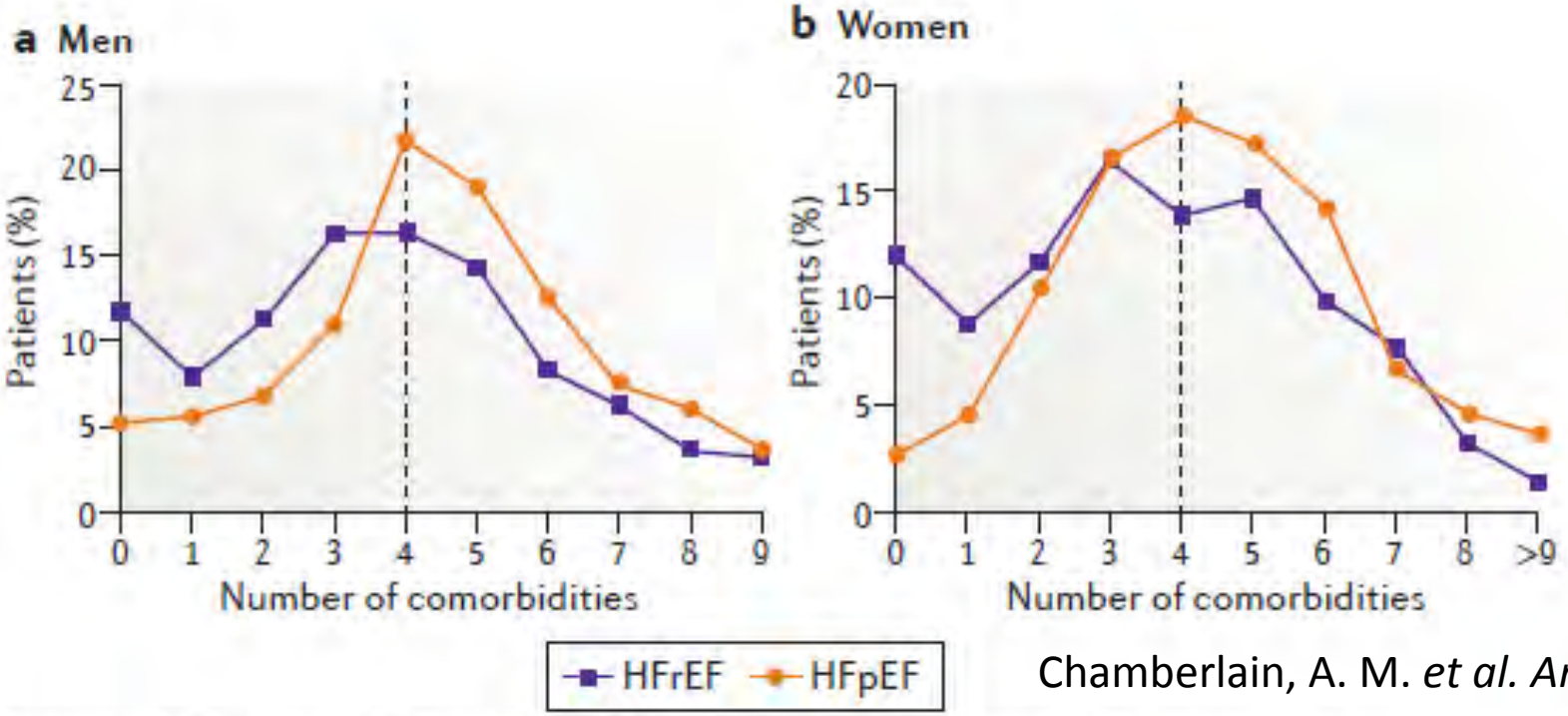
HFrEF – 45% vs HFpEF – 28%



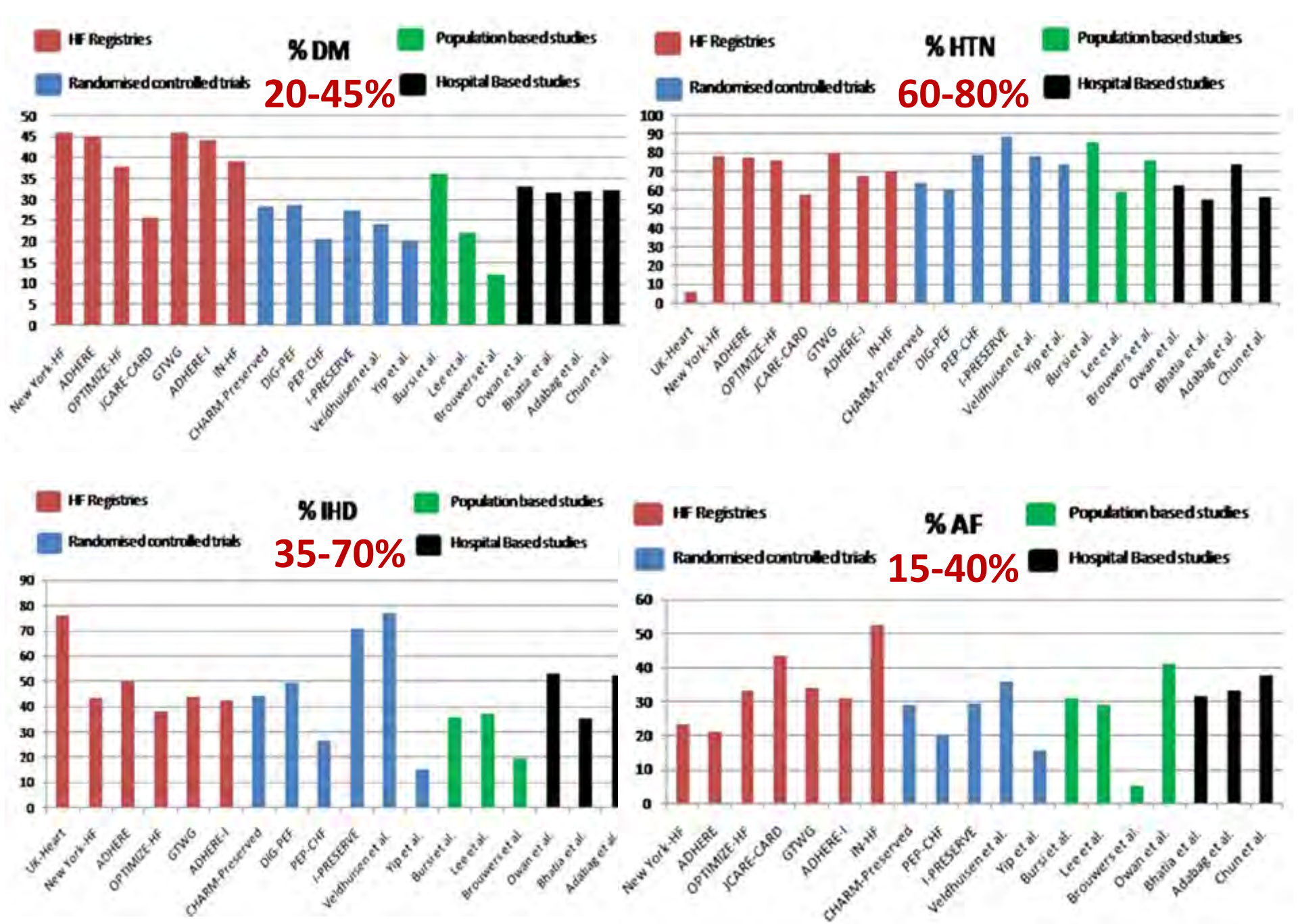
Gerber, Y. *et al JAMA Intern. Med. 2015*



Dunlay, S. M. *et al. Circ. Heart Fail 2012*



Chamberlain, A. M. *et al. Am. J. Med 2015*

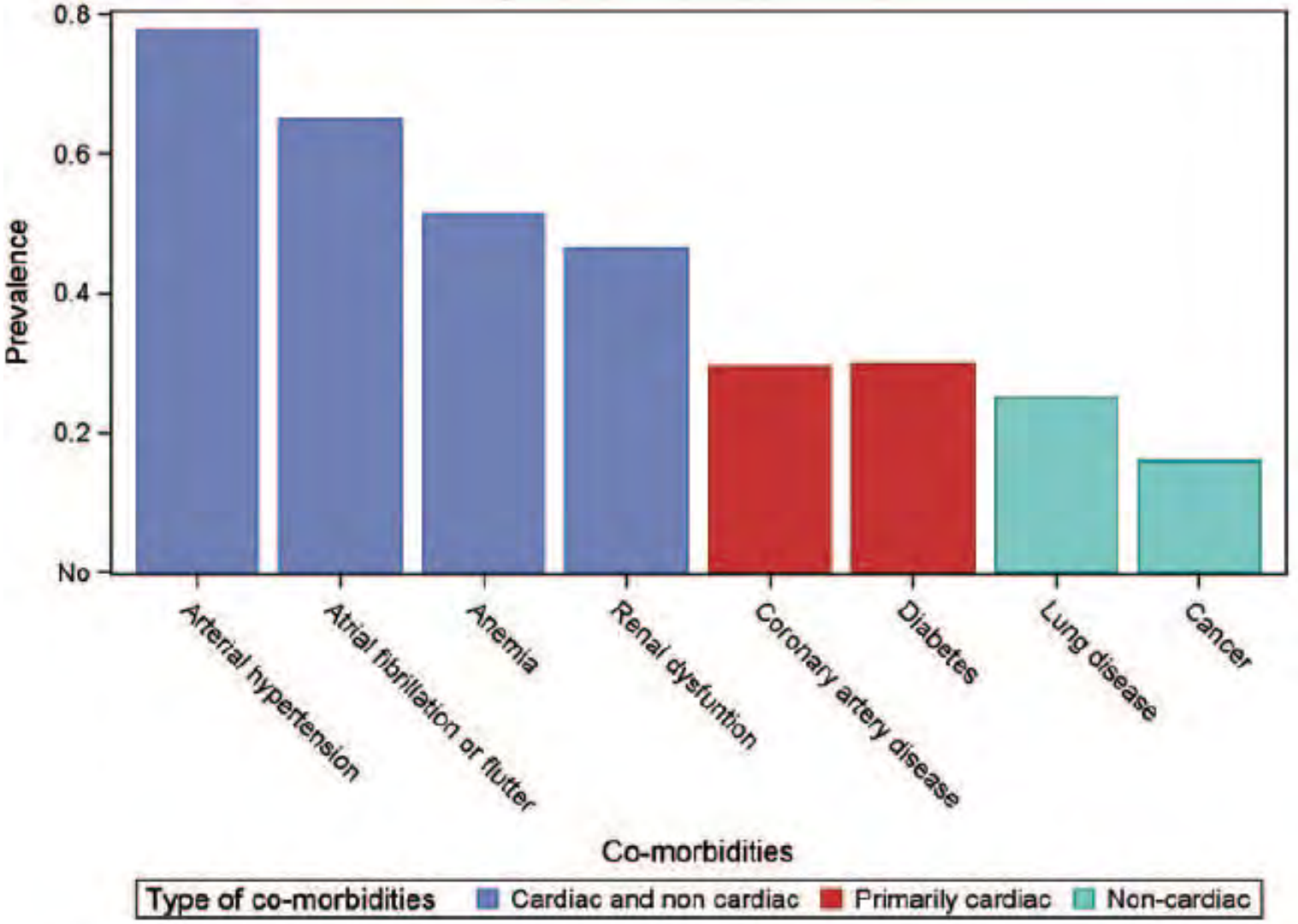


Dhingra A. et al, Curr Heart Fail Rep 2014

KaRen study

539 pts 56% donne

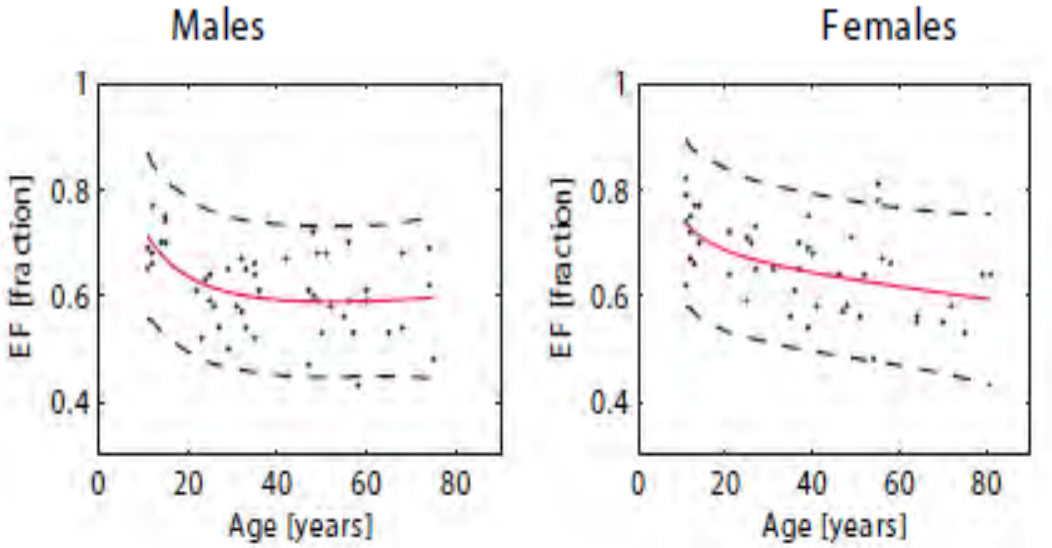
F.U. 18 mesi

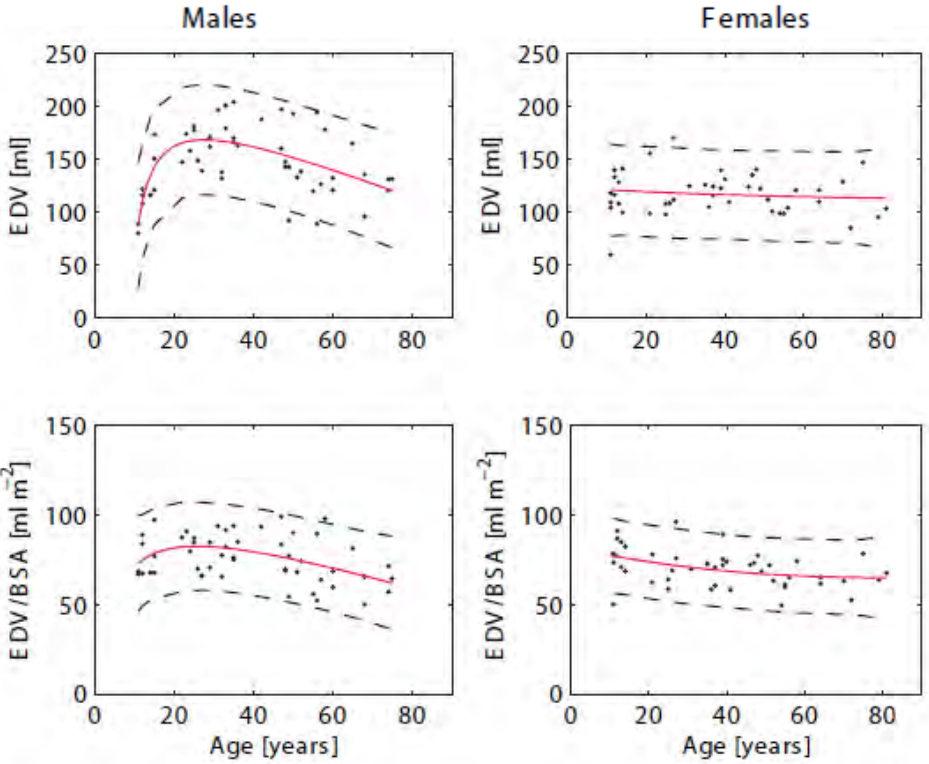


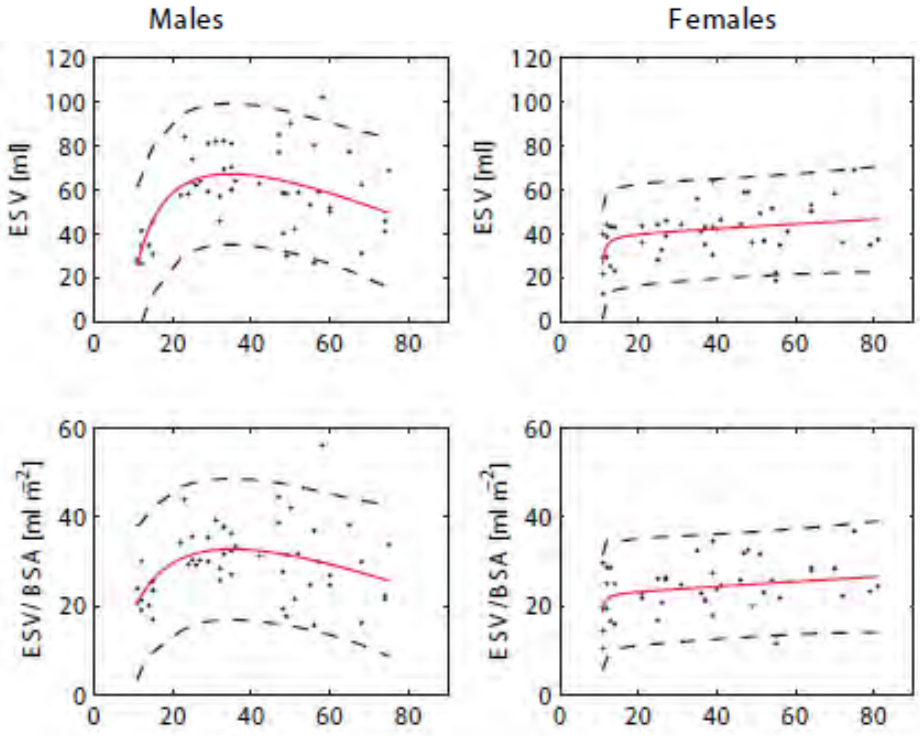
Lund L.H. et al Eur J Heart Fail 2014

Why Me, God?

- RM
  (volumi, massa, funzione VS)
- 96 volontari sani
  (50 M; 11-81 aa)







Cain P. A. et alBMC Medical Imaging 2009

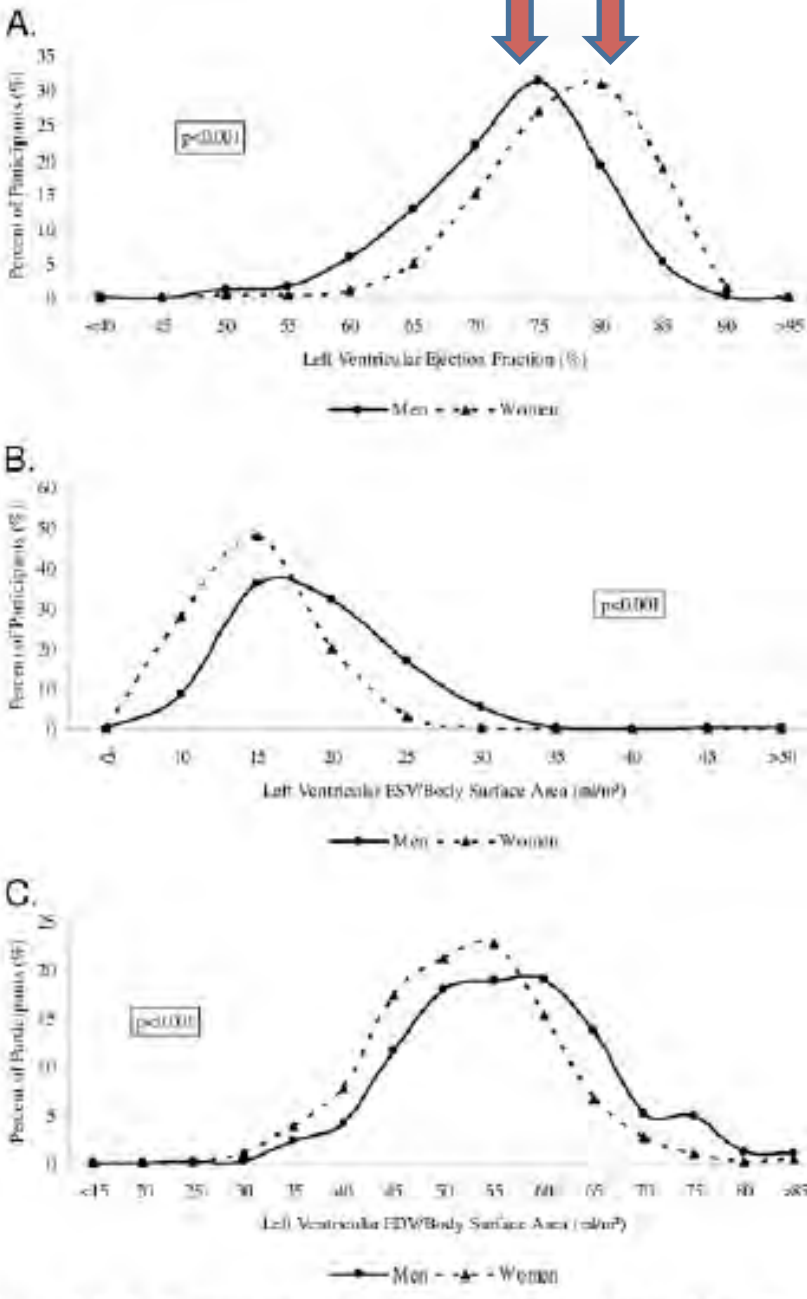
TABLE 1. Demographic Data and Clinical Characteristics of Men and Women in DHS Participants Aged 30 to 65 Years

	Women (n=1435)	Men (n=1183)	P
Age, y	45±9	44±9	0.4
Body mass index, kg/m^2	31.5±7.9	29.1±5.9	<0.001
BSA, m^2	1.9±0.25	2.0±0.22	<0.001
Race/ethnicity			<0.001
Black	52	47	
White	29	34	
Hispanic	18	16	
Hypertension	33	30	0.06
Systolic blood pressure, mm Hg	125±18	129±16	<0.001
Diastolic blood pressure, mm Hg	78±10	79±10	0.2
Heart rate, bpm	77±11	75±12	<0.001
Cardiac output, L/min	5.3±1.4	5.7±1.4	<0.001
Cardiac index, L/min per m^2	2.8±0.6	2.8±0.6	0.2
Left ventricular mass, g	141.3±33.8	191.7±44.4	<0.001
LVM/body surface area, g/m^2	74.2±14.2	94.1±18.4	<0.001
LVM/fat-free mass, g/kg	3.0±0.5	3.0±0.6	0.7
Concentricity (LVM/EDV)	1.6±0.4	1.8±0.4	<0.001
CAC >10 Agatston units	14	27	<0.001
Diabetes	11.4	10.6	0.5
History of myocardial infarction	1.7	2.7	0.07
Congestive heart failure	2.6	2.2	0.5
Heavy alcohol use	1.8	7.2	<0.001
Self-reported cocaine use	9.6	18.4	<0.001
Past or present tobacco use	39	55	<0.001

All numbers are percentages for categorical variables or mean±SD for continuous variables.

DALLAS HEART STUDY

RM

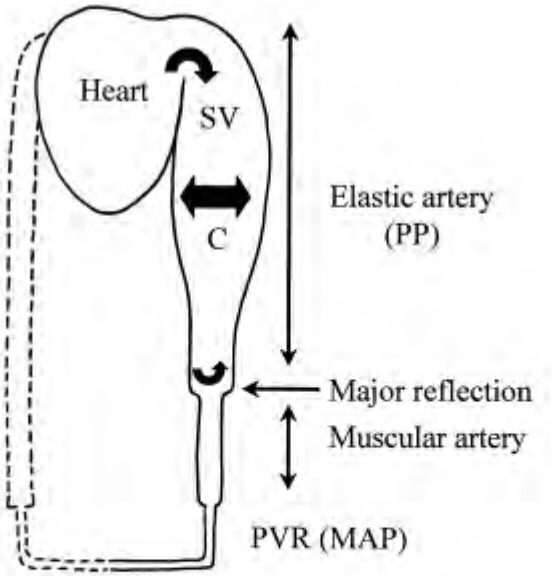


Chung A.K. Et al Circulation 2006

Proprietà biomeccaniche delle grandi arterie:

> rigidità prima della pubertà
e dopo la menopausa

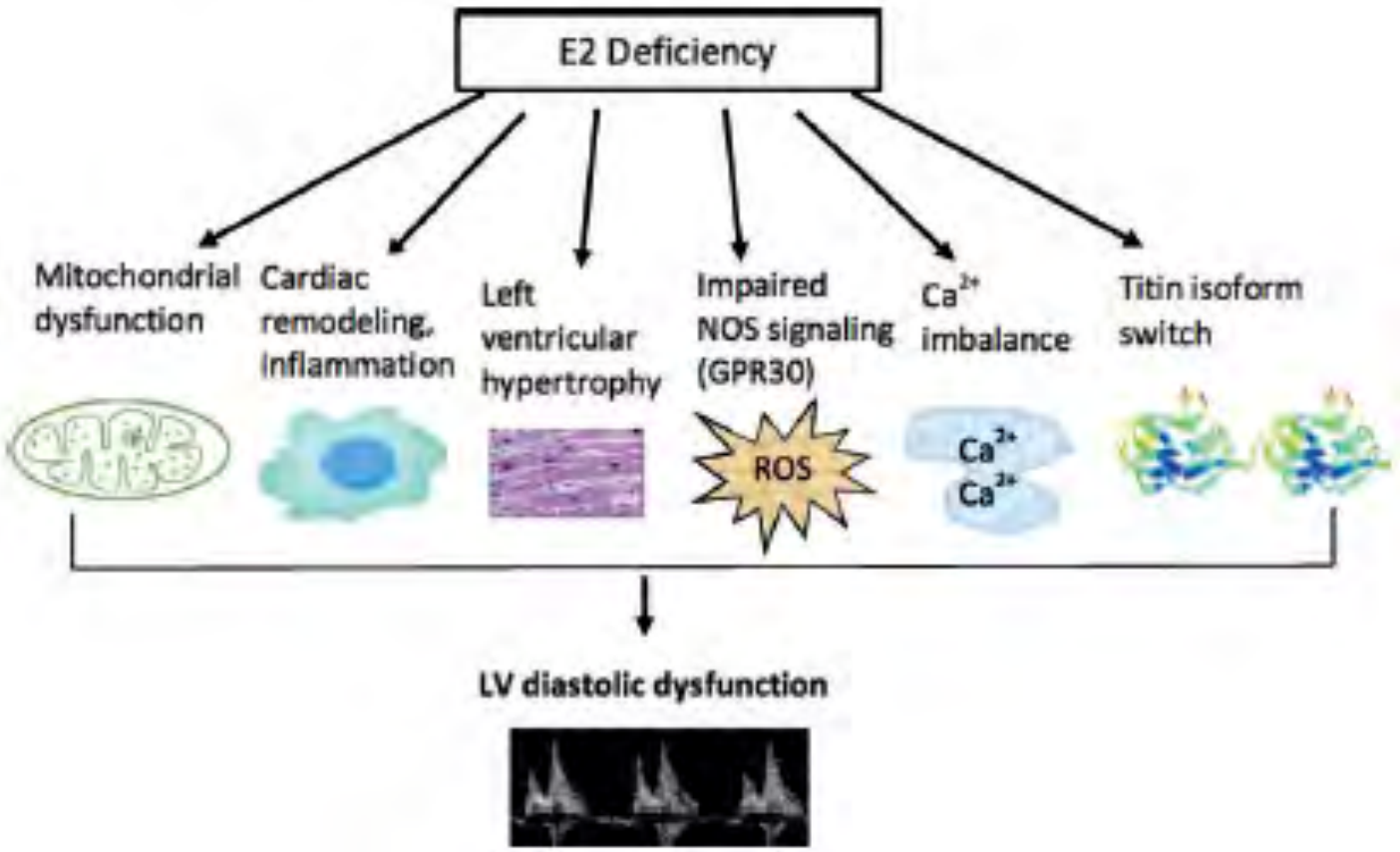
aumento lineare
della rigidità con l'età



Rossia P. et al J of Hyp 2011

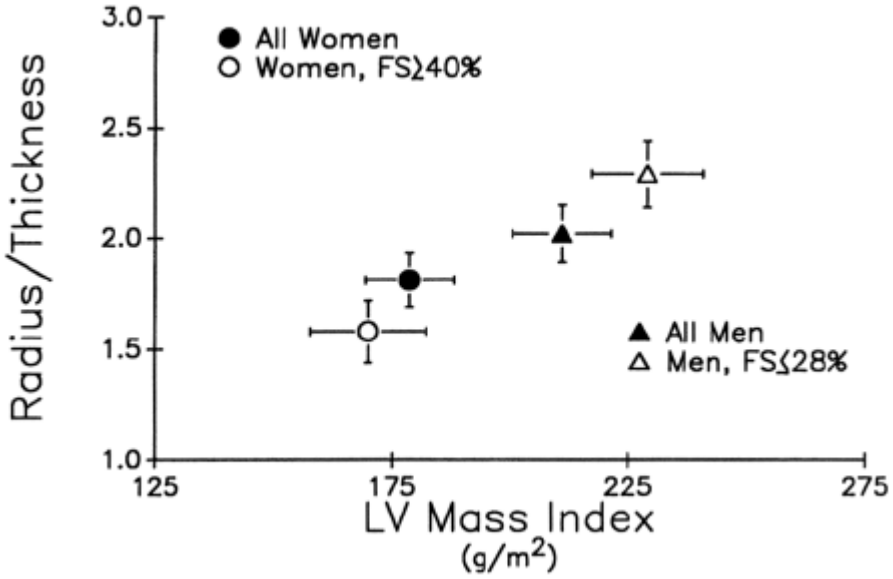
Dart A.M. et al JACC 2001

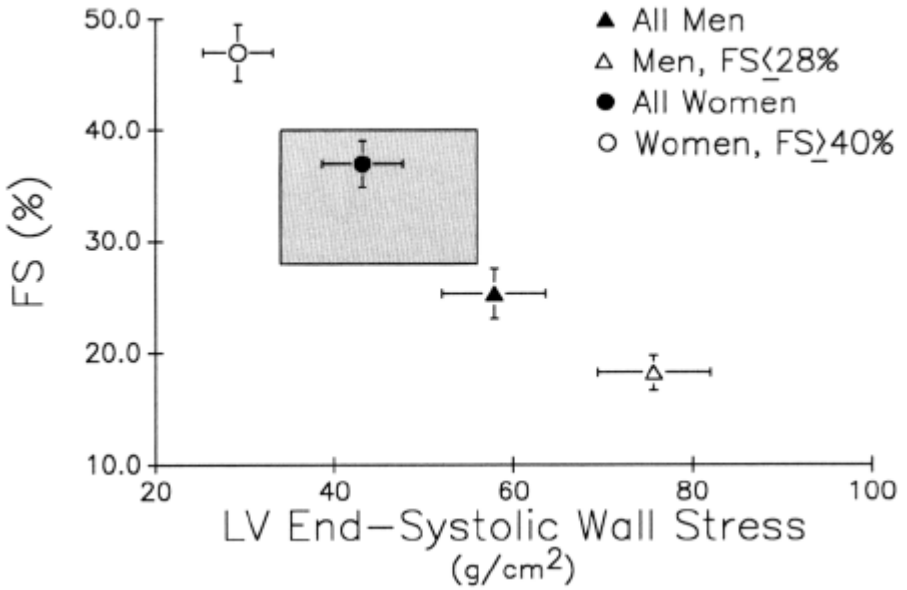
Estrogeni e funzione diastolica



Shumin l. et al Houston Methodist Debakey J 2017

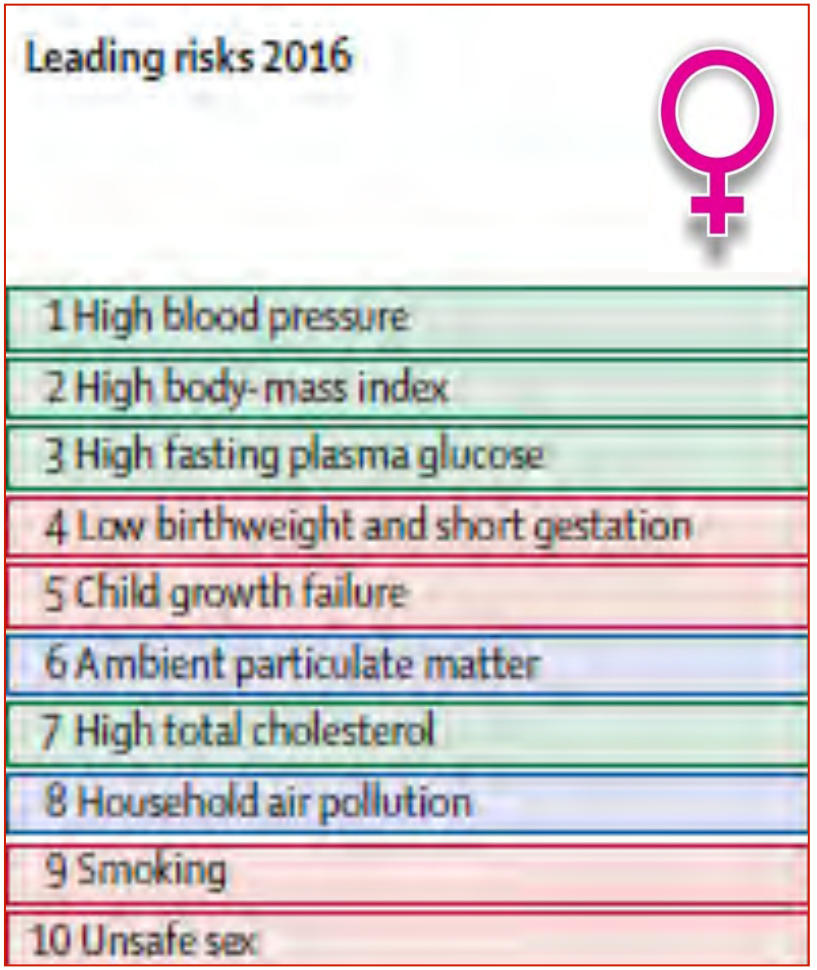
Adattamento al sovraccarico di pressione collegato al sesso





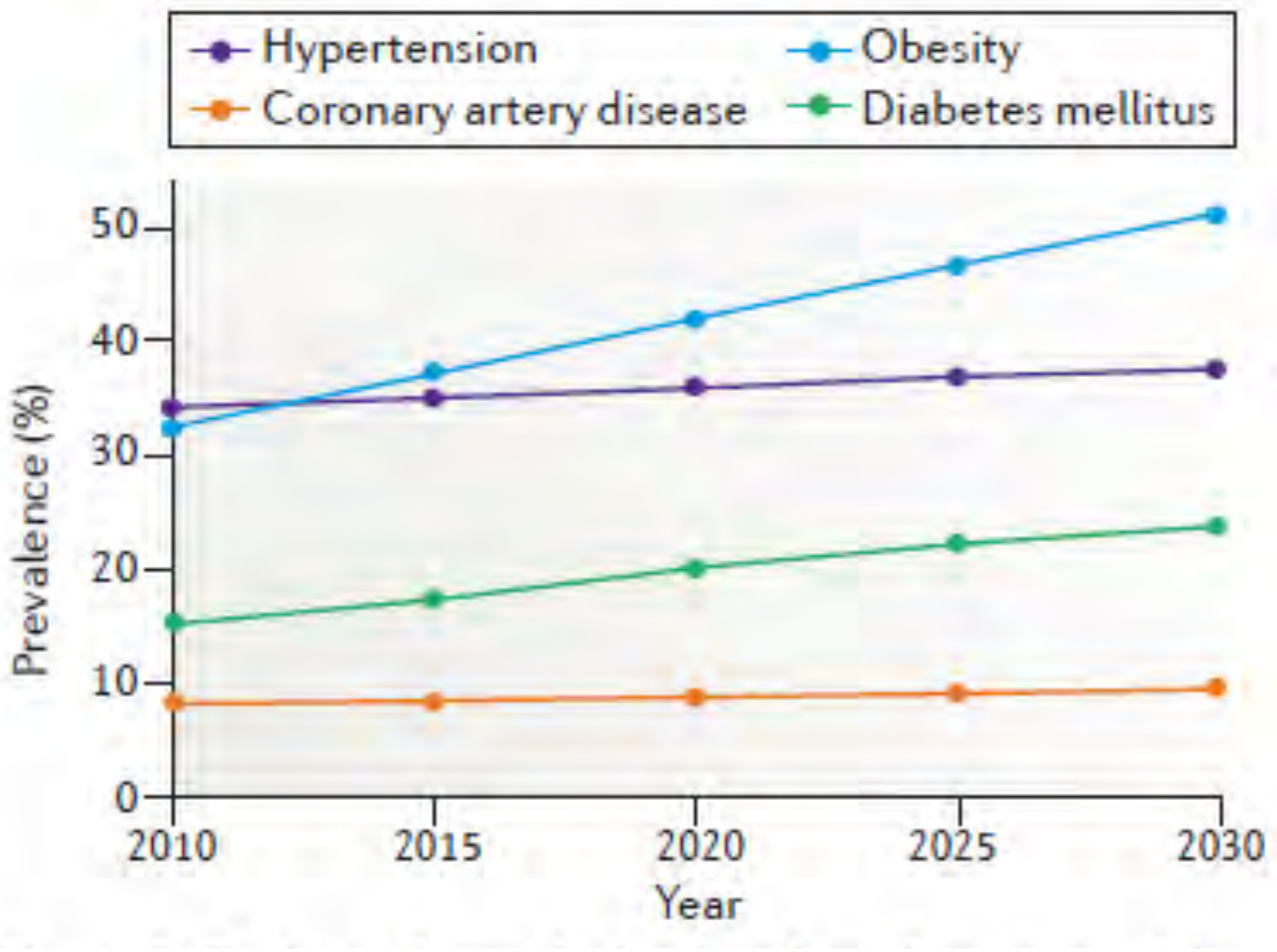
Carroll J.D. et al Circulation 1992

GLOBAL BURDEN of DISEASES 2016



GBD 2016 Risk Factors Collaborators Lancet 2017

Proiezioni sui fattori di rischio per HF



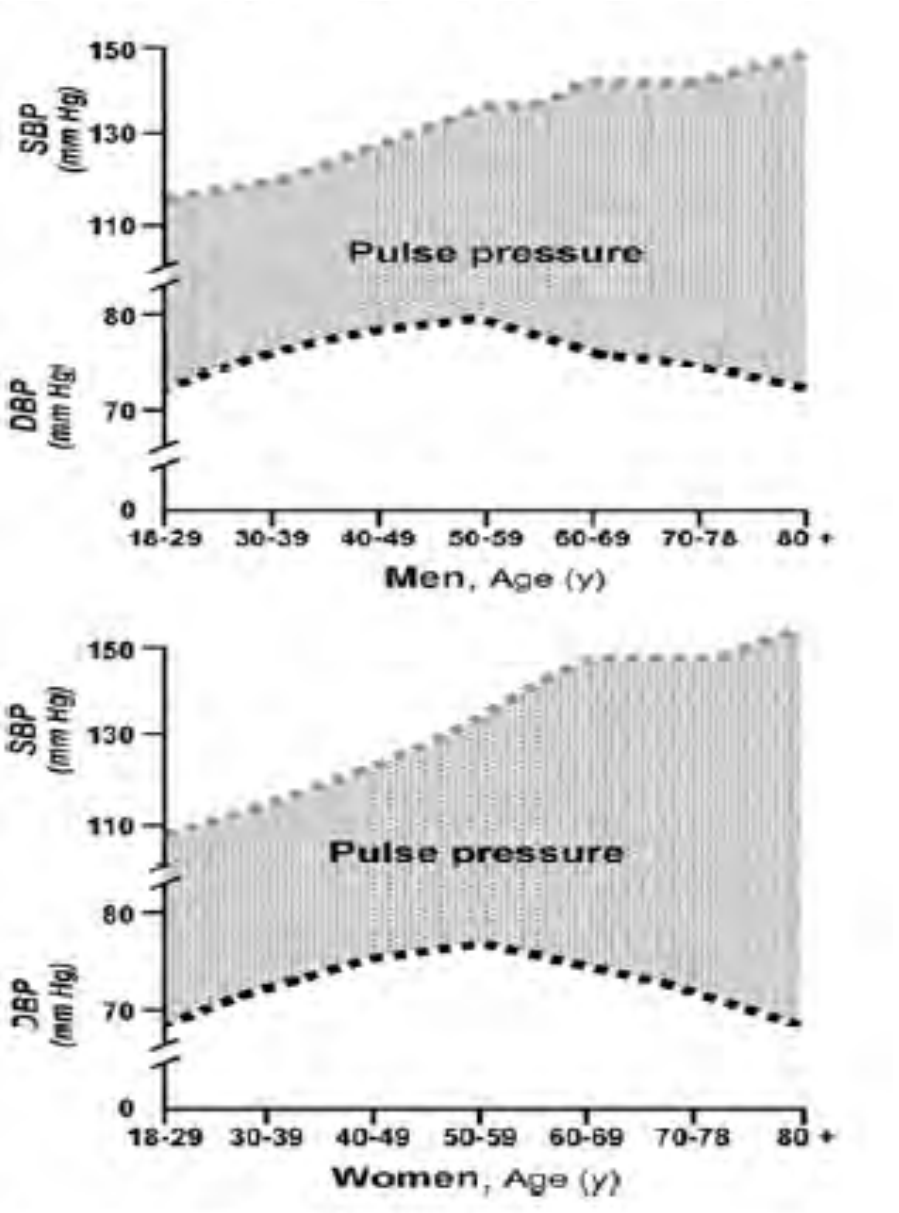
Dunlay S.M. et al, Nature Reviews- Cardiology 2017

Ipertensione arteriosa

- Prevalenza ipertensione in Europa:

  60% > USA-Canada

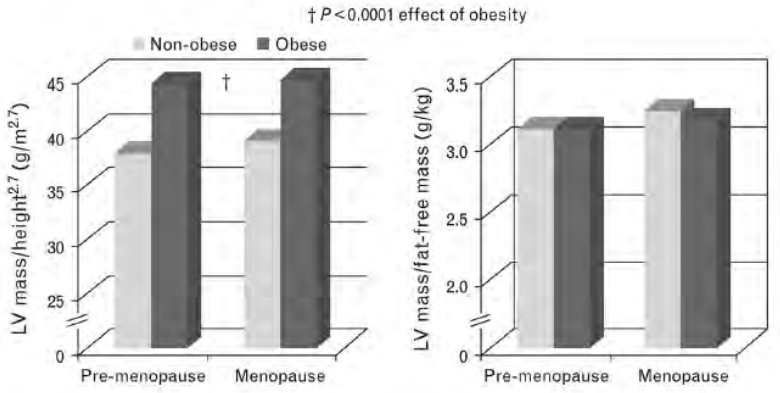
- Regola delle metà…



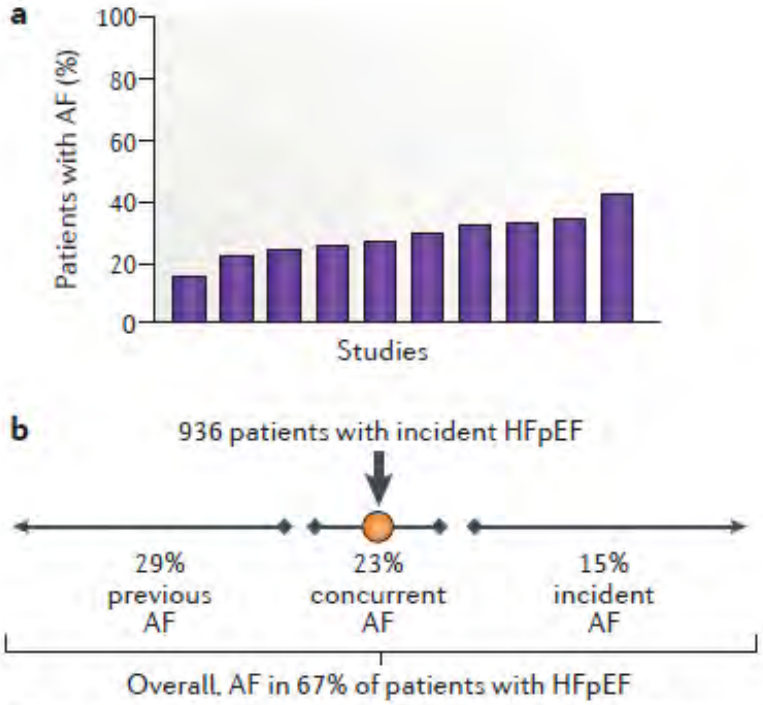
Vishram J.K.K. Dan Med J 2014

Pedrotty D.M. , Jessup M. Circ Cardiovsc Qual Outcomes 2015

“Frailty, Thy Name Is Woman”



De Simone G. et al J Hypertens 2011



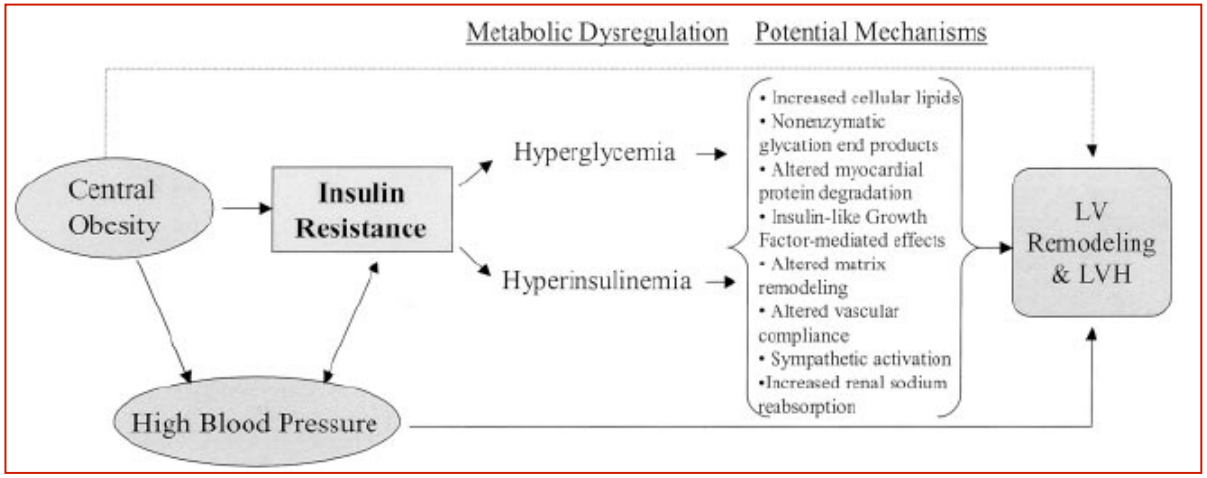
Dunlay S.M. et al, Nature Reviews- Cardiology 2017

PREDIABETE/DIABET E E LV

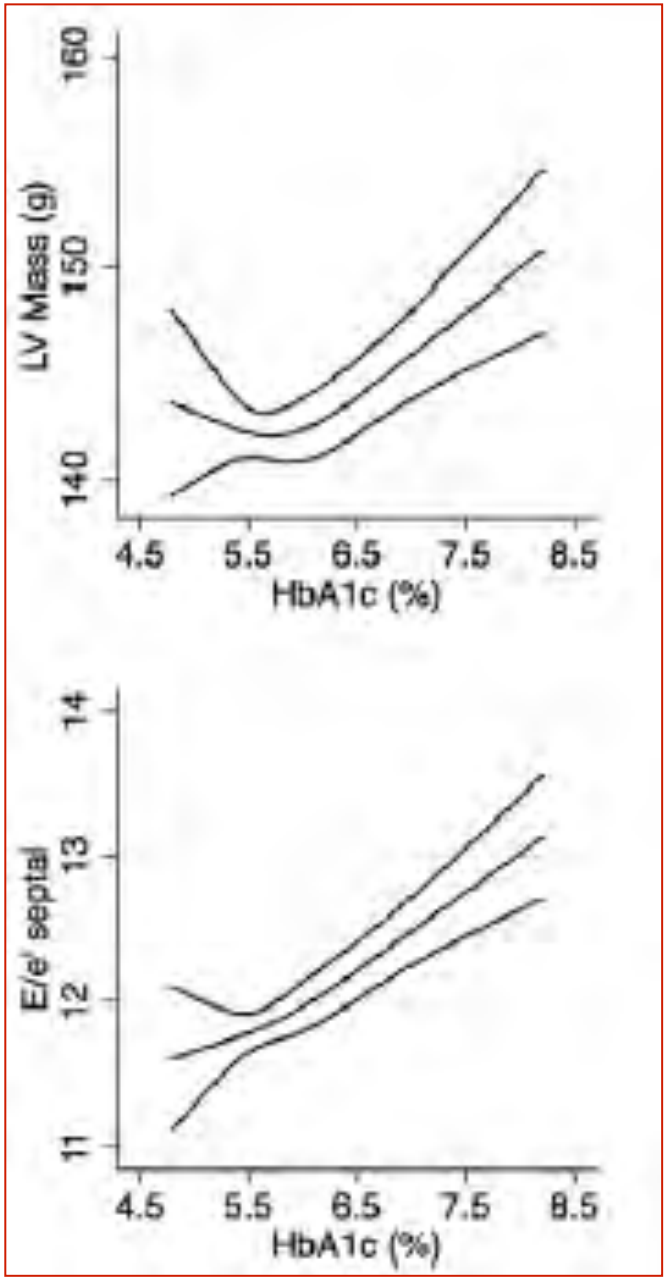
2623 soggetti FHS
(1514 donne
età media 53 aa)

LVM aumenta con gravità intolleranza glicidica

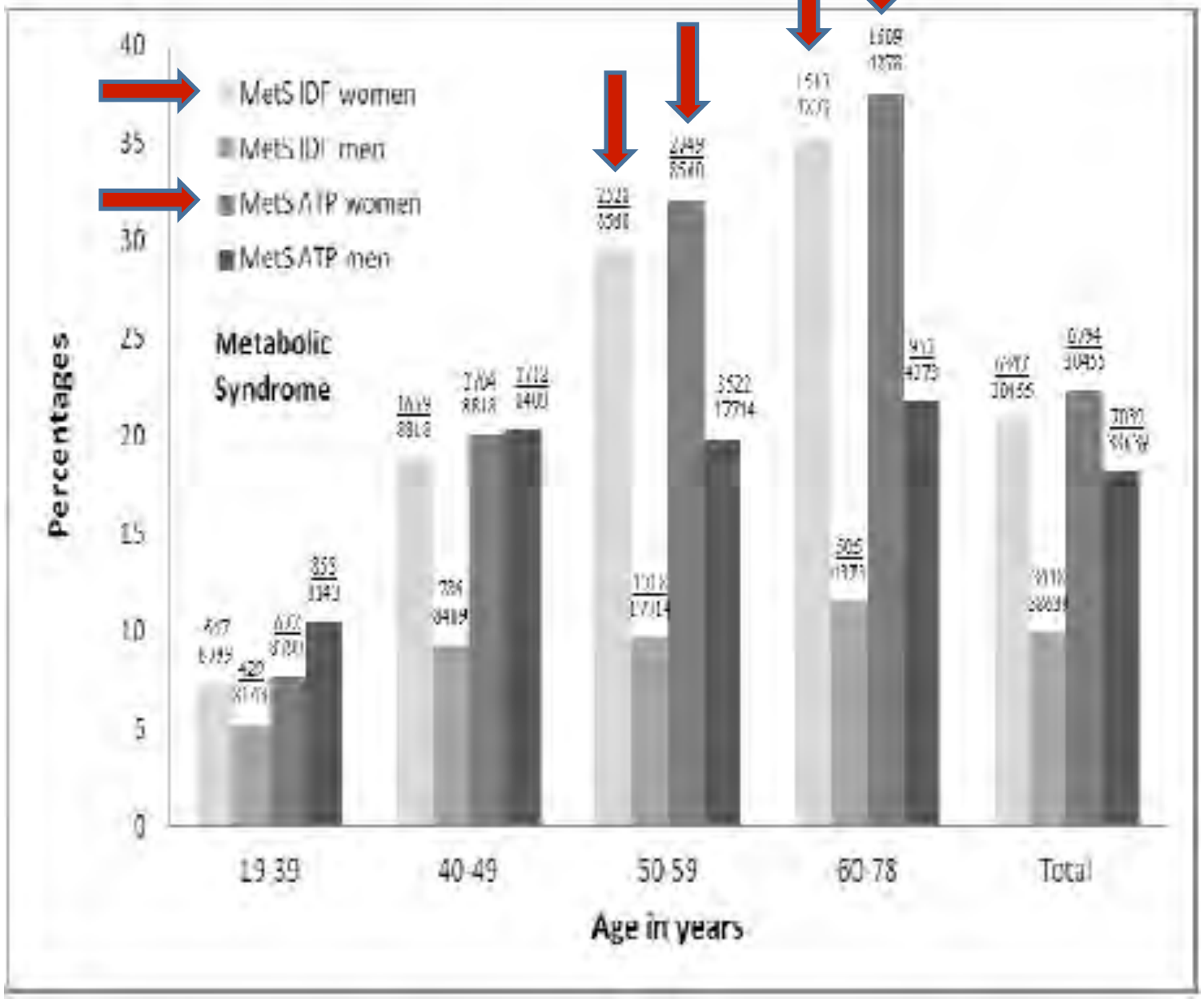
SOPRATTUTTO nelle DONNE



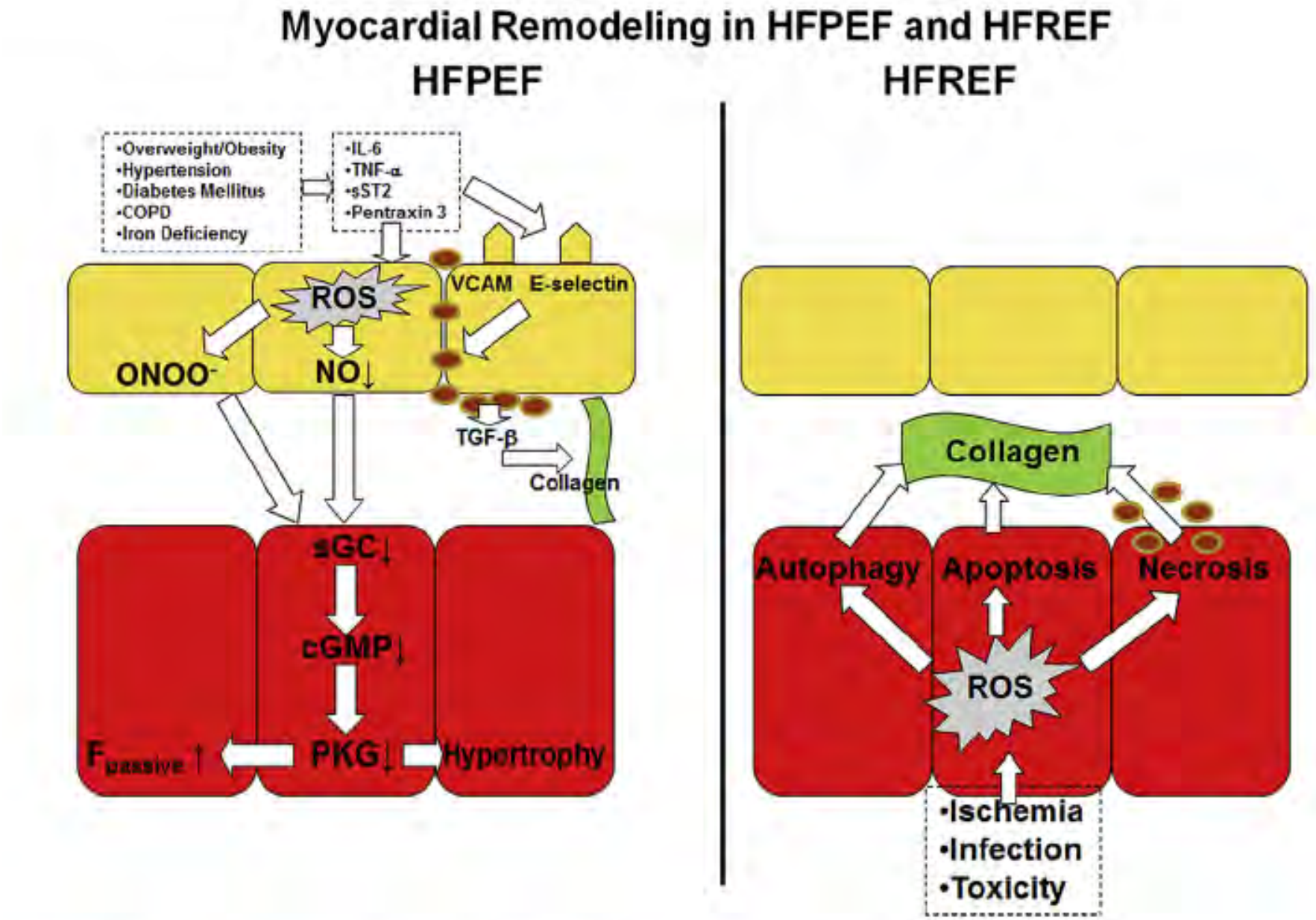
Rutter M K et al , **Framinham Heart Study**
Circulation 2003



Skali H et al, **ARIC Study**
Circ Heart Fail. 2015



Vishram J.K.K. Dan Med J 2014



Paulus W.J. et al JACC 2013

CONCLUSIONI

Le donne:

- sono…deboli di diastole
- vanno incontro più spesso a comorbilità che danneggiano la diastole
- evolvono più spesso in HFpEF

Quindi:

- prevenzione mirata
- terapie specifiche dell'HFpEF

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

- Prevalenza HF: 1-2% → ≥ 10% oltre i 70 aa
- Incidenza HF: ↓ soprattutto per HFrEF

- **HFpEF e HFrEF: ≠ epidemiologia ed eziologia**

- HFpEF: donne, età avanzata, ipertensione, FA
- HFrEF: uomini, età meno avanzata, CAD

Sindrome metabolica: definizioni

MetS Criteria	WHO (1999)	EGIR (1999)	NCEP-ATPIII (2001)	AACE (2002)	NCEP-ATPIII (2004)	IDF (2005)	New Joint (2009)
Absolutely required:	One of: DM2, IGT, IFG, and/or IR	IR[¶]		MetS diagnosis dependes on clinical judgment based on risk factors[‡]		WC	
Other criteria:	≥ 2	≥ 2	≥ 3		≥ 3	2	≥ 3
Blood pressure (mmHg)	≥ 140/90 and/or	≥ 140/90 and/or	≥ 130/85 and/or	≥ 130/85	≥ 130/85 or	SBP ≥ 130 or DBP ≥ 85 or	SBP ≥ 130 and/or DBP ≥ 85 or
Antihypertensive drugs	yes	yes	yes		yes	yes	yes
Dyslipidemia Triglyceride (mmol/L)	≥ 1.695 and/or	≥ 2.0 and/or	≥ 1.7 and/or	≥ 1.69 and/or	≥ 1.7 and/or	≥ 1.7 and/or	≥ 1.7 and/or
HDL-C (mmol/L)	≤ 0.9 (M) < 1.0 (W)	< 1.0 or	< 1.03 (M) < 1.29 (W)	< 1.04 (M) < 1.29 (W)	< 1.03 (M) < 1.29 (W)	< 1.03 (M) or < 1.29 (W) or	< 1.0 (M) or < 1.3 (W) or
Lipid lowering drugs		yes				yes	yes
Central obesity Waist:hip ratio	>0.90 (M) and/or >0.85 (W) and/or						
WC (cm)		≥ 94 (M) ≥ 80 (W)	≥ 102 (M) ≥ 88 (W)		> 102 (M) > 88 (W)	ethnicity specific[*] or	ethnicity specific[*]
BMI (kg/m^2)	> 30			≥ 25		> 30	
Dysglycemia DM 2	One of: yes	no				yes	
IGT (mmol/L)	≥ 7.8 and < 11.1	≥ 7.8 and < 11.1		> 7.8 and < 11.1			
IFG/ FG (mmol/L)	≥ 6.1 and < 7.0	≥ 6.1 and < 7.0	≥ 6.1	> 6.1 and < 7.0	≥ 5.6 or	≥ 5.6[†] or	≥ 5.6 or
IR	yes	yes					
Anti-diabetic drugs					yes	yes	yes
Microalbuminuria	UAER≥20 µg/min or ACR ≥30 mg/g						

Vishram J.K.K. Dan Med J 2014

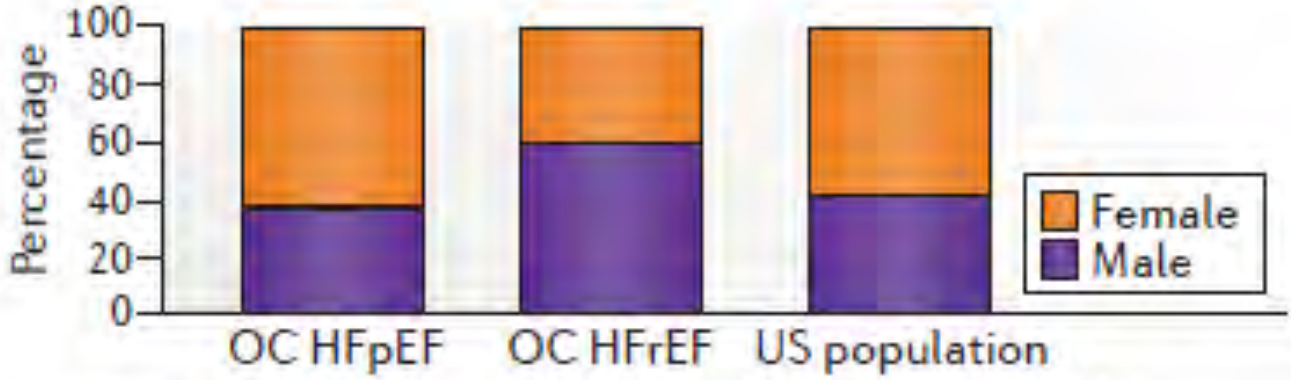
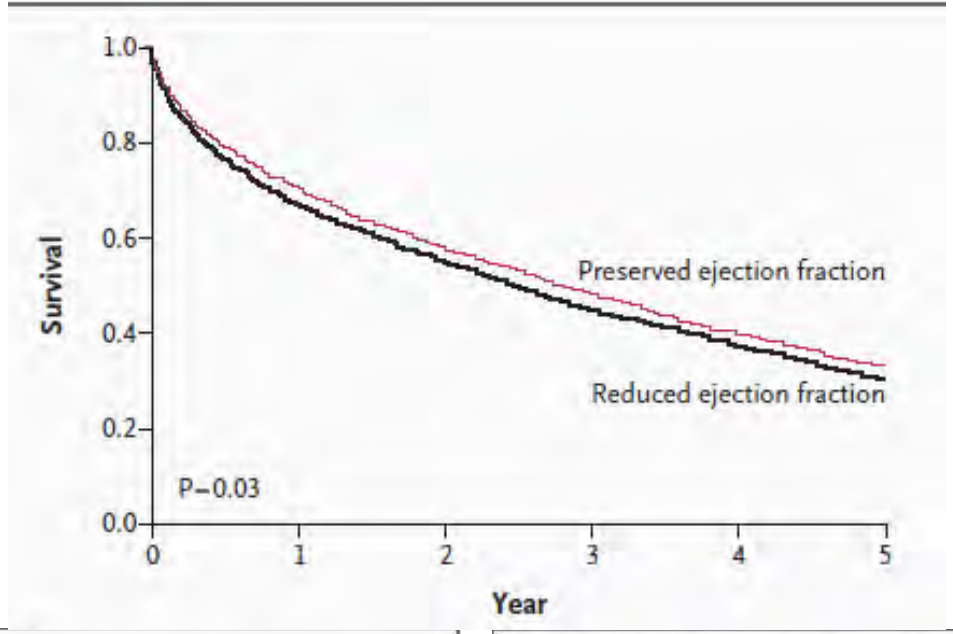
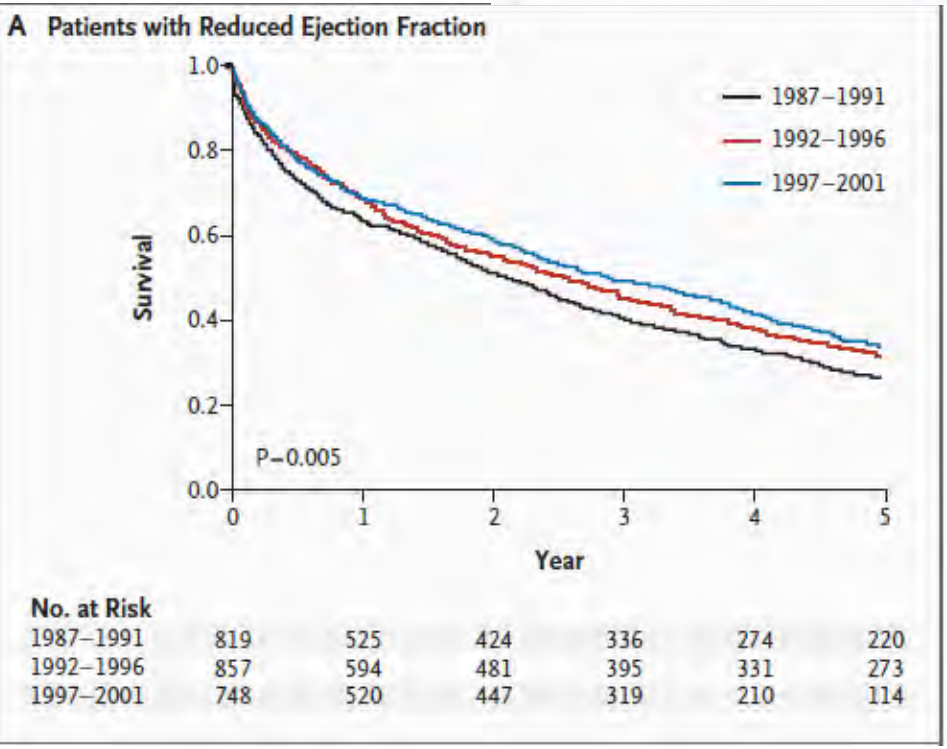
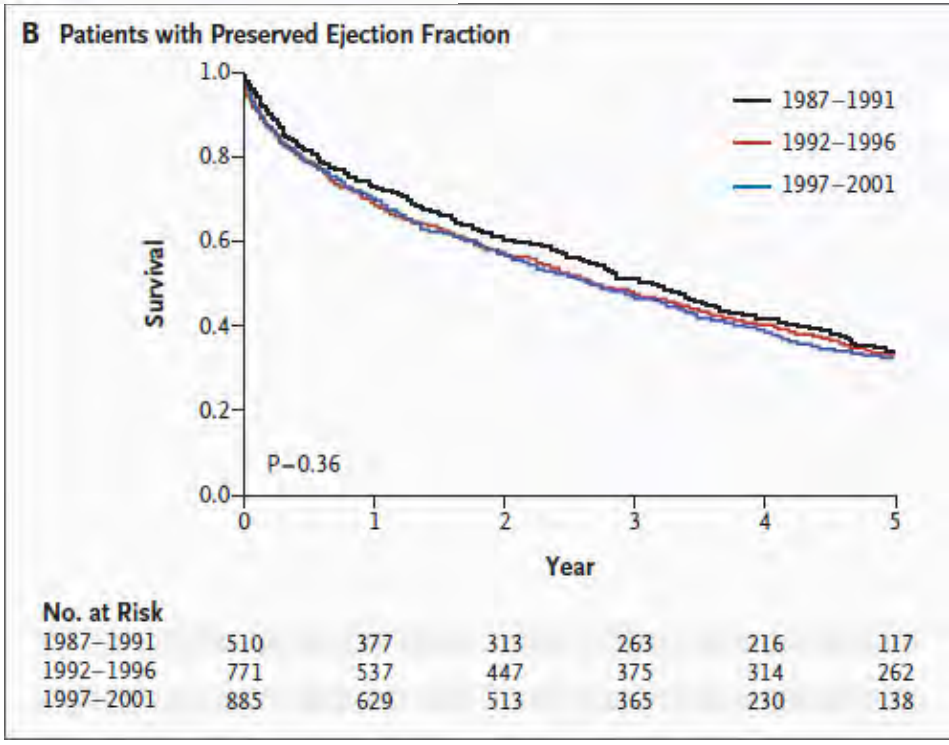


Figure 6 | **Summary of incident HFpEF and HFrEF in Olmsted County, Minnesota, USA.** The sex-specific distribution of all incident cases of heart failure with preserved ejection fraction (HFpEF; *n* = 1,089; mean age = 78 years) and heart failure with reduced ejection fraction (HFrEF; *n* = 971; mean age = 73 years) in Olmsted County (OC) over the study period (2000–2010), and the sex-specific distribution of the US population aged >75 years.





No. at Risk						
1987–1991	819	525	424	336	274	220
1992–1996	857	594	481	395	331	273
1997–2001	748	520	447	319	210	114



No. at Risk						
1987–1991	510	377	313	263	216	117
1992–1996	771	537	447	375	314	262
1997–2001	885	629	513	365	230	138

Owan T.E. et al N Engl J Med 2006

Table 2 Clinical trials in patients with HFpEF

Trial name/author	Year	Intervention	No. of subjects	LVEF as inclusion criterion	Outcome(s)	Findings
Setaro et al. [70]	1990	Verapamil vs placebo	20	>45 %	Mean EF Systolic BP Peak filling rate Exercise capacity	No effect on mean EF and systolic BP Exercise capacity improved by 33 %, peak filling rates by 30 %
Aronow et al. [71]	1993	Enalapril	21	Normal	Exercise time	Improved exercise time
Aronow et al. [72]	1997	Propanolol	158	>40 %	Mortality	Decreased mortality (by 35 %) Decreased mortality + non-fatal MI (by 37 %)
CHARM-Preserved/Yusuf et al. [39]	2003	Candesartan vs placebo	3023	>40 %	Hospitalisation Mortality	No effect on mortality Decreased hospitalisation when adjusted for baseline characteristics (HR=0.84; p=0.047)
Nodari et al. [73]	2003	Nebivolol vs atenolol	26	>50 %	Haemodynamic parameters during exercise	Nebivolol associated with greater hemodynamic improvement than atenolo
Takeda et al. [74]	2004	Carvedilol vs standard therapy	40	≥45 %	Plasma BNP levels	Decreased plasma BNP levels
PEP-CHF/Cleland et al. [41]	2006	Perindopril vs placebo	846	>40 %	Re-hospitalisation at 1 year Mortality	No effect on mortality Decreased 1-year re-hospitalisation (HR=0.63; p=0.033)
SENIORS/Flather et al. [75]	2006	Nebivolol vs placebo	752	>35 %	Mortality CV-related hospitalisation	No effect on mortality or hospitalisation in patients with EF >40 %
DIG-PEF/Ahmed et al. [40]	2006	Digoxin vs placebo	988	>45 %	Hospitalisation Mortality	No effect
I-PRESERVE/ Massie et al. [43]	2008	Irbesartan vs placebo	4128	≥45 %	Hospitalisation Mortality	No effect
Yip et al. [42]	2008	Diuretics vs diuretics + ACEi/ARBs	150	>45 %	Quality of life (QoL) 6-min walk test (6-MWT) LVEF BP NT-pro-BNP levels	Improved QoL, 6-MWT and systolic and diastolic BP. No effect of adding ACEi/ARB No change in LVEF NT-pro-BNP levels declined only with addition of ACEi/ARB
Tehrani et al. [76]	2010	Statin vs controls	270	≥50 %	Hospitalisation Mortality	Decreased mortality (RR=0.65; p=0.028) No effect on hospitalisation
PARAMOUNT/ Solomon et al. [77]	2012	LCZ696 vs Valesartan	301	≥45 %	NT-pro-BNP levels	LCZ696 caused significantly greater reduction in NT-pro-BNP levels
Aldo-DHF/ Edelmann et al. [78]	2013	Spironolactone vs placebo	422	≥50 %	LV diastolic function Maximal exercise capacity	Improved LV diastolic function No improvement in exercise capacity or quality of life
J-DHF/Yamamoto et al. [79]	2013	Carvedilol vs controls	245	>40 %	Cardiovascular mortality and unplanned hospitalisation for HF	No improvement
RALI-DHF/Maier et al. [80]	2013	Ranolazine vs placebo	20	≥45 %	LVEDP and PCWP Echocardiographic changes	LVEDP and PCWP improved 30 min after infusion No long-term improvement in the echocardiographic parameters
Pitt et al. [45]	2014	Spironolactone vs placebo	3445	≥45 %	Cardiovascular mortality Hospitalisation for HF	Decreased hospitalisation for HF (HR=0.83, p=0.04) No effect on mortality

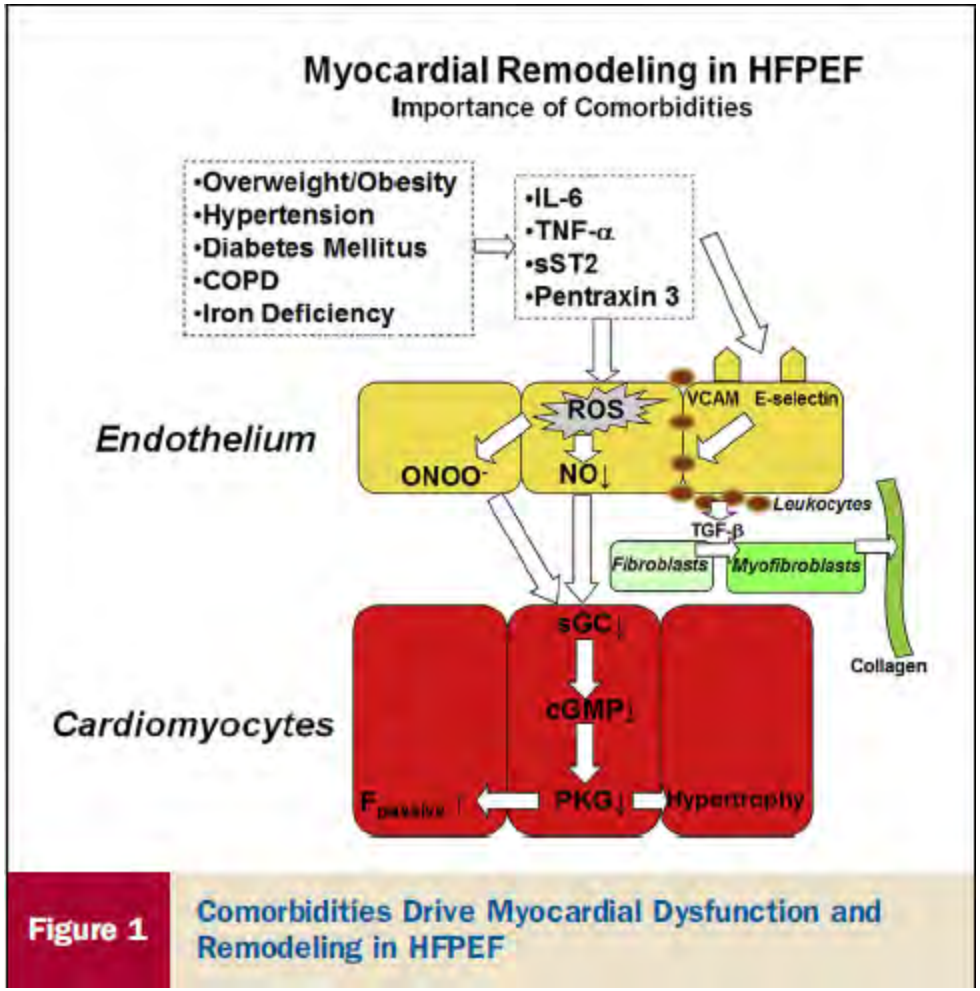


Figure 1 Comorbidities Drive Myocardial Dysfunction and Remodeling in HFPEF

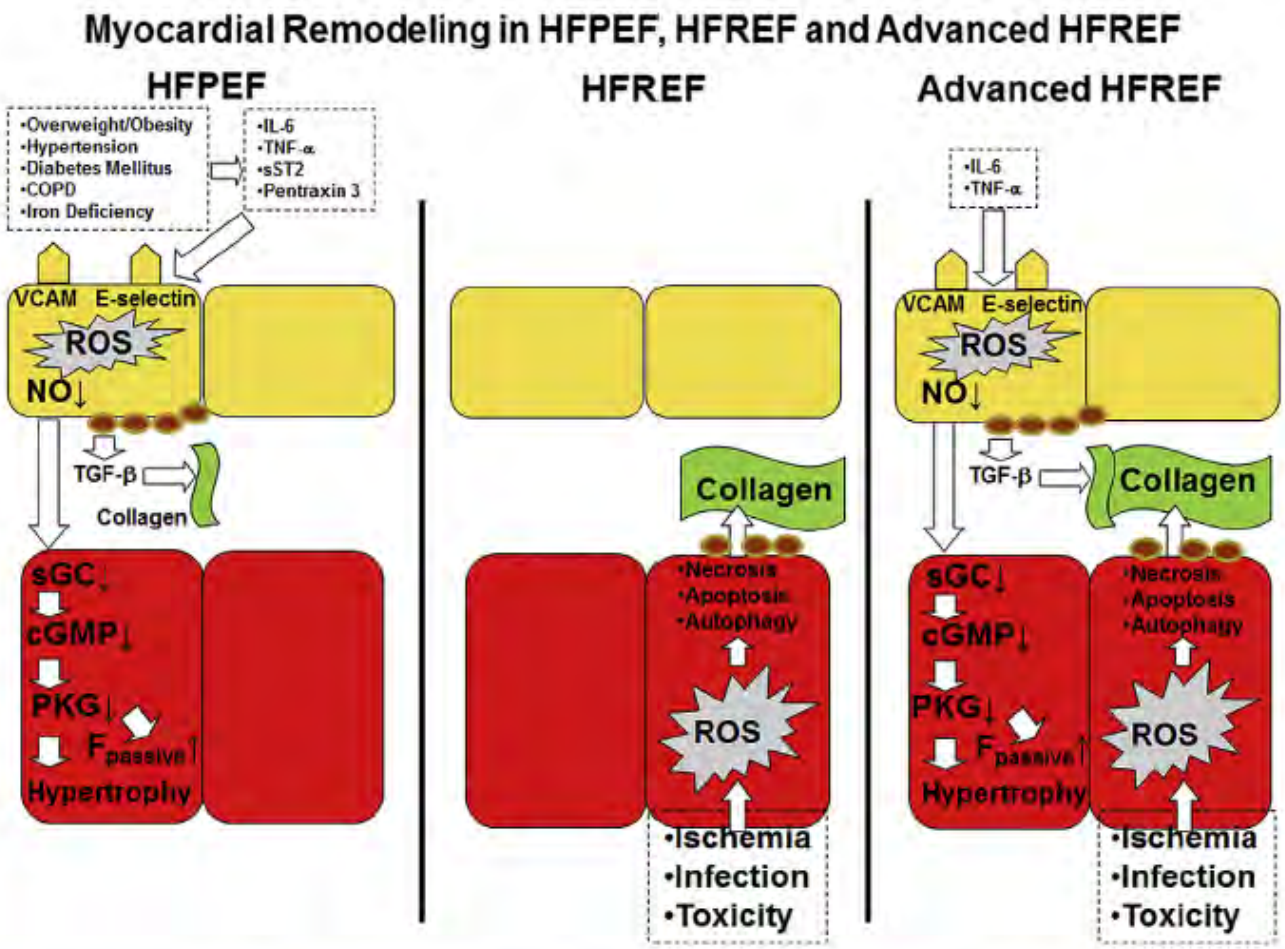


Figure 3 Myocardial Dysfunction and Remodeling in HFPEF, HFREF, and Advanced HFREF

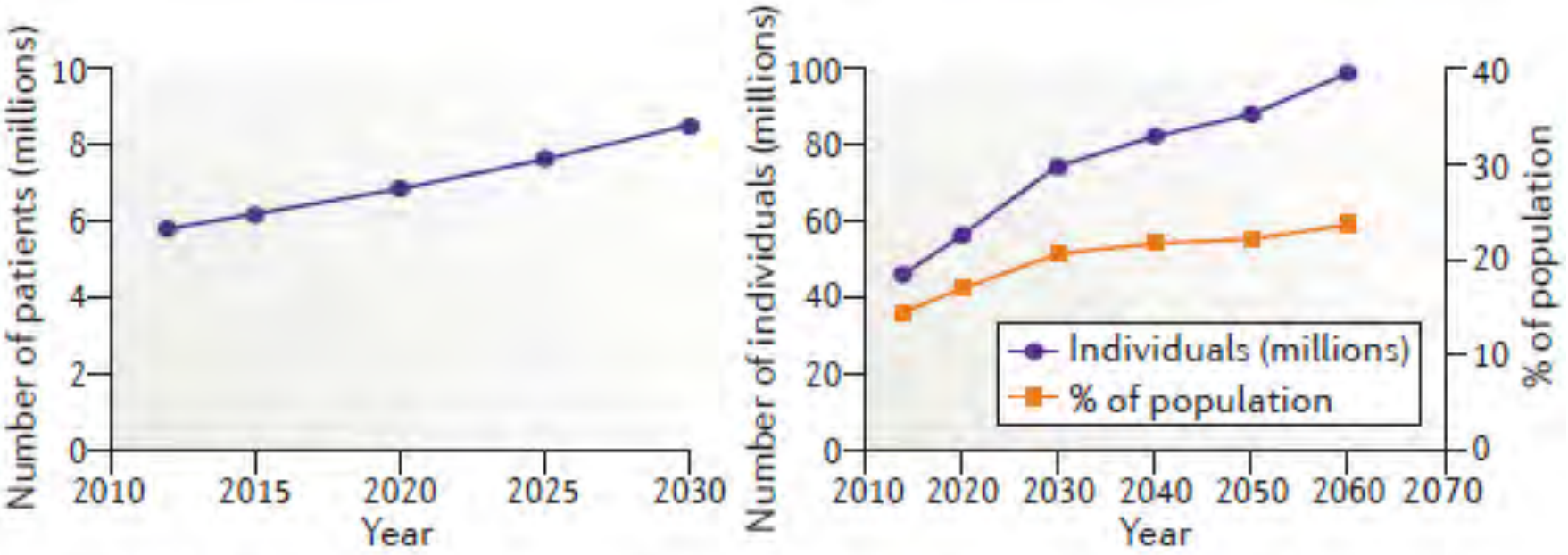


Figure 1 | **Projected population burden of heart failure in the USA. a** | Projected increases in the number of patients with heart failure in the USA from 2012 to 2030 assuming stable age-specific, sex-specific, and ethnicity-specific incidences[1]. **b** | Increases are caused largely by the projected changes in population demographics, with increases in the number and percentage of individuals aged >65 years[5].

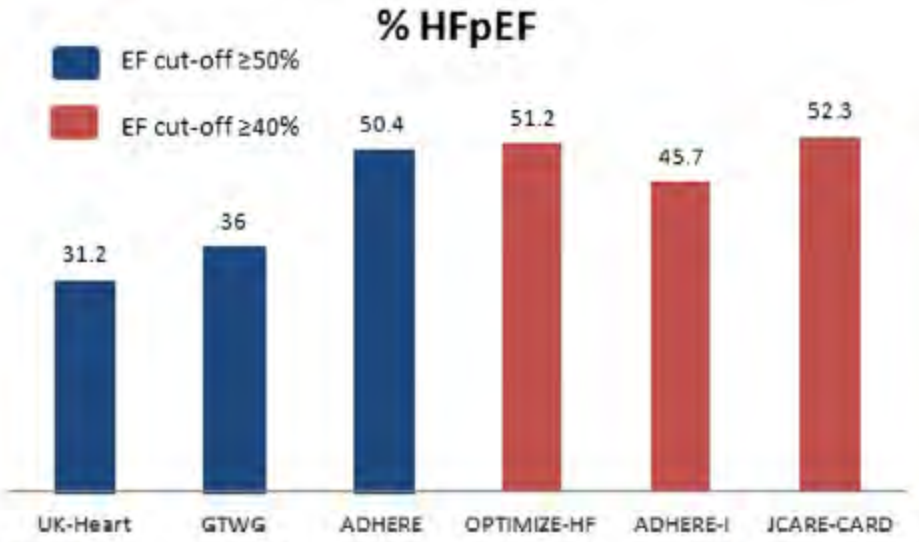


Fig. 1 Proportion of heart failure patients with preserved ejection fraction based on heart failure registries. *EF* ejection fraction, *GTWG* Get with the Guidelines, *ADHERE-I* ADHERE International, *JCARE-CARD* Japanese Cardiac Registry of Heart Failure in Cardiology

Dhingra A. et al, Curr Heart Fail Rep 2014

Mayo Clinic -Olmested County Minnesota

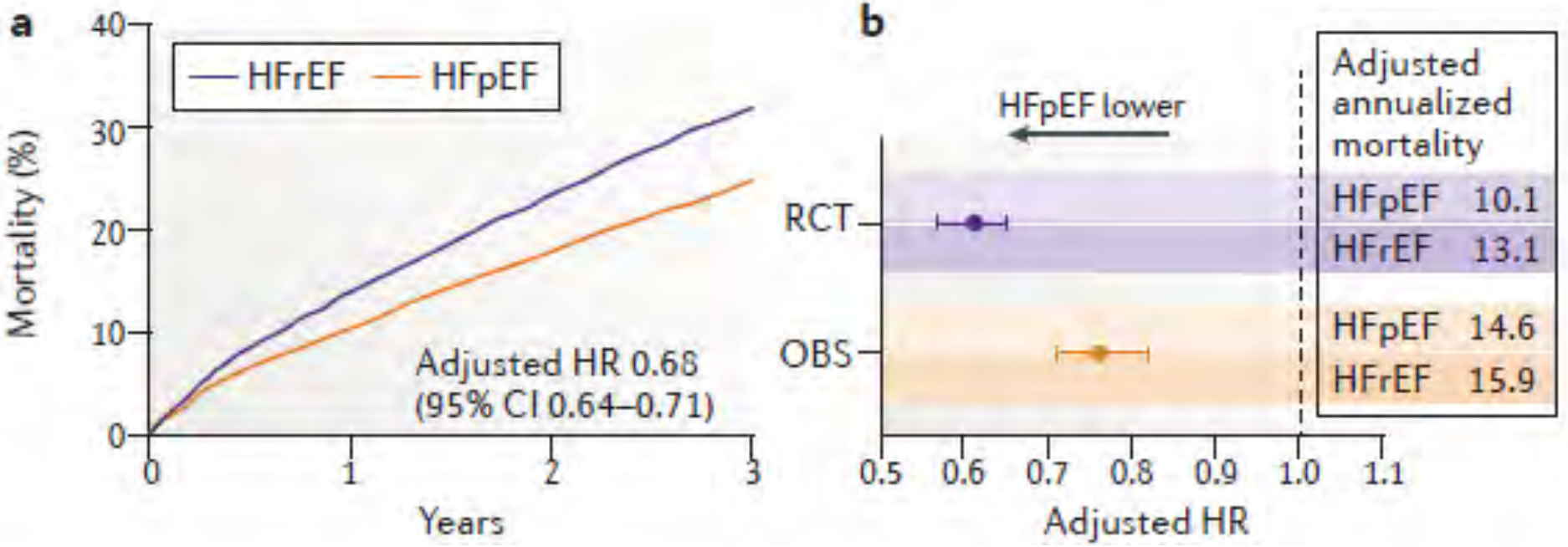
6076 pts ospedalizzati per HF dal 1987 al 2001

53% HFrEF e 47% HFpEF

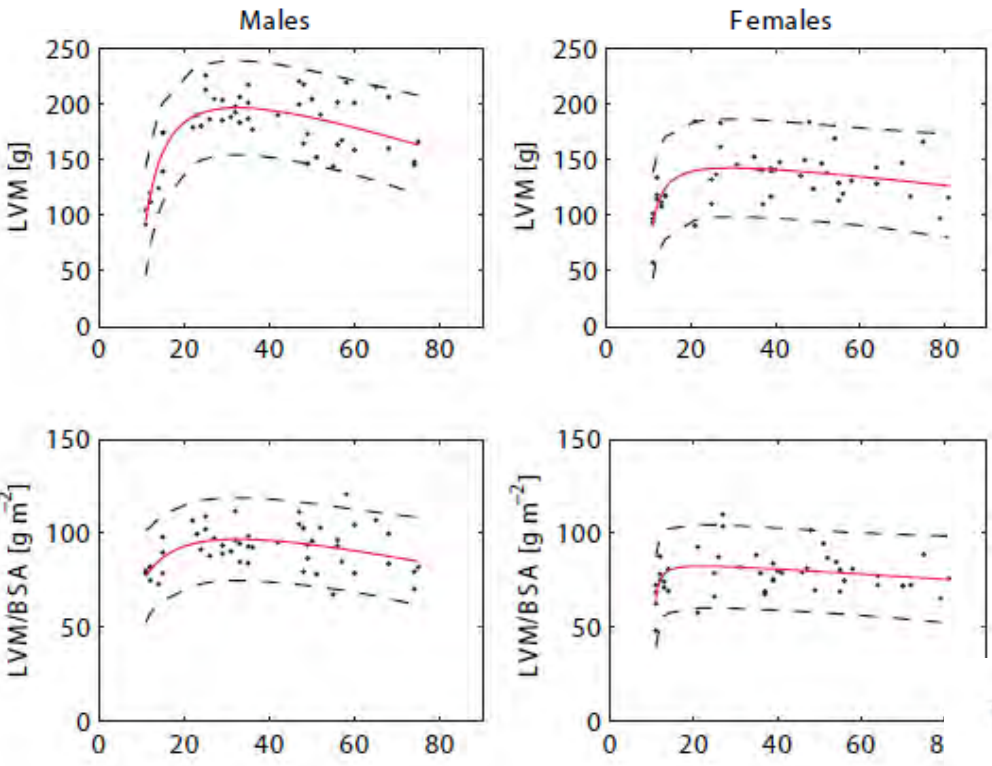
Table 1. Characteristics of Patients with Heart Failure and Preserved or Reduced Ejection Fraction.*

Characteristic	Reduced Ejection Fraction (N=2429)	Preserved Ejection Fraction (N=2167)	P Value	Adjusted P Value†
Age (yr)	71.7±12.1	74.4±14.4	<0.001	NA
Male sex (% of patients)	65.4	44.3	<0.001	<0.001
Body-mass index‡	28.6±7.0	29.7±7.8	0.002	0.17
Obesity (% of patients)‡§	35.5	41.4	0.007	0.002
Serum creatinine on admission (mg/dl)	1.6±1.0	1.6±1.1	0.31	0.30
Hemoglobin on admission (g/dl)	12.5±2.0	11.8±2.1	<0.001	<0.001
Hypertension (% of patients)	48.0	62.7	<0.001	<0.001
Coronary artery disease (% of patients)	63.7	52.9	<0.001	<0.001
Atrial fibrillation (% of patients)	28.5	41.3	<0.001	<0.001
Diabetes (% of patients)	34.3	33.1	0.42	0.61
Substantial valve disease (% of patients)	6.5	2.6	<0.001	0.05
Ejection fraction (%)	29±10	61±7	<0.001	NA

Owan T.E. et al N Engl J Med 2006



Comparative mortality in HFpEF and HFrEF from the MAGGIC study51. a | Age-adjusted and comorbidity-adjusted all-cause mortality in heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) are shown. b | Adjusted hazard ratios for mortality in HFpEF versus HFrEF according to types of studies (randomized clinical trials [RCT] or observational studies [OBS]) are shown along with the adjusted annualized mortality


Males
Females
LVM [g]
LVM/BSA [g m^{-2}]

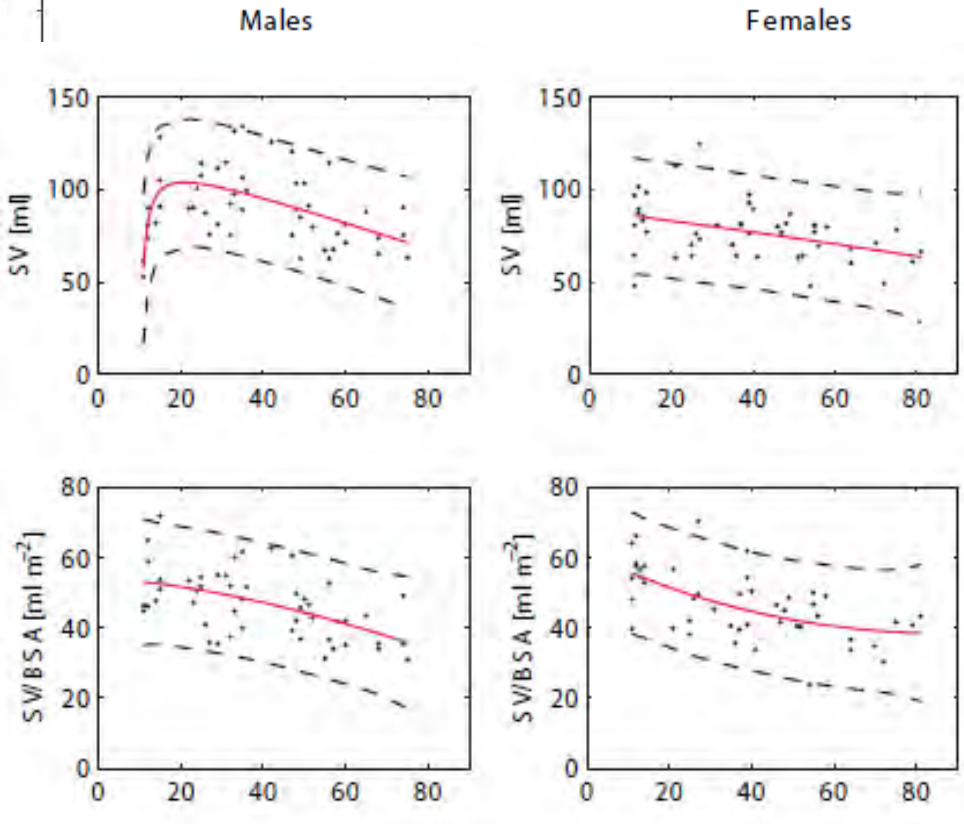
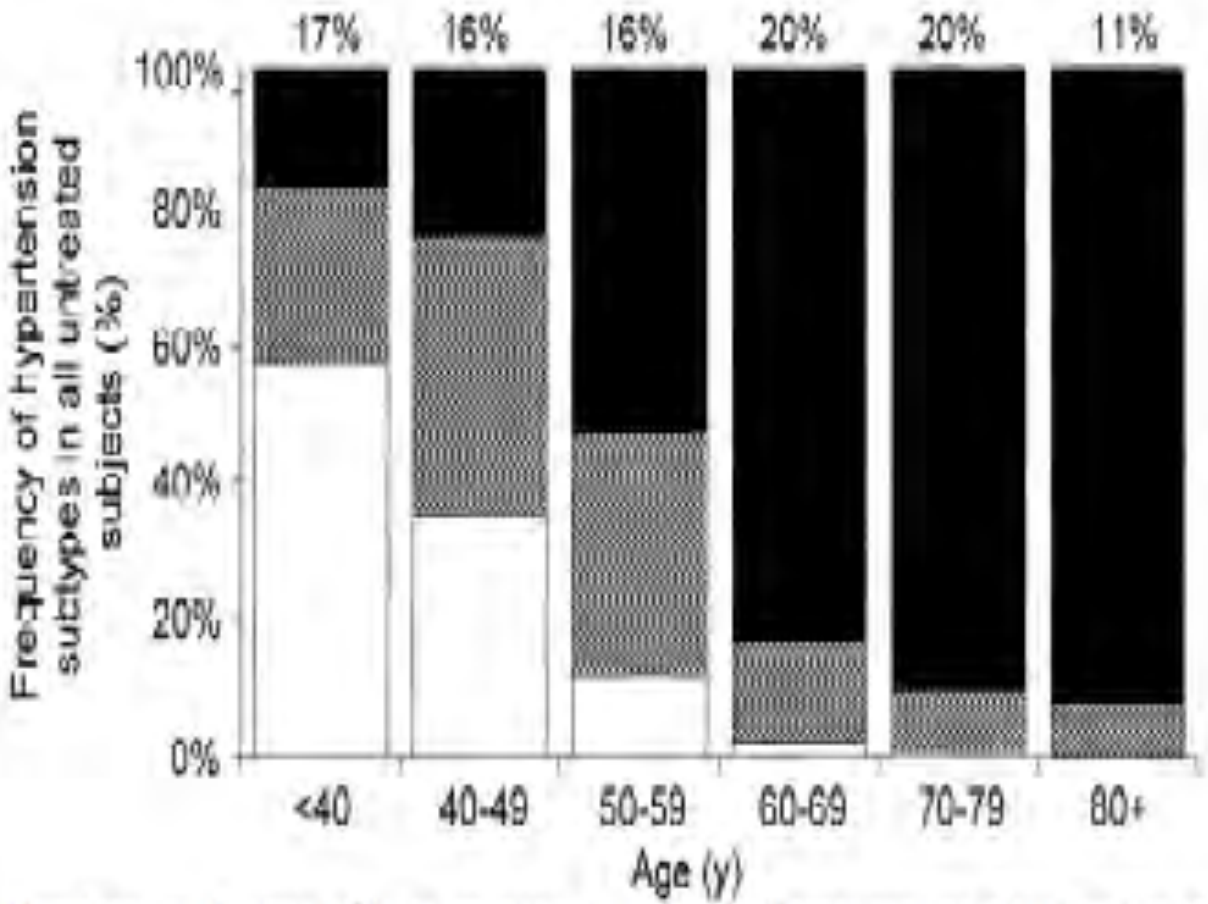

Males
Females
SV [ml]
SV/BSA [ml m^{-2}]

Table 3: Study characteristics

Paper	I	II	III
Number of:			
Participants	68 551	85 772	69 094
Cohorts	34	42	36
European countries	10	11	10
Non-European countries		1	
Years of follow-up	13·2	13·3	12·2
Endpoints	total stroke	mortality from stroke CHD all-causes	total stroke total CHD CVD mortality

Figure 2: Frequency of hypertension subtypes in untreated hypertensive individuals in different age groups



Numbers at the top of bars represent the overall percentage distribution of all subtypes of untreated hypertension in that age group. Black colour indicates isolated systolic hypertension (SBP ≥140 mmHg and DBP <90 mmHg); striped colour, systolic-diastolic hypertension (SBP ≥140 mmHg and DBP ≥90 mmHg); and white colour, isolated diastolic hypertension (SBP <140 mmHg and DBP ≥90 mmHg). From Franklin et al [71].

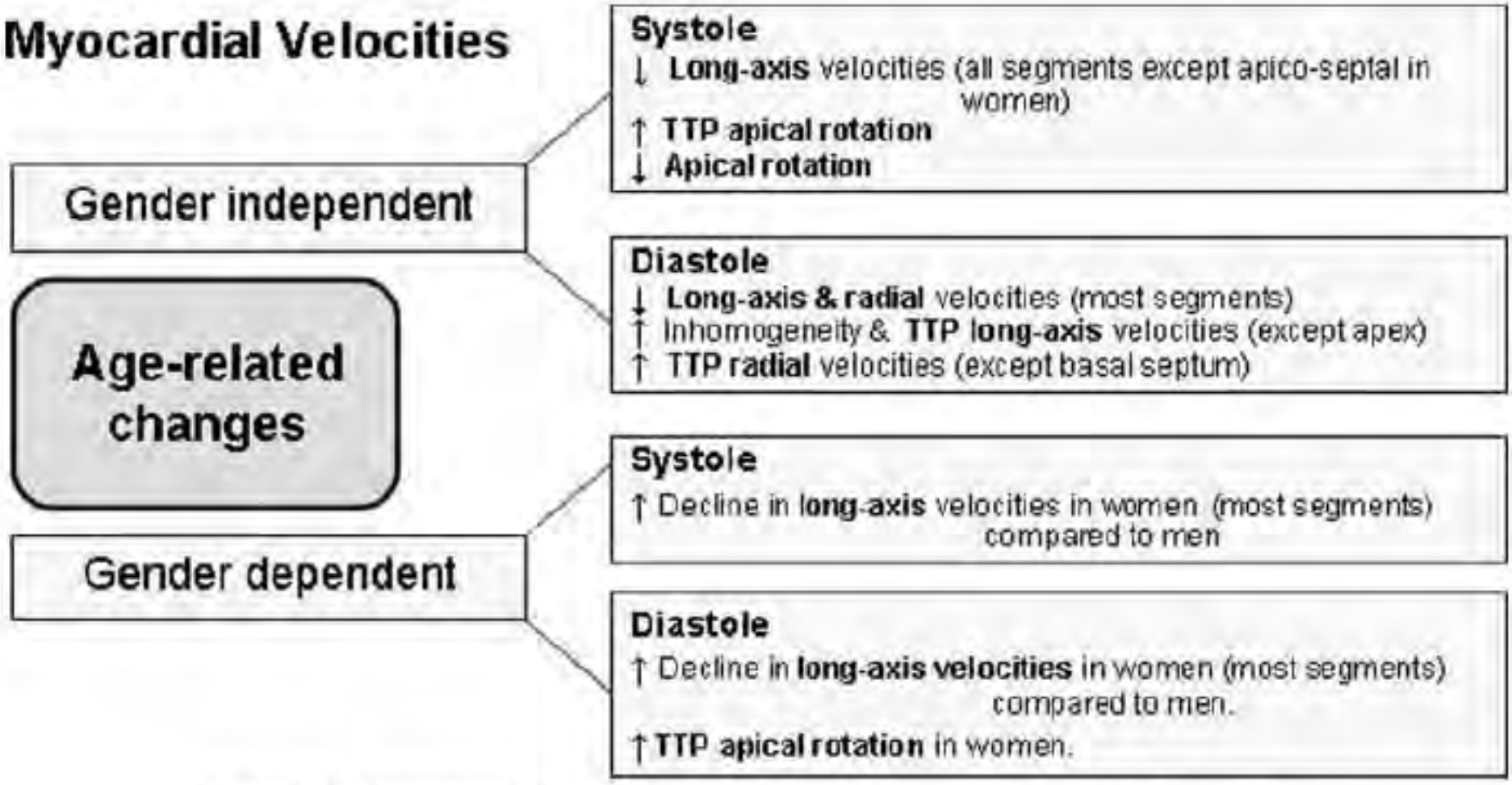
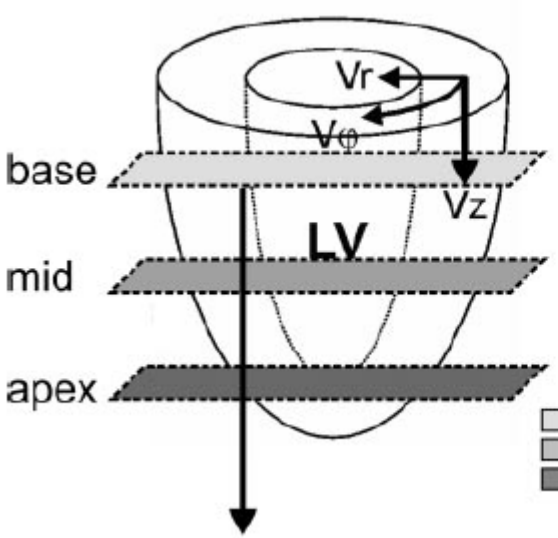
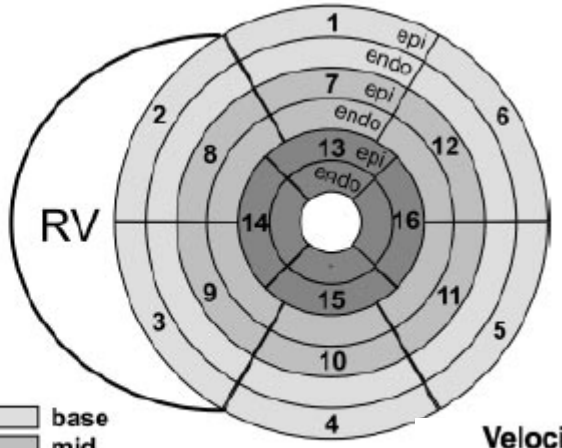
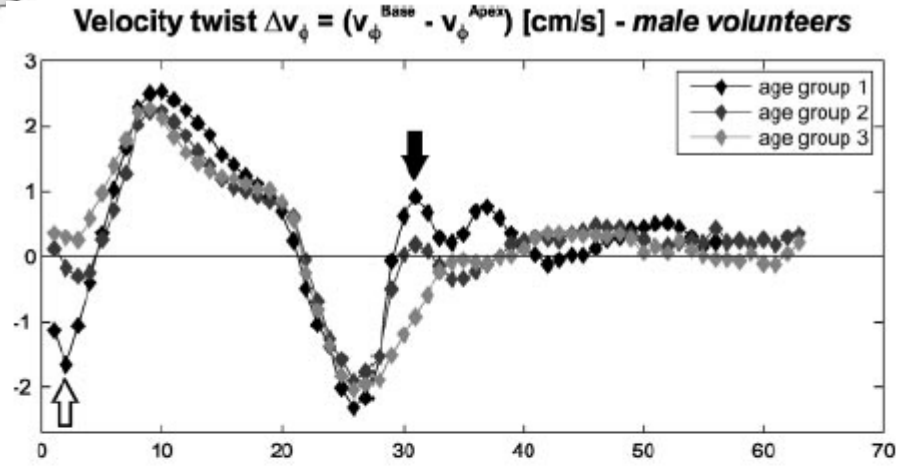
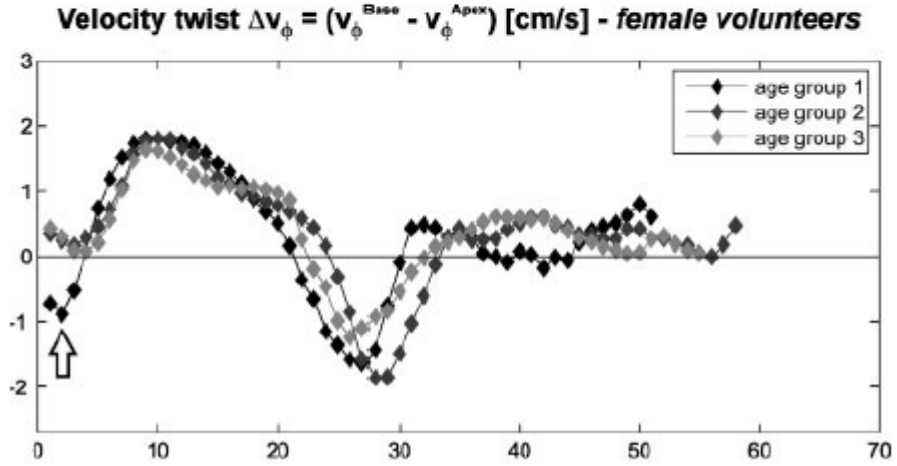


Figure 6. Summarizing figure of age-related myocardial motion changes.


Vr
Vφ
Vz
base
mid
apex
LV


RV
1
epi
endo
2
3
4
5
6
7
epi
endo
8
9
10
11
12
13
epi
endo
14
15
16
base
mid
apex


Velocity twist Δv_φ = (v_φ^Base - v_φ^Apex) [cm/s] - male volunteers
age group 1
age group 2
age group 3
3
2
1
0
-1
-2
0
10
20
30
40
50
60
70


Velocity twist Δv_φ = (v_φ^Base - v_φ^Apex) [cm/s] - female volunteers
age group 1
age group 2
age group 3
3
2
1
0
-1
-2
0
10
20
30
40
50
60
70
cardiac time frame

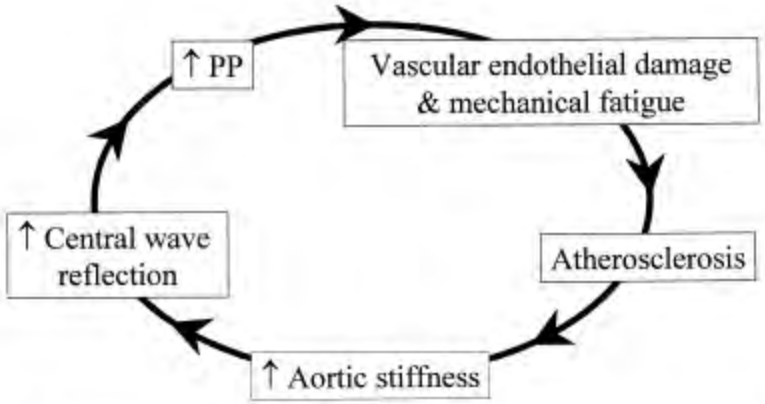


Figure 2. Schematic diagram illustrating the concept of bidirectionality in the relationship between pulse pressure (PP) and atherosclerosis. Elevated PP promotes vascular damage, an antecedent to atherosclerosis, which results in large-vessel stiffening and increased wave reflection, thus, further amplifying PP. While it is not clear which is the incipient event in this cycle, it is clear that, once initiated, a vicious cycle promoting disease progression ensues.