Heart Failure with Preserved Ejection Fraction: Is it a Kidney Disorder ?

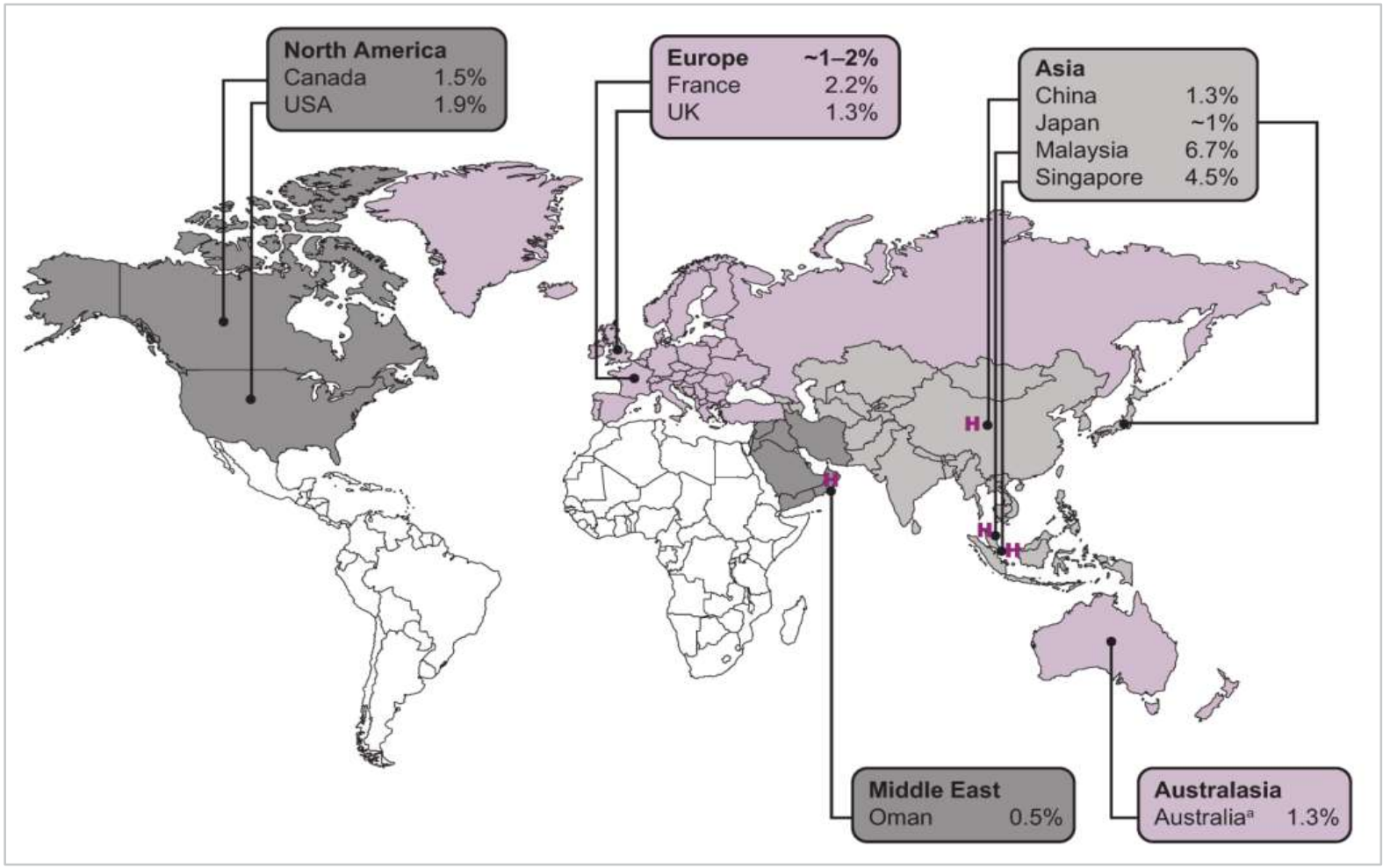
Amir A. Nassiri, M.D, D.I.U

Heart Failure Definition

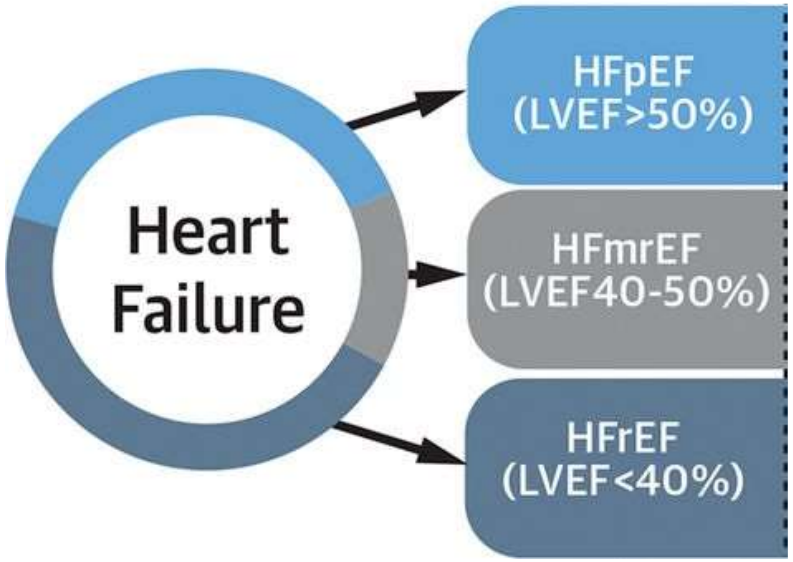
- **The inability to provide adequate cardiac output to the body at rest or with exertion, or to do so only in the setting of elevated cardiac filling pressures.**

-E. Braunwald modified by B. Borlaug and M. Redfield

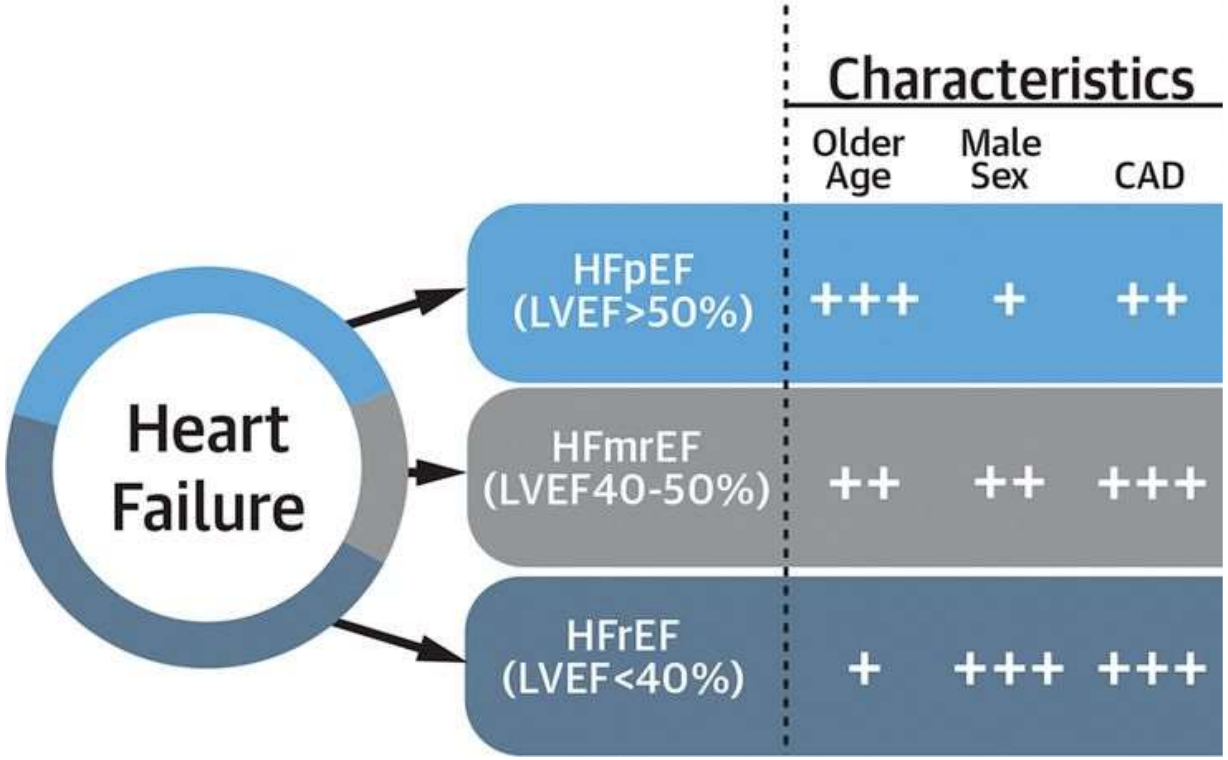
Heart Failure Prevalence



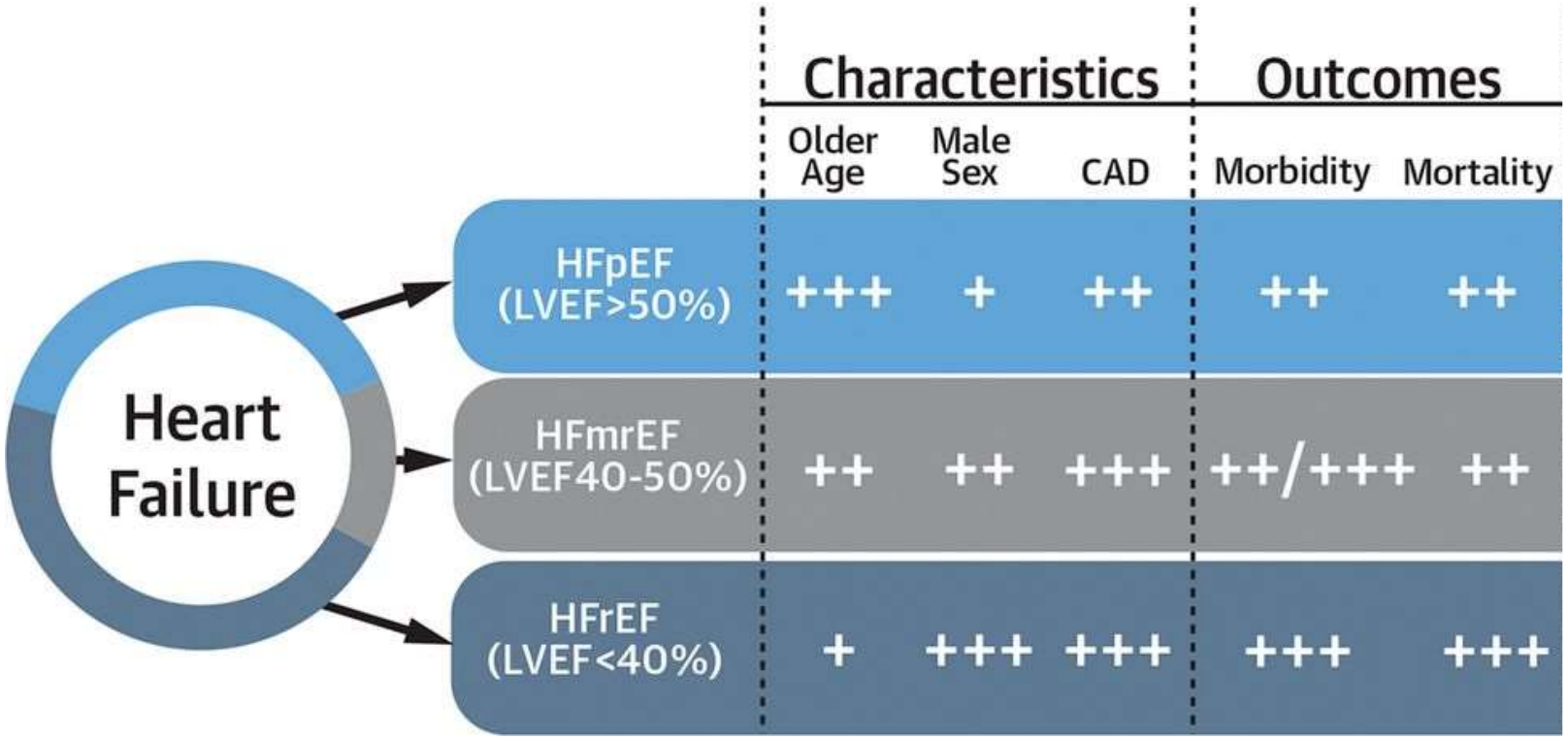
Heart Failure Classification



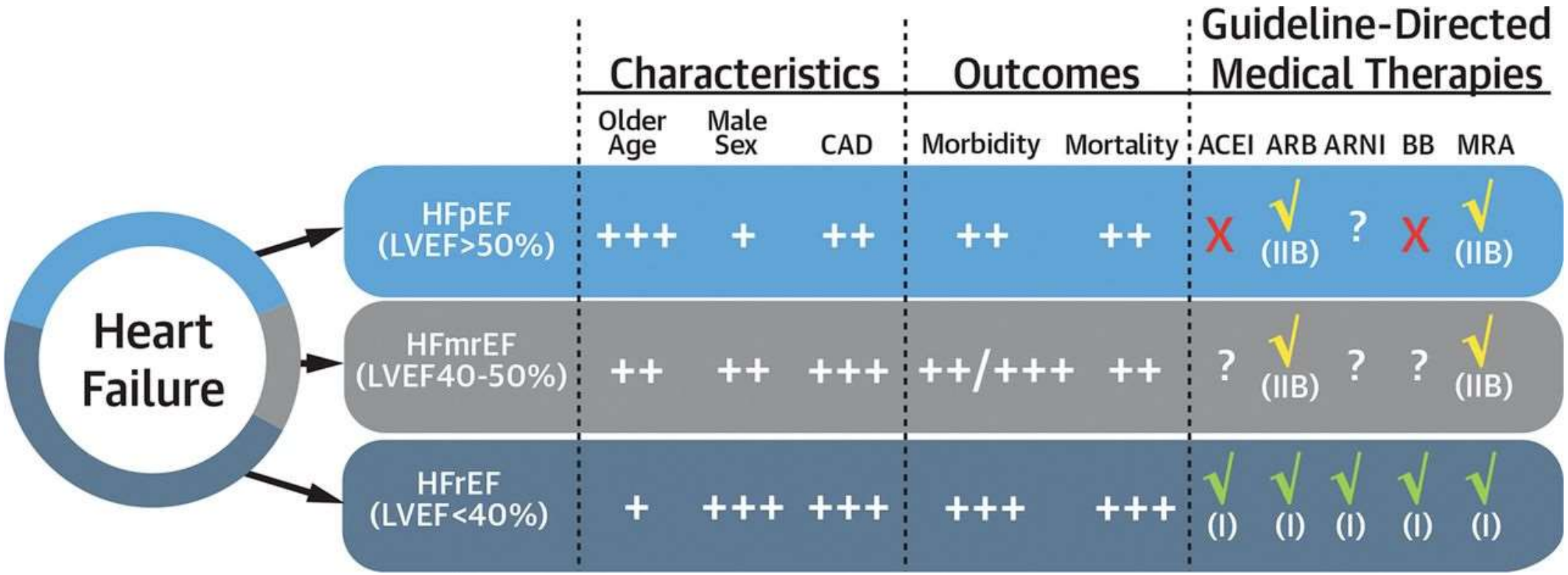
Heart Failure Classification



Heart Failure Classification



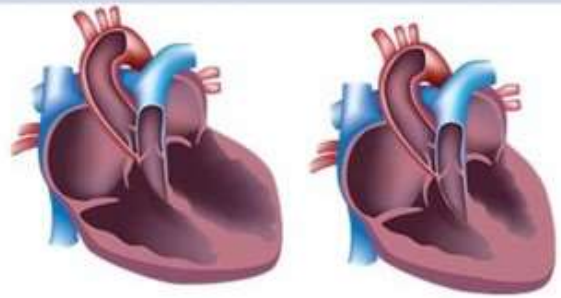
Heart Failure Classification



Characteristic	HFrEF	HFpEF	HFmrEF
Dysfunction	Systolic, Diastolic	Diastolic	Mild systolic, Diastolic
LVEF	<40%	≥50%	40%-49%
Etiology	CAD, MI	Hypertension, AF, Diabetes	CAD (Primary cause), Hypertension, Diabetes
LV remodeling	Eccentric	Concentric	Eccentric or Concentric
Prognostication under Medical treatments	Improved	Not improved	Resemble HFrEF

- ↑ EDV
- ↓ Wall thickness
- ↓ Cardiac contractility

- Normal EDV or EDV↓
- ↑ Wall thickness
- ↑ Myocardial stiffness
- ↓ LV relaxation time



Intermediate between HFrEF and HFpEF

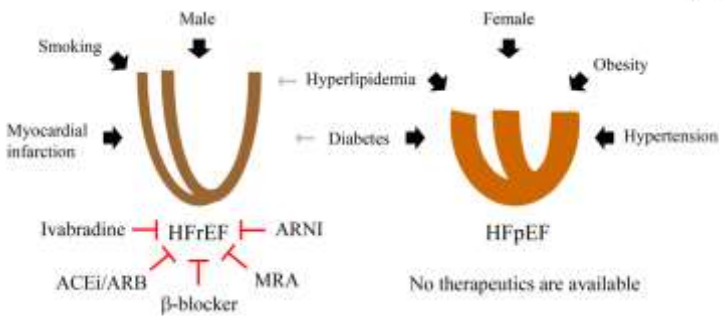
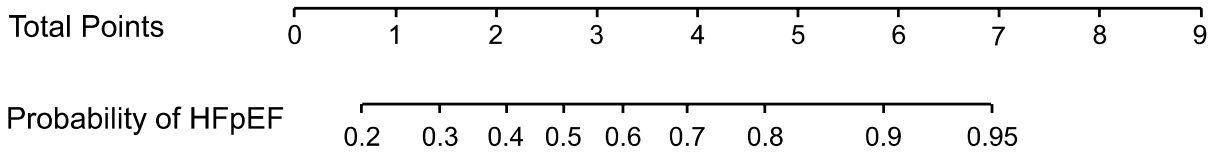


Table 1. Guideline and Clinical Trial Definitions of HFpEF

	ACC/AHA	ESC	HFSA	TOPCAT	PARAGON	I-PRESERVE	RELAX
Reference	Yancy C, Circ, 2013	Ponikowsky P, Eur Heart J, 2016	Lindenfeld J, JCF, 2010	Pitt B, N Engl J Med, 2014	Solomon SD, JACC HF, 2017	Massie B, N Engl J Med, 2008	Redfield MM, JAMA, 2013
Symptoms	√	√	√	√	√	√	√
Signs		±√	√	√		Alt to HF admission*	√
Echo		LVH, LAE, or DD and not dilated	cLVH, LAE (in absence of AF), DD		LAE or LVH	Alt to HF admission*	Alt to HF admission: LAE with diuretic
HF admission				√		√	√
CV admission			√				
Exclude	Noncardiac causes		Nonmyocardial disease				
NT-proBNP		≥125		Alt to HF admission: >360	Different cut-offs depending on HF admission and AF history		≥400 or elevated filling pressures
CPET						Alt to HF admission*	Peak Vo_2 <=60% pred
Other		Alt: rPCWP ≥15			Chronic diuretic age >50	Age ≥60	Alt to HF admission: previous invasive documented elevated filling pressures

H2FPEF Score for the Dx of HFpEF

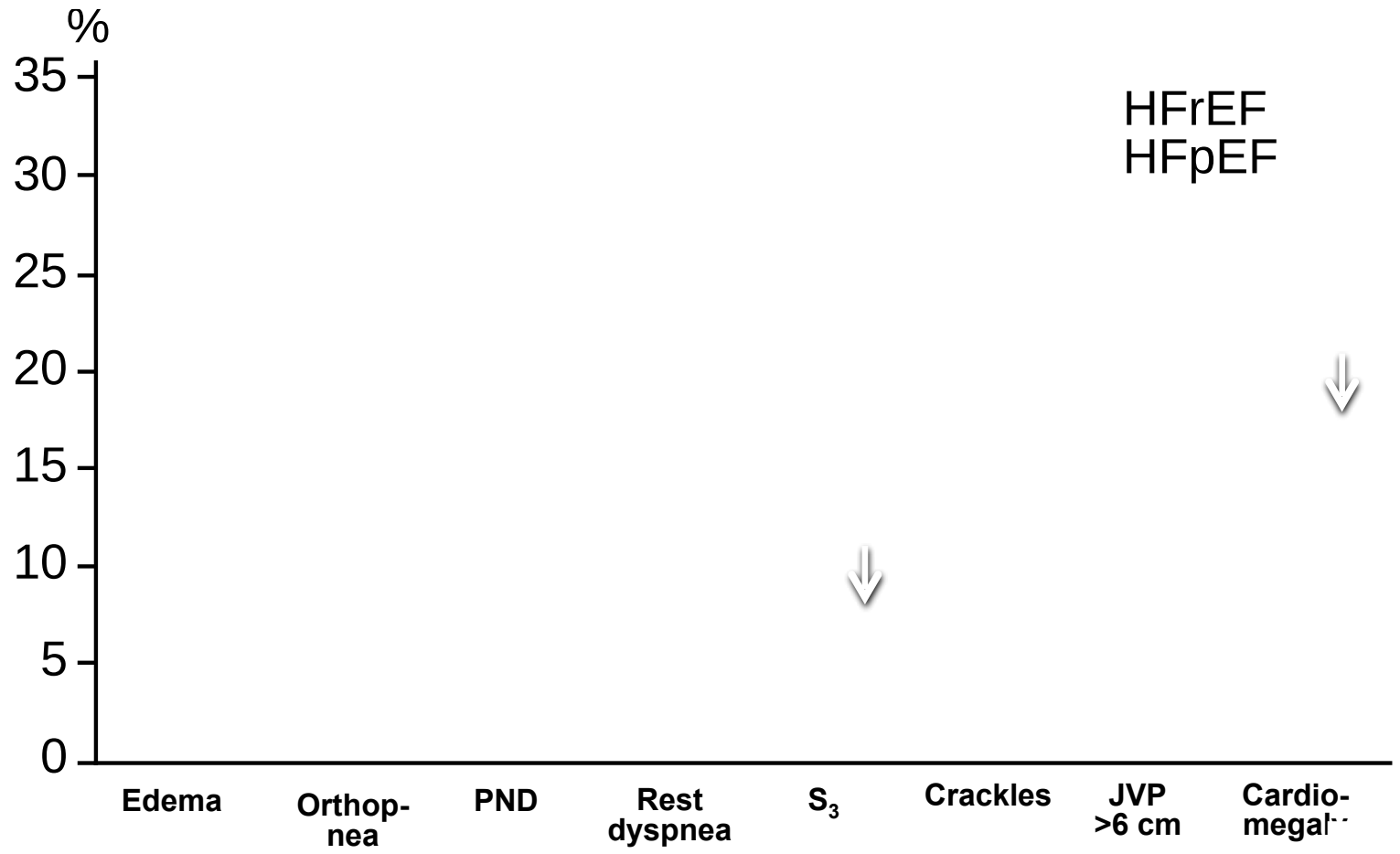
	Clinical Variable	Values	Points
H_2	**H**eavy	Body mass index > 30 kg/m^2	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial **F**ibrillation	Paroxysmal or Persistent	3
P	**P**ulmonary Hypertension	Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg	1
E	**E**lder	Age > 60 years	1
F	**F**illing Pressure	Doppler Echocardiographic E/e' > 9	1
H_2FPEF score			Sum (0-9)



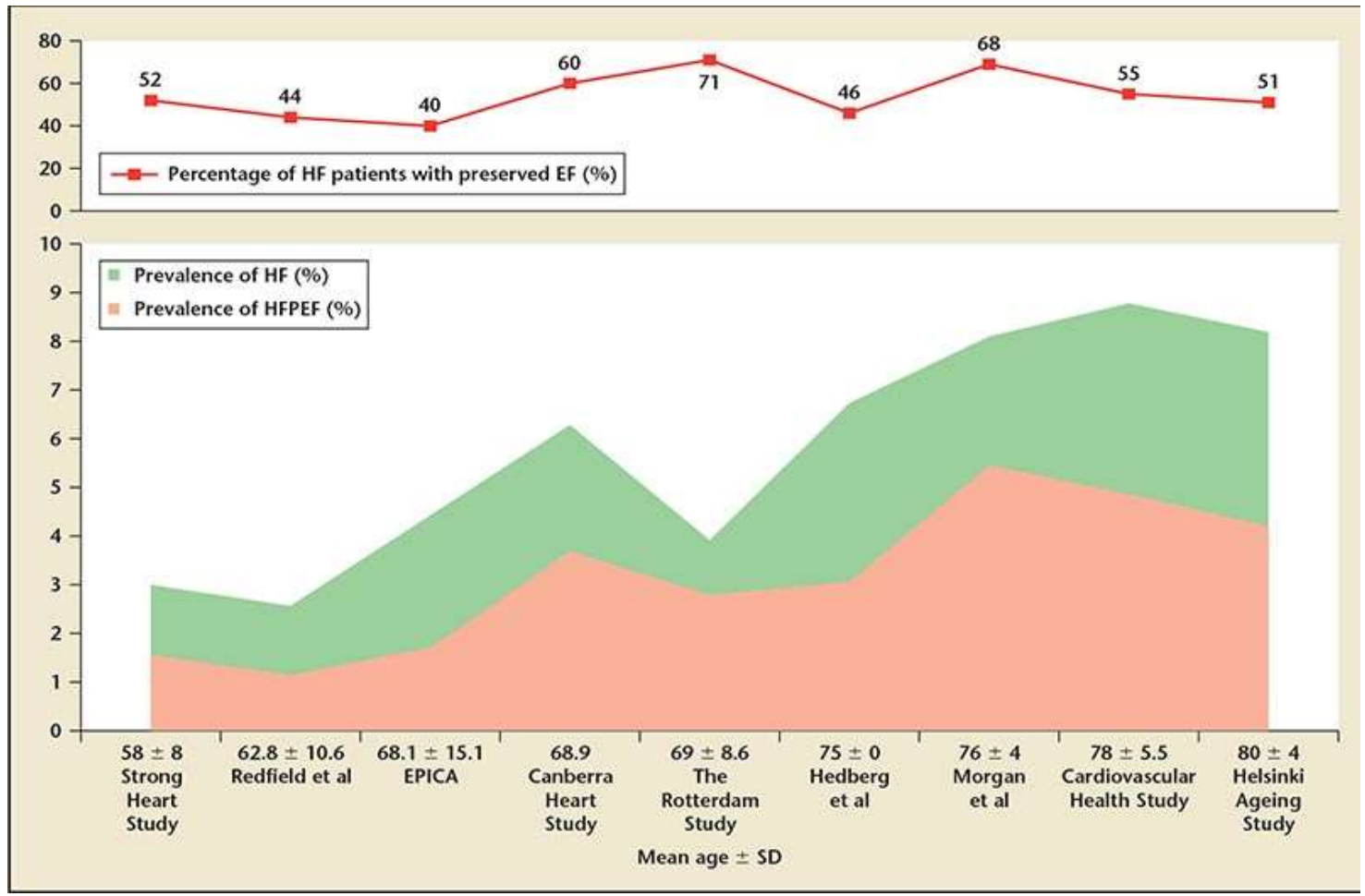
HFpEF represents a heterogeneous collection of conditions

- **the presence of a left ventricular ejection fraction ≥50%,**
- **evidence of impaired diastolic function and elevated natriuretic peptide levels,**
- **all within the context of typical heart failure signs and symptoms.**

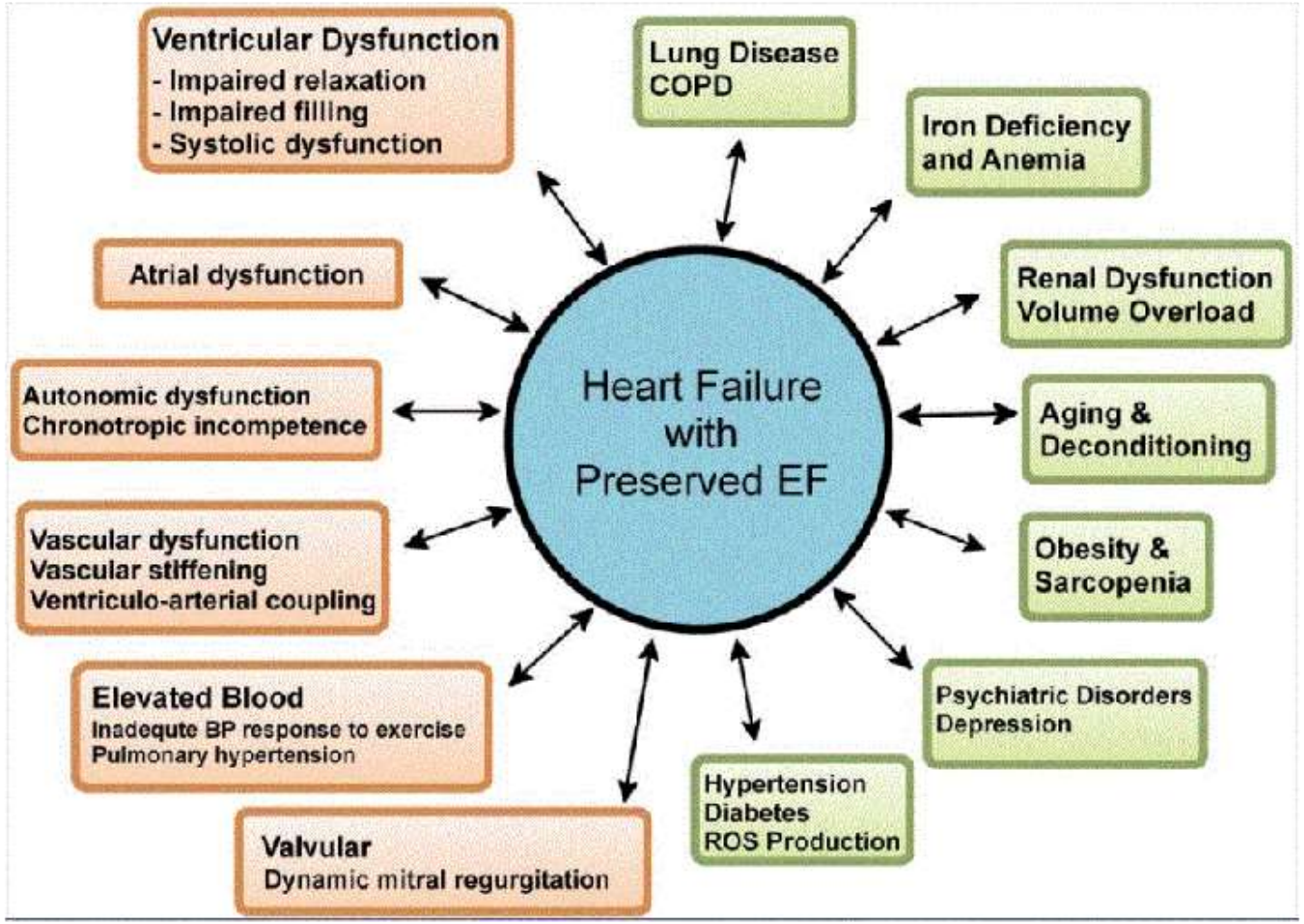
S & S in pts with HFpEF & HFrEF



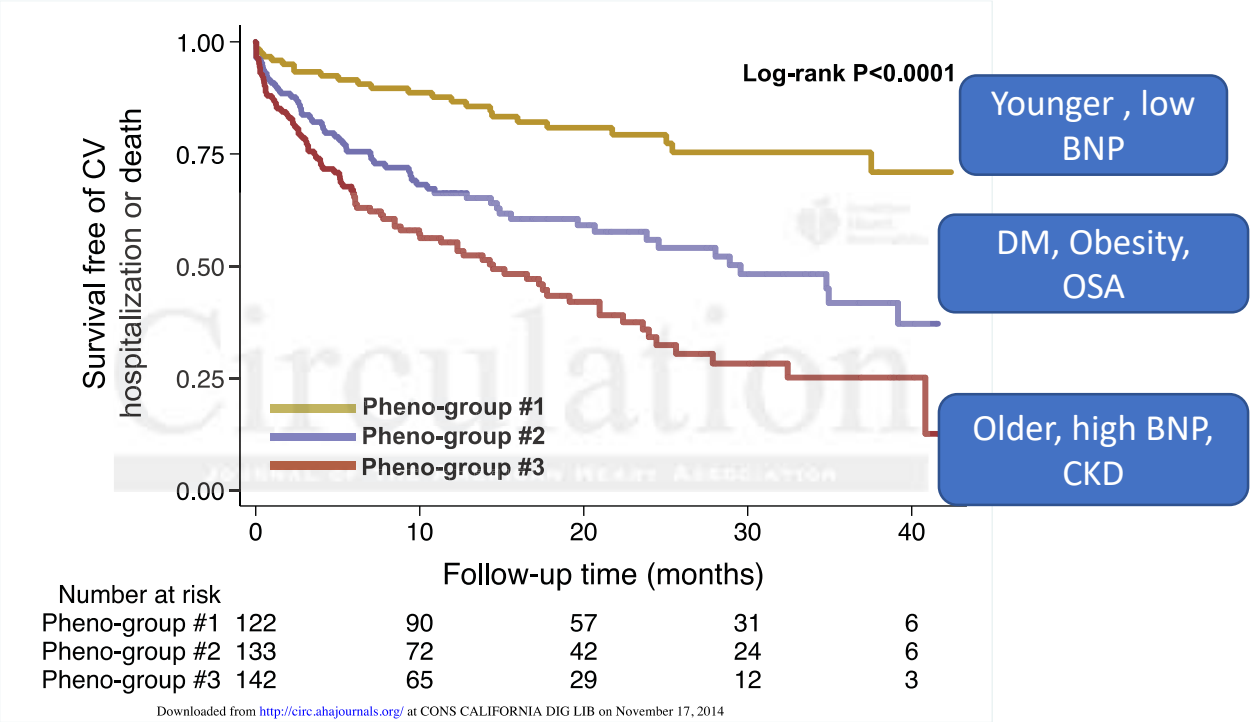
HFpEF is steadily becoming
“the predominant form of heart failure”

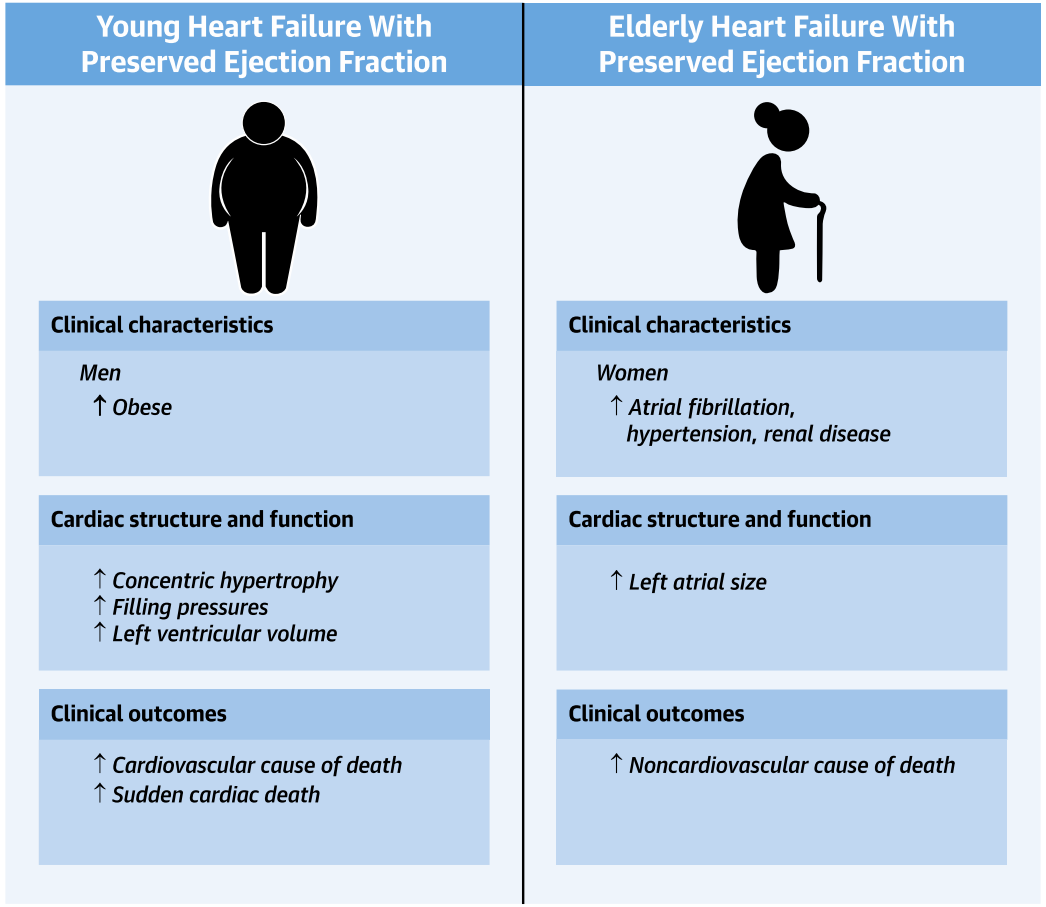

80
60
40
20
0
52
44
40
60
71
46
68
55
51
Percentage of HF patients with preserved EF (%)
10
9
8
7
6
5
4
3
2
1
0
Prevalence of HF (%)
Prevalence of HFPEF (%)
58 ± 8 Strong Heart Study
62.8 ± 10.6 Redfield et al
68.1 ± 15.1 EPICA
68.9 Canberra Heart Study
69 ± 8.6 The Rotterdam Study
75 ± 0 Hedberg et al
76 ± 4 Morgan et al
78 ± 5.5 Cardiovascular Health Study
80 ± 4 Helsinki Ageing Study
Mean age ± SD

HFpEF is a very heterogenous condition

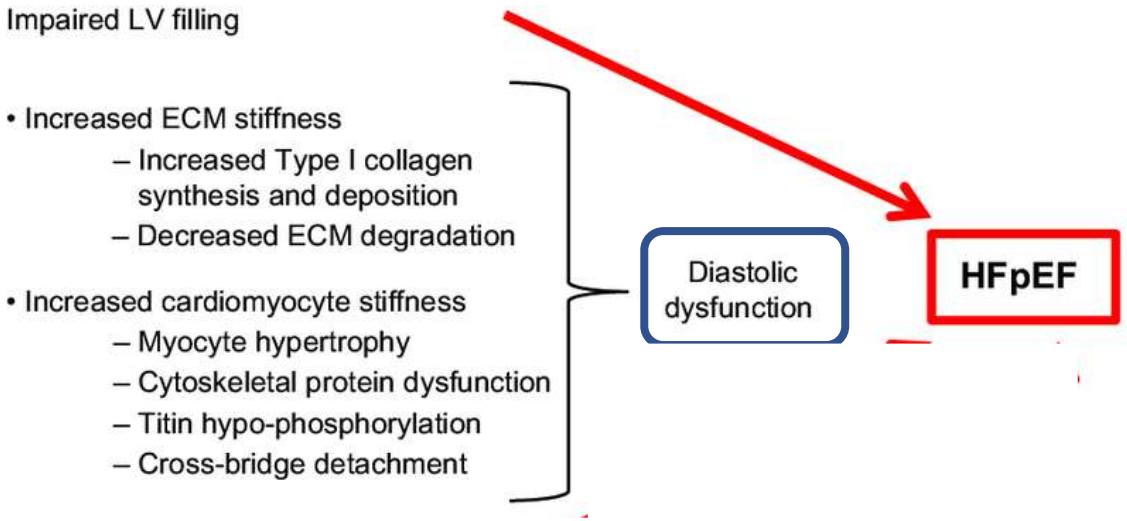


Distinct Phenotypes

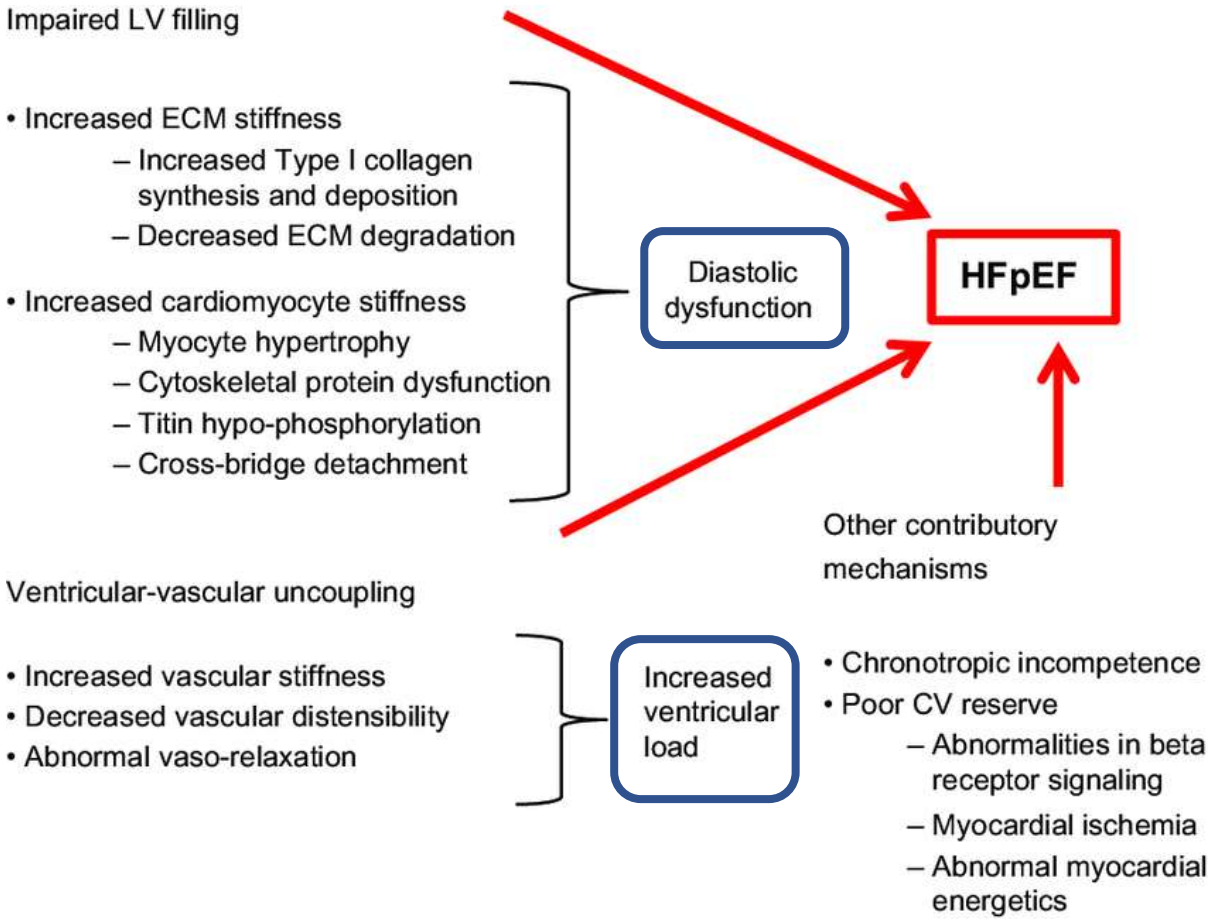




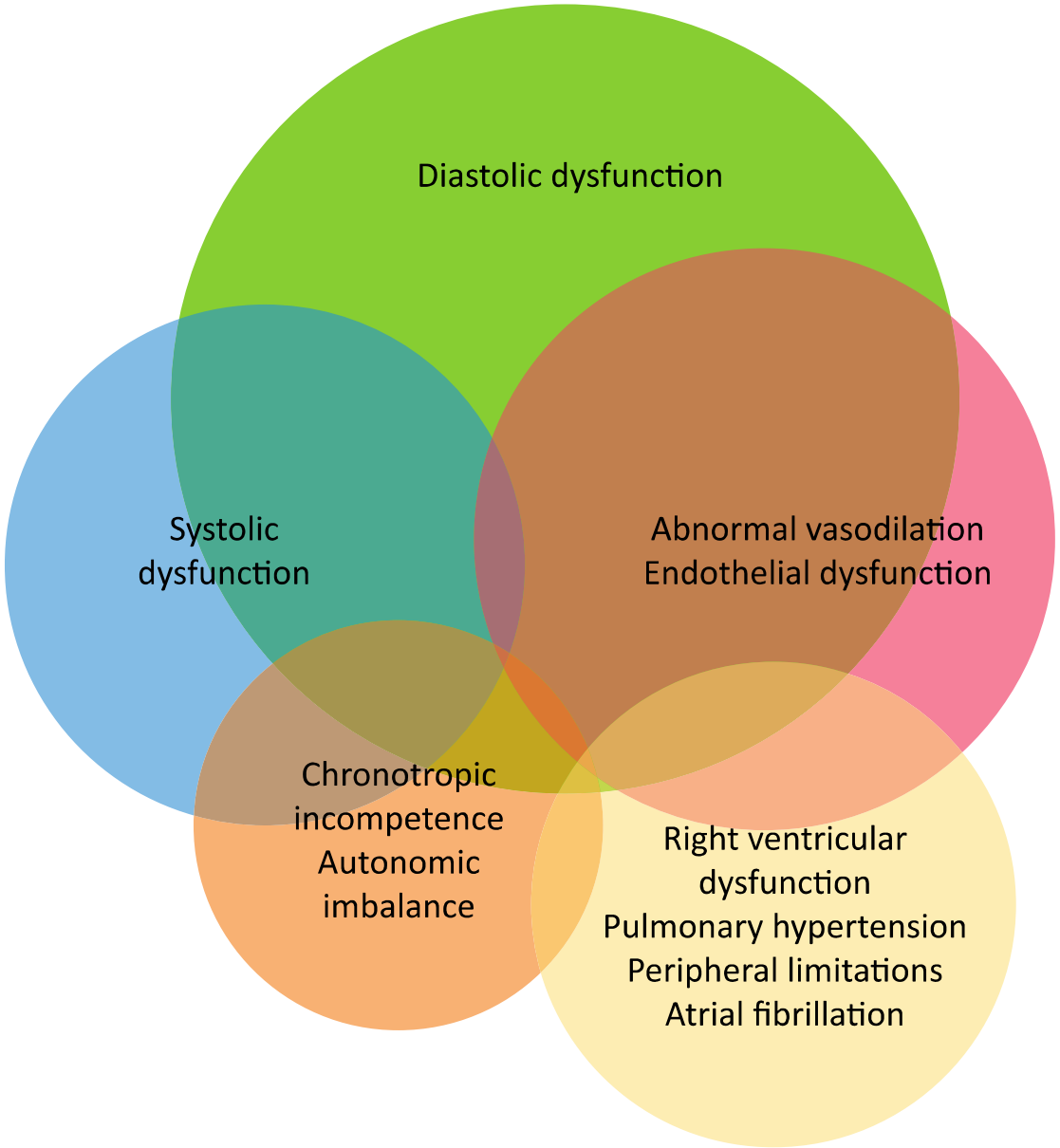
HFpEF is not equal to DD

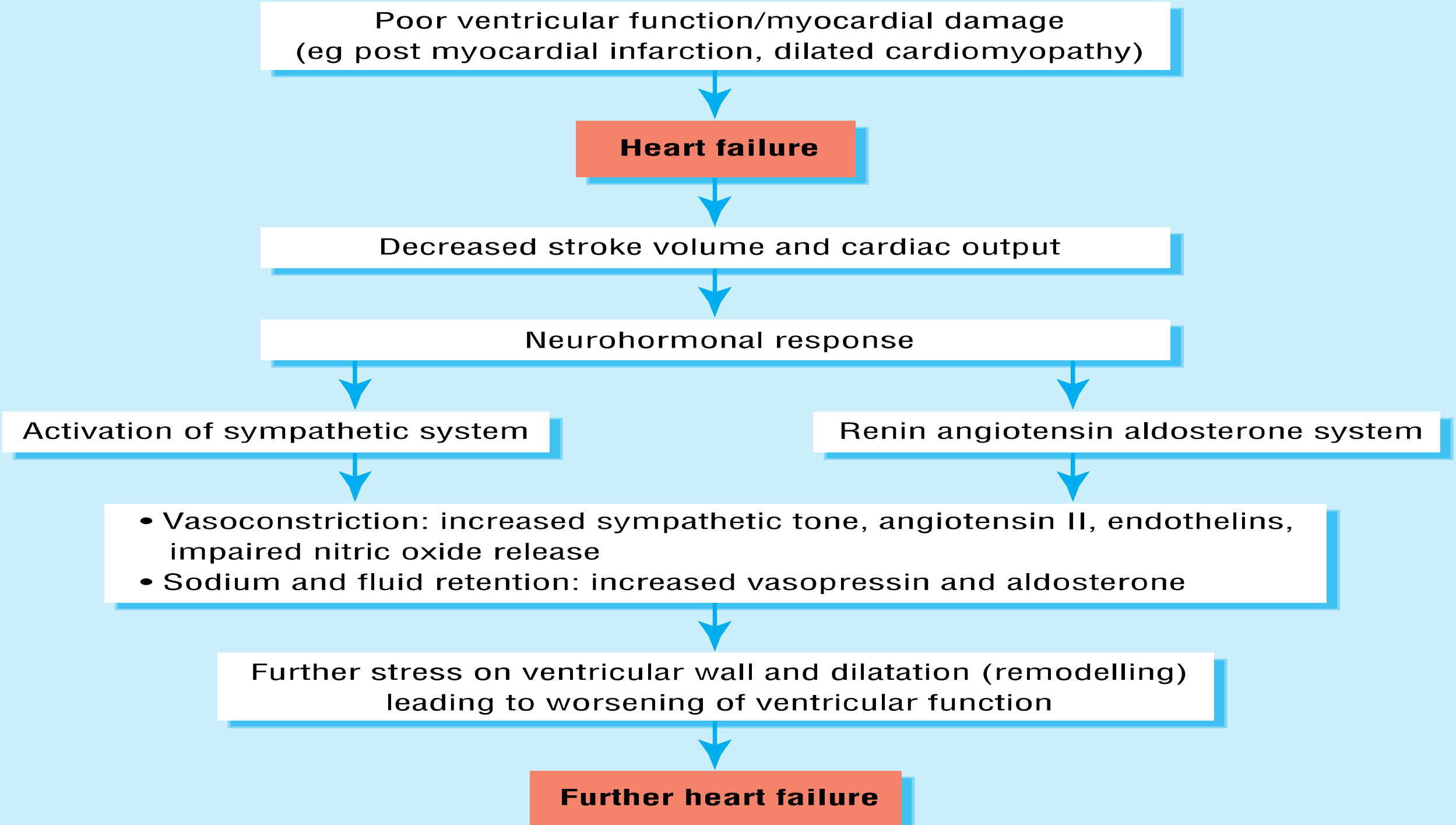


HFpEF is not equal to DD

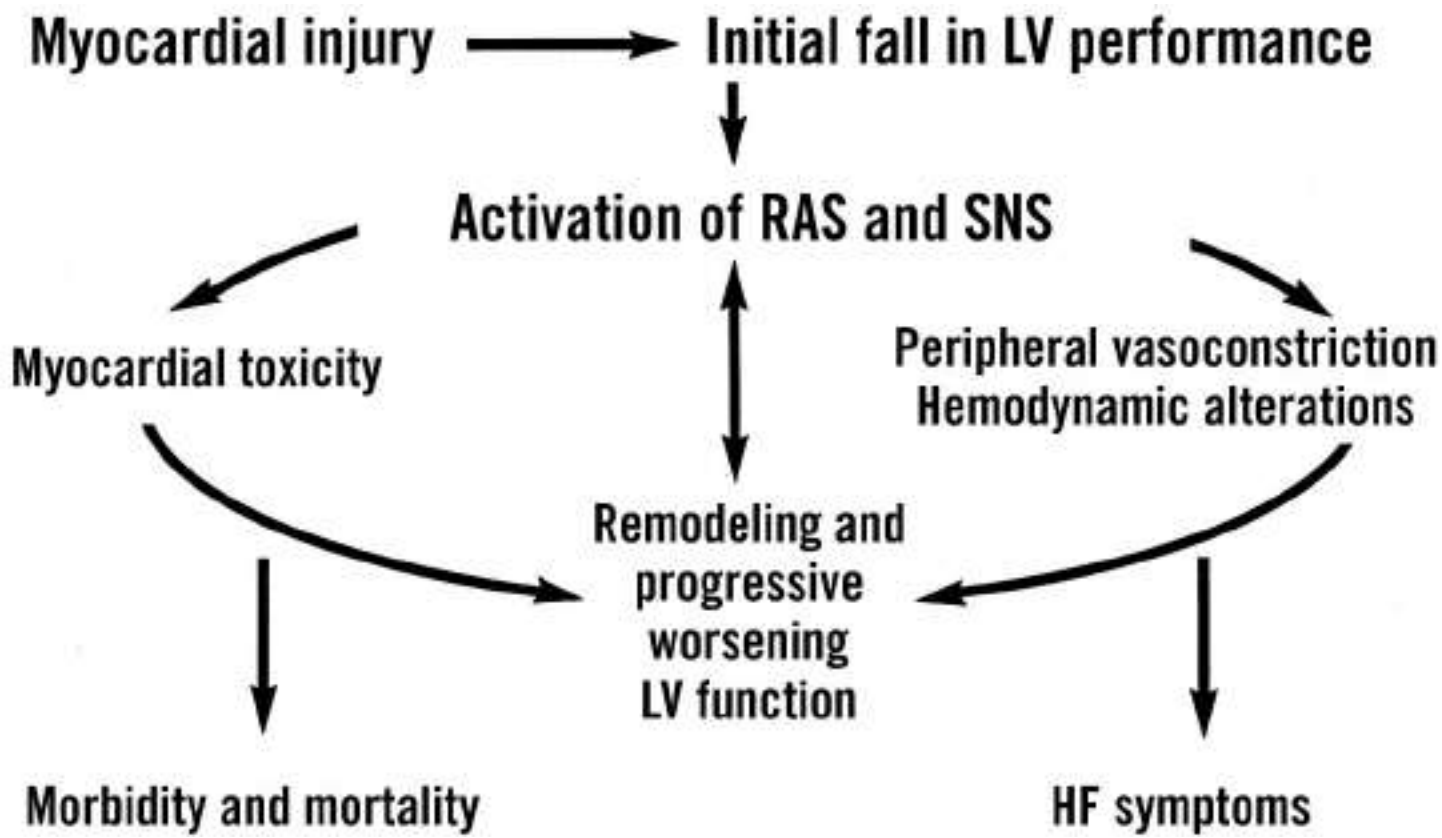


HFpEF represents a collection of heterogeneous conditions that can **sufficiently elevate left atrial pressures** and precipitate **clinical features of HF**, in the context of a **LVEF ≥50%.**


Diastolic dysfunction
Systolic dysfunction
Abnormal vasodilation
Endothelial dysfunction
Chronotropic incompetence
Autonomic imbalance
Right ventricular dysfunction
Pulmonary hypertension
Peripheral limitations
Atrial fibrillation


Poor ventricular function/myocardial damage
(eg post myocardial infarction, dilated cardiomyopathy)
Heart failure
Decreased stroke volume and cardiac output
Neurohormonal response
Activation of sympathetic system
Renin angiotensin aldosterone system
• Vasoconstriction: increased sympathetic tone, angiotensin II, endothelins, impaired nitric oxide release
• Sodium and fluid retention: increased vasopressin and aldosterone
Further stress on ventricular wall and dilatation (remodelling) leading to worsening of ventricular function
Further heart failure

In HFpEF
the evil is Na/water
overload


Myocardial injury
Initial fall in LV performance
Activation of RAS and SNS
Myocardial toxicity
Peripheral vasoconstriction
Hemodynamic alterations
Remodeling and
progressive
worsening
LV function
Morbidity and mortality
HF symptoms

Is this paradigm true for HFpEF ?

- 1- Cardio-Vascular stimulation >>> neuro-hormonal activation
- 2- Neuro-Hormonal activation (“measure” NH activity)
- 3- Antagonizing the NH activation >>> improved outcome

we cannot find a primary cardiac stimulus for NH activation

- if the heart is the problem >>> **there should be a low COP to explain the NH activation**
- **may be there is an art under-filling** >>> look at the SVR >>> no difference
- we can not find a paper showing a primary CV stimulus for NH activation !

Hemodynamics of HFpEF & HTN pts

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Heart Failure

Global Cardiovascular Reserve Dysfunction in Heart Failure With Preserved Ejection Fraction

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Rochester, Minnesota

Objectives The purpose of this study was to comprehensively examine cardiovascular reserve function with exercise in patients with heart failure and preserved ejection fraction (HFpEF).

Background Optimal exercise performance requires an integrated physiologic response, with coordinated increases in heart rate, contractility, lusitropy, arterial vasodilation, endothelial function, and venous return. Cardiac and vascular responses are coupled, and abnormalities in several components may interact to promote exertional intolerance in HFpEF.

Methods Subjects with HFpEF (n = 21), hypertension without heart failure (n = 19), and no cardiovascular disease (control, n = 10) were studied before and during exercise with characterization of cardiovascular reserve function by Doppler echocardiography, peripheral arterial tonometry, and gas exchange.

Results Exercise capacity and tolerance were reduced in HFpEF compared with hypertensive subjects and controls, with lower VO_2 and cardiac index at peak, and more severe dyspnea and fatigue at matched low-level workloads. Endothelial function was impaired in HFpEF and in hypertensive subjects as compared with controls. However, blunted exercise-induced increases in chronotropy, contractility, and vasodilation were unique to HFpEF and resulted in impaired dynamic ventricular-arterial coupling responses during exercise. Exercise capacity and symptoms of exertional intolerance were correlated with abnormalities in each component of cardiovascular reserve function, and HFpEF subjects were more likely to display multiple abnormalities in reserve.

Conclusions HFpEF is characterized by depressed reserve capacity involving multiple domains of cardiovascular function, which contribute in an integrated fashion to produce exercise limitation. Appreciation of the global nature of reserve dysfunction in HFpEF will better inform optimal design for future diagnostic and therapeutic strategies. (J Am Coll Cardiol 2010;56:845–54) © 2010 by the American College of Cardiology Foundation

Exercise intolerance is a defining symptom in patients with heart failure and preserved ejection fraction (HFpEF), yet its mechanisms remain poorly understood (1). Reductionist strategies to studying human disease are predicated on the concept that a single unifying process causes a specific disease phenotype. However, HFpEF is principally a disease of the elderly (2), and in geriatric medicine, it is more likely that multiple processes and age-related comorbidities coexist in the same patient (3). These processes interact synergistically to produce a clinical phenotype. Because exercise requires coordinated changes in ventricular function, arterial tone, endothelial function, venous return, and autonomic signaling, it would be expected that abnormalities in many such components exist and interact to promote subjective and objective exercise limitation in HFpEF (4,5).

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Accordingly, the present study sought to examine multiple components of exercise reserve responses in patients with HFpEF, including assessment of chronotropic, preload, contractile, endothelial and global vascular reserve functions, and importantly, ventricular-arterial coupling reserve responses. Because population-based studies have shown that patients with HFpEF are typically older, hypertensive, and female (2), and because each of these features may independently affect cardiovascular function, we compared reserve responses in HFpEF to a predominantly female, elderly hypertensive control group without HF, in addition to an apparently healthy control group free of cardiovascular disease.

From the Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic, Rochester, Minnesota. Dr. Borlaug was supported by the Mayo Clinic Center for Translational Science Activities, the National Institutes of Health (UL RR024150), and the Marie Ingalls Career Development Award in Cardiovascular Research. Dr. Lerman serves on the advisory board for Itamar Medical. All other authors have reported that they have no relationships to disclose.

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Table 1 Clinical Characteristics and Resting Cardiovascular Function

	Control (n = 10)	Hypertension (n = 19)	HFpEF (n = 21)	p Value
Clinical characteristics				
Age, yrs	62 ± 7	65 ± 11	67 ± 11	0.4
Sex, female	70	74	76	0.9
Body mass index, kg/m^2	31.2 ± 7.9	28.3 ± 3.0	34.3 ± 6.6*	0.004
KCCQ score	99 ± 4	94 ± 16	69 ± 18*†	<0.001
Hypertension	0	100†	86†	<0.001
Coronary artery disease	0	11	33†	0.02
Diabetes mellitus	0	5	43*†	0.003
Smoking	0	0	9	0.2
GFR, ml/min	87 ± 17	81 ± 20	81 ± 38	0.9
Plasma BNP, pg/ml	38 ± 40	60 ± 50	152 ± 106*†	0.001
Hemoglobin, g/dl	13.0 ± 2.2	14.2 ± 1.5	13.0 ± 1.3	0.06
Beta-blockers	0	42†	57†	<0.001
ACEI or ARB	0	53†	67†	<0.001
Loop diuretic	0	0	57*†	<0.001
Lipid lowering	40	63	90†	0.009
LV mass index, mg/m^2	68.2 ± 19.8	90.7 ± 21.8	88.0 ± 27.1	<0.05
Resting function				
Heart rate, beats/min	70 ± 8	71 ± 12	68 ± 12	0.9
Pre-load				
LVEDVI, ml/m^2	54 ± 8	59 ± 12	58 ± 19	0.6
E/E′ ratio	12 ± 4	12 ± 5	20 ± 7*†	0.003
Contractility				
PWRI, mm Hg/s	330 ± 80	348 ± 59	339 ± 69	0.8
PRSW, g/cm^2	79 ± 19	77 ± 19	81 ± 40	0.9
Ees, mm Hg/ml	1.48 ± 0.38	1.72 ± 0.38	1.79 ± 0.76	0.4
Vascular function				
Systolic BP, mm Hg	123 ± 16	136 ± 12	131 ± 21	0.2
Ea, mm Hg/ml	1.88 ± 0.40	1.97 ± 0.51	1.77 ± 0.62	0.3
SVRI, dyne·m^2/s·cm^{-5}	3,430 ± 920	3,430 ± 750	3,100 ± 880	0.4
Log RHI	1.33 ± 0.34	0.92 ± 0.38†	0.85 ± 0.42†	0.009
Endothelial dysfunction	0	28	42†	0.016
Ventricular arterial coupling				
Coupling ratio, Ea/Ees	1.32 ± 0.34	1.16 ± 0.24	1.08 ± 0.35	0.2
Ejection fraction, %	58 ± 7	58 ± 5	60 ± 6	0.5
Cardiac index, l/min·m^2	2.2 ± 0.5	2.4 ± 0.6	2.3 ± 0.6	0.7

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B-Type Natriuretic Peptide Strongly Reflects Diastolic Wall Stress in Patients With Chronic Heart Failure

Comparison Between Systolic and Diastolic Heart Failure

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OBJECTIVES We explored the stimulus for B-type natriuretic peptide (BNP) secretion in the clinical setting of heart failure (HF).

BACKGROUND Increasingly, plasma BNP levels are being incorporated into the clinical assessment and management of systolic heart failure (SHF) as well as diastolic heart failure (DHF). However, heterogeneity in BNP levels among individuals with HF can cause some confusion in interpreting results.

METHODS In 160 consecutive patients presenting with HF, we measured plasma BNP levels and performed echocardiography and cardiac catheterization. Systolic and diastolic meridional wall stress was calculated from echocardiographic and hemodynamic data.

RESULTS Although plasma BNP had a significant correlation ($r^2 = 0.296$ [$p < 0.001$]) with left ventricular end-diastolic pressure (EDP) as previously reported, the correlation between plasma BNP and end-diastolic wall stress (EDWS) ($r^2 = 0.887$ [$p < 0.001$]) was more robust. In a subanalysis of 62 patients with DHF, a similar result was obtained ($r^2 = 0.143$ for EDP and $r^2 = 0.704$ for EDWS). In a comparison between SHF and DHF, the BNP level was significantly higher in SHF ($p < 0.001$). Although EDP did not show any difference, EDWS was significantly higher in SHF than in DHF ($p < 0.001$).

CONCLUSIONS The present study shows that plasma BNP levels reflect left ventricular EDWS more than any other parameter previously reported, not only in patients with SHF, but also in patients with DHF. The relationship of left ventricular EDWS to plasma BNP may provide a better fundamental understanding of the interindividual heterogeneity in BNP levels and their clinical utility in the diagnosis and management of HF. (J Am Coll Cardiol 2006;47:742–8)

Plasma B-type natriuretic peptide (BNP) levels are reported not only to be a strong marker of left ventricular (LV) dysfunction, but also a marker to predict morbidity and mortality accurately in patients with chronic heart failure (HF) (1,2). Recently, BNP-guided therapy for chronic HF has been suggested. Troughton et al. (3) demonstrated that pharmacotherapy guided by BNP levels reduces cardiovascular events and delays time to first cardiovascular event compared with intensive clinically guided therapy. Recent reports also demonstrated the contribution of LV diastolic function to plasma BNP levels and the usefulness of BNP in the diagnosis of diastolic HF (4).

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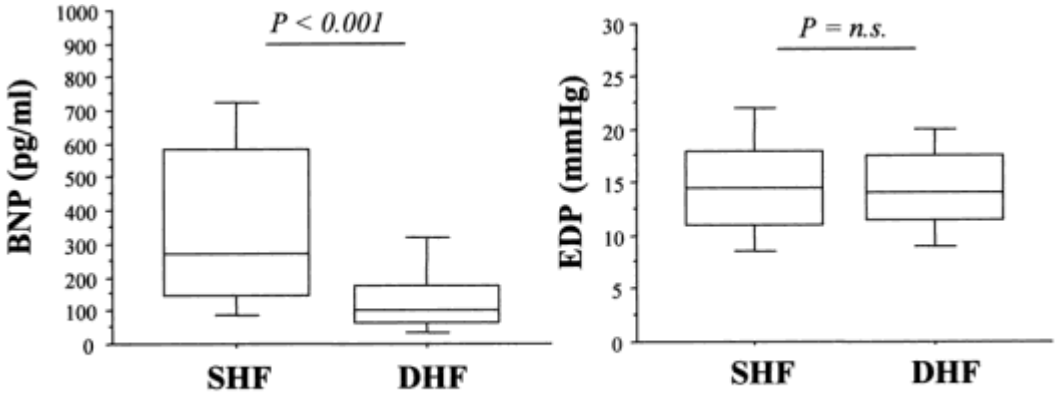
However, heterogeneity in BNP levels among individuals with HF has been recognized, and it has caused some confusion in interpreting results (5). Previous human studies have suggested correlations between BNP levels and cardiac functional or dimensional indexes such as end-diastolic pressure (EDP), ejection fraction (EF), pulmonary capillary wedge pressure, and LV volume, none of which sufficiently explain the heterogeneity (6–9). Therefore, it is essential to determine the stimulus for BNP secretion in the clinical setting of HF. In vitro studies have clarified the mechanism of secretion and regulation of BNP precisely (10). Stretch of cardiomyocytes is reported to be the most important stimulus of BNP regulation (11). It is also believed that BNP in humans may be released from the heart in response to increased wall stress. However, there have been few human studies exploring a direct relationship between wall stress and BNP regulation (12). Vanderheyden et al. (13) have very recently demonstrated, for the first time, in 40 patients with aortic stenosis (AS), a significant correlation of BNP with LV end-diastolic wall stress (EDWS). In their study, however, subjects were limited to patients with AS. Hence, there now is a need for the same assessment in patients



ORIGINAL ARTICLE

Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction

Barry M. Massie, M.D., Peter E. Carson, M.D., John J. McMurray, M.D., Michel Komajda, M.D., Robert McKelvie, M.D., Michael R. Zile, M.D., Susan Anderson, M.S., Mark Donovan, Ph.D., Erik Iverson, M.S., Christoph Staiger, M.D., and Agata Ptaszynska, M.D., for the I-PRESERVE Investigators*

ABSTRACT

BACKGROUND

Approximately 50% of patients with heart failure have a left ventricular ejection fraction of at least 45%, but no therapies have been shown to improve the outcome of these patients. Therefore, we studied the effects of irbesartan in patients with this syndrome.

METHODS

We enrolled 4128 patients who were at least 60 years of age and had New York Heart Association class II, III, or IV heart failure and an ejection fraction of at least 45% and randomly assigned them to receive 300 mg of irbesartan or placebo per day. The primary composite outcome was death from any cause or hospitalization for a cardiovascular cause (heart failure, myocardial infarction, unstable angina, arrhythmia, or stroke). Secondary outcomes included death from heart failure or hospitalization for heart failure, death from any cause and from cardiovascular causes, and quality of life.

RESULTS

During a mean follow-up of 49.5 months, the primary outcome occurred in 742 patients in the irbesartan group and 763 in the placebo group. Primary event rates in the irbesartan and placebo groups were 100.4 and 105.4 per 1000 patient-years, respectively (hazard ratio, 0.95; 95% confidence interval [CI], 0.86 to 1.05; P=0.35). Overall rates of death were 52.6 and 52.3 per 1000 patient-years, respectively (hazard ratio, 1.00; 95% CI, 0.88 to 1.14; P=0.98). Rates of hospitalization for cardiovascular causes that contributed to the primary outcome were 70.6 and 74.3 per 1000 patient-years, respectively (hazard ratio, 0.95; 95% CI, 0.85 to 1.08; P=0.44). There were no significant differences in the other prespecified outcomes.

CONCLUSIONS

Irbesartan did not improve the outcomes of patients with heart failure and a preserved left ventricular ejection fraction. (ClinicalTrials.gov number, NCT00095238.)

From the University of California, San Francisco, and San Francisco Veterans Affairs Medical Center, San Francisco (B.M.M.); Georgetown University and Washington DC Veterans Affairs Medical Center, Washington, DC (P.E.C.); British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (J.J.M.); Université Paris 6 and Hospital Pitié–Salpêtrière, Paris (M.K.); Hamilton Health Sciences, McMaster University, Hamilton, ON, Canada (R.M.); Ralph H. Johnson Veterans Affairs Medical Center and Medical University of South Carolina, Charleston (M.R.Z.); University of Wisconsin, Madison (S.A., E.I.); Bristol-Myers Squibb, Princeton, NJ (M.D., A.P.); and Sanofi-Aventis, Bridgewater, NJ (C.S.). Address reprint requests to Dr. Massie at the Veterans Affairs Medical Center, 111C, 4150 Clement St., San Francisco, CA 94121, or at barry.massie@va.gov.

*Committee members and investigators in the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE) are listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

This article (10.1056/NEJMoa0805450) was published at www.nejm.org on November 11, 2008.

N Engl J Med 2008;359:2456-67.

Table 2. Primary Outcome with Component Events.*

Outcome	Placebo (N=2061)		Irbesartan (N=2067)		Hazard Ratio (95% CI)	P Value
	No. of Patients with Event	Event Rate per 1000 Patient-Yr	No. of Patients with Event	Event Rate per 1000 Patient-Yr		
Primary outcome	763	105.4	742	100.4	0.95 (0.86–1.05)	0.35
Death	226		221			
Hospitalization for protocol-specified cardiovascular cause	537		521			
Worsening heart failure	314		291			
Myocardial infarction	54		60			
Unstable angina	19		20			
Stroke	79		68			
Atrial arrhythmia	68		77			
Ventricular arrhythmia	3		5			

* Event rates were normalized for the duration of follow-up before the event occurrence.

ARB (Irbesartan) >>> did not work !

Table 2. Primary Outcome with Component Events.*

Outcome	Placebo (N=2061)		Irbesartan (N=2067)		Hazard Ratio (95% CI)	P Value
	No. of Patients with Event	Event Rate per 1000 Patient-Yr	No. of Patients with Event	Event Rate per 1000 Patient-Yr		
Primary outcome	763	105.4	742	100.4	0.95 (0.86–1.05)	0.35
Death	226		221			
Hospitalization for protocol-specified cardiovascular cause	537		521			
Worsening heart failure	314		291			
Myocardial infarction	54		60			
Unstable angina	19		20			
Stroke	79		68			
Atrial arrhythmia	68		77			
Ventricular arrhythmia	3		5			

* Event rates were normalized for the duration of follow-up before the event occurrence.

HF hospitalization
the clinical manifestation of salt / water overload

- no impact on it !

Table 3. Secondary Outcomes.*

Outcome	Placebo (N=2061)		Irbesartan (N=2067)		Hazard Ratio (95% CI)	P Value
	No. of Patients with Event	Event Rate per 1000 Patient-Yr	No. of Patients with Event	Event Rate per 1000 Patient-Yr		
Death from any cause	436	52.3	445	52.6	1.00 (0.88–1.14)	0.98
Death from heart failure or hospitalization for heart failure†	438	57.4	428	54.8	0.96 (0.84–1.09)	0.51
Death from a cardiovascular cause or nonfatal myocardial infarction or stroke	400	49.4	402	48.9	0.99 (0.86–1.13)	0.84
Death from a cardiovascular cause	302	36.3	311	36.7	1.01 (0.86–1.18)	0.92
Hospitalization for a protocol-specified cardiovascular cause	537	74.3	521	70.6	0.95 (0.85–1.08)	0.44
Hospitalization for worsening heart failure	336	44.0	325	41.6	0.95 (0.81–1.10)	0.50
Hospitalization for any cause	1126	199.8	1152	203.6	1.02 (0.94–1.11)	0.64
Change in score on the Minnesota Living with Heart Failure scale at 6 mo‡						0.85
Median	−7		−8			
Interquartile range	−19 to 0		−19 to 1			
Change in NT pro-BNP at 6 mo (pg/ml)						0.14
Median	−2		−13			
Interquartile range	−125 to 119		−149 to 100			

* Event rates were normalized for the duration of follow-up before the event occurrence.
† Death from heart failure includes death due to pump failure and sudden death. NT pro-BNP denotes plasma N-terminal pro B–type natriuretic peptide.
‡ Possible scores range from 0 to 105, with lower scores indicating a better quality of life.

there must be sub-group !

Subgroup	Irbesartan	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients/no. of events (%)			
All patients	742/2067 (36)	763/2061 (37)	0.95 (0.86–1.05)	
Age				0.60
<65 yr	86/376 (23)	86/364 (24)	0.96 (0.71–1.30)	
65–74 yr	331/994 (33)	322/981 (33)	1.01 (0.87–1.18)	
≥75 yr	325/697 (47)	355/716 (50)	0.90 (0.78–1.05)	
Sex				0.78
Female	392/1227 (32)	420/1264 (33)	0.94 (0.82–1.08)	
Male	350/840 (42)	343/797 (43)	0.96 (0.83–1.12)	
Ejection fraction				0.28
≤59%	433/1054 (41)	423/1027 (41)	0.98 (0.85–1.12)	
>59%	309/1011 (31)	339/1033 (33)	0.92 (0.79–1.07)	
Use of ACE inhibitor				0.36
No	529/1529 (35)	566/1551 (36)	0.93 (0.82–1.04)	
Yes	213/538 (40)	197/510 (39)	1.03 (0.85–1.25)	
Use of beta-blocker				0.14
No	299/842 (36)	336/859 (39)	0.87 (0.75–1.02)	
Yes	443/1225 (36)	427/1202 (36)	1.02 (0.89–1.16)	
Diabetes				0.28
No	491/1495 (33)	494/1496 (33)	0.99 (0.87–1.12)	
Yes	251/570 (44)	269/564 (48)	0.88 (0.74–1.04)	
Hospitalization for heart failure within 6 mo				0.81
No	323/1157 (28)	334/1155 (29)	0.96 (0.82–1.12)	
Yes	419/910 (46)	429/906 (47)	0.94 (0.82–1.08)	
Geographic region				0.50
Europe	518/1475 (35)	534/1464 (36)	0.95 (0.84–1.07)	
North America	87/190 (46)	99/195 (51)	0.85 (0.64–1.14)	
Other	137/402 (34)	130/402 (32)	1.07 (0.84–1.35)	

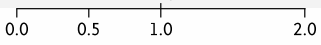


Figure 2. Primary Outcome According to Prespecified Subgroups.

The plot shows hazard ratios and 95% confidence intervals for the primary outcome, with patients stratified according to eight subgroups prespecified in the statistical analysis plan. No heterogeneity was observed for these subgroups.

Original Investigation

Association Between Use of β-Blockers and Outcomes 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; Leif Friberg, MD, PhD

IMPORTANCE Heart failure with preserved ejection fraction (HFPEF) may be as common and may have similar mortality as heart failure with reduced ejection fraction (HFREF). β-Blockers reduce mortality in HFREF but are inadequately studied in HFPEF.

OBJECTIVE To test the hypothesis that β-blockers are associated with reduced all-cause mortality in HFPEF.

DESIGN Propensity score–matched cohort study using the Swedish Heart Failure Registry. Propensity scores for β-blocker use were derived from 52 baseline clinical and socioeconomic variables.

SETTING Nationwide registry of 67 hospitals with inpatient and outpatient units and 95 outpatient primary care clinics in Sweden with patients entered into the registry between July 1, 2005, and December 30, 2012, and followed up until December 31, 2012.

PARTICIPANTS From a consecutive sample of 41 976 patients, 19 083 patients with HFPEF (mean [SD] age, 76 [12] years; 46% women). Of these, 8244 were matched 2:1 based on age and propensity score for β-blocker use, yielding 5496 treated and 2748 untreated patients with HFPEF. Also we conducted a positive-control consistency analysis involving 22 893 patients with HFREF, of whom 6081 were matched yielding 4054 treated and 2027 untreated patients.

EXPOSURES β-Blockers prescribed at discharge from the hospital or during an outpatient visit, analyzed 2 ways: without consideration of crossover and per-protocol analysis with censoring at crossover, if applicable.

MAIN OUTCOMES AND MEASURES The prespecified primary outcome was all-cause mortality and the secondary outcome was combined all-cause mortality or heart failure hospitalization.

RESULTS Median follow-up in HFPEF was 755 days, overall; 709 days in the matched cohort; no patients were lost to follow-up. In the matched HFPEF cohort, 1-year survival was 80% vs 79% for treated vs untreated patients, and 5-year survival was 45% vs 42%, with 2279 (41%) vs 1244 (45%) total deaths and 177 vs 191 deaths per 1000 patient-years (hazard ratio [HR], 0.93; 95% CI, 0.86-0.996; P = .04). β-Blockers were not associated with reduced combined mortality or heart failure hospitalizations: 3368 (61%) vs 1753 (64%) total for first events, with 371 vs 378 first events per 1000 patient-years (HR, 0.98; 95% CI, 0.92-1.04; P = .46). In the matched HFREF cohort, β-blockers were associated with reduced mortality (HR, 0.89; 95% CI, 0.82-0.97, P=.005) and also with reduced combined mortality or heart failure hospitalization (HR, 0.89; 95% CI, 0.84-0.95; P = .001).

CONCLUSIONS AND RELEVANCE In patients with HFPEF, use of β-blockers was associated with lower all-cause mortality but not with combined all-cause mortality or heart failure hospitalization. β-Blockers in HFPEF should be examined in a large randomized clinical trial.

Editorial page 1977

Supplemental content at jama.com

CME Quiz at jamanetworkcme.com and CME Questions 2034

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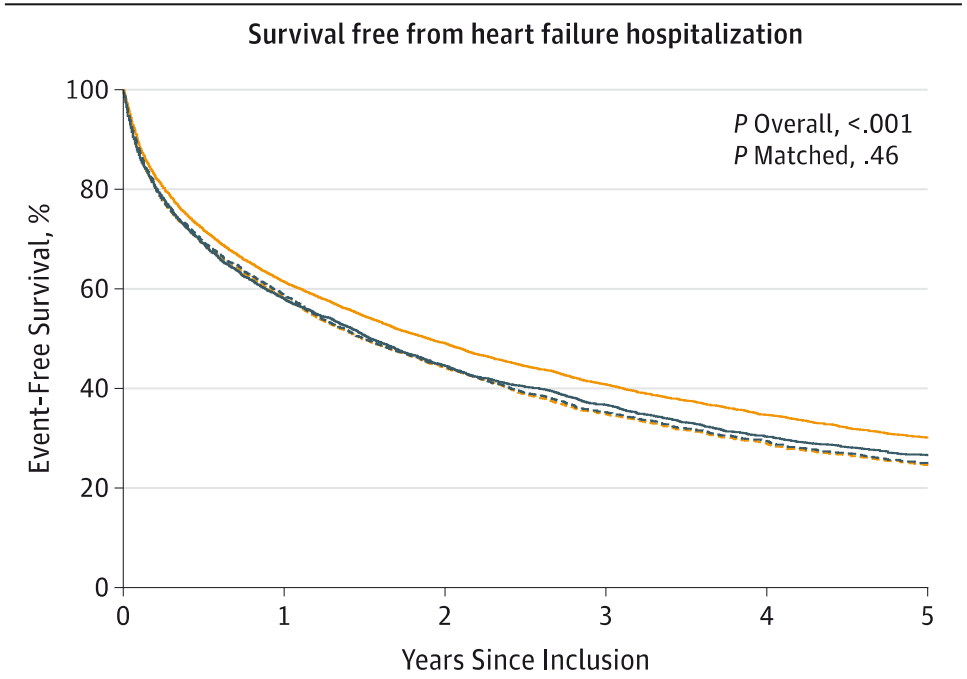
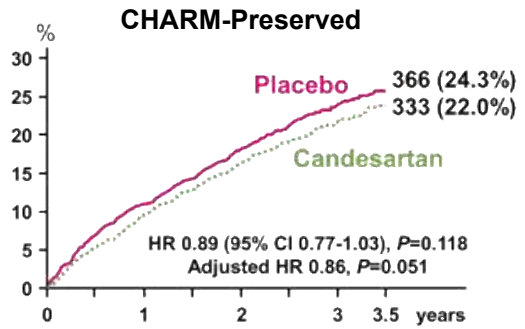
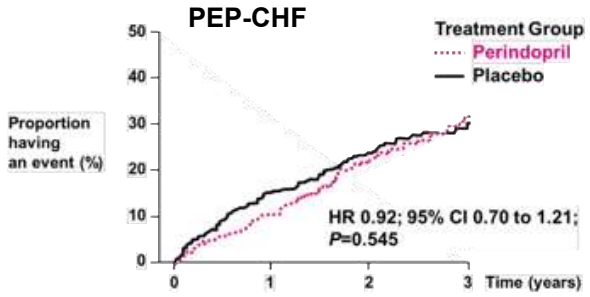
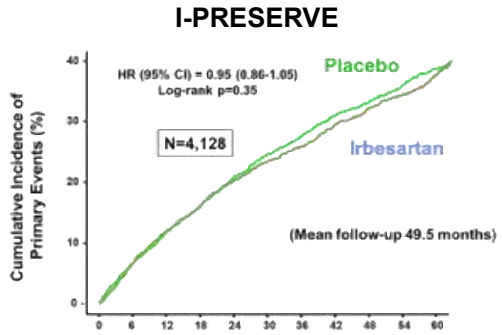
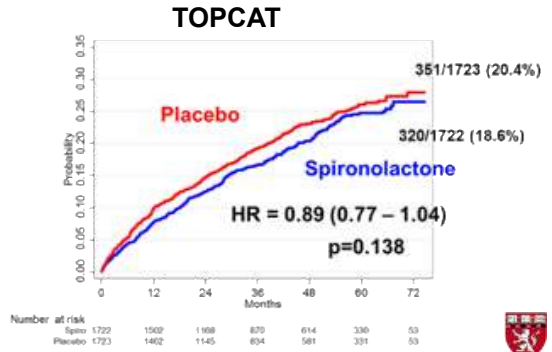


Outcomes Trials in HFpEF









IMPORTANT
Is HFpEF really a kind of Hear Failure ?

- when we are talking about HF
- in order to tell that HFpEF is a kind of HF >>> for which salt water retention & VO is originating within the heart >>> but we cant show that !

Are Systolic and Diastolic Heart Failure Overlapping or Distinct Phenotypes Within the Heart Failure Spectrum?

Diastolic and Systolic Heart Failure Are Distinct Phenotypes Within the Heart Failure Spectrum

Barry A. Borlaug, MD; Margaret M. Redfield, MD

Heart failure (HF) is a major worldwide public health problem. One in 5 people aged 40 years in the United States will develop HF during his or her lifetime,[1] and HF remains the leading cause for hospitalization among the elderly.[2] Although age- and sex-specific HF incidence is not increasing,[3] overall HF survival has improved, and the number of people aged >65 years is increasing rapidly. Thus, the absolute number of patients with HF will continue to increase. Half of the patients with HF have a preserved ejection fraction (HFpEF), and the remainder display reduced ejection fraction (HFrEF).[4–6] The proportion of patients with normal ejection fraction (EF) is increasing steadily because of increased incidence and/or increasing physician recognition of the syndrome.[4] Resource utilization associated with HF is high in both the inpatient and outpatient settings, regardless of EF.

Response by De Keulenaer and Brutsaert on p 2014

Heart failure is a syndrome that can be defined clinically by a collection of symptoms (dyspnea, fatigue, exertional intolerance) and signs (edema, gallop, rales) that are attributable to a cardiac disorder.[2] Heart failure may also be defined hemodynamically by an inability to provide adequate cardiac output to the body at rest or with exertion, or to do so only in the setting of elevated cardiac filling pressures. The cardiovascular system responds to a wide variety of insults (eg, myocardial disease, ischemia, valvular or pericardial disease) in a finite number of ways, both hemodynamically (elevated filling pressures, depressed output) and symptomatically (dyspnea, fatigue, angina). However, these similarities in clinical expression do not indicate that the underlying mechanisms of disease are the same or that treatment will be similar. For example, a headache may be noted with a migraine or brain tumor; dyspnea may be reported with HF, emphysema, or neuromuscular disease; and diarrhea may be observed with infection, dysmotility, or sprue. In each case, common treatments (analgesics, oxygen, and rehydration) will improve symptoms, but only unique interventions targeted to the specific insults causing each disease will be effective to modify long-term outcomes.

HFpEF and HFrEF share the same clinical phenotype. Signs, symptoms, exercise intolerance, hemodynamics, and outcomes may be identical or highly similar in each form of HF,[5–11] but this does not indicate that these disorders are due to a common pathogenesis, or that they should be treated in the same way. Indeed, the principal rationale to taxonomically distinguish diseases is based on cause and treatment. In this review, we examine the wealth of evidence proving that, despite multiple similarities in clinical expression, HFpEF and HFrEF represent 2 distinct disorders in the HF spectrum and, as such, should be studied and treated separately.

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The online-only Data Supplement is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.110.954388/DC1.
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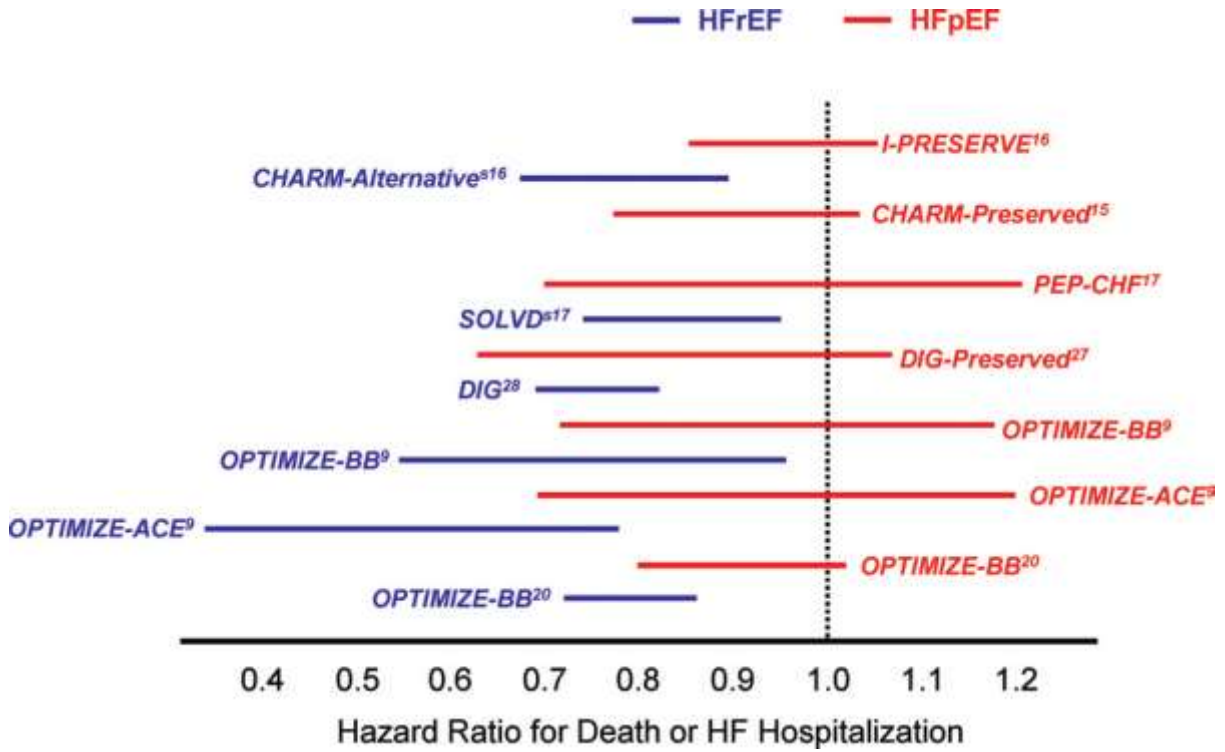
***Circulation* is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.110.954388**



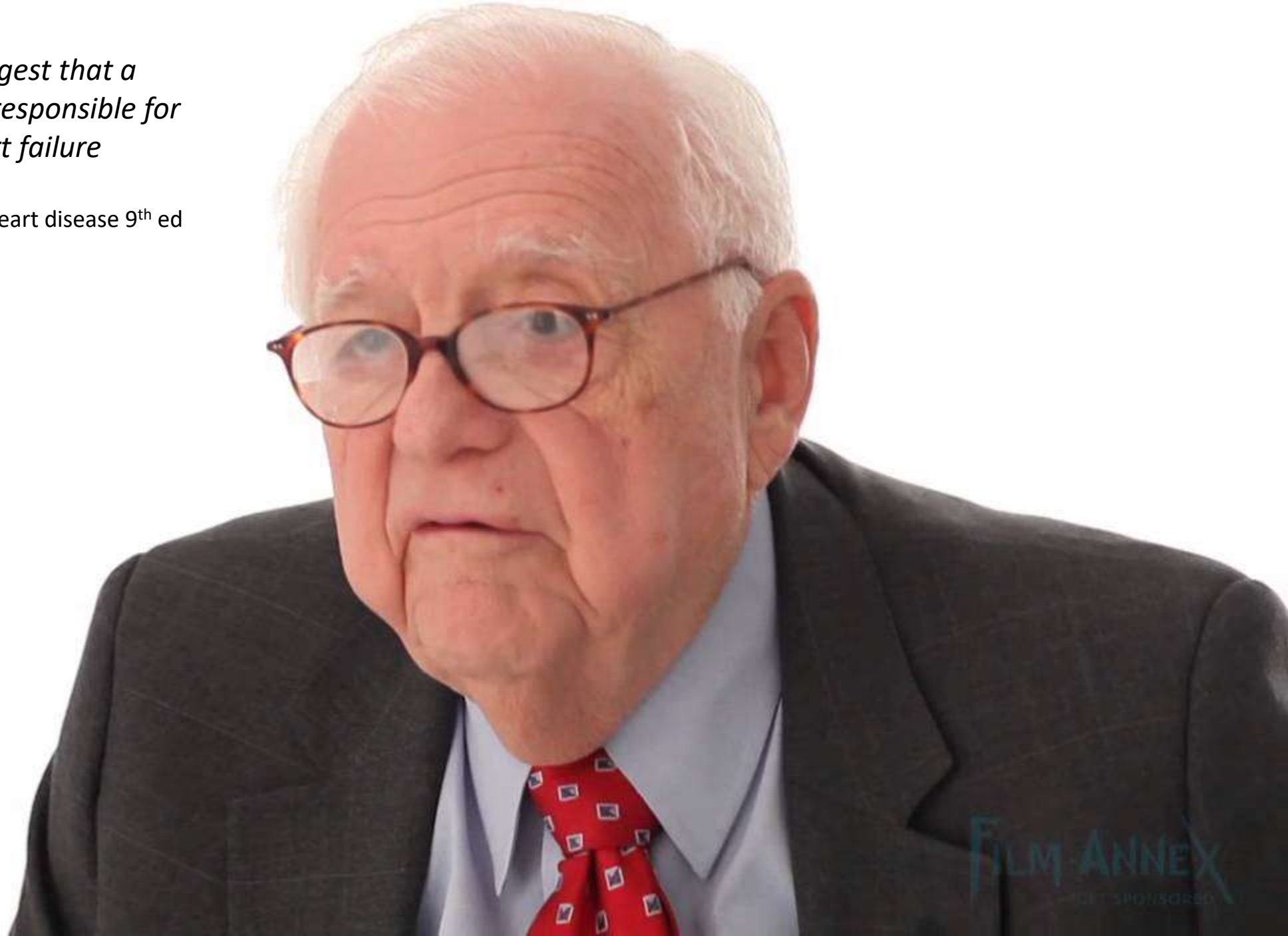
may be we are going to think more deeply >>> may be the problem is not the heart after all !


May be the heart is not the problem

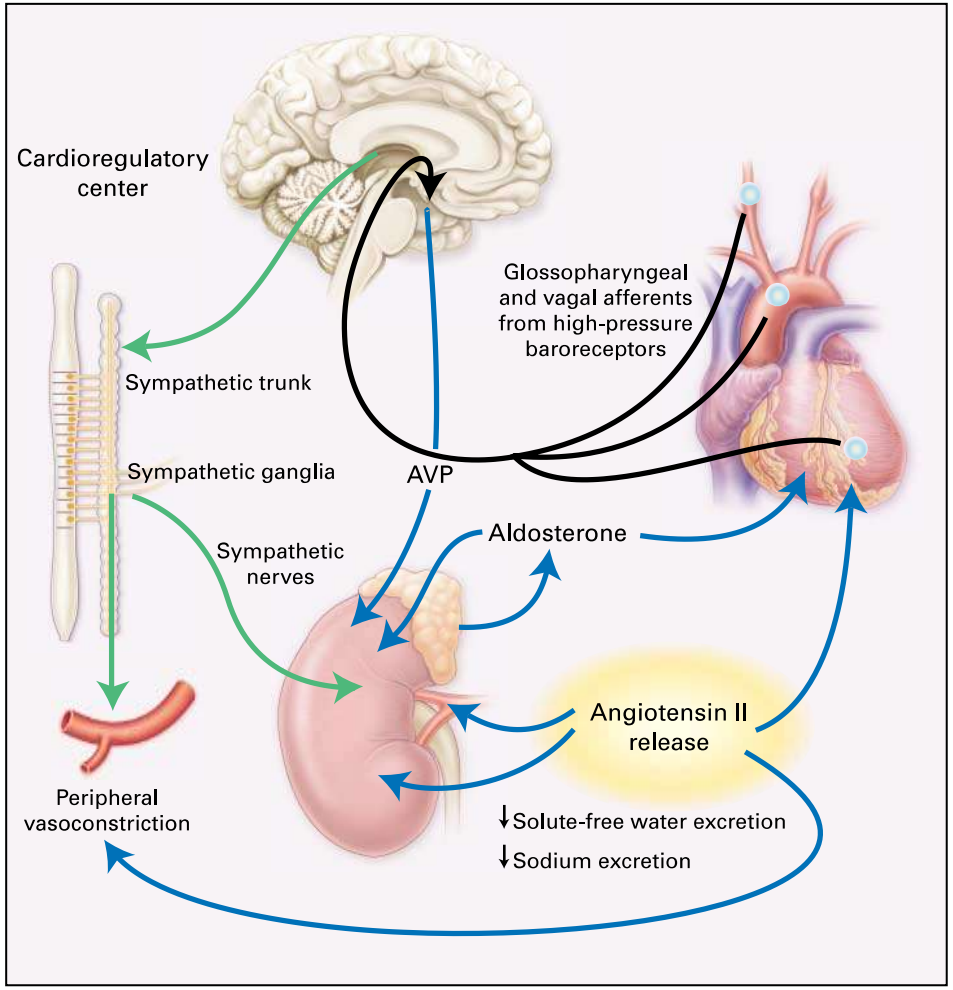
“the kidney has a very special place in the heart”

“there is little evidence to suggest that a primary renal abnormality is responsible for excessive Na retention in heart failure

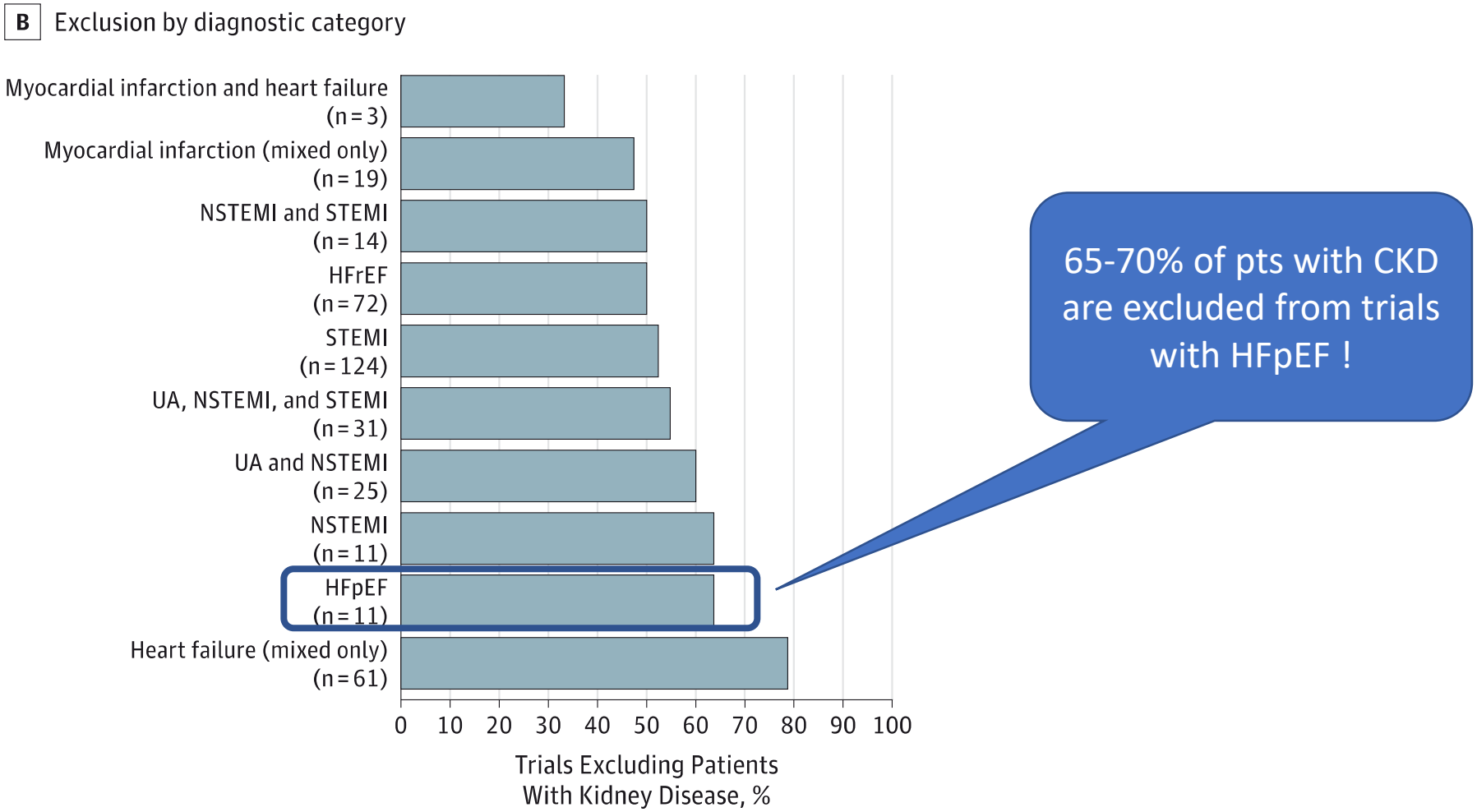
Braunwald’s Heart disease 9th ed



HF: a syndrome of volume overload



the literature ?



If Na & fluid avidity not being driven by neuro-hormonal stimulation (which is central for HFrEF) , then perhaps the kidney must be doing so “inappropriately” eg: a renal disorder.

James C. Fang, MD

if the kidney is responsible >>> these things and observation would be supportive

- Renal Impairement is common in HFpEF & associated with outcomes
- the issue of measuring the GFR
- RI can presage HFpEF >>> epidemiolog evidence why RI predispose to getting HFpEF in contrast to HFrEF
- RI can mediate CV dysfunction

Original Article

Chronic Kidney Disease and Outcomes in Heart Failure With Preserved Versus Reduced Ejection Fraction

The Cardiovascular Research Network PRESERVE Study

David H. Smith, RPh, MHA, PhD; Micah L. Thorp, DO, MPH; Jerry H. Gurwitz, MD; David D. McManus, MD, ScM; Robert J. Goldberg, PhD; Larry A. Allen, MD, MHS; Grace Hsu, MPH; Sue Hee Sung, MPH; David J. Magid, MD, MPH; Alan S. Go, MD

Background—There is scant evidence on the effect that chronic kidney disease (CKD) confers on clinically meaningful outcomes among patients with heart failure with preserved left ventricular ejection fraction (HF-PEF).

Methods and Results—We identified a community-based cohort of patients with HF. Electronic medical record data were used to divide into HF-PEF and reduced left ventricular EF on the basis of quantitative and qualitative estimates. Level of CKD was assessed by estimated glomerular filtration rate (eGFR) and by dipstick proteinuria. We followed patients for a median of 22.1 months for outcomes of death and hospitalization (HF-specific and all-cause). Multivariable Cox regression estimated the adjusted relative-risk of outcomes by level of CKD, separately for HF-PEF and HF with reduced left ventricular EF. We identified 14 579 patients with HF-PEF and 9762 with HF with reduced left ventricular EF. When compared with patients with eGFR between 60 and 89 mL/min per 1.73 m^2, lower eGFR was associated with an independent graded increased risk of death and hospitalization. For example, among patients with HF-PEF, the risk of death was nearly double for eGFR 15 to 29 mL/min per 1.73 m^2 and 7× higher for eGFR<15 mL/min per 1.73 m^2, with similar findings in those with HF with reduced left ventricular EF.

Conclusions—CKD is common and an important independent predictor of death and hospitalization in adults with HF across the spectrum of left ventricular systolic function. Our study highlights the need to develop new and effective interventions for the growing number of patients with HF complicated by CKD. **(*Circ Cardiovasc Qual Outcomes*. 2013;6:333-342.)**

Key Words: chronic kidney disease ■ heart failure ■ hospitalization ■ mortality

Heart failure (HF) currently affects ≈5.7 million adults in the United States and is associated with an estimated $29 billion in hospital charges annually.[1] Driven by a variety of factors, the prevalence of HF is a current and increasing public health problem nationally and internationally. Many patients with HF also have chronic kidney disease (CKD), most frequently manifest as a reduced glomerular filtration rate (GFR), and the risk of developing HF is substantially increased with worsening stage of CKD.[2] Many of the same factors contribute to the development of both chronic diseases, including age, diabetes mellitus, and hypertension.[2,3] Although patients with HF suffer poor outcomes, including a death rate of ≈50% within 5 years of diagnosis,[1] the co-occurrence of CKD and HF seems to confer an even higher rate of poor outcomes, especially in those with HF and reduced left ventricular ejection fraction (HF-REF).[4]

The physiological relations between CKD and HF are multifactorial and causally intertwined. For example, kidney dysfunction contributes to HF by increased salt retention and volume expansion, upregulation of neurohormonal pathways, proinflammatory mechanisms, and likely other mechanisms. HF worsens CKD by decreasing renal perfusion and activation of the catecholaminergic and renin–angiotensin–aldosterone system.[5–7] In addition, both CKD and HF can cause or worsen other comorbid conditions, including anemia,[8] coronary and peripheral atherosclerosis,[9] and malnutrition.[10]

Because the population prevalence of HF has increased, so has the proportion of patients with HF preserved left ventricular EF (HF-PEF).[11] Few studies have, however, examined how CKD affects clinically meaningful outcomes among patients with HF-PEF. Existing data have largely come from studies

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***Circ Cardiovasc Qual Outcomes* is available at http://circoutcomes.ahajournals.org** **DOI: 10.1161/CIRCOUTCOMES.113.000221**

	Hospitalization for Heart Failure Adjusted Hazard Ratio (95% Confidence Interval)	
	Preserved Systolic Function* (n=14 579)	Reduced Systolic Function† (n=9752)
eGFR (mL/min per 1.73 m^2) category, n (%)		
90–130	0.99 (0.83–1.17)	1.04 (0.82–1.32)
60–89	Reference	Reference
45–59	1.17 (1.07–1.29)	1.24 (1.12–1.38)
30–44	1.54 (1.40–1.69)	1.39 (1.24–1.55)
15–29	1.91 (1.71–2.13)	2.05 (1.79–2.35)
<15	2.28 (1.83–2.84)	1.95 (1.45–2.64)
Dialysis	1.35 (1.14–1.60)	1.19 (0.97–1.46)
Urine dipstick protein excretion		
Negative/trace or undocumented	Reference	Reference
1+	1.40 (1.29–1.53)	1.35 (1.22–1.50)
2+	1.60 (1.45–1.77)	1.43 (1.25–1.64)
3+	1.64 (1.44–1.86)	1.52 (1.29–1.79)

eGFR indicates estimated glomerular filtration rate.

	Hospitalization From Any Cause Adjusted Hazard Ratio (95% Confidence Interval)	
	Preserved Systolic Function* (n=14 579)	Reduced Systolic Function† (n=9752)
eGFR (mL/min per 1.73 m^2) category, n (%)		
90–130	1.15 (1.05–1.25)	1.04 (0.94–1.16)
60–89	Reference	Reference
45–59	1.08 (1.02–1.13)	1.07 (1.01–1.14)
30–44	1.16 (1.09–1.22)	1.09 (1.02–1.17)
15–29	1.32 (1.24–1.41)	1.47 (1.35–1.60)
<15	1.73 (1.50–2.00)	1.85 (1.52–2.25)
Dialysis	1.87 (1.71–2.04)	1.71 (1.53–1.92)
Urine dipstick protein excretion		
Negative/trace or undocumented	Reference	Reference
1+	1.28 (1.22–1.34)	1.30 (1.23–1.38)
2+	1.33 (1.26–1.40)	1.37 (1.27–1.48)
3+	1.36 (1.26–1.47)	1.42 (1.27–1.57)

eGFR indicates estimated glomerular filtration rate.

there is an independent grade association with mortality

Table 3. Multivariable Association Between Kidney Function and Hospitalization for Heart Failure Among 24 331 Adults With Heart Failure Stratified by Preserved and Reduced Left Ventricular Systolic Function (2005–2008)

	Hospitalization for Heart Failure Adjusted Hazard Ratio (95% Confidence Interval)	
	Preserved Systolic Function* (n=14 579)	Reduced Systolic Function† (n=9752)
eGFR (mL/min per 1.73 m²) category, n (%)		
90–130	0.99 (0.83–1.17)	1.04 (0.82–1.32)
60–89	Reference	Reference
45–59	1.17 (1.07–1.29)	1.24 (1.12–1.38)
30–44	1.54 (1.40–1.69)	1.39 (1.24–1.55)
15–29	1.91 (1.71–2.13)	2.05 (1.79–2.35)
<15	2.28 (1.83–2.84)	1.95 (1.45–2.64)
Dialysis	1.35 (1.14–1.60)	1.19 (0.97–1.46)
Urine dipstick protein excretion		
Negative/trace or undocumented	Reference	Reference
1+	1.40 (1.29–1.53)	1.35 (1.22–1.50)
2+	1.60 (1.45–1.77)	1.43 (1.25–1.64)
3+	1.64 (1.44–1.86)	1.52 (1.29–1.79)

eGFR indicates estimated glomerular filtration rate.

*Adjusted for age, sex, prevalent heart failure, acute myocardial infarction, coronary artery bypass surgery, ischemic stroke or transient ischemic attack, atrial fibrillation or flutter, mitral or aortic valve disease, peripheral arterial disease, pacemaker, dyslipidemia, hypertension, diabetes mellitus, hospitalized bleeds, diagnosed depression, chronic lung disease, mechanical fall, hemoglobin, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, year of study entry, and sites.

†Adjusted for age, sex, prevalent heart failure, acute myocardial infarction, unstable angina, ischemic stroke or transient ischemic attack, other thromboembolic event, atrial fibrillation or flutter, mitral or aortic valve disease, peripheral arterial disease, cardiac resynchronization therapy, pacemaker, dyslipidemia, hypertension, diabetes mellitus, hospitalized bleeds, diagnosed depression, chronic liver disease, chronic lung disease, hemoglobin, systolic blood pressure, cholesterol, cholesterol, year of study entry, and sites.

Table 4. Multivariable Association Between Kidney Function and Hospitalization From Any Cause Among 24 331 Adults With Heart Failure Stratified by Preserved and Reduced Left Ventricular Systolic Function (2005–2008)

	Hospitalization From Any Cause Adjusted Hazard Ratio (95% Confidence Interval)	
	Preserved Systolic Function* (n=14 579)	Reduced Systolic Function† (n=9752)
eGFR (mL/min per 1.73 m²) category, n (%)		
90–130	1.15 (1.05–1.25)	1.04 (0.94–1.16)
60–89	Reference	Reference
45–59	1.08 (1.02–1.13)	1.07 (1.01–1.14)
30–44	1.16 (1.09–1.22)	1.09 (1.02–1.17)
15–29	1.32 (1.24–1.41)	1.47 (1.35–1.60)
<15	1.73 (1.50–2.00)	1.85 (1.52–2.25)
Dialysis	1.87 (1.71–2.04)	1.71 (1.53–1.92)
Urine dipstick protein excretion		
Negative/trace or undocumented	Reference	Reference
1+	1.28 (1.22–1.34)	1.30 (1.23–1.38)
2+	1.33 (1.26–1.40)	1.37 (1.27–1.48)
3+	1.36 (1.26–1.47)	1.42 (1.27–1.57)

eGFR indicates estimated glomerular filtration rate.

*Adjusted for age, sex, prevalent heart failure, acute myocardial infarction, unstable angina, percutaneous coronary intervention, ischemic stroke or transient ischemic attack, atrial fibrillation or flutter, mitral or aortic valve disease, peripheral arterial disease, pacemaker, dyslipidemia, hypertension, diabetes mellitus, hospitalized bleeds, diagnosed depression, chronic lung disease, mechanical fall, hemoglobin, systolic blood pressure, high-density lipoprotein cholesterol, year of study entry, and sites.

†Adjusted for age, sex, prevalent heart failure, acute myocardial infarction, unstable angina, percutaneous coronary intervention, ischemic stroke or transient ischemic attack, other thromboembolic event, atrial fibrillation or flutter, ventricular tachycardia or fibrillation, mitral or aortic valve disease, peripheral arterial disease, pacemaker, cardiac resynchronization therapy, implantable cardioverter defibrillator, dyslipidemia, hypertension, diabetes mellitus, hospitalized bleeds, diagnosed depression, chronic lung disease, mechanical fall, hemoglobin, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, year of study entry, and sites.

common to both diseases, including increased inflammatory cytokines,[23] malnutrition,[24] and neurohormonal changes.[23] For example, CKD contributes to HF by volume expansion through increased renin production and decreased erythropoietin production; HF worsens CKD by decreasing renal perfusion. HF is a cause of renal impairment, [15,25,26] and HF causes CKD progression.[26] In addition, the presence of HF is more common among patients with CKD than the general population, and decreased renal function is linearly associated with increased prevalence of congestive HF.[27,28]

For patients with HF-PEF, we observed a U-shaped relationship between level of renal function and death,[29] and to a lesser extent between level of renal function and all-cause hospitalization (Tables 2 and 4), even though we excluded individuals with baseline eGFR >130 mL/min per 1.73 m² and censored patients when their eGFR increased beyond that level. Our findings confirm that the effect of eGFR on outcomes is not linear, highlighting the need for investigators to allow for this nonlinearity when modeling eGFR. Development of eGFR >130 mL/min per 1.73m² during follow-up was independently associated with worse outcomes, and the low serum creatinine concentrations that drive these high GFR estimates likely represent either malnutrition or fluid overload and more impaired ventricular function, which would contribute to the poorer prognosis.

Our study had several strengths. We assembled a large, contemporary, community-based HF cohort that reflects real-world outcomes. We were also able to longitudinally characterize level of eGFR across a wide range of kidney function and examine its association with multiple clinically and public health-relevant outcomes after accounting for a large set of potential confounders and the presence and severity of documented proteinuria. We used the CKD-Epidemiology Collaboration formula[19] to estimate eGFR, an estimating equation recently shown to more accurately categorize end-stage renal disease risk and mortality risk, compared with the Modification of Diet in Renal Disease formula.[30] Using the older estimating equation would likely have attenuated our relative-risk estimates.

25000 pts 50% HFrEF & 50% HFpEF >>> epidemiologic study >>> a graded association with Systolic HF & lowering the GFR + the exact same thing with HfpEF >>> suggesting the primacy of this issue

CLINICAL RESEARCH
Heart failure/cardiomyopathy

Clinical outcome of renal tubular damage in chronic heart failure†

Kevin Damman[1*], Serge Masson[2], Hans L. Hillege[1,3], Aldo P. Maggioni[4], Adriaan A. Voors[1], Cristina Opasich[5], Dirk J. van Veldhuisen[1], Laura Montagna[6], Franco Cosmi[7], Gianni Tognoni[8], Luigi Tavazzi[9], and Roberto Latini[2]

Aims Both reduced glomerular filtration and increased urinary albumin excretion independently determine outcome in patients with chronic heart failure (HF). However, tubulo-interstitial injury might indicate renal damage, even in the presence of normal glomerular filtration. We studied the relationship between tubular damage, glomerular filtration, urinary albumin excretion, and outcome in HF patients.

Methods and results In 2130 patients participating in the GISSI-HF trial, we measured urinary albumin-to-creatinine ratio (UACR), estimated glomerular filtration rate (eGFR), and three urinary markers of tubular damage: N-acetyl-beta-D-glucosaminidase (NAG), kidney injury molecule 1 (KIM-1), and neutrophil gelatinase-associated lipocalin (NGAL). We assessed the relationship between the individual tubular damage markers and the combined endpoint of all-cause mortality and HF hospitalizations. Mean age was 67 ± 11 years, and 21% were female. Urinary NAG 13.7 (7.8–22) U/gCr, KIM-1 1939 (671–3871) ng/gCr, and NGAL 36 (14–94) mg/gCr were markedly elevated above normal levels. All individual tubular markers were independently associated with the combined endpoint: NAG: adjusted hazard ratio (HR) 1.22; 95% confidence interval (CI), 1.10–1.36; P, 0.001, KIM-1 HR 1.13; 95% CI, 1.02–1.24; P ¼ 0.018 and NGAL HR 1.10; 95% CI, 1.00–1.20; P ¼ 0.042; all per log standard deviation increase). Even in patients with a normal eGFR, increased tubular markers were related to a poorer outcome. The combination of impaired eGFR, increased UACR and high NAG was associated with a HR of 3.00; 95% CI, 2.29–3.95; P, 0.001, compared with those without these abnormalities.

Conclusion Tubular damage is related to a poor clinical outcome in HF patients even when eGFR is normal. ClinicalTrials.gov Identifier: NCT00336336 (for the main study).

Keywords Renal function † Heart failure † Tubular damage † Prognosis

Introduction

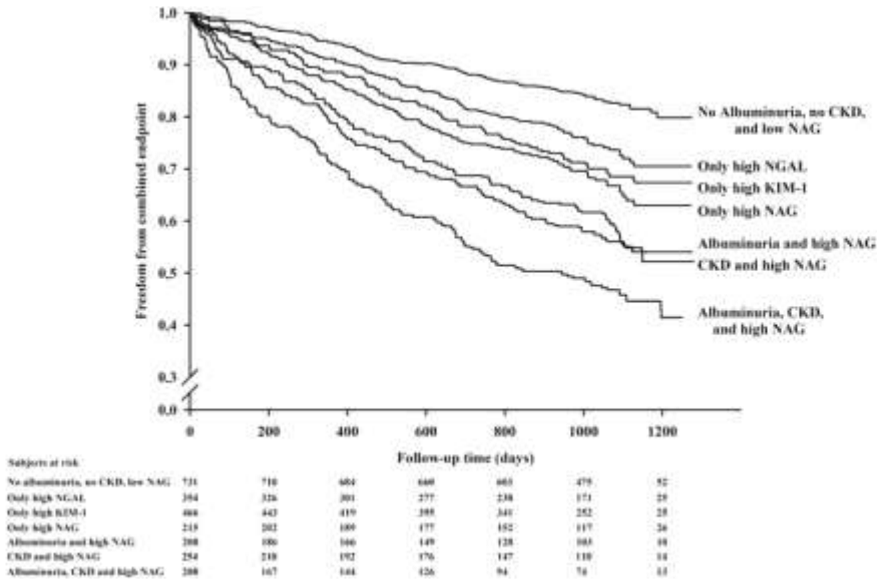

Figure 1 Survival function for the combined endpoint stratified by different combinations of renal markers low NAG = urinary NAG ≤ 14.12 U/gCr, high NAG = urinary NAG > 14.12 U/gCr, high KIM-1 = urinary KIM-1 > 3172 ng/gCr, and high NGAL = urinary NGAL > 32 mg/gCr. eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); KIM-1, kidney injury molecule 1; NAG, N-acetyl-beta-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin.

Reduced Kidney Function as a Risk Factor for Incident Heart Failure: The Atherosclerosis Risk in Communities (ARIC) Study

Anna Kottgen,*† Stuart D. Russell,‡ Laura R. Loehr,§ Ciprian M. Crainiceanu,‖ Wayne D. Rosamond,§ Patricia P. Chang,§¶ Lloyd E. Chambless,**and Josef Coresh*†‡‖

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Reduced kidney function is a risk factor for cardiovascular morbidity and mortality, and both heart failure (HF) and kidney failure incidences are increasing. This study therefore sought to determine the effect of decreased kidney function on HF incidence in a population-based study of middle-aged adults. From 1987 through 2002, 14,857 participants of the Atherosclerosis Risk in Communities (ARIC) study who were free of prevalent HF at baseline were followed for incident HF hospitalization or death (*International Classification of Diseases, Ninth Revision/10th Revision* 428/I50). Estimated GFR (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation, and kidney function was categorized as normal (eGFR ≥90 ml/min per 1.73 m^2; *n* = 7143), mildly reduced (eGFR 60 to 89 ml/min per 1.73 m^2; *n* = 7311), and moderately/severely reduced (eGFR <60 ml/min per 1.73 m^2; *n* = 403). Cox proportional hazards models were used to control for demographic and cardiovascular risk factors; analyses were stratified by the presence of coronary heart disease at baseline. During a mean follow-up of 13.2 yr, 1193 participants developed HF. The incidence of HF was three-fold higher for individuals with eGFR <60 ml/min per 1.73 m^2 compared to the reference group with eGFR ≥90 ml/min per 1.73 m^2 (18 *versus* 6 per 1000 person-years). The overall adjusted relative hazard of developing HF was 1.94 (1.49 to 2.53) for individuals with eGFR <60 ml/min per 1.73 m^2 compared to the reference group and was significantly increased for individuals with and without prevalent coronary heart disease at baseline. A substantially greater decline in kidney function occurred in individuals concomitant with HF hospitalization/death compared to those who did not develop HF. In summary, middle-aged adults with moderately/severely reduced kidney function are at high risk for developing HF.

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Reduced kidney function has been established as a risk factor for cardiovascular disease (CVD) in several recent studies, both in populations at high risk for CVD and in the general population (1–7). Moderately reduced kidney function is very common, affecting an estimated 8.3 million US adults (8). Specifically, reduced kidney function has been proposed as a risk factor for deterioration of prevalent heart failure (HF) as well as a risk factor for incident HF (9–15). However, most previous studies were restricted to subgroups such as elderly individuals (9–11,13), predominantly white individuals (16), or individuals with preexisting coronary heart disease (CHD) (12). These individuals might be at increased risk for incident HF as a result of advanced age or comorbidities. Therefore, we sought to determine the role of impaired kidney function as a risk factor for incident HF in a large, population-based, biracial study of middle-aged US adults, the Atherosclerosis Risk in Communities (ARIC) Study. We hypothesized that individuals with reduced kidney function are at increased risk for incident HF and sought to estimate both the absolute risk and the adjusted relative risk.

Chronic kidney disease (CKD) and HF often occur together (1,14,17,18), but relatively few studies have data on the decline in kidney function in relation to incident HF. A recent study of individuals with left ventricular systolic dysfunction reported significantly higher mortality for those with a more rapid compared to those with a slower decline in kidney function (19). Using data from multiple ARIC study visits, we also investigated the changes in kidney function in the years before and after the first HF hospitalization.

Finally, previous studies did not account for the impact of measurement error and biologic variability in serum creatinine on the association between reduced kidney function and incident HF. Therefore, it is useful to use models that take into account variability in estimated kidney function that is assessed using a creatinine-based estimating equation, a procedure that is feasible in a large population-based study but subject to

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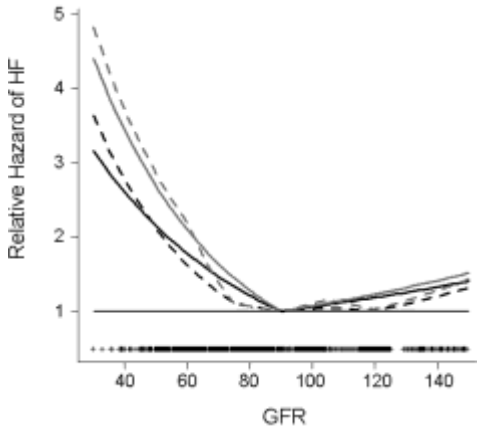

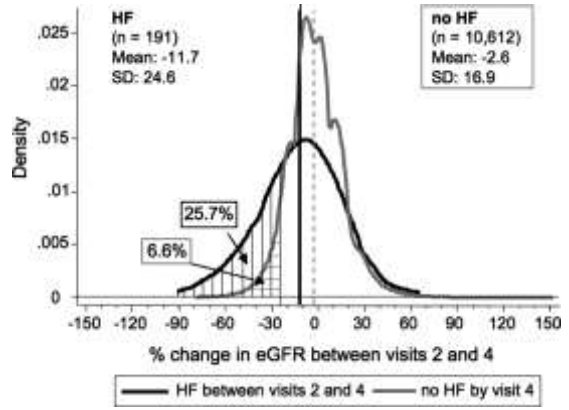

Renal Dysfunction is a Clinical Risk for Incident HFpEF but not HFrEF

CLINICAL RESEARCH
Heart failure/cardiomyopathy

Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND

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See page 1208 for the editorial comment on this article (doi:10.1093/eurheartj/eht117)

Aims Differences in clinical characteristics and outcome of patients with established heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) are well established. Data on epidemiology and prediction of new onset HFpEF, compared with HFrEF, have not been described.

Methods and results In 8592 subjects of the Prevention of Renal and Vascular End-stage Disease (PREVEND), a community-based, middle-aged cohort study, we performed cause-specific hazard analyses to study the predictive value of risk factors and established cardiovascular biomarkers on new onset HFrEF vs. HFpEF (left ventricular ejection fraction ≤40 and ≥50%, respectively). A *P*-value for competing risk (P_{cr}), 0.10 between HFrEF and HFpEF was considered statistically significant. All potential new onset heart failure cases were reviewed and adjudicated to HFrEF or HFpEF by an independent committee. During a median follow-up of 11.5 years, 374 (4.4%) subjects were diagnosed with heart failure, of which 125 (34%) with HFpEF and 241 (66%) with HFrEF. The average time to diagnosis of new onset HFrEF was 6.6 + 3.6 years; it was 8.3 + 3.3 years for HFpEF (P_{cr} 0.001). Male gender was associated with new onset HFrEF, whereas female gender with new onset HFpEF (P_{cr} 0.001). Higher age and increased N-terminal pro-B-type natriuretic peptide (NT-proBNP) increased the risk for both HFpEF and HFrEF, although for age this was stronger for HFpEF (P_{cr} ¼ 0.018), whereas NT-proBNP was stronger associated with risk for HFrEF (P_{cr} ¼ 0.083). Current smokers, increased highly sensitive troponin T, and previous myocardial infarction conferred a significantly increased risk for HFrEF, but not for HFpEF (P_{cr} ¼ 0.093, 0.091, and 0.061, respectively). Conversely, a history of atrial fibrillation, increased urinary albumin excretion (UAE), and cystatin C were significantly more associated with the risk for HFpEF, but not for HFrEF (P_{cr} 0.001, 0.061, and 0.033, respectively). The presence of obesity at baseline was associated with comparable prognostic information for both HFpEF and HFrEF.

Conclusion Higher age, UAE, cystatin C, and history of atrial fibrillation are strong risk factors for new onset HFpEF. This underscores differential pathophysiological mechanisms for both subtypes of heart failure.

Keywords New onset heart failure † HFpEF † HFrEF † Epidemiology

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Cyt-c & Alburia has no impact on systolic HF but did seems to predict HfpEF !

Table 2 Cox regression: cause-specific hazard (risk) ratios

	Adjusted for age and sex		Mutually adjusted[a]		HFrEF	HFpEF	P^b_{cr}
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	HR (95% CI)	
Age (per 10 years)	–	–	1.81 (1.47–2.24)	<0.001	1.61 (1.24–2.09)	2.53 (1.93–3.30)	0.018
Males	–	–	1.48 (1.03–2.13)	0.035	2.43 (1.49–3.95)	0.56 (0.31–1.01)	<0.001
Obesity	1.93 (1.37–2.73)	<0.001	1.62 (1.10–2.37)	0.014	–	–	0.750
Heart rate (per 5 b.p.m.)	1.05 (0.98–1.13)	0.155					
Hypertension	1.99 (1.37–2.89)	<0.001	1.17 (0.77–1.77)	0.458	–	–	0.288
Myocardial infarction	3.45 (2.38–4.99)	<0.001	2.27 (1.54–3.34)	<0.001	2.77 (1.73–4.43)	1.25 (0.64–2.45)	0.058
Smoking or quit smoking <1 year	1.31 (0.96–1.79)	0.087	1.24 (0.87–1.77)	0.228	1.51 (0.96–2.36)	0.80 (0.46–1.41)	0.086
Atrial fibrillation	2.64 (1.23–5.66)	0.013	1.10 (0.55–2.19)	0.787	0.42 (0.19–0.93)	3.79 (1.64–8.77)	<0.001
Diabetes mellitus	2.41 (1.51–3.85)	<0.001	1.66 (0.99–2.78)	0.056	–	–	0.794
Hypercholesterolaemia (mmol/L)	1.65 (1.21–2.26)	0.002	1.34 (0.95–1.88)	0.096	–	–	0.713
Log Creatinine (per doubling)	1.00 (0.84–1.20)	0.973					
eGFR >60 mL/min/kg	1.07 (0.66–1.74)	0.782					
Log Cystatine C (per doubling)	1.43 (1.23–1.68)	<0.001	1.08 (0.94–1.24)	0.295	0.98 (0.86–1.11)	1.45 (1.03–2.04)	0.033
Log UAE (per doubling)	1.35 (1.22–1.50)	<0.001	1.01 (0.91–1.14)	0.798	0.96 (0.84–1.09)	1.21 (0.98–1.48)	0.061
Log hs-C-reactive protein (per doubling)	1.41 (1.17–1.70)	<0.001	1.14 (0.92–1.41)	0.228	–	–	0.230
Log NT-proBNP (per doubling)	2.11 (1.79–2.49)	<0.001	1.68 (1.39–2.04)	<0.001	1.85 (1.42–2.41)	1.35 (1.06–1.72)	0.082
Log hs-TnT (per doubling)	1.67 (1.51–1.86)	<0.001	1.33 (1.17–1.52)	<0.001	1.38 (1.18–1.60)	1.10 (0.90–1.36)	0.091

Univariate and multivariate endpoint: total incident HF. All variables from multivariate regression are tested for competing risk between HFrEF and HFpEF.
Obesity, body mass index >30 kg/m^2; HDL-cholesterol, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; UAE, urinary albumin excretion; hs-C-reactive protein, highly sensitive C-reactive protein; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; hs-TnT, highly sensitive troponin T.
[a]Adjusted for age, sex, and all variables from the univariate analyses with a *P*-value < 0.10.
[b]P_{cr} = *P*-value for competing risk: heart failure with reduced vs. preserved ejection fraction.

8592 pts 28-75 yo PREVEND Study 11 y F/U UAE > 10 mg/L vs control

Table 2 Cox regression: cause-specific hazard (risk) ratios

	Adjusted for age and sex		Mutually adjusted[a]		HFrEF	HFpEF	P_{cr}^{b}
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Univariate and multivariate endpoint: total incident HF. All variables from multivariate regression are tested for competing risk between HFrEF and HFpEF.
Obesity, body mass index >30 kg/m^2; HDL-cholesterol, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; UAE, urinary albumin excretion; hs-C-reactive protein, highly sensitive C-reactive protein; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; hs-TnT, highly sensitive troponin T.
[a]Adjusted for age, sex, and all variables from the univariate analyses with a *P*-value < 0.10.
[b]P_{cr} = *P*-value for competing risk: heart failure with reduced vs. preserved ejection fraction.

if measure of CKD >>> more prtend HfpEF ! so Cyt-c & Alburia has no impact on systolic HF but did seems to predict HfpEF !

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Association of chronic kidney disease with abnormal cardiac mechanics and adverse outcomes in patients with heart failure and preserved ejection fraction

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Aims Chronic kidney disease (CKD) is associated with worse outcomes in heart failure with preserved ejection fraction (HFpEF). Whether this association is due the effect of CKD on intrinsic abnormalities in cardiac function is unknown. We hypothesized that CKD is independently associated with worse cardiac mechanics in HFpEF.

Methods and Results We prospectively studied 299 patients enrolled in the Northwestern University HFpEF Program. Using the creatinine-based CKD-Epi equation to calculate estimated glomerular filtration rate (eGFR), study participants were analysed by CKD status (using eGFR <60 mL/min/1.73 m^2 to denote CKD). Indices of cardiac mechanics (longitudinal strain parameters) were measured using speckle-tracking echocardiography. Using multivariable-adjusted linear and Cox regression analyses, we determined the association between CKD and echocardiographic parameters and clinical outcomes (cardiovascular hospitalization or death). Of 299 study participants, 48% had CKD. CKD (dichotomous variable) and reduced eGFR (continuous variable) were both associated with worse cardiac mechanics indices including left atrial (LA) reservoir strain, LV longitudinal strain, and right ventricular free wall strain even after adjusting for potential confounders, including co-morbidities, EF, and volume status. For example, for each 1-SD decrease in eGFR, LA reservoir strain was 3.52% units lower ($P < 0.0001$) after multivariable adjustment. Reduced eGFR was also associated with worse outcomes [adjusted hazard ratio (HR) 1.28, 95% confidence interval (CI) 1.01–1.61 per 1-SD decrease in eGFR, $P = 0.039$]. The association was attenuated after adjustment for indices of cardiac mechanics ($P = 0.064$).

Conclusion In HFpEF, CKD is independently associated with worse cardiac mechanics, which may explain why HFpEF patients with CKD have worse outcomes.
Trial registration: NCT01030991

Keywords Diastolic heart failure • Chronic kidney disease • Cardiac mechanics • Outcomes

Introduction

Due to overlapping risk factors, chronic kidney disease (CKD) and heart failure with preserved ejection fraction (HFpEF) are becoming more prevalent.[1,2] Whether due to a common aetiology or arising independently, CKD and HFpEF are often coincident in patients. Furthermore, the patient population with both problems is expanding. Importantly, studies published [illegible] years ago found that renal dysfunction is associated with worse outcomes and higher mortality in HFpEF patients,[3–5] and the trajectory of

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†Deceased.

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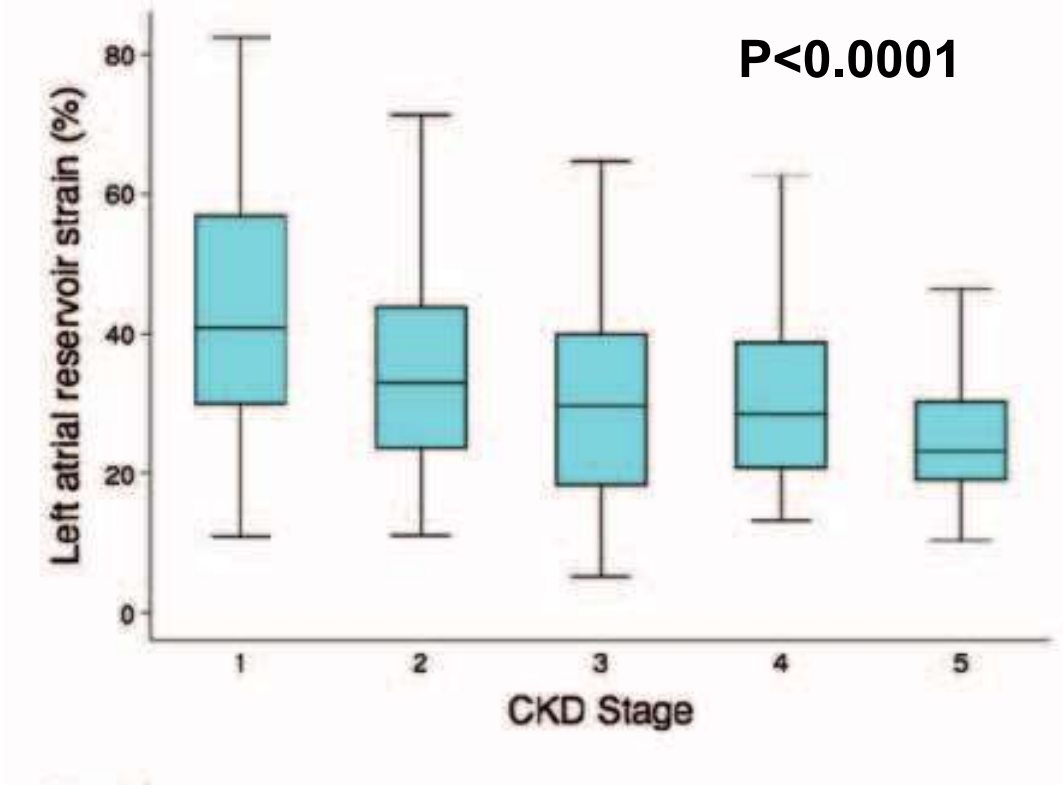
CKD influences HFpEF



Stepwise Increase in Arterial Stiffness Corresponding With the Stages of Chronic Kidney Disease

Ming-Cheng Wang, MD, Wei-Chuan Tsai, MD, Ju-Yi Chen, MD, and Jeng-Jong Huang, MD

• ***Background:*** **Patients with end-stage renal disease on maintenance dialysis therapy have a high prevalence of cardiovascular risk factors and cardiovascular disease (CVD). A similar finding is noted in patients with chronic kidney disease (CKD). The important contributors are premature and accelerated atherosclerosis and vascular calcification. We assessed the severity of arterial stiffness in 102 patients with CKD by using pulse wave velocity (PWV) and sought to identify associated risk factors.** ***Methods:*** **PWV was measured by calculating the distance traveled by the flow wave and divided by the time delay. Correlations between PWV and traditional cardiovascular risk factors, estimated glomerular filtration rate (GFR) per 1.73 m^2, blood pressure (BP), and pulse pressure (PP) were analyzed.** ***Results:*** **PWV values in patients with CKD stages 1 to 2 and the age-matched control group were similar. There was a significant trend for a stepwise increase in PWV corresponding to advance in CKD stage ($P < 0.0001$). Univariate linear regression analysis showed that age, prior CVD, diabetes, hypertension, any high risk, estimated GFR per 1.73 m^2, systolic BP, and PP correlated with PWV. In the multivariate model, decreased estimated GFR per 1.73 m^2 and increased systolic BP were independently associated with increased PWV in patients with CKD (model $R^2 = 0.539$; $P < 0.0001$).** ***Conclusion:*** **This is the first study to show a greater PWV in patients with more advanced CKD from stages 1 to 5. Estimated GFR per 1.73 m^2 and systolic BP were the major clinical determinants of arterial stiffness in patients with CKD independent of conventional risk factors for CVD.** ***Am J Kidney Dis*** **45: 494-501.**

INDEX WORDS: Arterial stiffness; atherosclerosis; cardiovascular disease (CVD); chronic kidney disease (CKD); pulse wave velocity (PWV).

THERE IS A GREATER age-adjusted mortality rate in patients with end-stage renal disease (ESRD) than in the general population, and cardiovascular disease (CVD) is the leading cause of death. Patients with ESRD on maintenance dialysis therapy have a very high prevalence of cardiovascular risk factors, and approximately 40% have clinical coronary artery disease. The increased risk for death from CVD is greatest in younger patients, although the percentage of total deaths caused by CVD is similar in all age groups.[1,2] Many clinical and epidemiological investigations have shown that atherosclerosis and vascular calcification contribute to the high cardiovascular mortality in patients with ESRD,[3-6] and evidence suggests the development of premature and accelerated atherosclerosis. Vascular calcification develops at 2 sites of arterial wall. Arterial intimal calcification represents an advanced stage of atherosclerosis, and arterial medial calcification commonly is associated with aging, diabetes mellitus (DM), and ESRD. Both types of vascular calcification contribute to the loss of arterial compliance.[7-9] Increased arterial stiffness associated with arterial calcification is found in patients with ESRD and is associated with increased cardiovascular mortality in these patients, as in the general population. Aortic pulse wave velocity (PWV), a standard method to measure arterial stiffness, has been reported to be a strong independent predictor of overall and cardiovascular mortality in patients with ESRD.[10-13]

The development of atherosclerotic CVD (ASCVD) seems to begin early in the course of chronic kidney disease (CKD). In the Second National Health and Nutrition Examination Survey, mild to moderate renal insufficiency was independently associated with subsequent death from CVD.[14] In addition to the general population, an impact of minor renal dysfunction on the development of ASCVD can be found in a hypertensive and elderly population; patients with left

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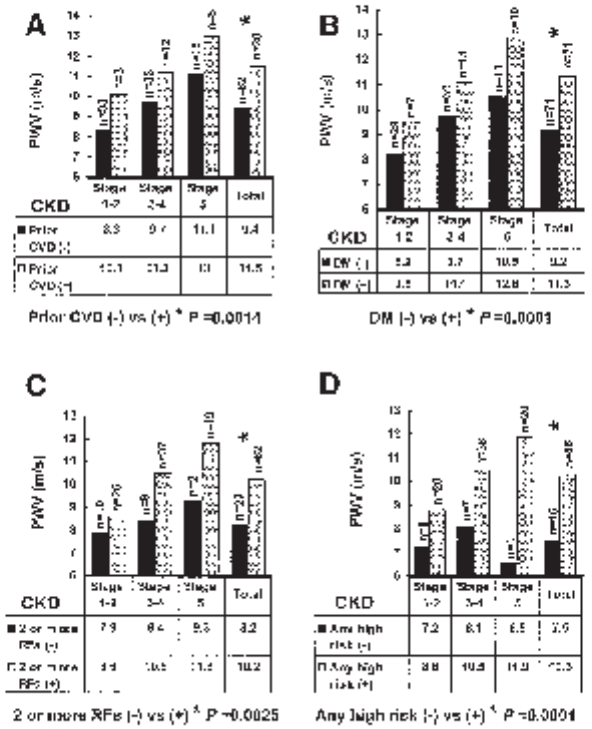
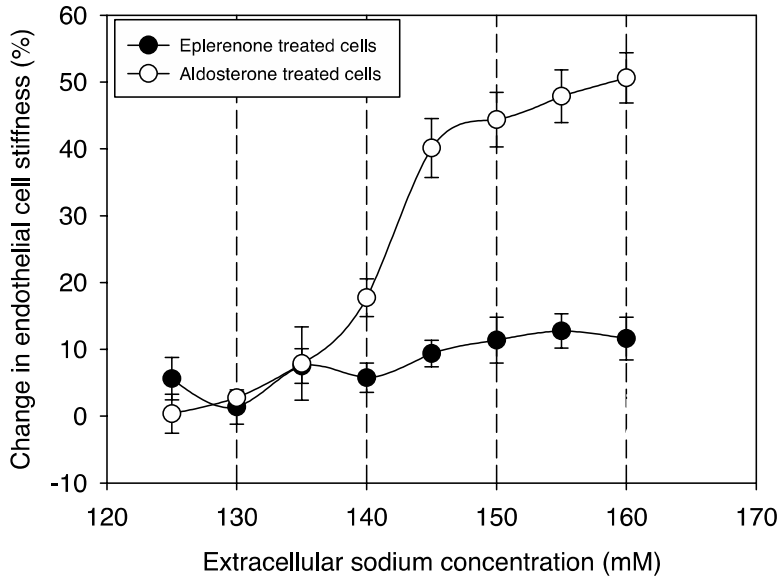
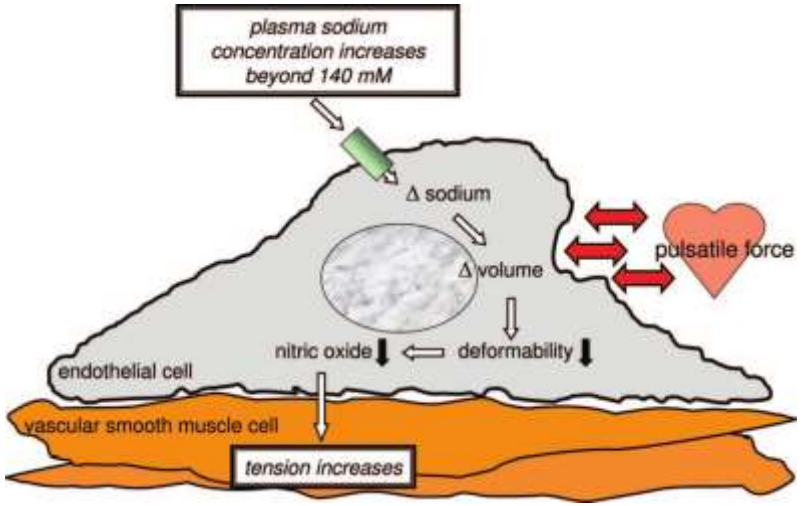
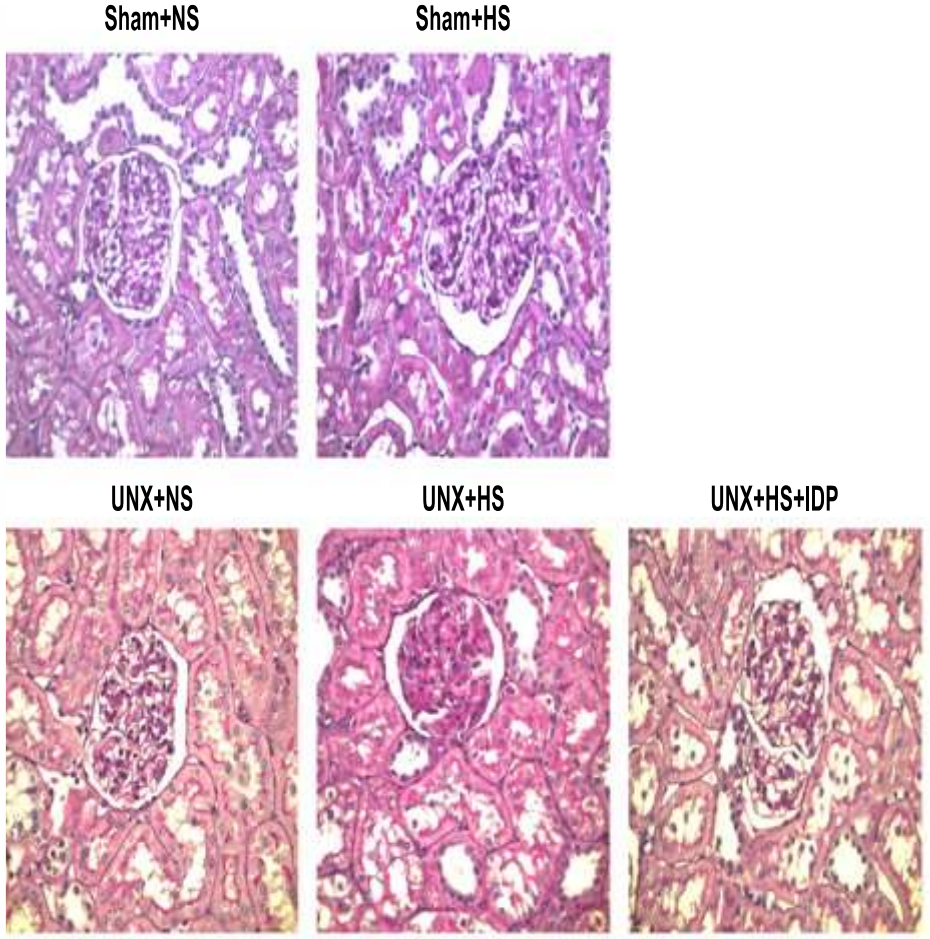
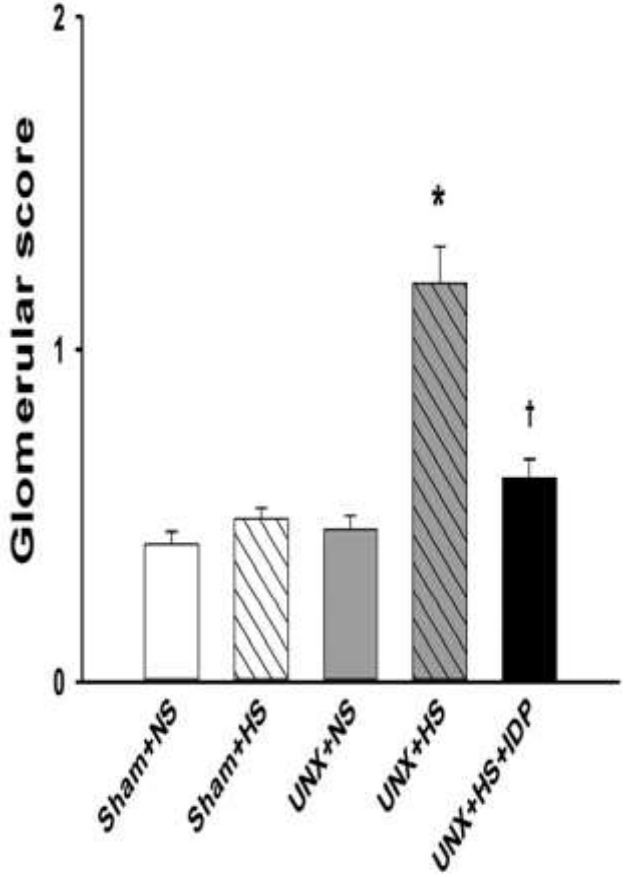


Fig 2. PWV in patients with different stages of CKD with or without (A) prior CVD, (B) DM, (C) 2 or more risk factors (RFs), and (D) any high risk.


Eplerenone treated cells
Aldosterone treated cells
Change in endothelial cell stiffness (%)
60
50
40
30
20
10
0
-10
120
130
140
150
160
170
Extracellular sodium concentration (mM)


plasma sodium concentration increases beyond 140 mM
Δ sodium
Δ volume
pulsatile force
nitric oxide
deformability
endothelial cell
vascular smooth muscle cell
tension increases


Sham+NS
Sham+HS
UNX+NS
UNX+HS
UNX+HS+IDP


Glomerular score
2
1
0
*
†
Sham+NS
Sham+HS
UNX+NS
UNX+HS
UNX+HS+IDP

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Spironolactone for Heart Failure with Preserved Ejection Fraction

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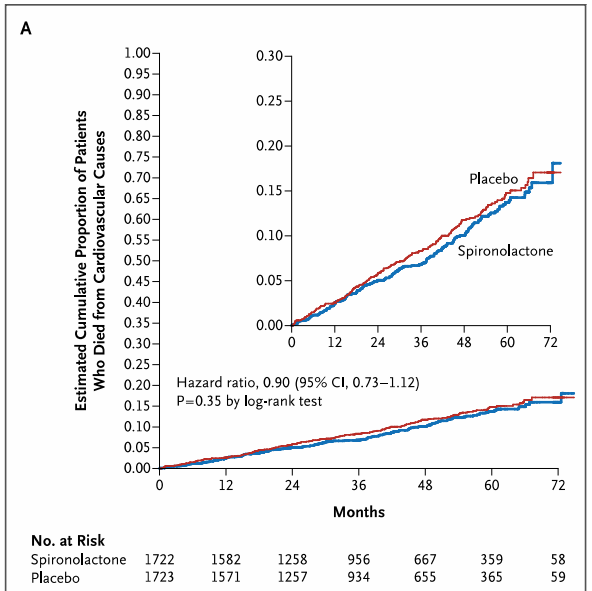


Figure 2. Kaplan–Meier Plots of Two Components of the Primary Outcome.

Panel A shows the time to confirmed death from cardiovascular causes, and Panel B the time to the first confirmed hospitalization for heart failure. The insets show the same data on an expanded y axis.

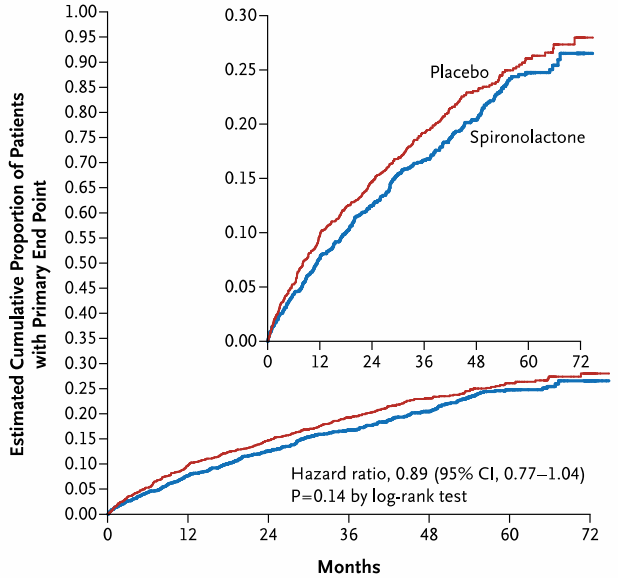


Figure 1. Kaplan–Meier Plot of Time to the First Confirmed Primary-Outcome Event.

The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure. The inset shows the same data on an expanded y axis.

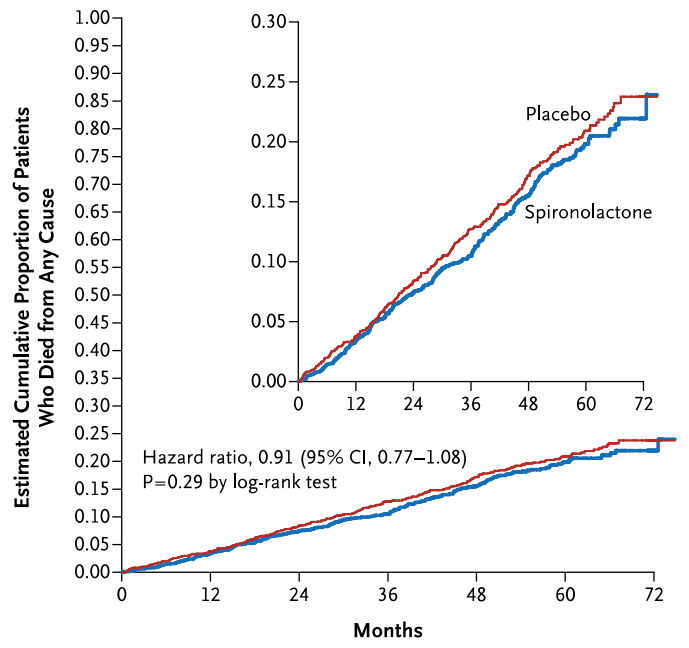
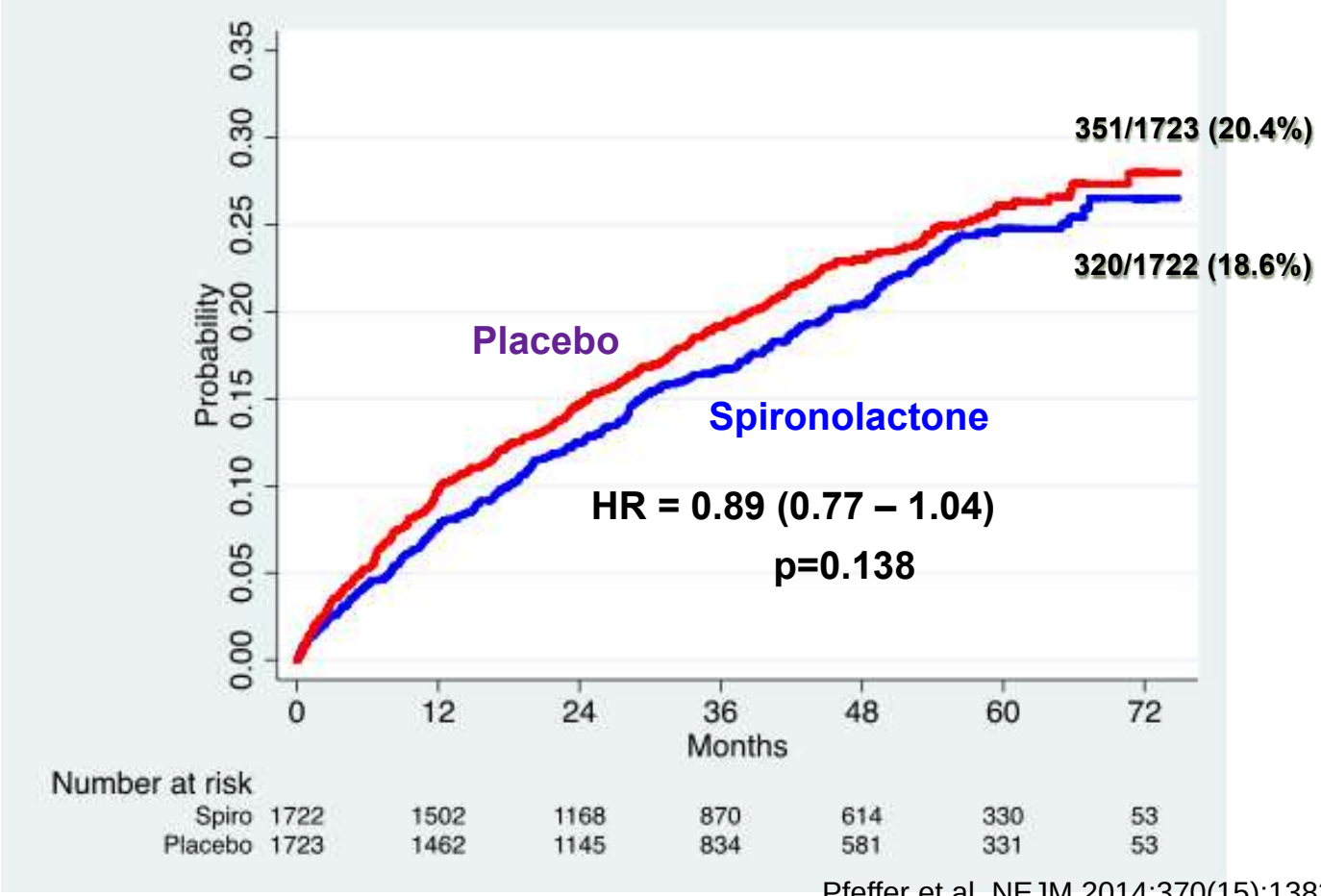


Figure 3. Kaplan–Meier Plot of Time to Death from Any Cause.

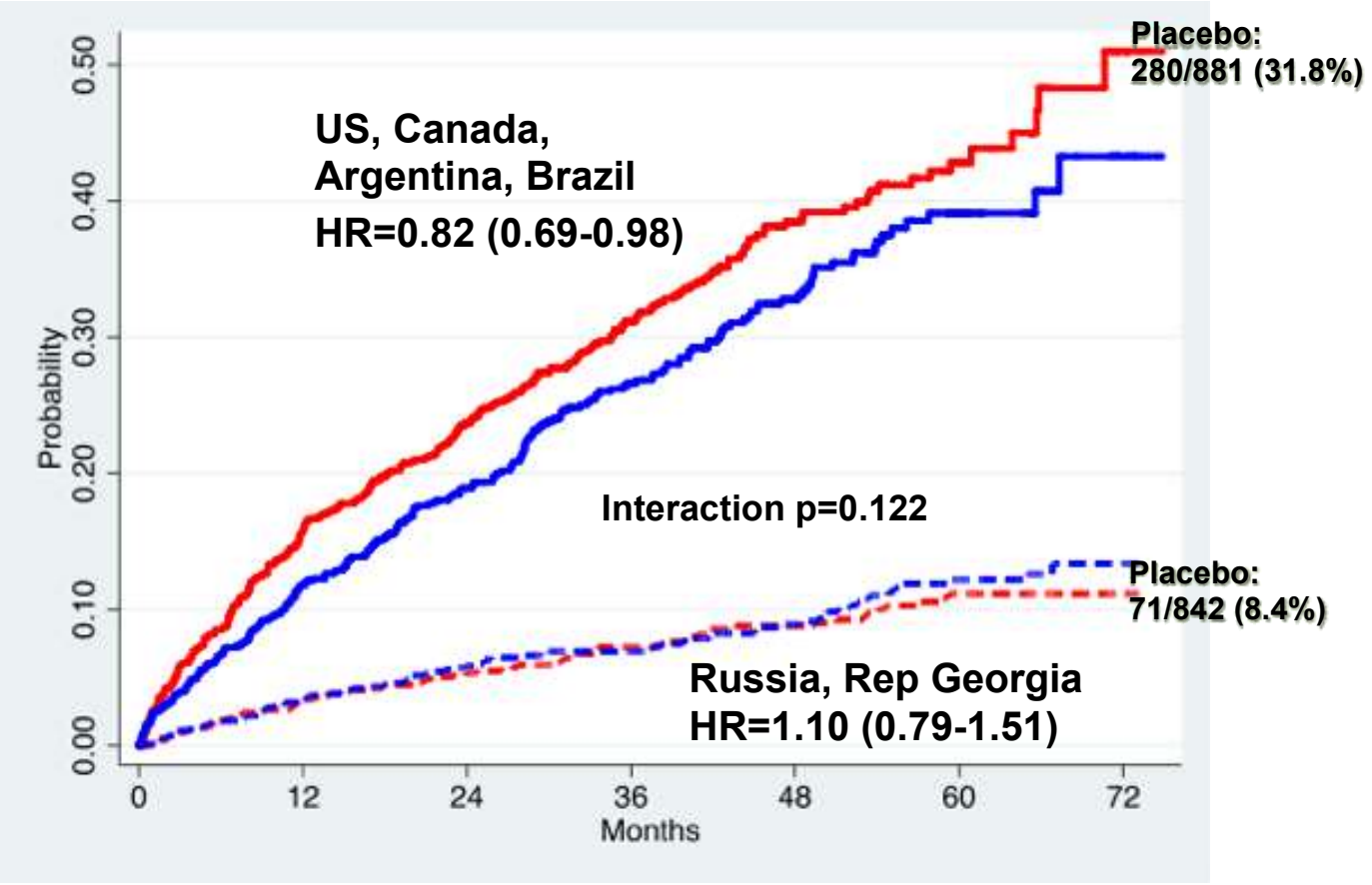
The inset shows the same data on an expanded y axis.

TOPCAT primary outcome (CV death, Hf Hosp)



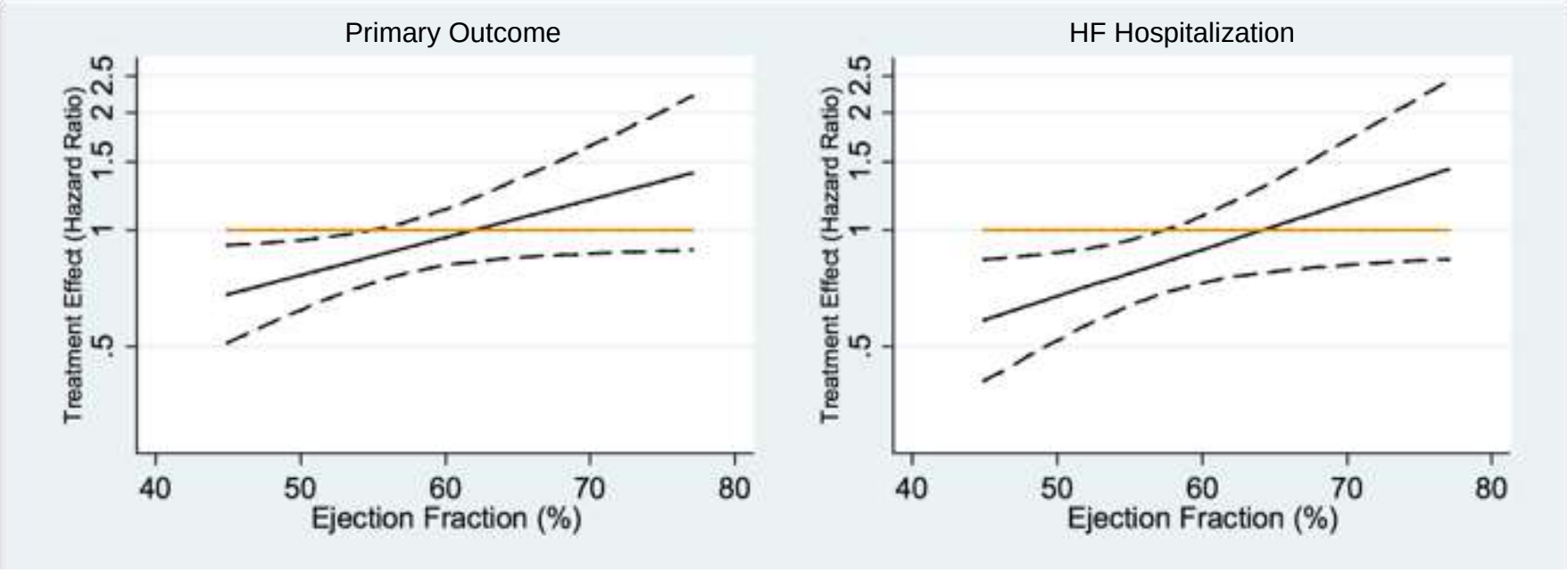
Pfeffer et al. NEJM 2014;370(15):1383-92

TOPCAT by Region

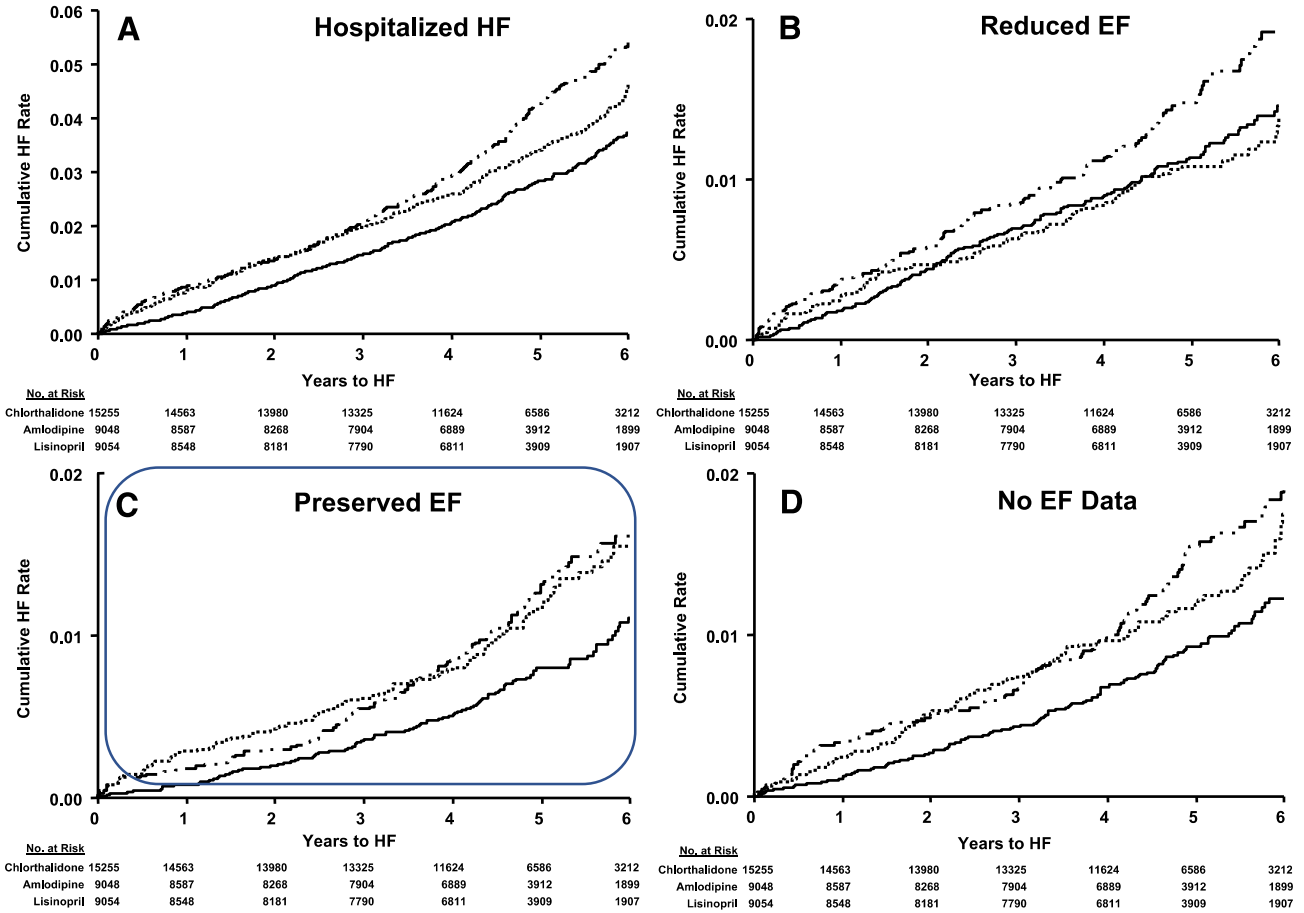


Pfeffer MA et al. Circulation. 2015 Jan 6;131(1):34-42

Benefit of Aldi diminishes with increasing EF



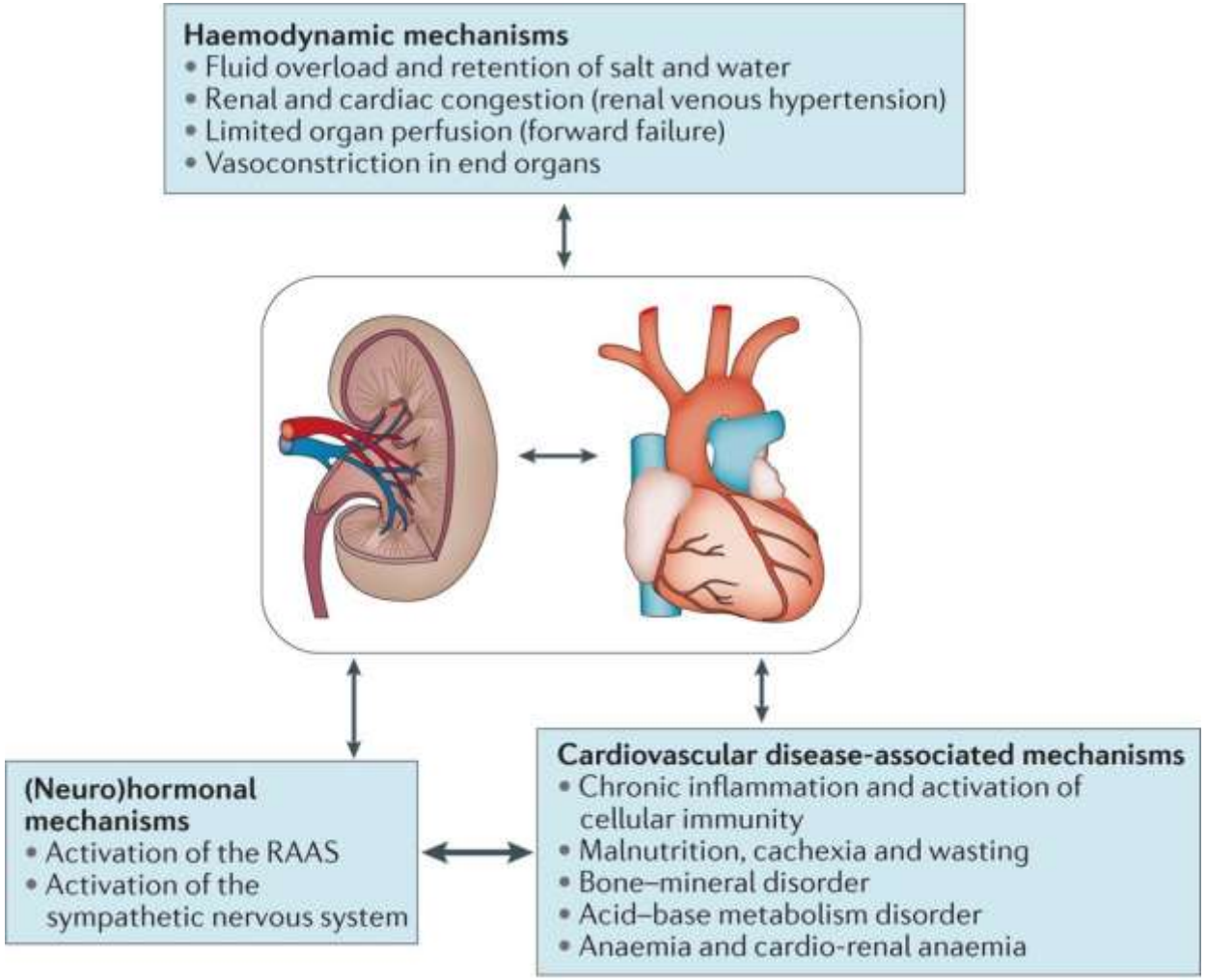
HfpEF & HFrEF in ALLHAT



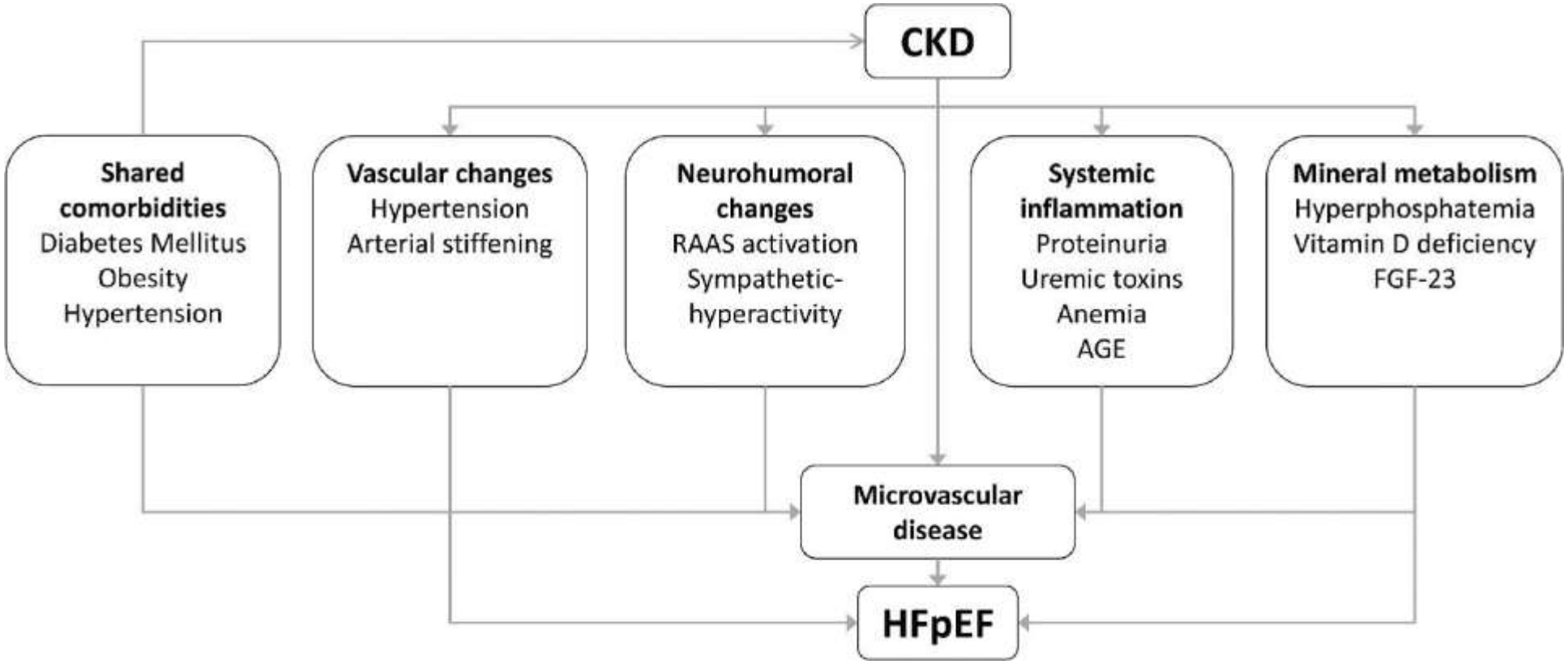
Consequences of Na & water overload
or
having overly distended veins & art

- stimulus for inflammation
- Oxid stress
- Elevated CVP
- Increased art stiffness (decreased distensibility)
- HTN (a load on the heart)
- strong stimulus for increased adrenergic activity

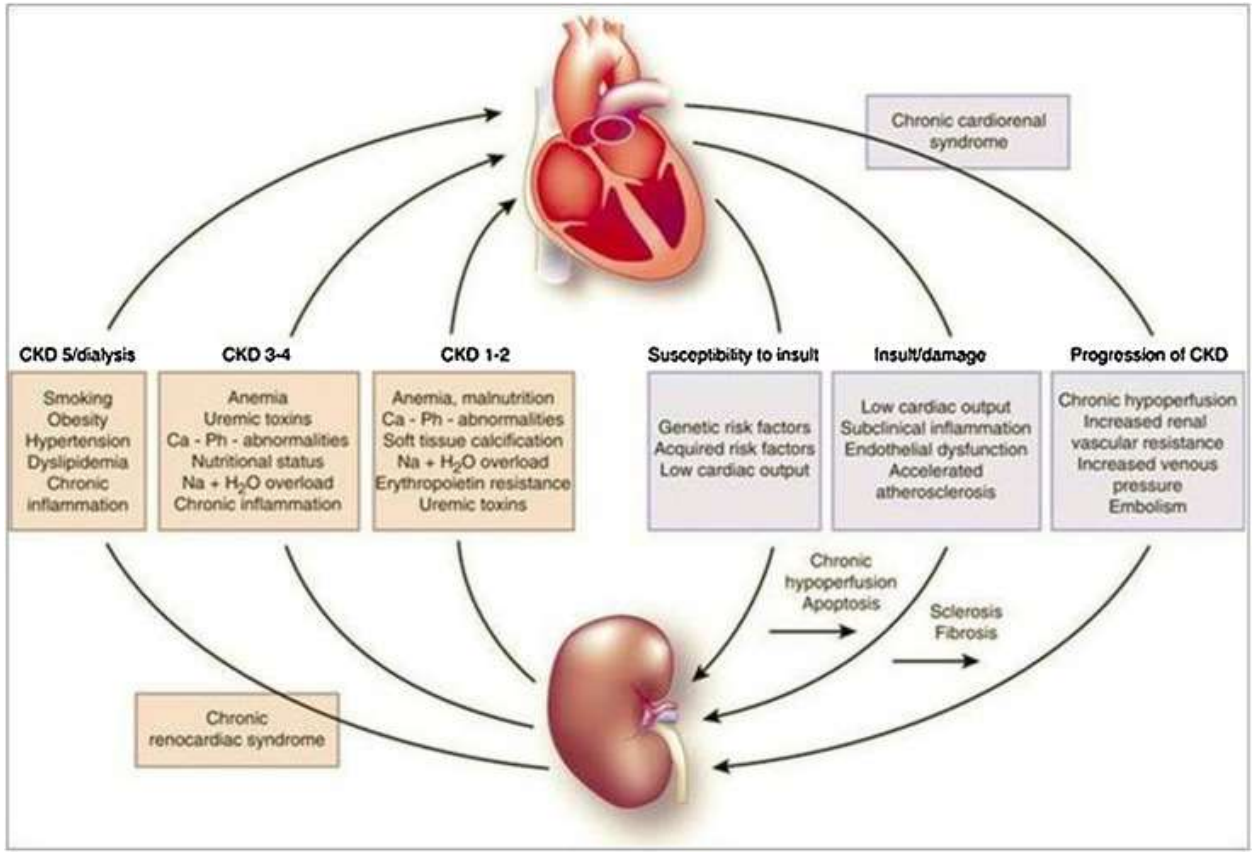
HFrEF is a Neuro-hormonal state
HFpEF is an Inflammatory state

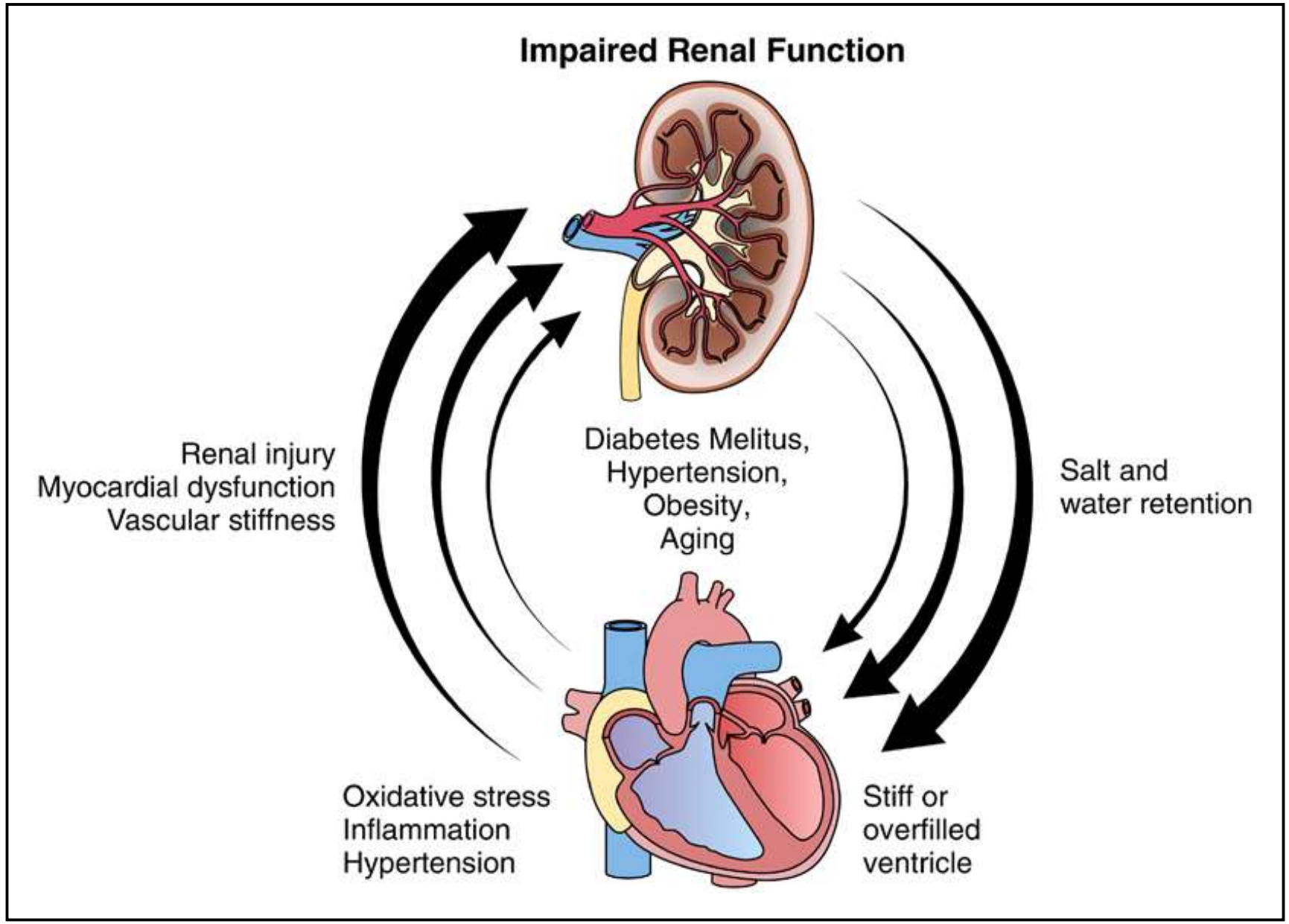


CKD as a risk factor for HFpEF



HFpEF is more ”reno” than “cardio”




Impaired Renal Function
Renal injury
Myocardial dysfunction
Vascular stiffness
Diabetes Melitus,
Hypertension,
Obesity,
Aging
Salt and
water retention
Oxidative stress
Inflammation
Hypertension
Stiff or
overfilled
ventricle

MERCI