Heart Failure with Preserved EF (HFPEF) Epidemiology and management

Karl Swedberg
Senior Professor of Medicine
Sahlgrenska Academy
University of Gothenburg
Gothenburg, Sweden
e-mail: *karl.swedberg@gu.se*

Disclosures
Received research support/honoraria from
Astrazeneca, Amgen, Novartis, Roche, Servier

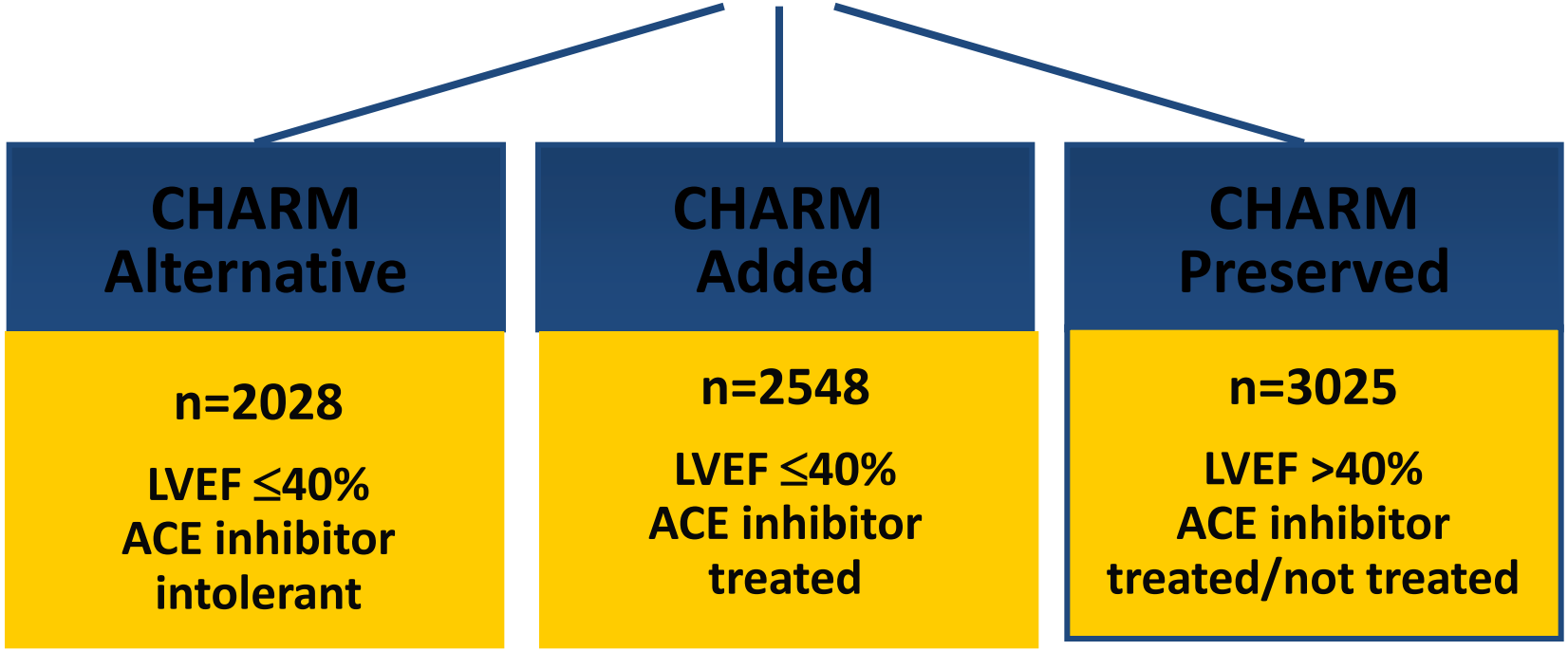
Diagnosis of HFPEF

The diagnosis of HF-REF requires three conditions to be satisfied:
1. Symptoms typical of HF
2. Signs typical of HF[a]
3. Reduced LVEF
The diagnosis of HF-PEF requires four conditions to be satisfied:
1. Symptoms typical of HF
2. Signs typical of HF[a]
3. Normal or only mildly reduced LVEF and LV not dilated
4. Relevant structural heart disease (LV hypertrophy/LA enlargement) and/or diastolic dysfunction (see Section 4.1.2)

McMurray et al: ESC Guidelines EHJ 2012

CHARM Programme

3 component trials (N=7601) comparing candesartan to placebo in patients with symptomatic heart failure



Primary outcome for each trial: CV death or CHF hospitalization

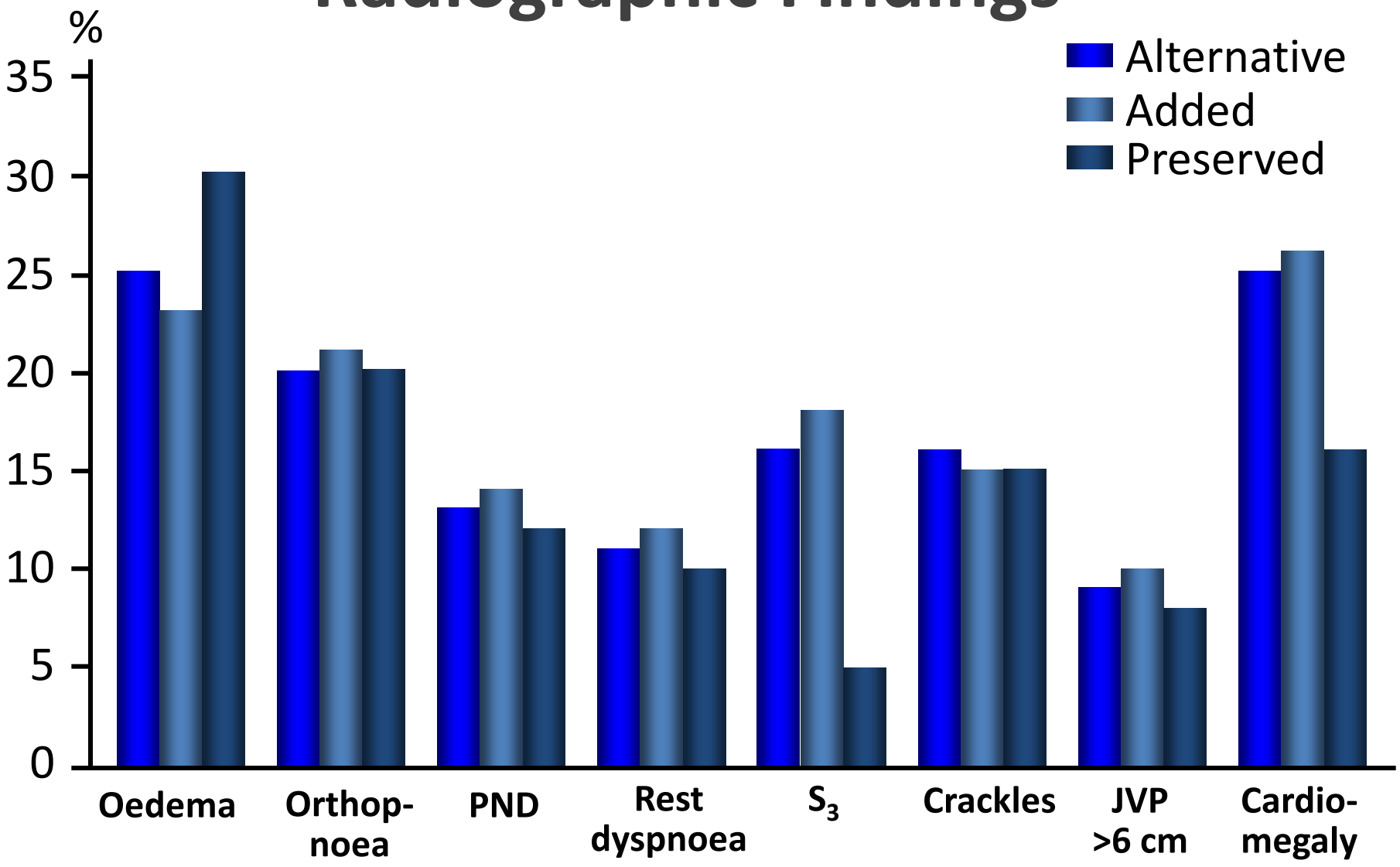
Pfeffer et al Lancet 2003

Baseline characteristics

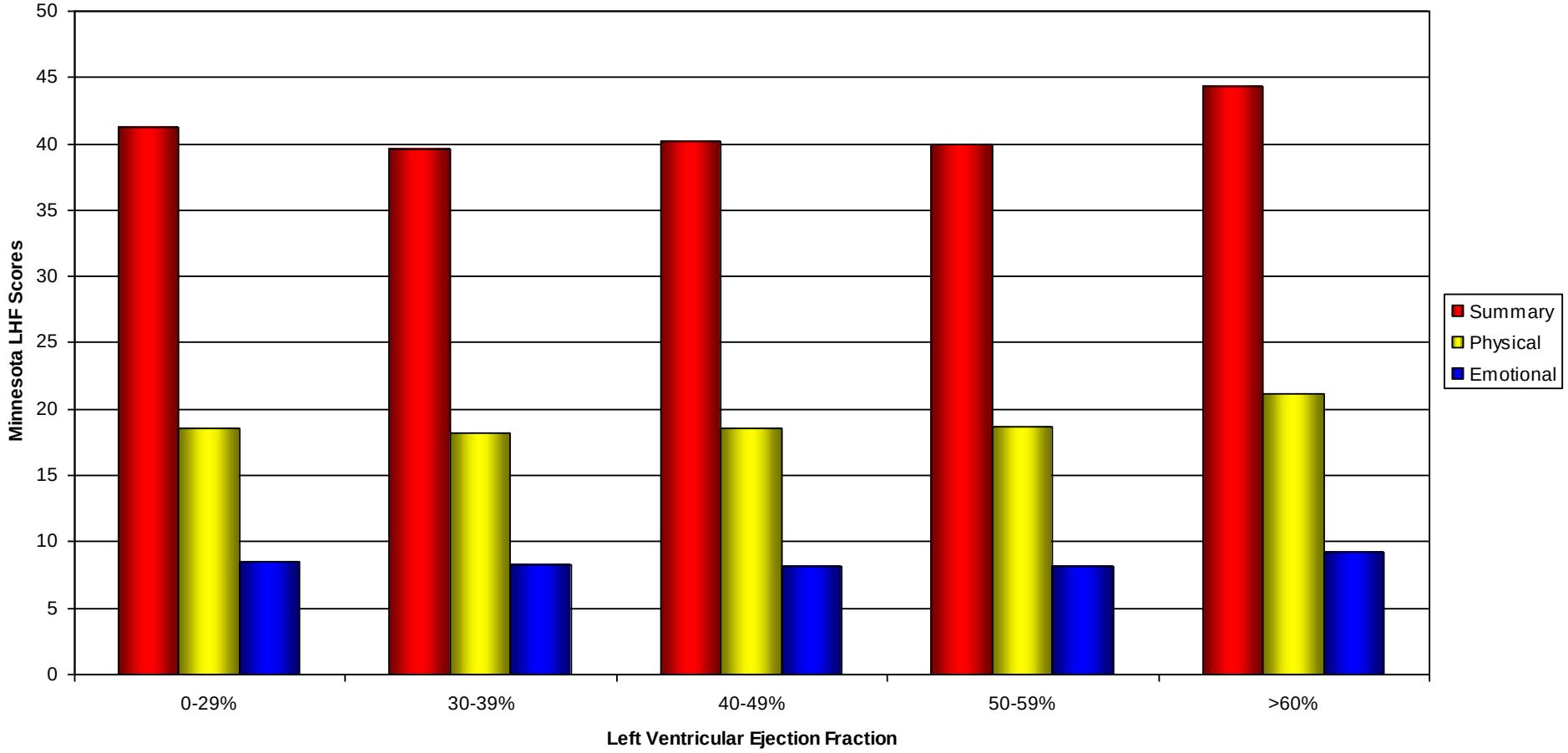
	Alternative n=2028	Added n=2548	Preserved n=3023	Overall n=7599
Mean age (years)	67	64	67	66
Women (%)	32	21	40	32
NYHA class (%)				
II	48	24	60	45
III	49	73	38	52
IV	3	3	2	3
Mean LVEF	30	28	54	39
Medical history (%)				
myocardial infarction	61	56	44	53
diabetes	27	30	28	28
hypertension	50	48	64	55
atrial fibrillation	25	26	29	27

Pfeffer et al Lancet 2003

CHF Signs, Symptoms and Radiographic Findings



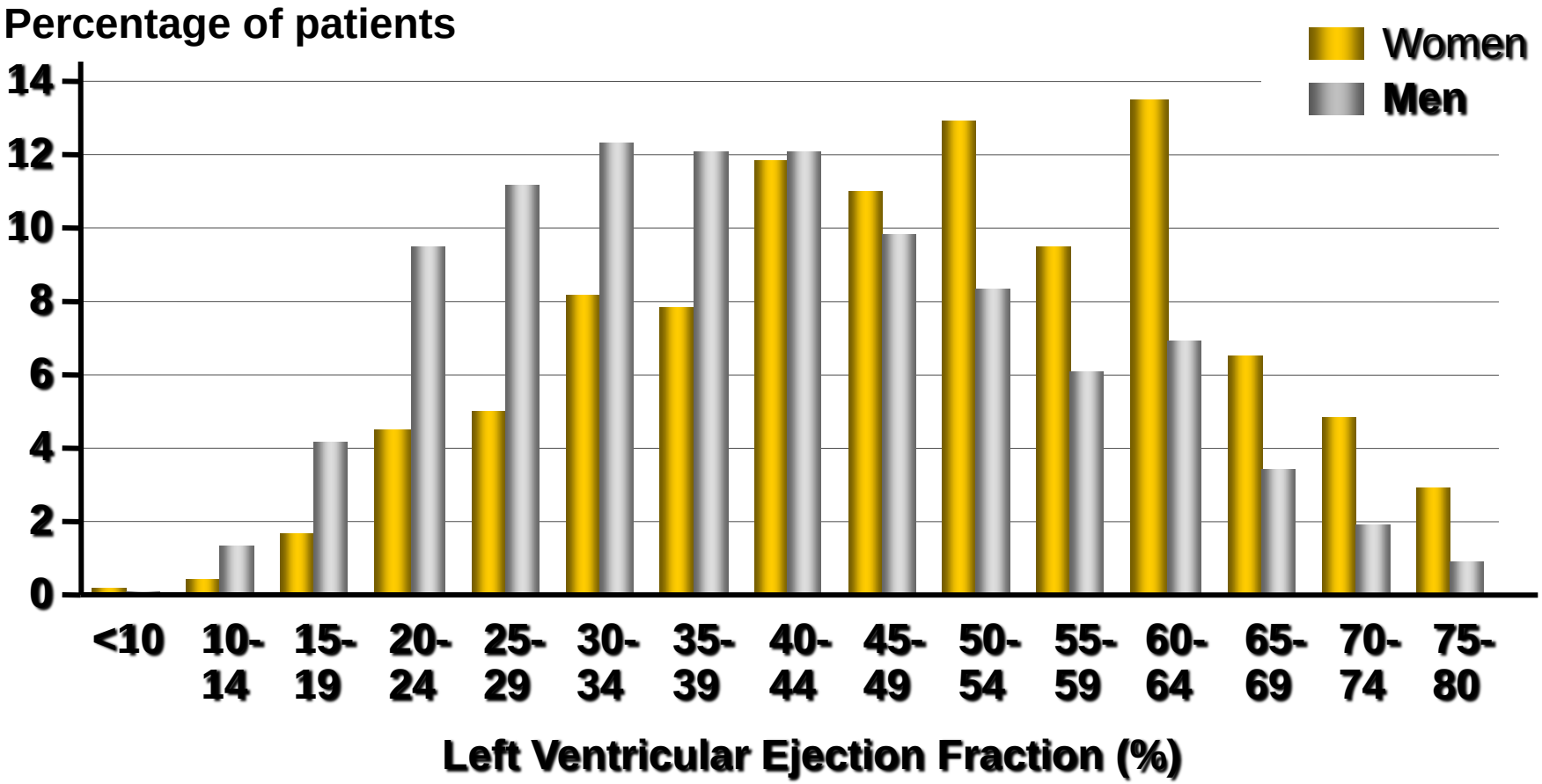
CHARM: Minnesota Living With Heart Failure and LVEF



Lewis et al EJHF 2006

Euroheart Failure
Distribution of ejection fraction

11,015 patients in 115 hospitals in 24 countries



Cleland et al Euroheart Survey EHJ 2003

Systolic HF & HFPHF in the Community

(Olmsted County, Minn)

- Surveillance HF patients in Olmsted County 2003-2005 (hospital and outpatient clinic)
- 556 patients – echo & 6 month mortality

EF	%Population	Diastolic Dysfunction
EF ≥ .50	55%	79%
EF < .50	45%	83%

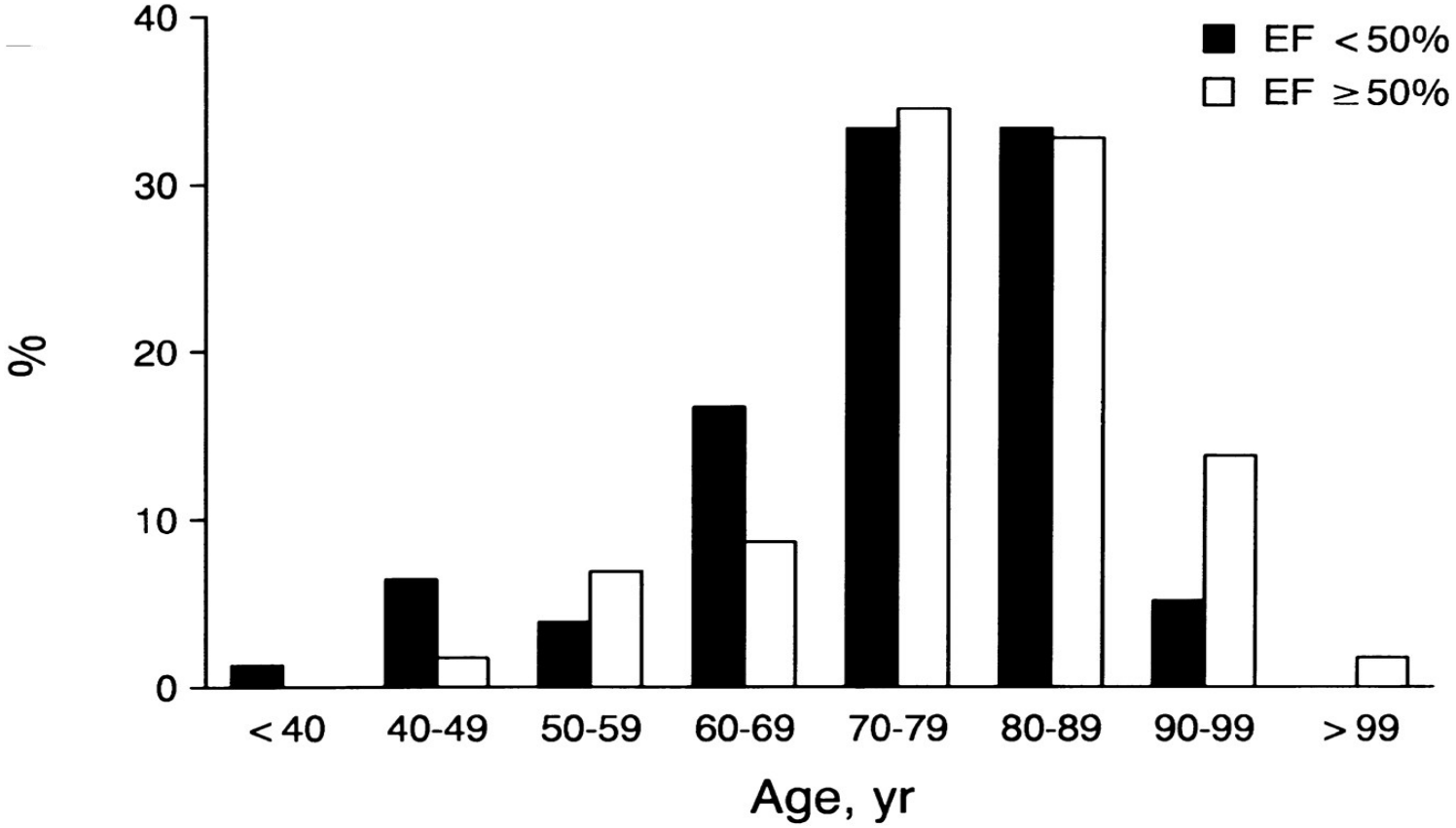
HFpEF – over half of HF in the community

DD present in ~ 80%, whether EF ≥ or < .50

Bursi, JAMA 2006;296:2209

Incidence

- **All patients with onset of heart failure 1991 in Olmsted County, Minnesota- Population 102 000**
- **216 patients identified (annual incidence 0.2%)**
- **137 (63%) had a recent echocardiographic assessment of LVEF**
- **54 (39%) had PSF and no valve disease.**



Senni M et al, Circulation 1998

European Heart Journal (2002) **23**, 877–885
doi:10.1053/euhj.2001.2973, available online at http://www.idealibrary.com on IDEAL®

Hospitalization of patients with heart failure

A population-based study

M. R. Cowie[1], K. F. Fox[1], D. A. Wood[1], C. Metcalfe[2], S. G. Thompson[2], A. J. S. Coats[1], P. A. Poole-Wilson[1] and G. C. Sutton[1]

[1]*Cardiac Medicine, Imperial College School of Medicine at the National Heart & Lung Institute, London, U.K.;*
[2]*MRC Biostatistics Unit, Institute of Public Health, Cambridge, U.K.*

Incidence, Bromley Heart study

- **Population 292000 in Bromley, South London, UK**
- **All local primary care physicians were asked to refer new cases of CHF to a special clinic;**
- **All local patients admitted to hospital with CHF were also identified.**
- **Of the 332 new cases of CHF detected between February 1996 and April 1997, 310 (93%) had an echocardiogram: (annual incidence 0.1%)**
- **16% of patients were found to have PEF**

Cowie et al EHJ 2002

Incidence discrepancies

- **Only 63 % in Olmstead study had echocardiograms while 93% in Bromley study**
- **Diagnostic criteria differed.**
- **Around 20% of Bromley patients included after an acute MI**
- **About 60% of Bromley patients recruited during hospitalization which may bias towards systolic dysfunction**

Journal of the American College of Cardiology
© 2004 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 43, No. 3, 2004
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2003.07.046

STATE-OF-THE-ART PAPER

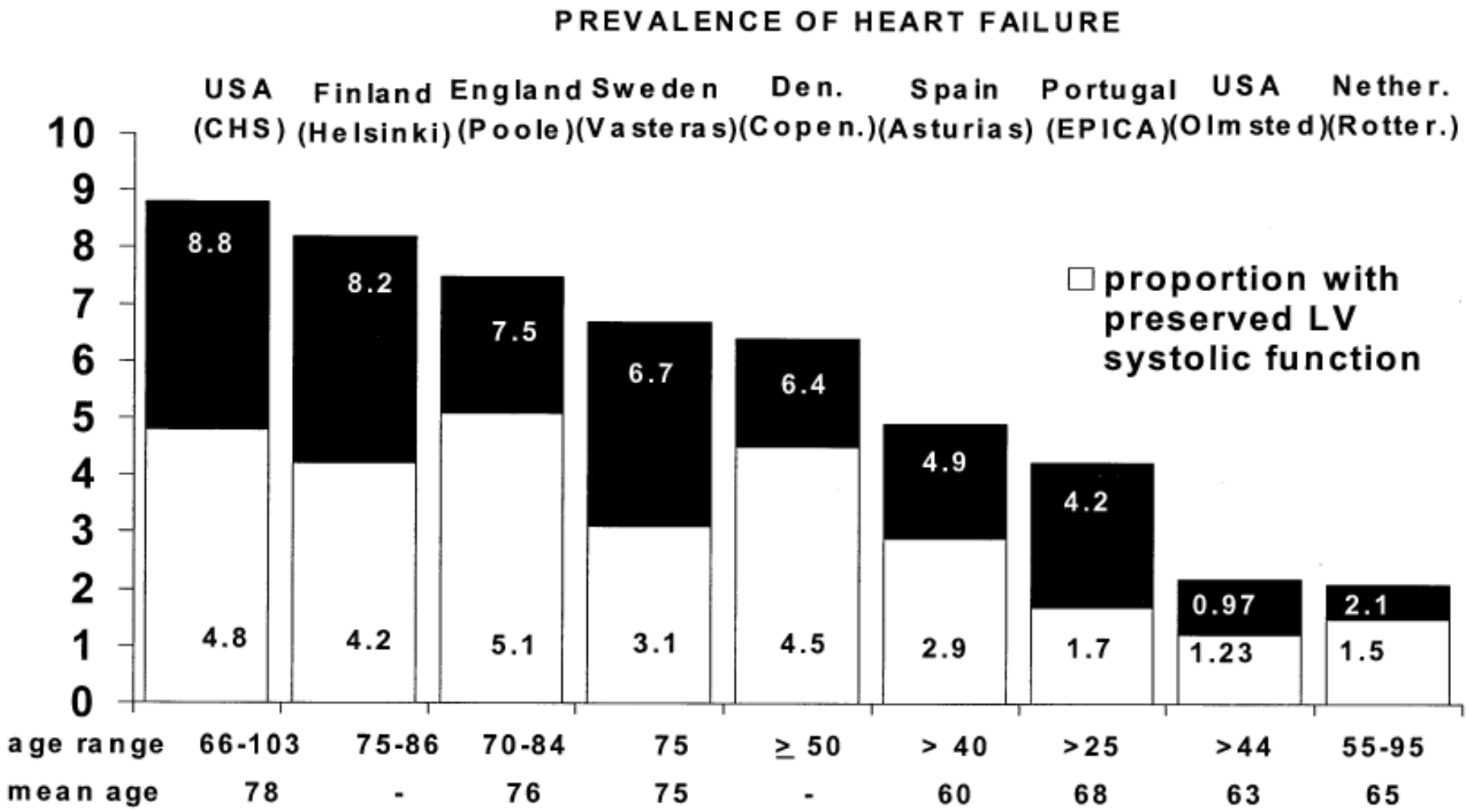
Heart Failure With Preserved Left Ventricular Systolic Function

Epidemiology, Clinical Characteristics, and Prognosis

Karen Hogg, BSC, MBChB, MRCP,* Karl Swedberg, MD, PhD,†
John McMurray, MD, FRCP, FESC, FACC*

Glasgow, Scotland; and Göteborg, Sweden

Prevalence



Hogg et al JACC 2004

Prevalence in Olmstead County, Mn

- **Population 106 000**
- **Prevalence of any diagnosis of CHF 2.6%**
- **Of these 41% had a and LVEF>50%**
- **Validated diagnosis of CHF 2.2% and of these LVEF >50% in 44%**

Redfield et al JAMA 2003

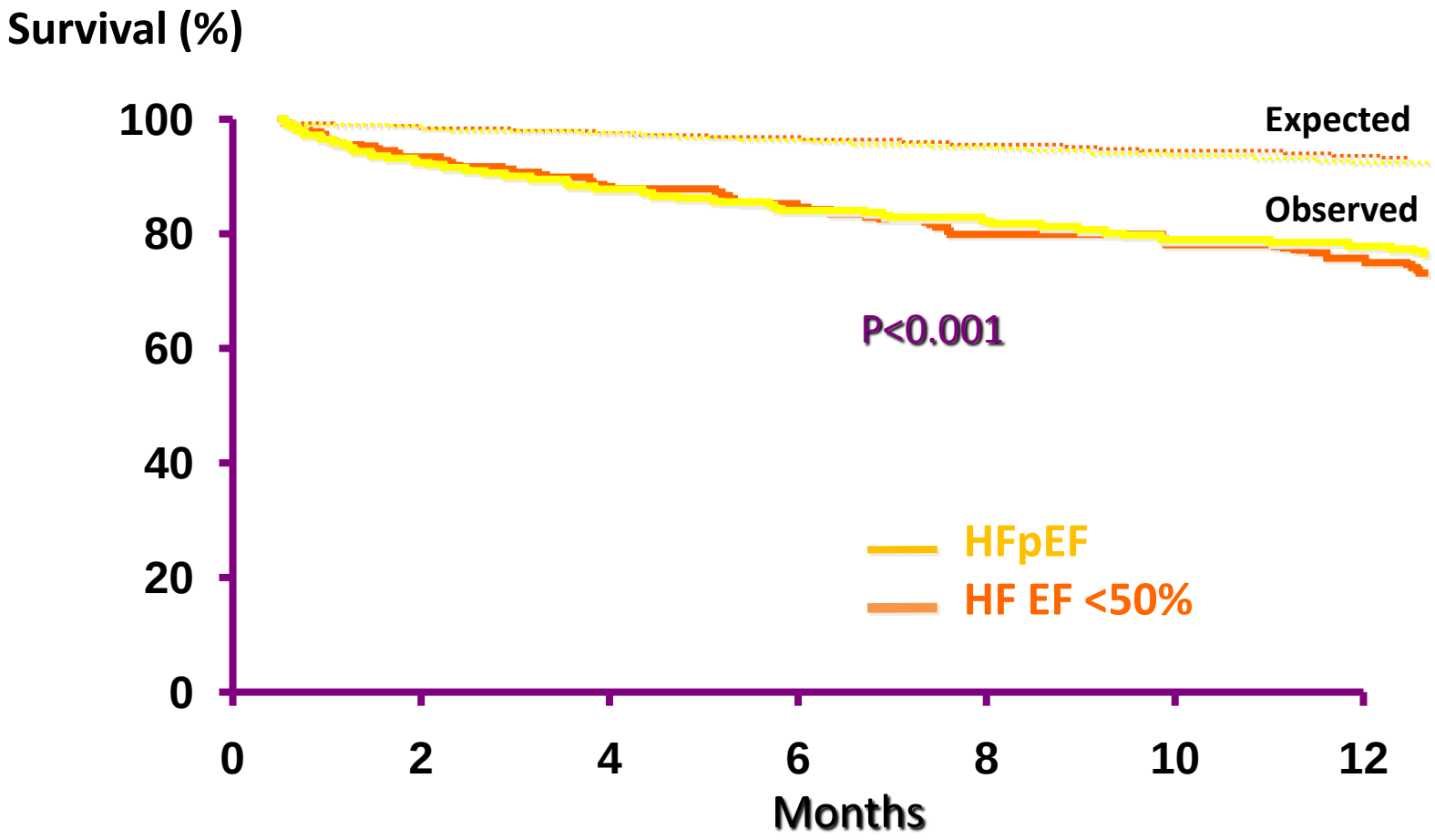
HFPEF - Inconsistancies in Prevalence

- Diagnostic criteria varies
- Comorbidities e.g. diabetes and obesitiy included, excluded or separately specified
- Age mix important
- Inclusion of community vs. Hospital based registries

Prognosis

Survival: HF↓EF & HFPEF

Olmsted County



No. at risk (observed cohort)	307	264	223	210	165	151	107
No. at risk (observed cohort)	247	213	182	161	145	114	85

Owan et al, NEJM 2006;355:251

EUROPEAN SOCIETY OF CARDIOLOGY®

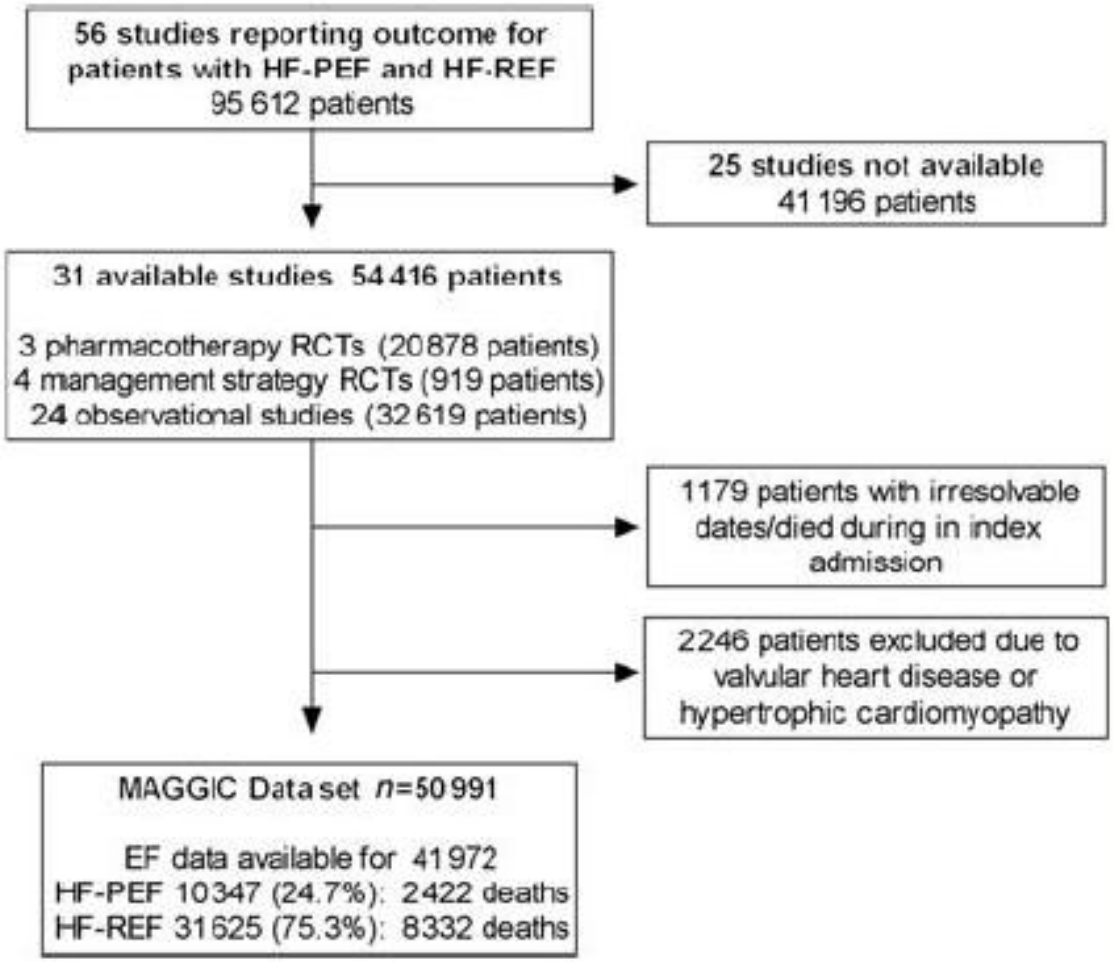
European Heart Journal (2012) **33**, 1750–1757
doi:10.1093/eurheartj/ehr254

CLINICAL RESEARCH
Heart failure/cardiomyopathy

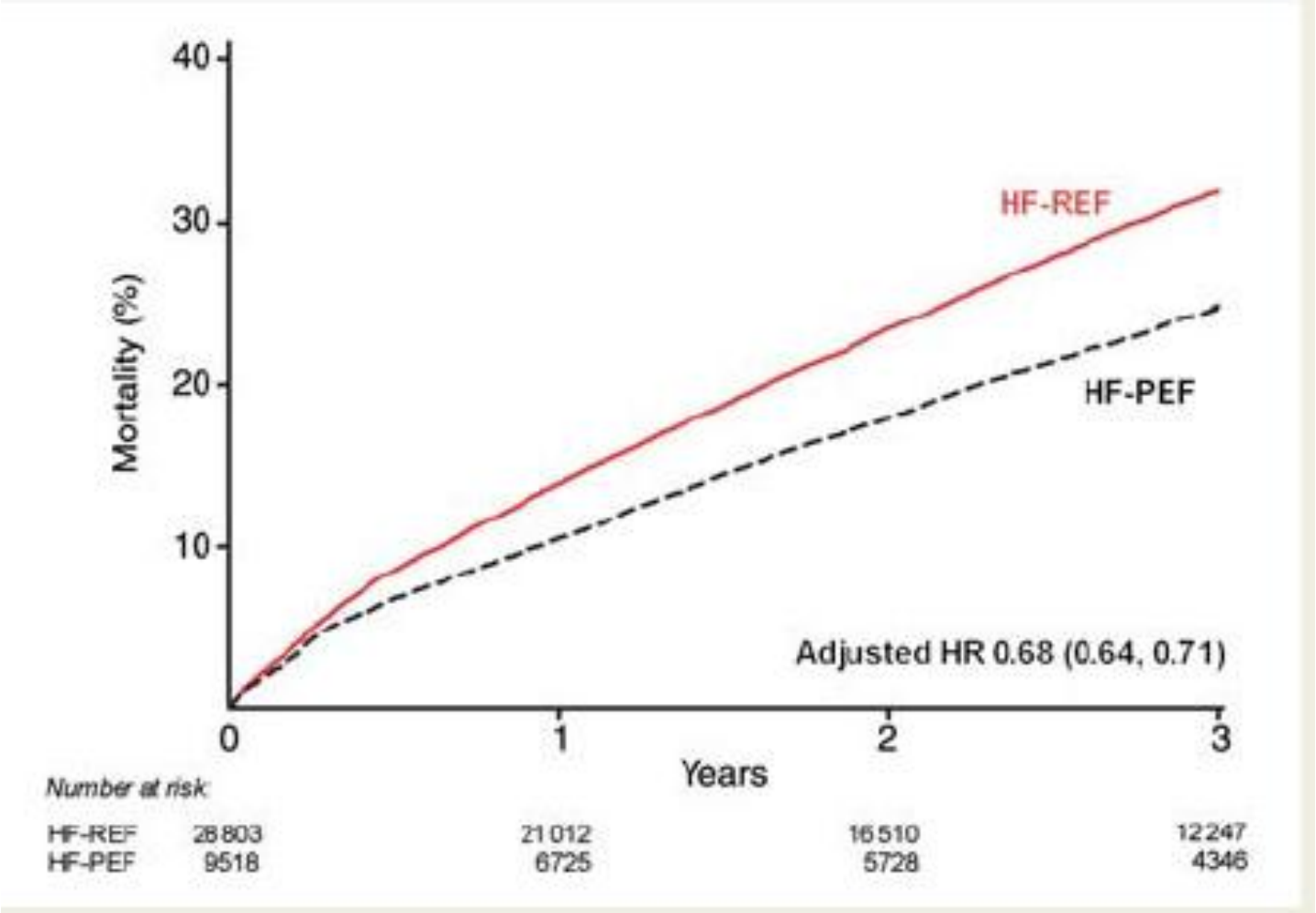
The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis

Meta-analysis Global Group in Chronic Heart Failure (MAGGIC)

CONSORT diagram MAGGIC



MAGGIC: HFREF and HFPEF



Prognosis

Long-Term Follow-Up of Participants With Heart Failure in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

Linda B. Piller, MD, MPH; Sarah Baraniuk, PhD; Lara M. Simpson, PhD; William C. Cushman, MD; Barry M. Massie, MD; Paula T. Einhorn, MD, MS; Suzanne Oparil, MD; Charles E. Ford, PhD; James F. Graumlich, MD; Richard A. Dart, MD; David C. Parish, MD, MPH; Tamrat M. Retta, MD, PhD; Aloysius B. Cuyjet, MD, MPH; Syed Z. Jafri, MD; Curt D. Furberg, MD, PhD; Mohammad G. Saklayen, MBBS; Udho Thadani, MD; Jeffrey L. Probstfield, MD; Barry R. Davis, MD, PhD; for the ALLHAT Collaborative Research Group

***Circulation*. 2011;124:1811-1818**

ALLHAT
All-cause mortality following new onset diagnosis of HF

- Participants were at least 55 years of age, with a systolic blood pressure of 140 mm Hg or higher and/or a diastolic blood pressure of 90 mm Hg or higher, and/or were taking antihypertensive medication (3 drugs) and had at least 1 additional CHD risk factor (including preexisting cardiovascular and/or cerebrovascular disease).
- Individuals with a history of symptomatic HF or left ventricular EF 35% were excluded
- Treatment part ended March 2002.
- Posttrial follow-up mortality through 2006 was obtained on participants who developed new-onset HF during the randomized (in-trial) phase of ALLHAT.
- Mean follow-up for the entire period was 8.9 years.
- Of 1761 participants with incident HF in-trial, 1348 died.

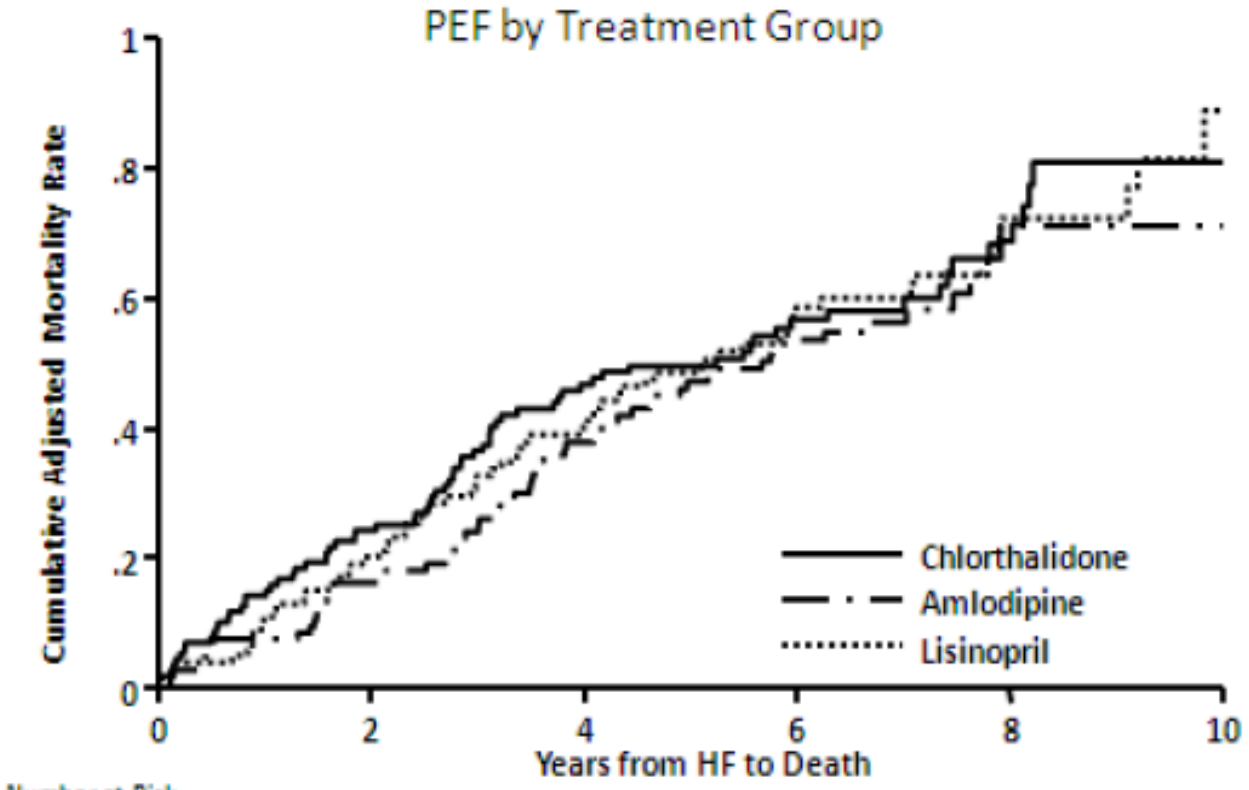
ALLHAT
All-cause mortality following new onset diagnosis of HF

Table 3. Adjusted Mortality Hazard Ratios for Hospitalized Heart Failure (Overall and by Ejection Fraction Status) Patients Comparing Those Who Developed Heart Failure Versus Those Who Did Not Develop Heart Failure (Heart Failure Treated as a Time-Varying Covariate)

	Total Mortality HR (95% CI), *P*	CVD Death HR (95% CI), *P*	HF Death HR (95% CI), *P*	Other CVD HR (95% CI), *P*	Non-CVD HR (95% CI), *P*
Overall					
Total	2.89 (2.69–3.11), <0.001	3.84 (3.49–4.23), <0.001	8.06 (6.38–10.18), <0.001	3.40 (3.05–3.78), <0.001	2.18 (1.95–2.43), <0.001
PEF*	2.42 (2.08–2.81), <0.001	2.73 (2.20–3.38), <0.001	3.81 (2.18–6.67), <0.001	2.60 (2.06–3.28), <0.001	2.15 (1.73–2.67), <0.001
REF*	3.06 (2.67–3.51), <0.001	4.27 (3.58–5.09), <0.001	6.80 (4.36–10.62), <0.001	3.99 (3.29–4.83), <0.001	2.05 (1.63–2.57), <0.001

Piller et al: Circulation 2011

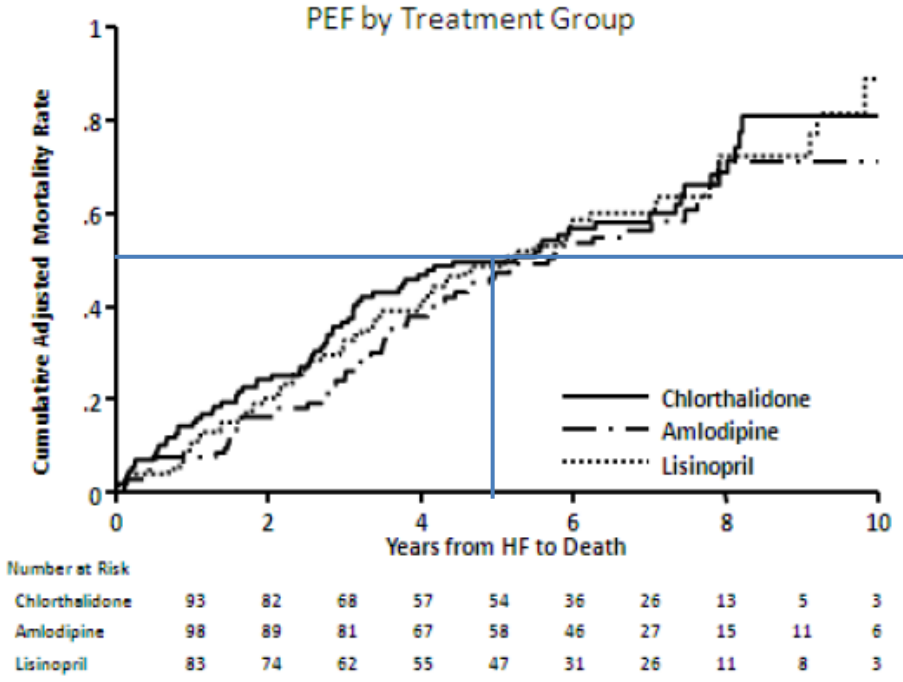
Prognosis after diagnosis of HF

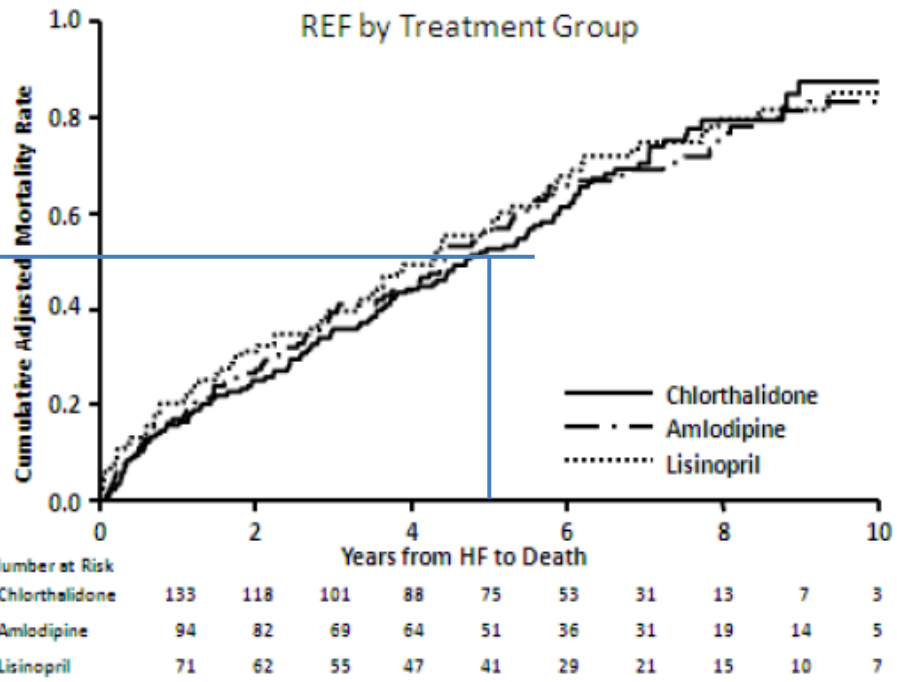


Number at Risk										
Chlorthalidone	93	82	68	57	54	36	26	13	5	3
Amlodipine	98	89	81	67	58	46	27	15	11	6
Lisinopril	83	74	62	55	47	31	26	11	8	3

Piller et al: Circulation 2011

5 year survival after diagnosis of HF by LV systolic function





Modified after Piller et al: Circulation 2011

HF with Preserved EF
Summary - Epidemiology

- Diagnostic criteria varies and influence estimates
- In the community, HF with preserved EF is as common as HF with systolic dysfuntion
- Prevalence is around 1%
- Incidence uncertain but around 0.1%/year
- Short term (1-3 years) prognosis better than HFREF
- Long term (>5 years) prognosis may be as poor as in HFREF

HFPEF

Management

HFPEF ESC Guidelines 2012

- No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HF-PEF.
- Diuretics are used to control sodium and water retention and relieve breathlessness and oedema as in HF-REF.

McMurray et al: ESC Guidelines EHJ 2012

HFPEF Therapy: general measures

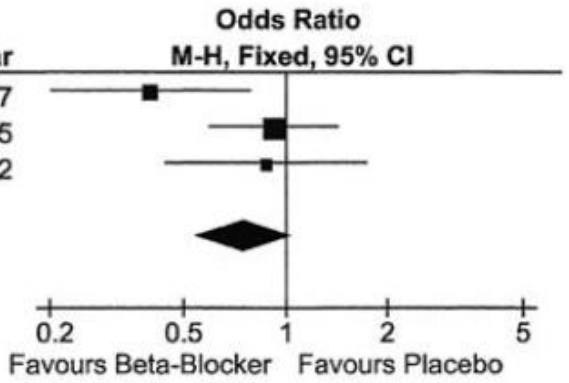
- Optimize hypertension therapy
- Lowest diuretic dose to relieve fluid excess
- Avoid HR extremes (chronotropic failure or rapid atrial fib)
- Beware co-morbidities e.g. sleep apnea, anemia, thyroid dysfunction
- Weight loss
- Exercise training

Beta-Blockers in HFPEF

Study or Subgroup	Beta-Blocker Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Aronow	44	79	60	79	31.2%	0.40 [0.20, 0.79]	1997
SENIORS	44	320	48	325	48.2%	0.92 [0.59, 1.43]	2005
J-DHF	18	120	21	125	20.5%	0.87 [0.44, 1.74]	2012
Total (95% CI)		**519**		**529**	**100.0%**	**0.75 [0.54, 1.03]**	
Total events	106		129				

Heterogeneity: $Chi^2 = 4.34$, $df = 2$ ($P = 0.11$); $I^2 = 54\%$

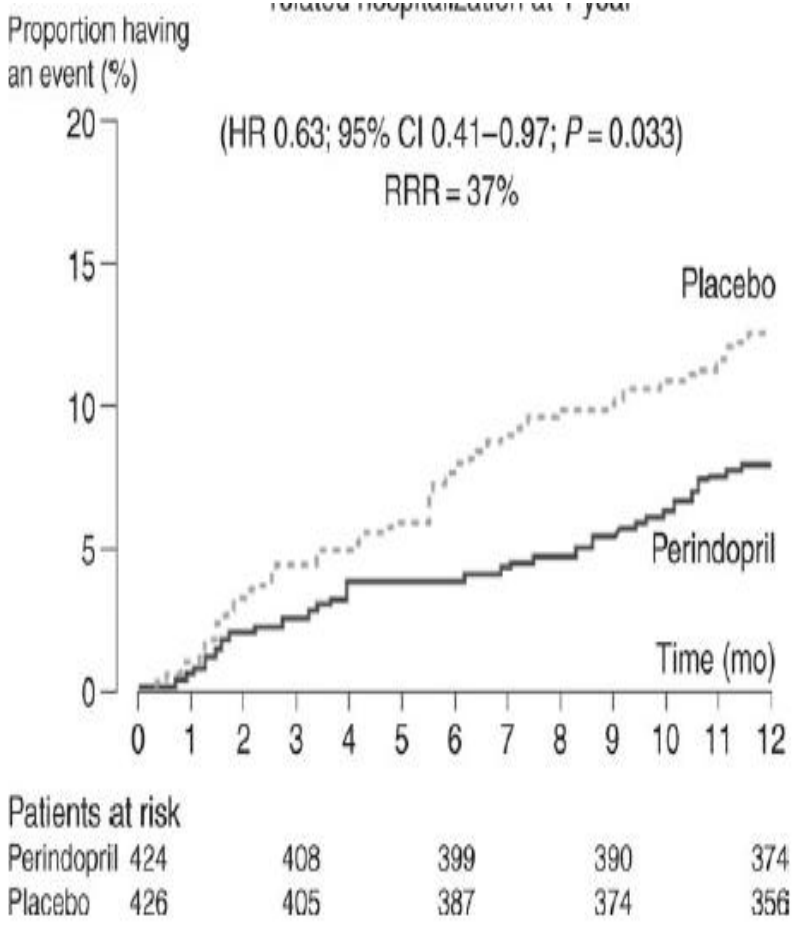
Test for overall effect: $Z = 1.76$ ($P = 0.08$)



v. Veldhuisen, McMurray EJHF 2013

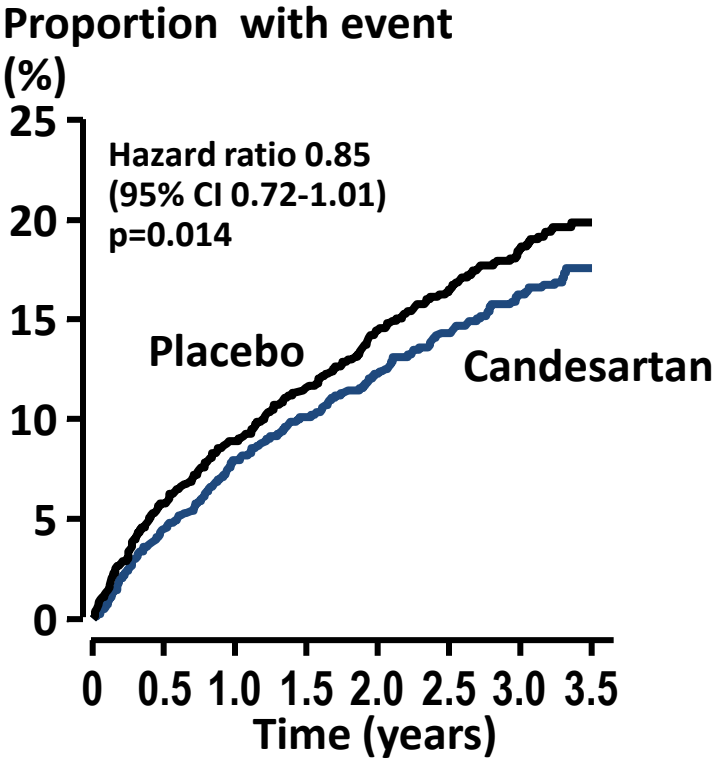
Trials in HF-PEF: HF hospitalization

PEP-CHF



Cleland et al EHJ 2006

CHARM Preserved



Number of patients at risk

Placebo	**1509**	**1331**	**1208**	**730**	**173**
Candesartan	**1514**	**1362**	**1241**	**749**	**169**

Yusuf et al Lancet 2003

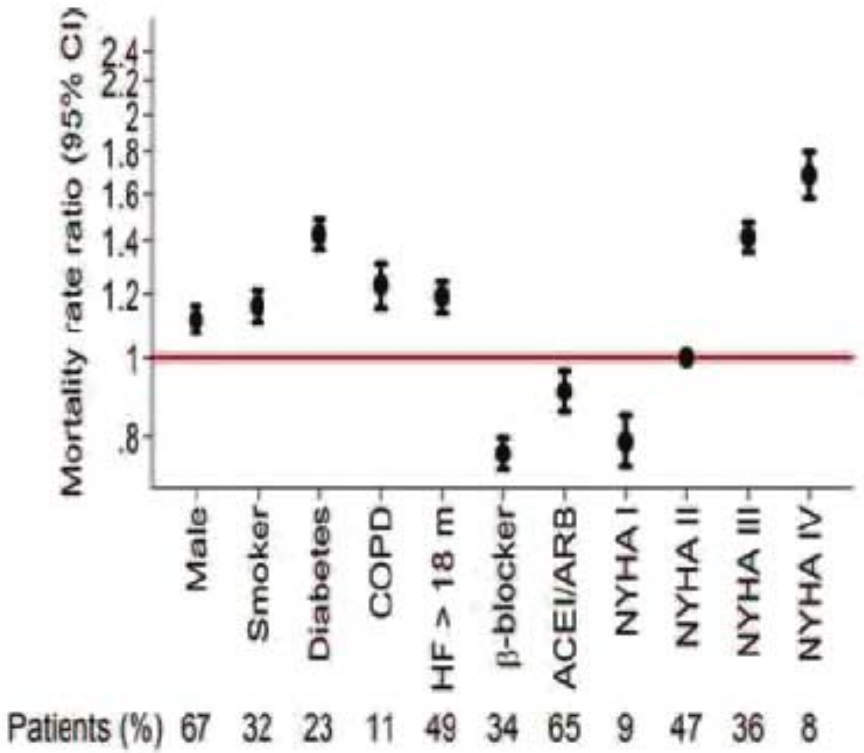
European Heart Journal Advance Access published October 24, 2012

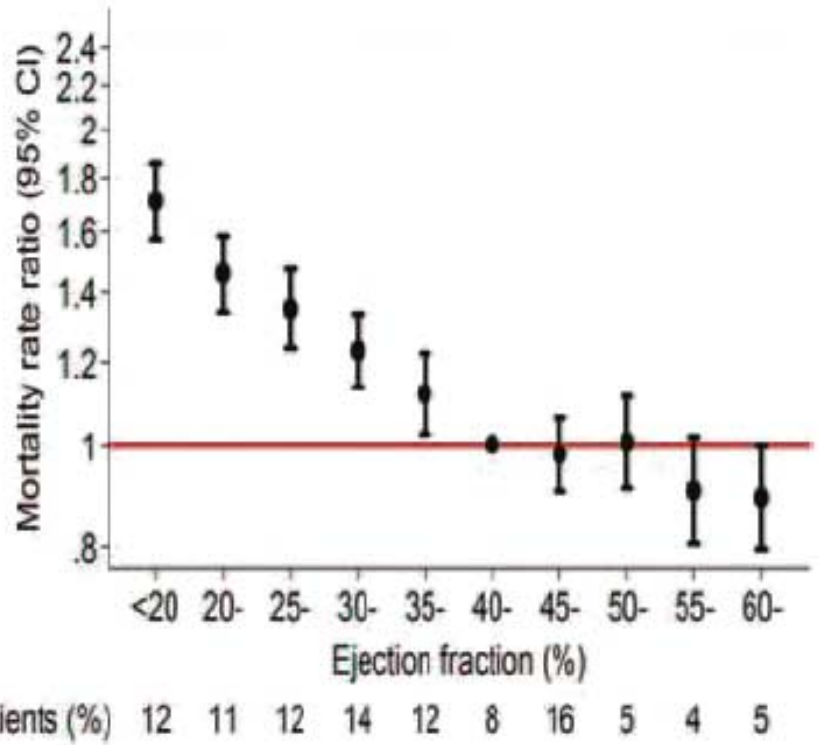
European Heart Journal
doi:10.1093/eurheartj/ehs337

CLINICAL RESEARCH

Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies

Stuart J. Pocock[1]*, Cono A. Ariti[1], John J.V. McMurray[2], Aldo Maggioni[3], Lars Køber[4], Iain B. Squire[5], Karl Swedberg[6], Joanna Dobson[1], Katrina K. Poppe[7], Gillian A. Whalley[7], and Rob N. Doughty[7], on behalf of the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC)


Mortality rate ratio (95% CI)
2.4
2.2
2
1.8
1.6
1.4
1.2
1
.8
Male
Smoker
Diabetes
COPD
HF > 18 m
β-blocker
ACEI/ARB
NYHA I
NYHA II
NYHA III
NYHA IV
Patients (%) 67 32 23 11 49 34 65 9 47 36 8


Mortality rate ratio (95% CI)
2.4
2.2
2
1.8
1.6
1.4
1.2
1
.8
<20
20-
25-
30-
35-
40-
45-
50-
55-
60-
Ejection fraction (%)
Patients (%) 12 11 12 14 12 8 16 5 4 5

MAGGIC risk score

Table 6 Main effects model for EF ≥40 (17 930 patients of whom 6951 died)

Variable	Rate ratio	95% CI	Z	P-value
Age (per 10 years)	1.589	(1.536, 1.643)	27.14	<0.001
Male	1.113	(1.053, 1.177)	3.77	<0.001
BMI (per 1 kg/m^2 increase up to 30 kg/m$^{2)}$	0.960	(0.951, 0.969)	−8.50	<0.001
Current smoker	1.174	(1.095, 1.258)	4.54	<0.001
SBP (per 10 mmHg)	0.982	(0.968, 0.998)	−2.30	0.024
Diabetes	1.401	(1.311, 1.498)	9.90	<0.001
NYHA class				
I	0.756	(0.682, 0.838)	−5.32	<0.001
II	1.000			
III	1.458	(1.361, 1.561)	10.83	<0.001
IV	1.756	(1.599, 1.928)	11.82	<0.001
COPD	1.284	(1.181, 1.396)	5.91	<0.001
HF duration >18 months	1.166	(1.088, 1.250)	4.37	<0.001
Creatinine (per 10 μmol/L up to 350 μmol/L)	1.035	(1.029, 1.041)	11.39	<0.001
Beta-blocker	0.798	(0.746, 0.855)	−6.47	<0.001
ARB/ACE-I	0.938	(0.842, 1.044)	−1.21	0.233

ORIGINAL CONTRIBUTION

Association Between Use of Renin-Angiotensin System Antagonists and Mortality in Patients With Heart Failure and Preserved Ejection Fraction

Lars H. Lund, MD, PhD
Lina Benson, MSc
Ulf Dahlström, MD, PhD
Magnus Edner, MD, PhD

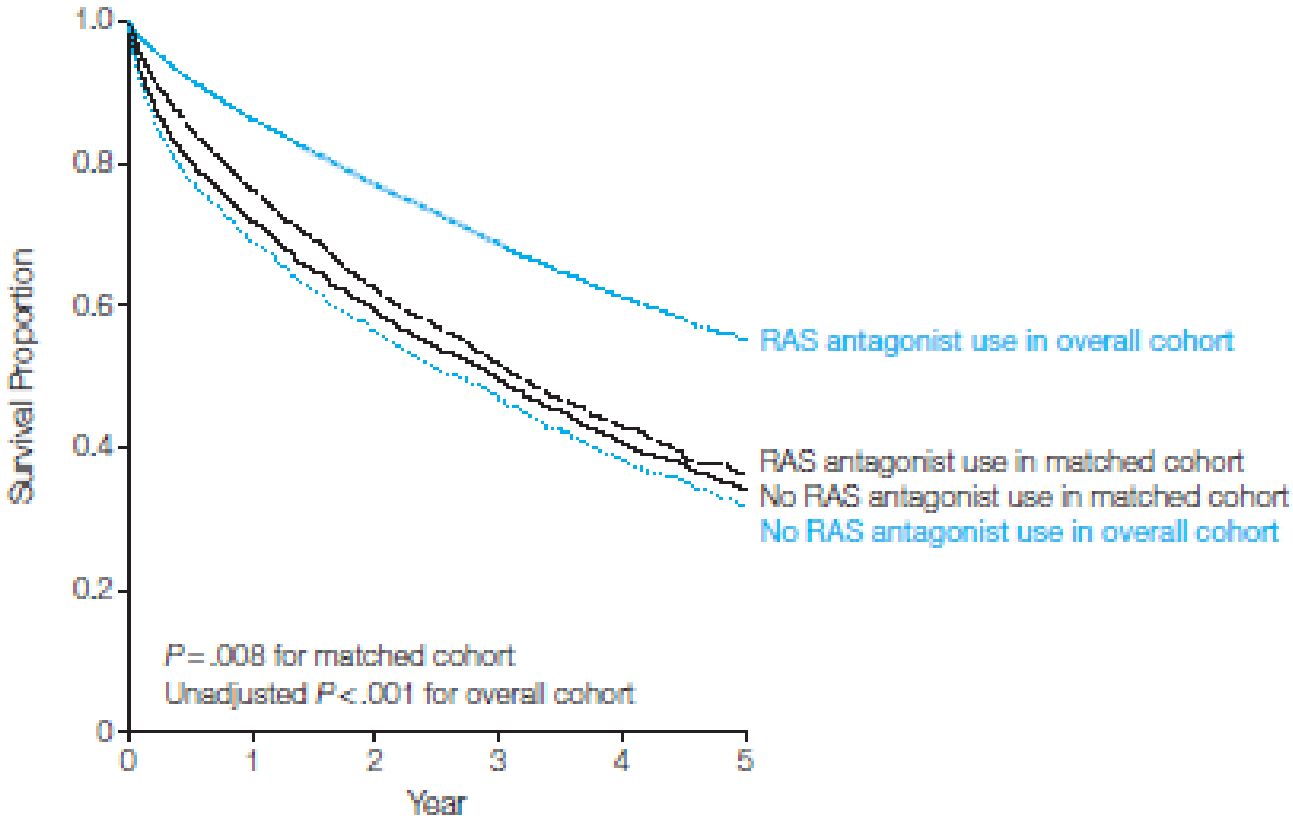
Context Heart failure with preserved ejection fraction (HFPEF) may be as common and as lethal as heart failure with reduced ejection fraction (HFREF). Three randomized trials of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ie, renin-angiotensin system [RAS] antagonists) did not reach primary end points but may have had selection bias or been underpowered.

JAMA 2013;308:2108

Table 1. Characteristics of the Overall and Matched Cohorts and the Standardized Differences Between the Treatment Groups[a]

	Overall Cohort (n = 16 216)				Matched Cohort (n = 6658)			
	RAS Antagonist Use				RAS Antagonist Use			
	No (n = 3673)	Yes (n = 12 543)	Standardized Difference, %[b]	*P* Value[c]	No (n = 3329)	Yes (n = 3329)	Standardized Difference, %[b]	*P* Value[c]
Follow-up, median (range), d	511 (0-3991)	782 (0-3907)			558 (0-3991)	609 (0-3651)		
No. of deceased patients	1900 (52)	3864 (31)			1639 (49)	1555 (47)		
Type of RAS antagonist[d]								
ACE inhibitor	0	9103 (73)			0	2457 (74)		
ARB	0	3172 (25)			0	832 (25)		
ACE inhibitor plus ARB	0	268 (2)			0	40 (1)		
None	3673 (100)	0			3329 (100)	0		

Survival by treatment with a RAS-antagonist



No. at risk						
Matched						
No RAS antagonist use	3329	2028	1349	846	453	229
RAS antagonist use	3329	2181	1447	880	475	238
Overall						
No RAS antagonist use	3673	2156	1425	884	467	234
RAS antagonist use	12543	9177	6580	4193	2340	1216

Table 3. All-Cause Mortality by Renin-Angiotensin System (RAS) Antagonist Use

	No./Total (%) by RAS Antagonist Use		Hazard Ratio (95% CI)	*P* Value
	Yes	No		
Cox regression model main analyses for heart failure preserved ejection fraction				
Univariable	12 543/16 216 (77)	3673/16 216 (23)	0.48 (0.45-0.51)	<.001
Matched by propensity for treatment[a]	3329/6658 (50)	3329/6658 (50)	0.91 (0.85-0.98)	.008
Overall cohort				
Adjusted for propensity score	12 543/16 216 (77)	3673/16 216 (23)	0.90 (0.85-0.96)	.001
Adjusted for age only	12 543/16 216 (77)	3673/16 216 (23)	0.64 (0.60-0.68)	<.001
Adjusted for creatinine clearance only	11 554/14 867 (78)	3313/14 867 (22)	0.71 (0.66-0.75)	<.001
Cox regression model consistency analyses				
Matched by propensity for dose for heart failure preserved ejection fraction[b]				
High dose vs no treatment	2647/7941 (33)	2647/7941 (33)	0.85 (0.78-0.93)	<.001
Low dose vs no treatment	2647/7941 (33)	2647/7941 (33)	0.94 (0.87-1.02)	.14
Matched by propensity for treatment for heart failure reduced ejection fraction	2005/4010 (50)	2005/4010 (50)	0.80 (0.74-0.86)	<.001

[a] Matched 1:1 treated to untreated, within differences in age of 5 years or less, and propensity score of 0.1 or less yielded 3329 patients in each group.
[b] Matched 1:1:1 for high dose vs low dose vs no treatment, within differences in age of 5 years or less, and propensity score of 0.1 or less yielded 2647 patients in each group. Details of matching and results appear in the online-only material at http://www.jama.com.

Future

Aldosterone antagonist for HF-PEF?

Funded by the NHLBI

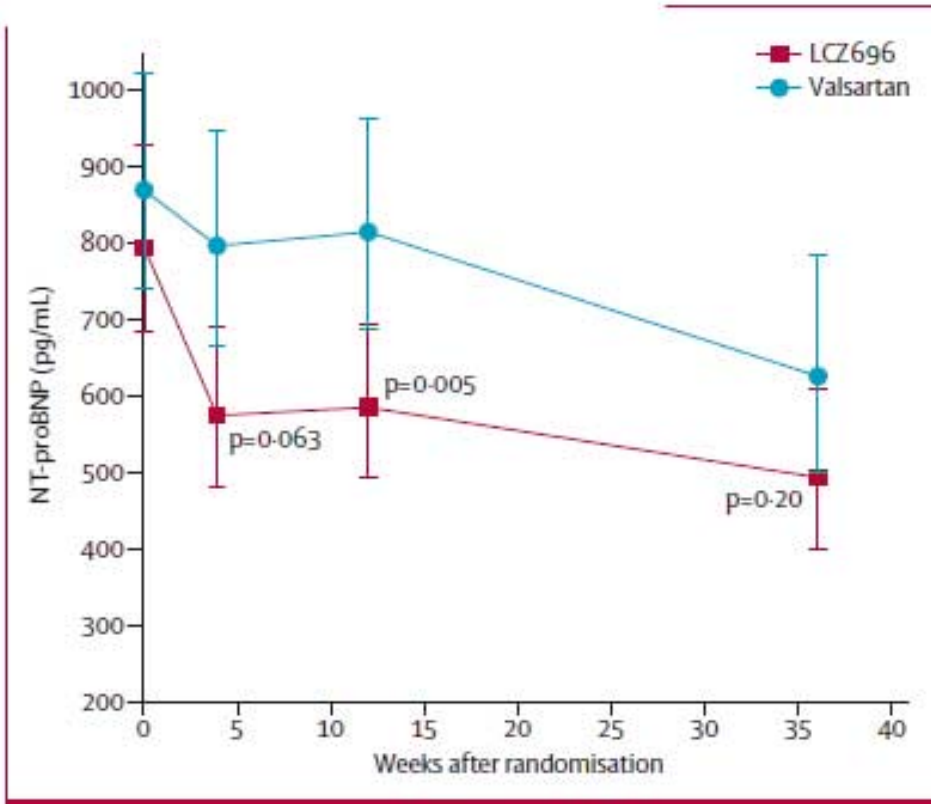
Treatment Of Preserved Cardiac function heart failure with an Aldosterone anTagonist

TOPCAT

- **Hypothesis:** Spironolactone will reduce morbidity and mortality in mild HF and preserved LV function
- **Population:** 4500 patients >50 yrs with NYHA II HF (and admission or elevated BNP), EF ≥45%
- **Intervention:** Spironolactone (15-45 mg) vs placebo
- **Primary endpoint:** CV death, RCA, HF hospitalisation
- **Status:** Recruitment ended Jan 31, 2012

The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial

*Scott D Solomon, Michael Zile, Burkert Pieske, Adriaan Voors, Amil Shah, Elisabeth Kraigher-Krainer, Victor Shi, Toni Bransford, Madoka Takeuchi, Jianjian Gong, Martin Lefkowitz, Milton Packer, John J V McMurray, for the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators**



Summary

- HFPEF is a serious syndrome which is as incapaciting as HFREF
- More common in women
- Short term prognosis better than in HFREF
- Long-term (>5 years) prognosis may be as bad as in HFREF
- Manage co-morbidities
- The value of pharmacological therapy is uncertain.
- Treatment with an ACEI/ARB in recommended dosages and a beta-blocker seems reasonable