HFpEF Prognostic stratification

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HF**r**EF and HF**p**EF

- HF**r**EF
  - Primary disease of the heart
  - Multi-organ adaptations: neuro-humoral, inflammatory and epi-genetic
  - Secondary changes due to deficient organ perfusion and/or due to maladaptive mechanisms
- HF**p**EF
  - Simultaneous dysfunction of heart, arteries, kidneys, pulmonary circulation and skeletal muscle
  - Maladaptive aging

Prognostic stratification Recent publications

- General approach starting from a population
  - I-PRESERVE, Randomized Controlled Trial
  - Karolinska-Rennes (KaRen) Population Study
- Echo substudies of RCT's & Registries
  - I-PRESERVE study
  - TOPCAT study
  - Olmsted County Registry
- Search for specific prognostic parameters
  - Worsening renal function and microalbuminuria
  - Arterial function (reflected waves, Pb, late-systolic hypertension)

Factors associated with outcome I-PRESERVE

- 4128 patients in the I-PRESERVE trial (Irbesartan in HFpEF)
- 58 baseline demographic, clinical, and biological variables to model outcome primary outcome of all-cause mortality or cardiovascular hospitalization (1505 events), all-cause mortality (881 events), and HF death or hospitalization (716 events)
- Age
  previous hospitalisation for HF
  diabetes
  NT-pro-BNP
  EF (mortality)
- Other factors: QOL, COPD, inflammation (neutrophile count),
  heart rate and estimated GFR

Komajda Circ Heart Fail. 2011;4:27-35.

I-PRESERVE
Models to predict outcome

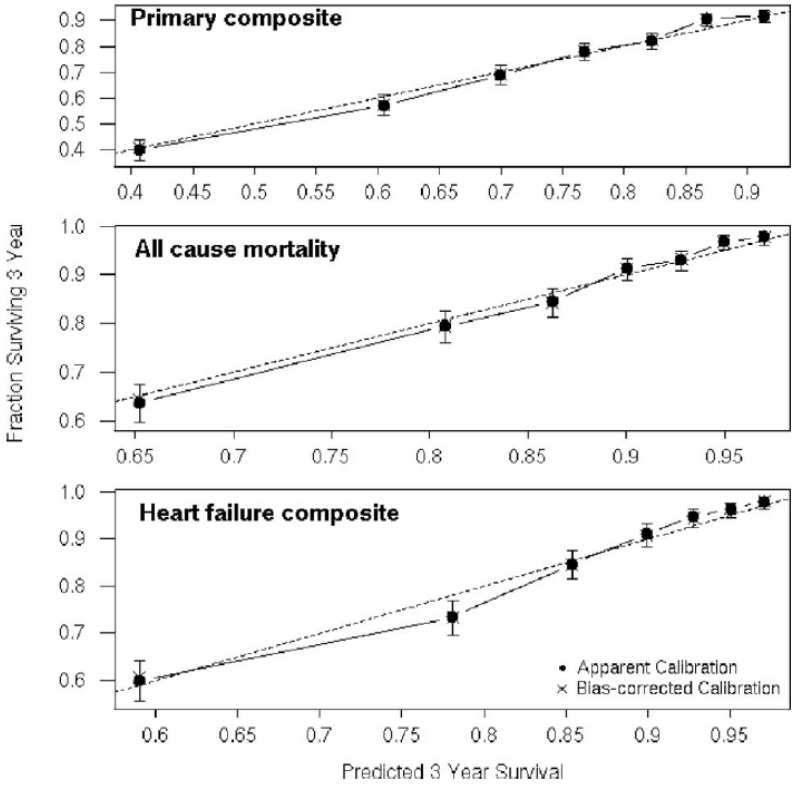


Figure 2. Calibration of model selection by using Efron bootstrap, with B=200 resamples and 7 equally divided groups of patients by 3-year survival probability. Fraction surviving (*y*-axis) is from Kaplan–Meier estimates. Predicted survival (*x*-axis) is from Cox proportional hazard model.

Komajda Circ Heart Fail. 2011;4:27-35.

KaRen Study

- **What?** prospective observational study designed to characterize HFpEF
- **Selection:** Framingham criteria, LVEF ≥45%, and NT-pro-BNP ≥300 ng/L or BNP ≥100 ng/L.
- **Population:** 539 patients age 79 (72–84) years
- **Endpoints:**
  - HF hospitalization or all-cause mortality
  - All-cause mortality

Lund EJHF (2014) 16, 992–1001

KaRen study

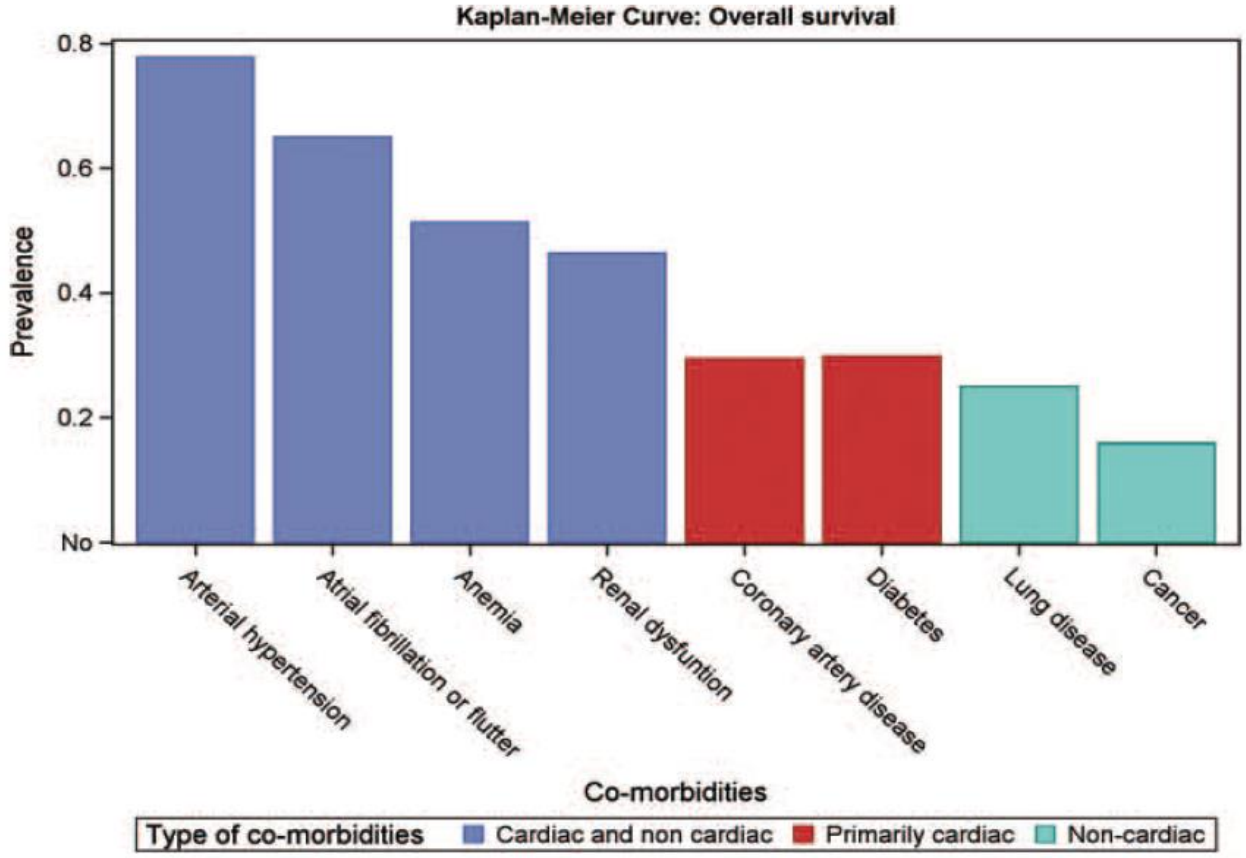


Figure 1 Barchart showing the prevalence of co-morbidities.

KaRen Conclusions

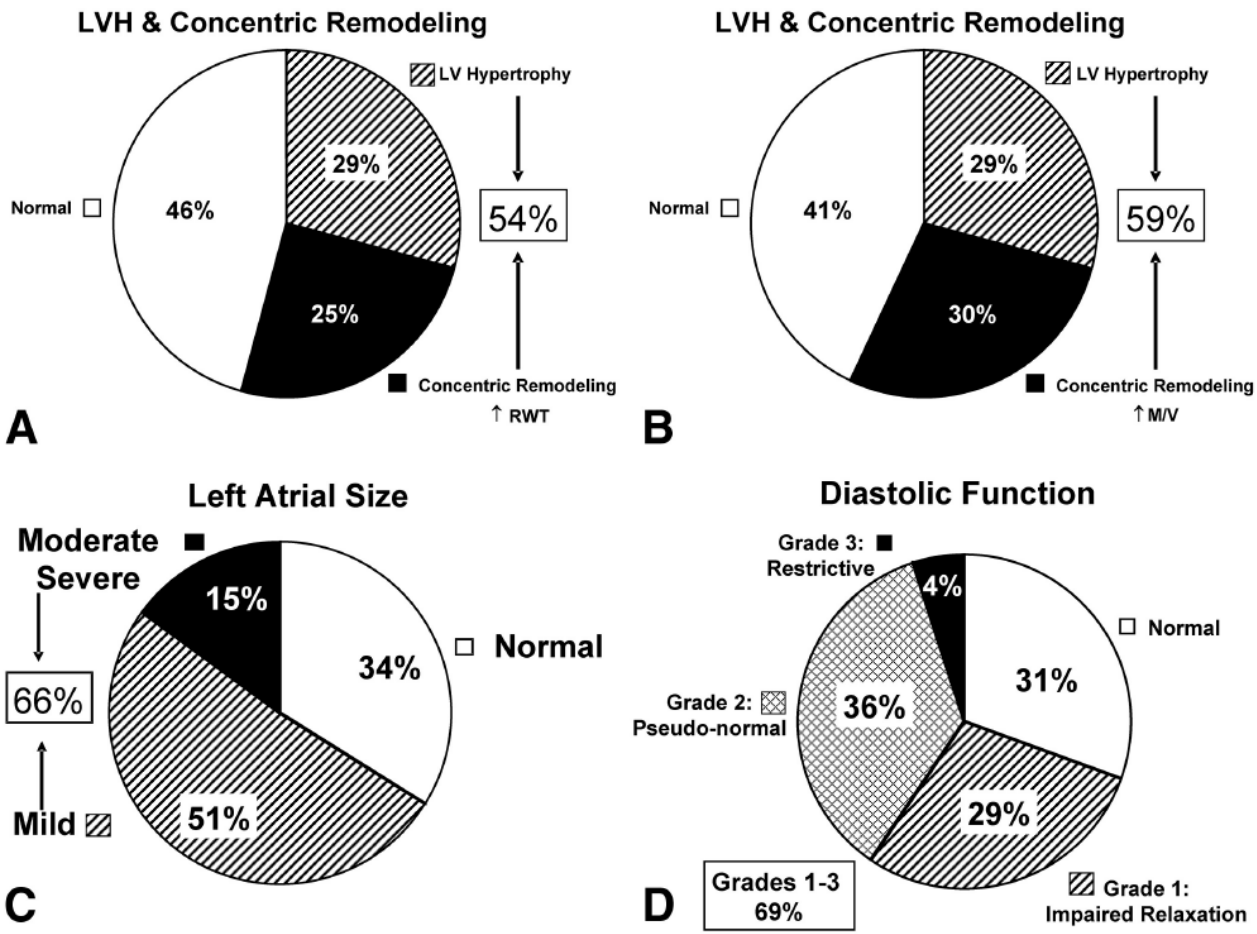
- Older population with less severe heart failure but more co-morbidities than in RCT's
- No independent predictors:
  male gender, diabetes, CAD, cerebrovascular disease, or peripheral vascular disease were not associated with increased risk
- Independent predictors:
  age, history of non-cardiovascular syncope, valve disease, anaemia, lower sodium, and higher potassium
- Use of RAS blocker and MCR antagonist associated with better prognosis. This was not observed in RCT's.

I-PRESERVE Echo

- The **Irbesartan** in HFpEF trial enrolled 4128 patients (mean 72)
- The **echo-substudy** enrolled 745 patients
- **Endpoints:**
  - Primary: death or cardiovascular hospitalization
  - Secondary: HF death or HF hospitalisation

Zile Circulation 2011;124:2491-2501

Prevalence of echo phenotypes



Zile Circulation 2011;124:2491–2501

I-PRESERVE Echo

- Multivariable analysis controlled for 7 clinical variables (including log NT-pro-BNP)
- LV mass (concentric remodelling) and LA size remained independently associated with an increased risk of morbidity and mortality
- Classification of diastolic dysfunction and lateral E/e' didn't survive multivariate analysis

Zile Circulation 2011;124:2491-2501

TOPCAT study

- Spironolactone to reduce cardiovascular morbidity and mortality in 3445 adults with signs and symptoms of HF and an LVEF ≥45%
- Echo substudy:
  - 935 patients, mean age 70 years
- Primary endpoint:
  - cardiovascular death, heart failure hospitalization, or aborted cardiac arrest

Amil Shah Circ Heart Fail 2014;7:740-751.

TOPCAT echo

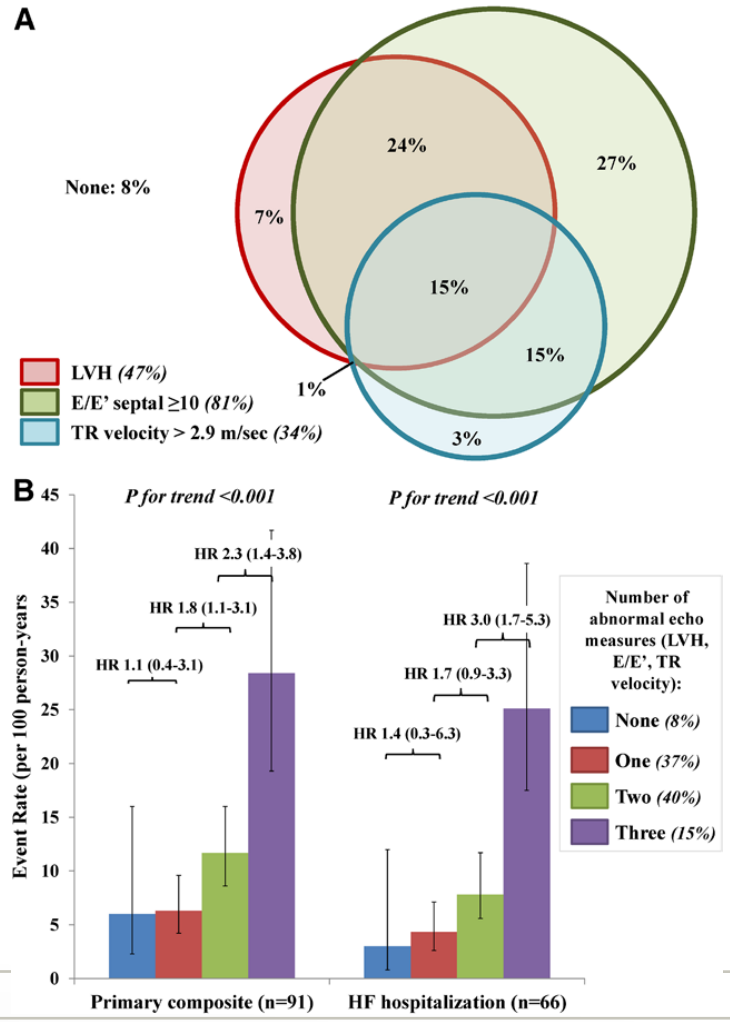


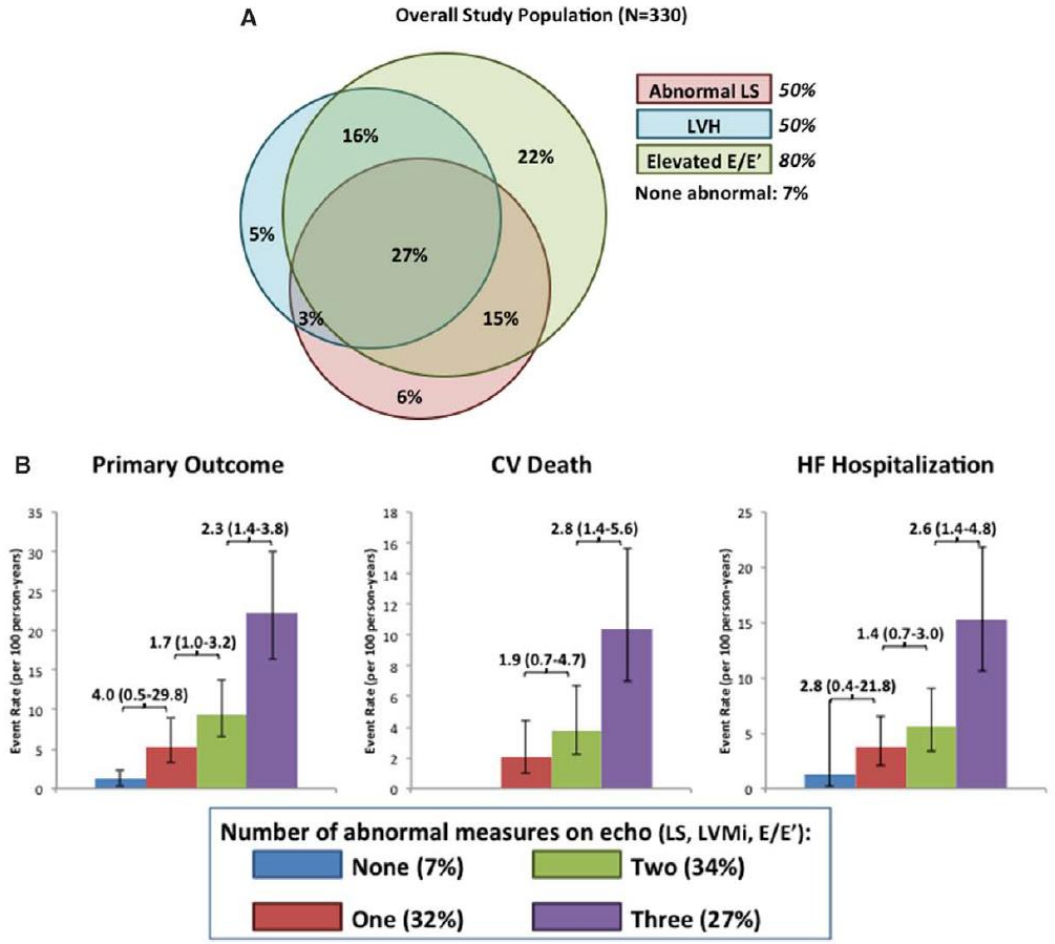
Figure 3. Interrelationship between left ventricular hypertrophy (LVH), E/E, and tricuspid regurgitation (TR) velocity among 303 patients with all 3 measures available.
A, Venn diagram demonstrating the overlap of these abnormalities.
B, Event rates (per 100 person-years) of the primary composite end point

TOPCAT echo

- LVH,
  higher filling pressures (septal E/e')
  and higher PAP
  were predictive of the primary composite end point and incident HF hospitalization
- These features coexist, and greater number of abnormalities is associated with higher risk
- These features alone or in combination identify patients with a particular high cardiovascular risk (improved C statistic, net reclassification)

Amil Shah Circ Heart Fail 2014;7:740-751.

TOPCAT echo GLS



Amil Shah Circulation. 2015;132:402-414.

TOPCAT echo GLS

- LVH,
  higher filling pressures (septal E/e')
  and higher PAP
  were predictive of outcome

- LVH,
  higher filling pressures (septal E/e')
  and decreased GLS
  were predictive of the primary composite end point

- Of note, GLS was related to decreased RV function, not to RV pressures (TR velocity)

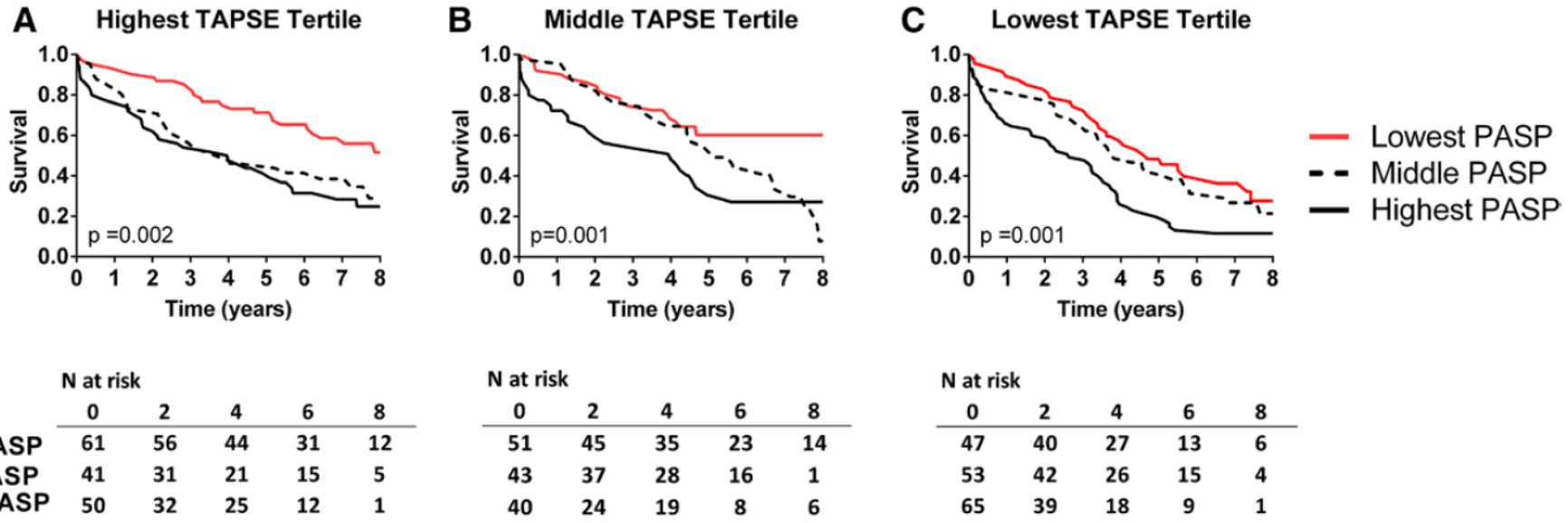
Amil Shah Circulation. 2015;132:402–414.

Olmsted County HFpEF cohort

- Prospectively identified HFpEF (Framingham HF criteria, ejection fraction ≥ 50%) patients (n=562)
- RV dysfunction:
  - TAPSE
  - semi-quantitative RV function
  - Severity of TR
- Endpoints:
  - Total and CV mortality.
  - HF hospitalisations
- RV systolic dysfunction may accompany HFpEF and portends a poorer prognosis, regardless of the severity of PH or comorbid conditions.

Mohammed Circulation 2014;130:2310-2320.

Olmsted County Survival



	N at risk				
	0	2	4	6	8
PASP	61	56	44	31	12
PASP	41	31	21	15	5
PASP	50	32	25	12	1

N at risk				
0	2	4	6	8
51	45	35	23	14
43	37	28	16	1
40	24	19	8	6

N at risk				
0	2	4	6	8
47	40	27	13	6
53	42	26	15	4
65	39	18	9	1

Kaplan–Meier survival curves for patients with heart failure with preserved ejection fraction (HFpEF) according to tertiles of y artery systolic pressure (PASP) among patients in the highest (tricuspid annular plane systolic excursion [TAPSE] ≥20 mm; **A**), APSE 16–19 mm; **B**), and lowest (TAPSE ≤15 mm; **C**) TAPSE tertile.

Mohammed Circulation 2014;130:2310–2320.

Worsening renal function I-PRESERVE

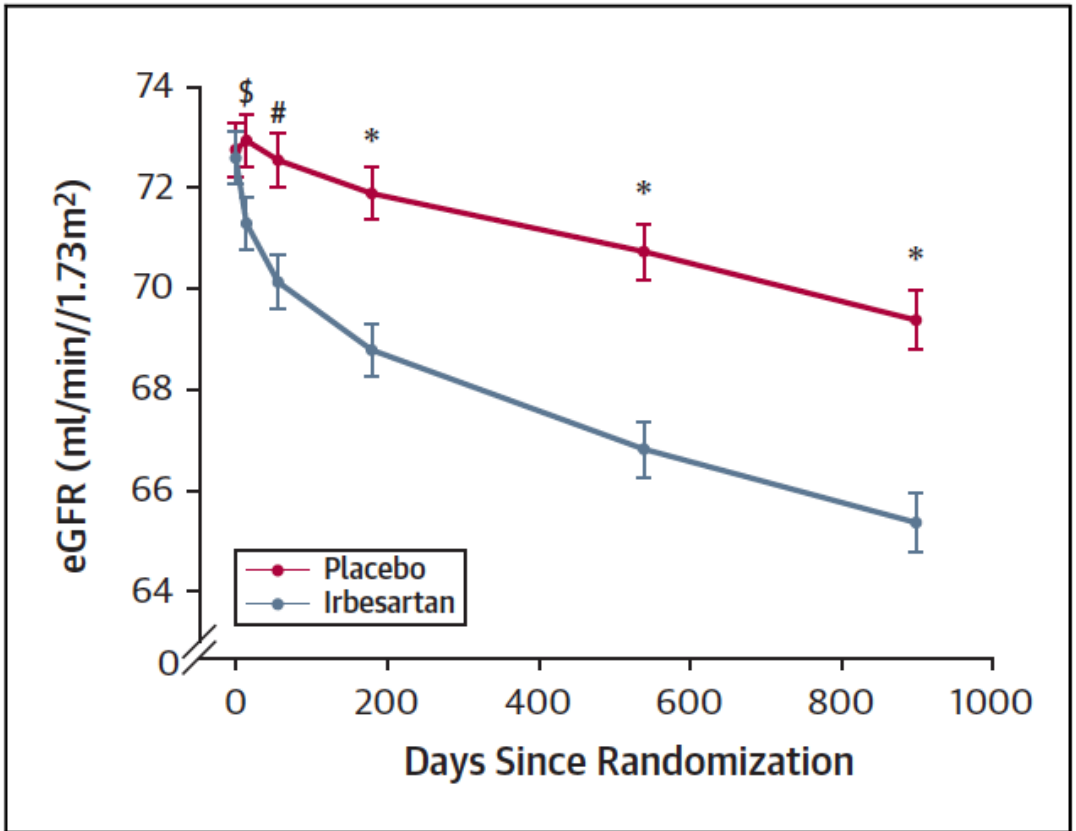


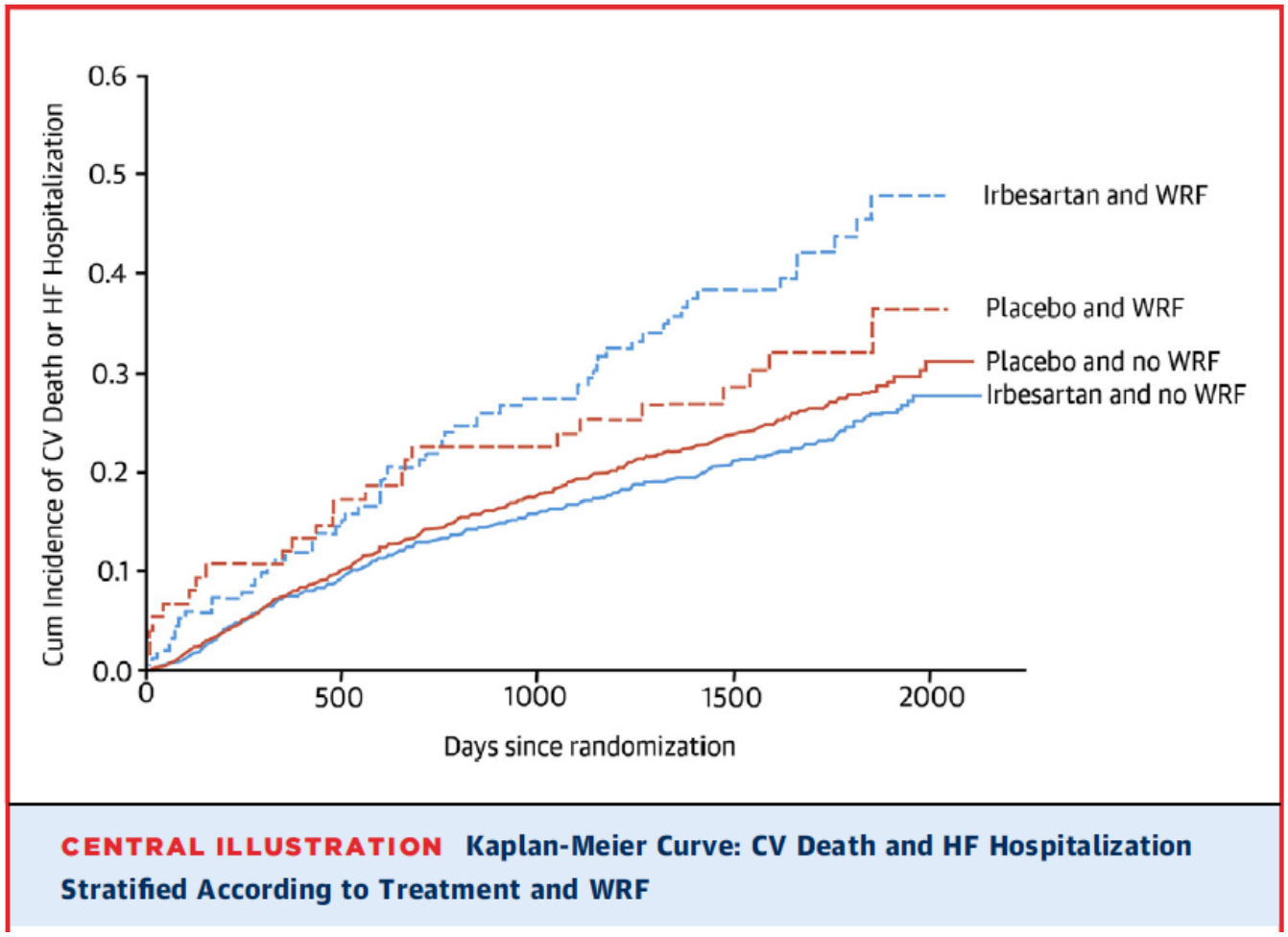
FIGURE 1 Change in eGFR Over Time Stratified According to Randomized Treatment Allocation

Damman J Am Coll Cardiol 2014;64:1106–13

WRF

SCr + 0.3 mg/dl and +25%

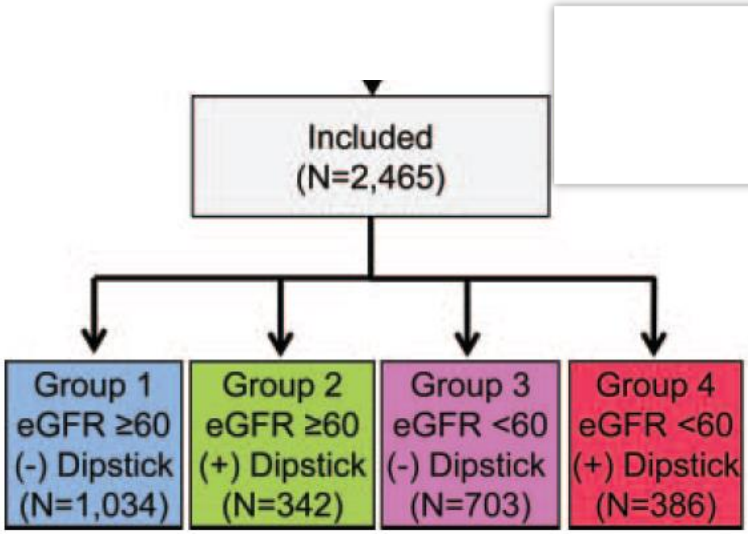
6,4% of the patients



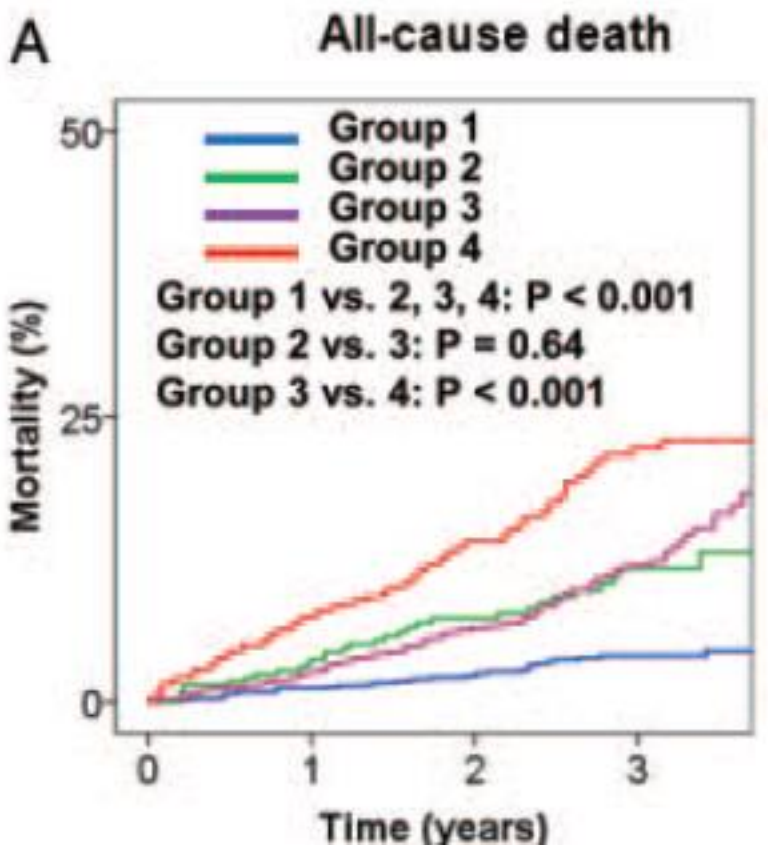
CENTRAL ILLUSTRATION **Kaplan-Meier Curve: CV Death and HF Hospitalization Stratified According to Treatment and WRF**

Damman J Am Coll Cardiol 2014;64:1106–13

Urinary Albumin CHART 2 study



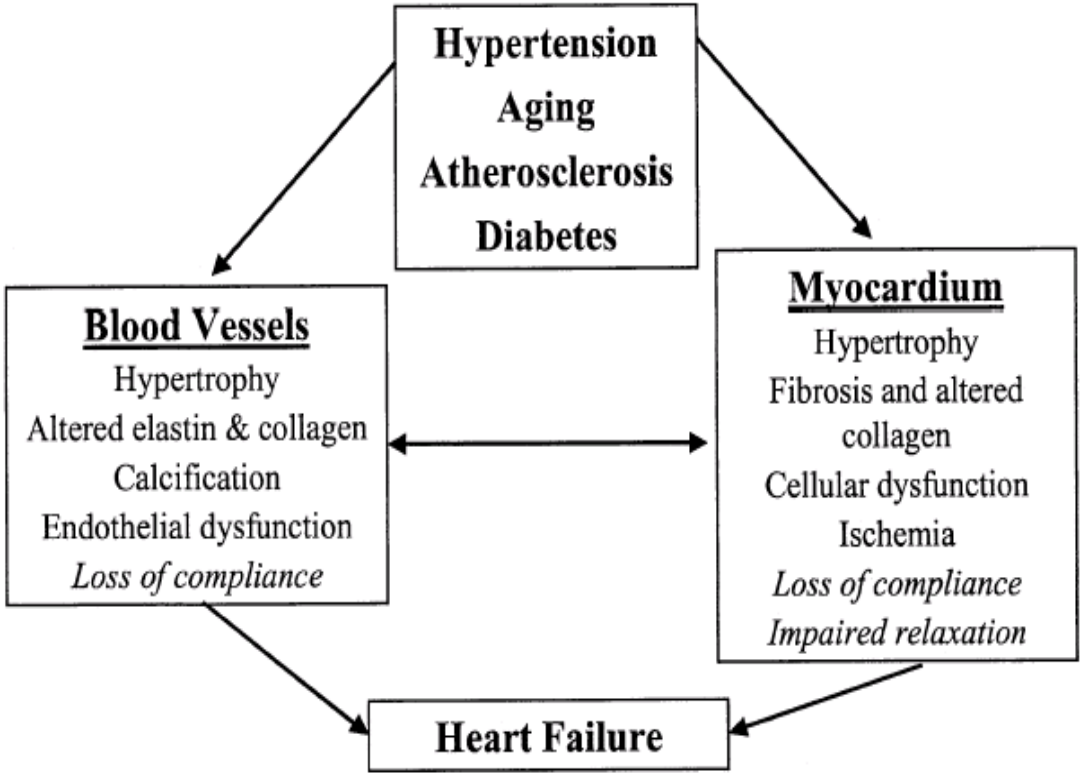
+ dipstick 30%



Miura EJHF (2012) 14, 367–376

HFpEF

Genetics
Physical inactivity
Overweight/Obesity

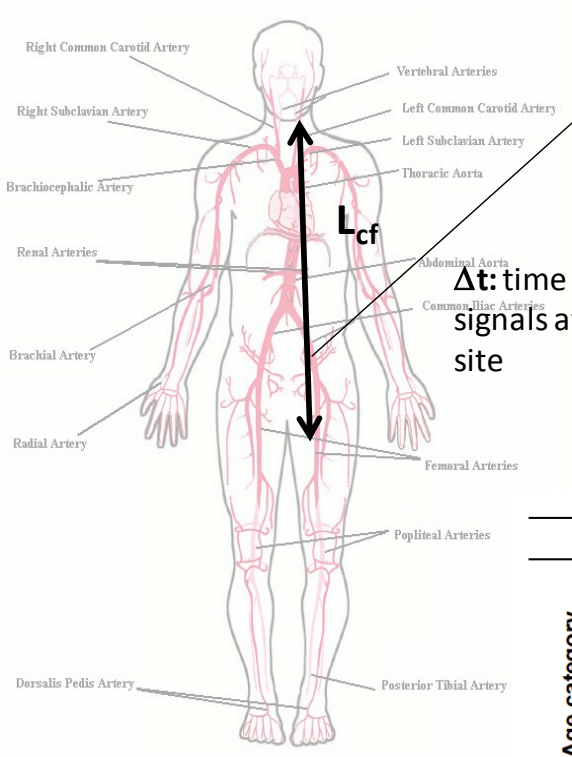


Massie, JACC, 2003

Measurement of carotid-femoral PWV, currently considered as gold standard measure of arterial stiffness

Carotid-Femoral PWV

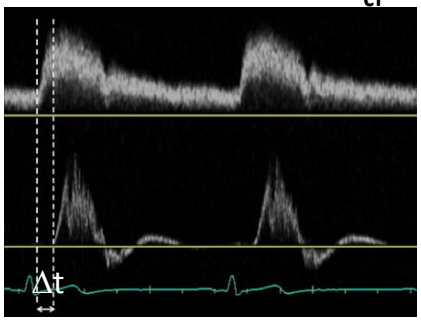
$PWV = \Delta x/\Delta t$



L_{cf} = carotid-femoral distance from body surface measurement

Δt: time delay between signals at carotid and femoral site

Distance **$\Delta x \sim 0.8\ L_{cf}$**



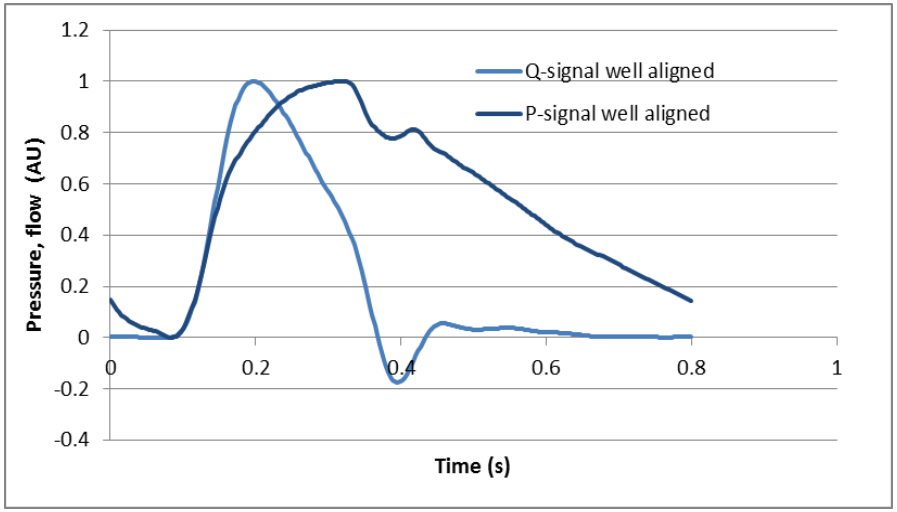
Normal values for PWV

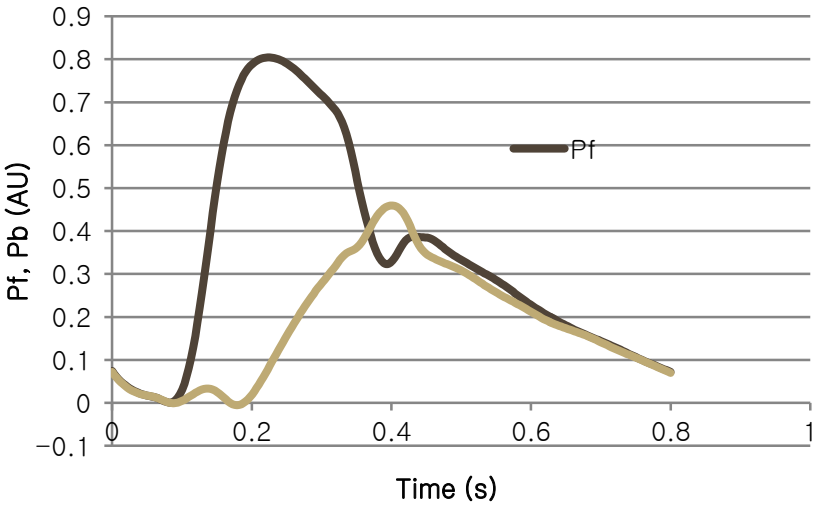
		Mean (SD)	Median (Q_1-Q_3)
Age category	<30 years	5.4 (0.7)	5.3 (4.9 - 5.8)
	30-39 years	5.6 (1.3)	5.4 (4.7 - 6.2)
	40-49 years	6.2 (1.2)	6.1 (5.5 - 6.8)
	50-59 years	7.4 (1.9)	7.2 (6.3 - 8.0)
	60-69 years	9.4 (2.3)	8.9 (7.7 - 10.8)
	≥70 years	9.9 (2.5)	9.6 (8.0 - 10.7)

Source: European Heart Journal 2010

Arterial Stiffness Collaboration Eur Heart J. 2010 Oct;31(19):2338-50.

Pulsatile load: Zc, Pf and Pb





The assessment of forward (Pf) and backward (Pb) travelling waves requires the following steps:

- measurement of two waveforms representative of pressure and flow
- assessment of characteristic impedance Zc
- wave separation Pf=0.5(P+Q*Zc); Pb=0.5(P−Q*Zc)
- computation of RM = Pb/Pf

Courtesy of Patrick Segers, Ghent University

Magnitude of the reflected wave

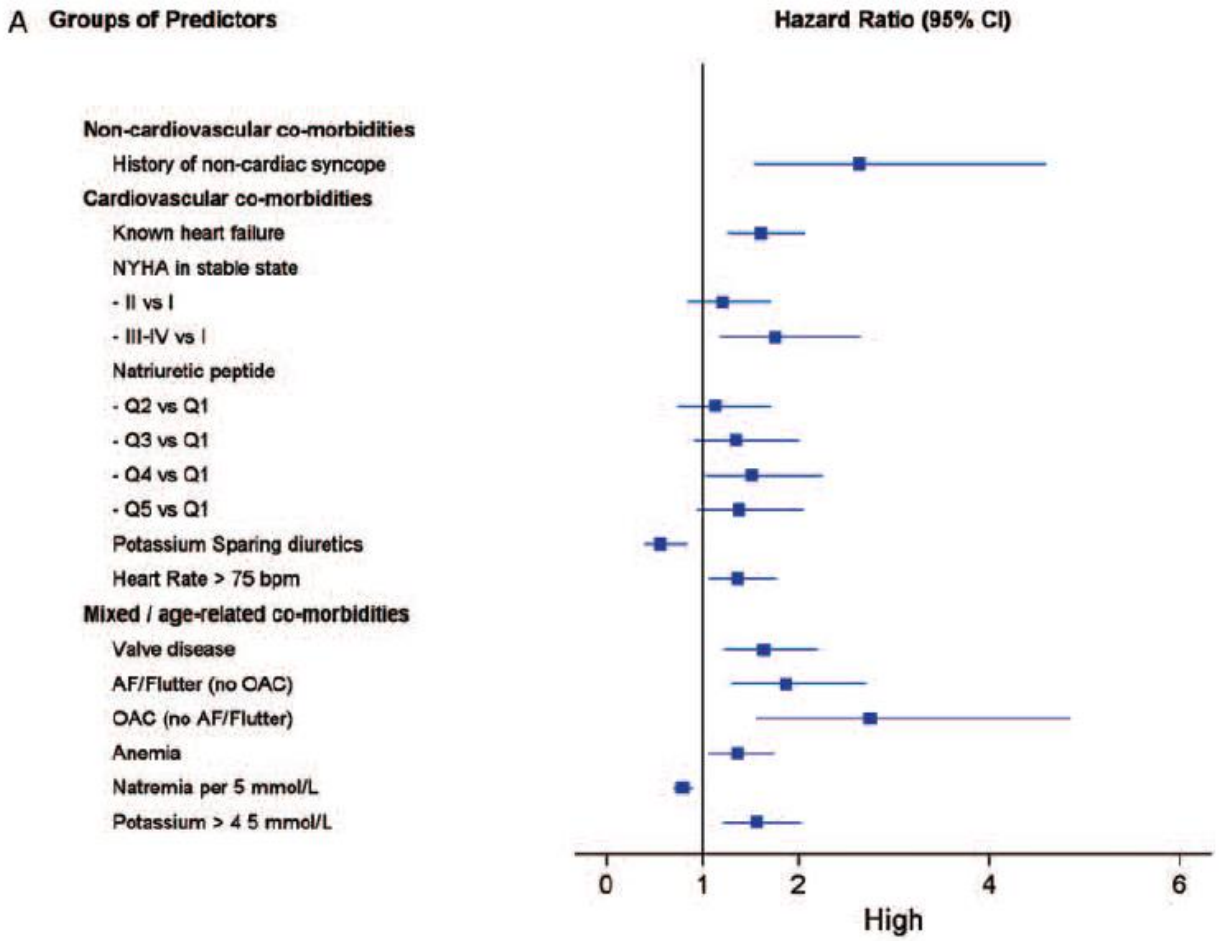
- Delays myocardial relaxation in animal models
  - Gillebert & Lew AJP Heart Circ Physiol.1991; 261: 805-13.
  - Leite-Moreira & Gillebert Circulation. 1994;90:2481-91.
- Is associated with decreased systolic and diastolic function
  - Borlaug et al. JACC 2007; 50:1570-7. Community subjects
  - Chirinos et al. Hypertension 2013;61:296-303. Asklepios population
- Is primarily responsible for increased LV mass (maladaptive hypertrophy)
  - Kobayashi et al. Circulation. 1996;94:3362-3368. Animal model.
  - Zamani et al. Hypertension. 2015;65:85-92. MESA population
- Is associated with
  - All CVE and incident heart failure.
    - Chirinos et al. JACC. 2012;60:2170-7. MESA population
  - All-cause mortality.
    - Zamani et al. Hypertension 2014;60:2170-7. MESA population

Take home messages
Prognostic stratification of HFpEF

- Clinical data
  - Age, diabetes, frailty (non-cardiovascular syncope), hospitalisation for HF
- Laboratory data
  - BNP (NT-pro-BNP)
  - eGFR, worsening GFR, sodium and potassium
  - Microalbuminuria
- Echocardiography and cardiac Doppler
  - LV mass, LA volume
  - Filling pressures (septal E/e') and PA pressures (TR velocities)
  - LV function (longitudinal GLS) and RV function (TAPSE)
  - Valvular heart diseases
  - Arterial function (wave reflection and end-systolic haemodynamics)

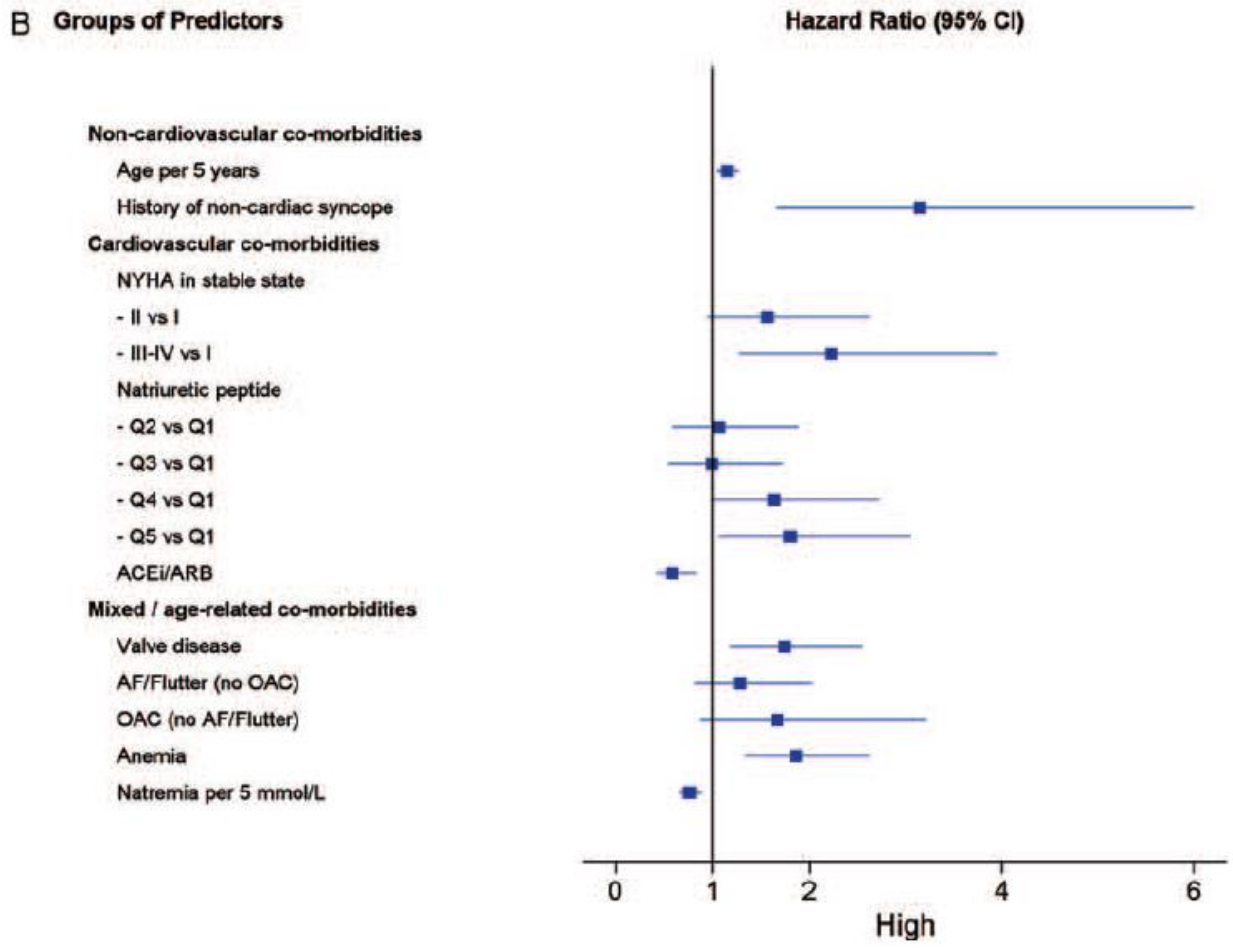
Gillebert EHJ-CVI 2015 (in press) doi:10.1093/ehjci/jev195

Primary endpoint (50%) Predictors



Lund EJHF (2014) 16, 992–1001

Secondary endpoint (20%) Predictors



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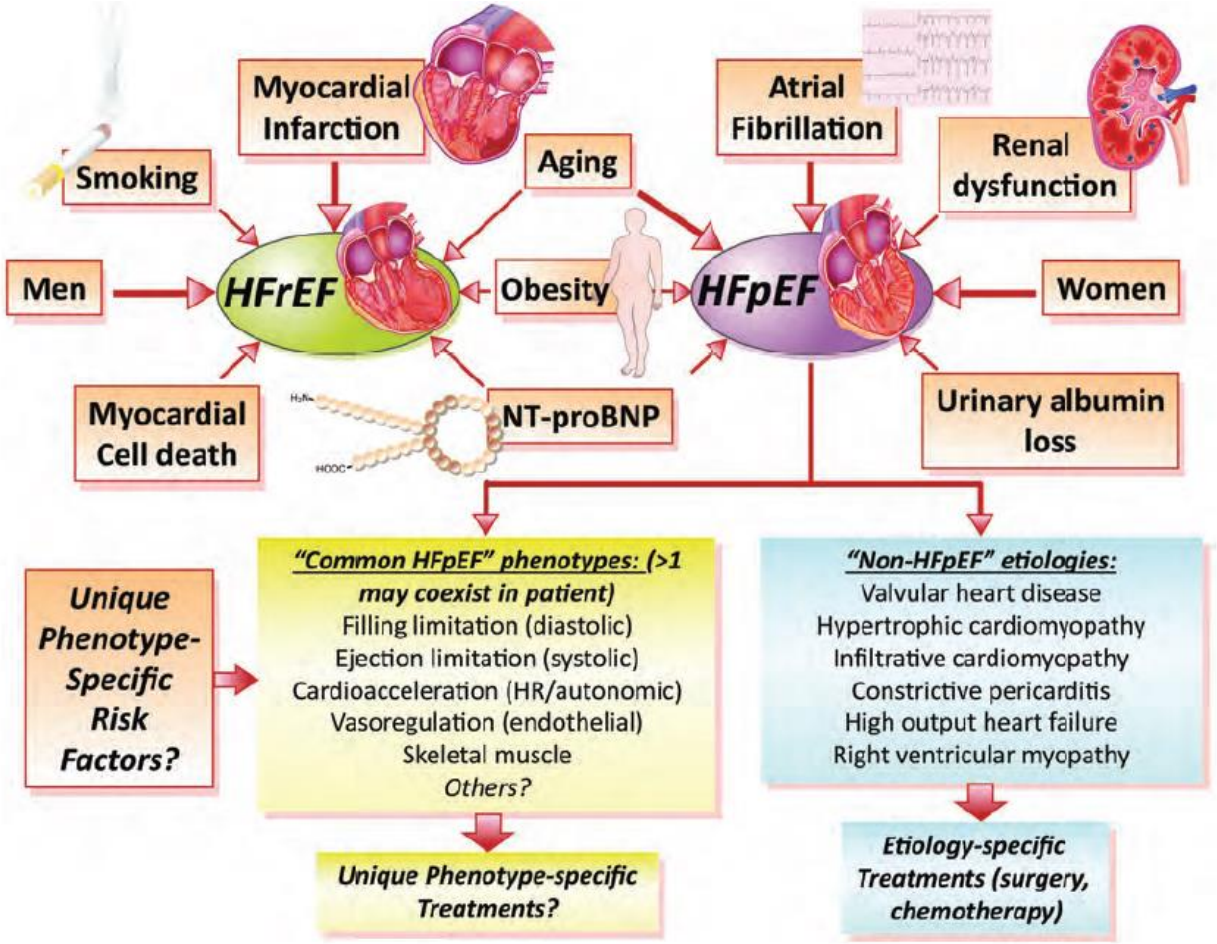
Different risk profiles for different diseases PREVEND study



Brouwers, Eur Heart J, 2013

Borlaug, Eur Heart J, 2013

Other prognostic determinants

- Coronary artery disease in HFpEF
  - Rusinaru EJHF (2014) 16, 967–976
  - In contrast to the situation in HFrEF, there is in HFpEF no association of CAD with CV death
- Anaemia in acute heart failure (ARIC cohort)
  - Caughey Am J Cardiol 2014;114:1850–1854
  - In HFpEF, anaemia is related to long term death and longer hospital stay (HR 2.1)
  - This effect is more pronounced than in HFrEF

NT-pro-CNP

- NT-pro-CNP levels in 567 hospitalized patients
- Endpoints:
  - The primary endpoint was a combined endpoint of all-cause mortality and HF hospitalization after 18 months
  - The secondary endpoint was all cause mortality after 3 years
- NT-proCNP is strongly predictive for the primary endpoint (HR=1.78) in patients with HFpEF, but not in patients with a reduced ejection fraction (HFrEF)

Lok EJHF (2014) 16, 958–966

Can we improve stratification with exercise echo?

Table 3
Univariate and multivariate analysis for prediction of the occurrence of adverse events.

Variables	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
LAEF_rest	0.87	0.80–0.95	0.001	0.92	0.83–1.05	0.094
E/e′ ratio_exercise	1.22	1.05–1.41	0.011	1.04	0.85–1.26	0.745
Heart rate_exercise	0.95	0.92–0.99	0.004	0.94	0.91–1.02	0.078
GLS_exercise	0.81	0.72–0.92	0.001	0.79	0.67–0.91	0.008

CI, confidence interval; E/e′ ratio, ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity; GLS, global longitudinal strain; HR hazard ratio; LAEF, left atrial ejection fraction.

Sanderson Am J Cardiol 2014;114:1850–1854

NT-pro-CNP

Table 4 Risk stratification improvement of N-terminal pro C-type natriuretic peptide levels on top of the COACH risk model for both endpoints in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction

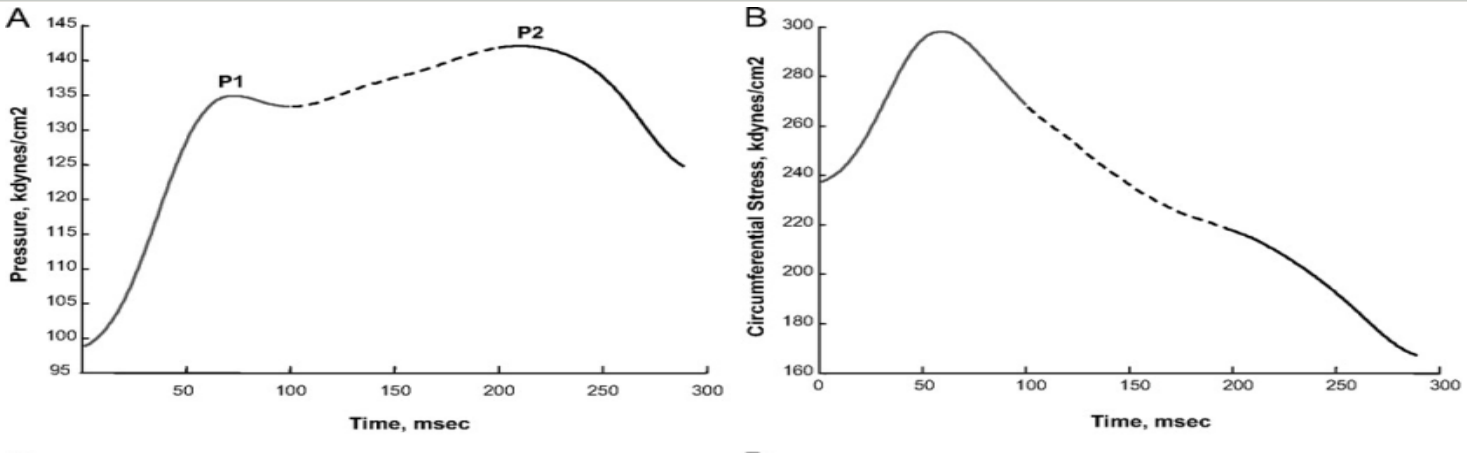
	NRI	*P*-value	IDI	*P*-value
HFrEF ($n = 353$)				
Combined endpoint	0.084	0.453	0.002	0.458
3-year all-cause mortality	0.157	0.166	0.002	0.233
HFpEF ($n = 107$)				
Combined endpoint	0.688	<0.001	0.064	0.003
3-year all-cause mortality	0.598	0.004	0.060	0.020

On top of the COACH risk engine including: age, sex, diastolic blood pressure, pulse pressure, previous heart failure hospitalization, history of myocardial infarction, stroke, diabetes, peripheral arterial disease, atrial fibrillation, renal function, and levels of NT-proBNP and sodium

HFpEF, heart failure with preserved ejection fraction; HFrEF, with reduced ejection fraction; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

Lok EJHF (2014) 16, 958–966

Arterial properties and load



- Early-systolic wall stress
  - Systemic vascular resistance (resistive load), HR and SV
  - Pf forward travelling wave (pulsatile load)
  - Proximal aortic Zc (pulsatile load)
  - Total aortic compliance (pulsatile load) (non-significant)
- Late-systolic wall stress
  - Systemic vascular resistance (resistive load), HR and SV
  - Pb backward travelling wave and Pb/Pf or reflection magnitude (pulsatile load)

Chirinos, Hypertension 2012;60:64-70.

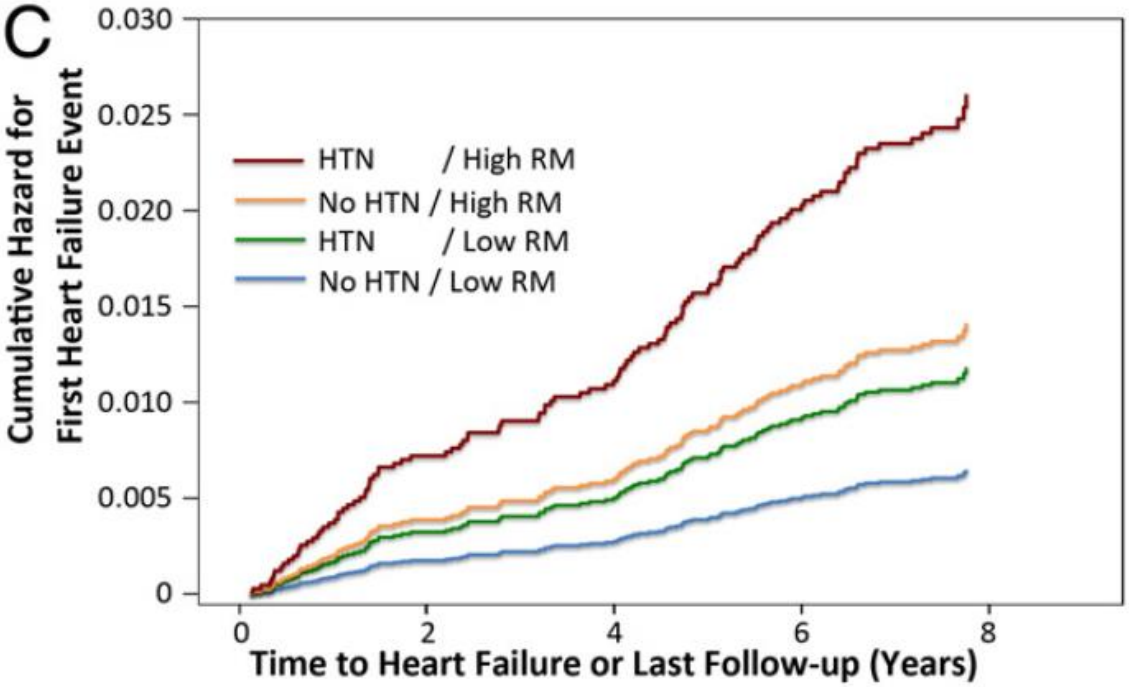
Predictors of incident heart failure
Chirinos et al. MESA study, n:5934.

Table 3 Predictors of Incident Heart Failure in Multivariate Analysis

Predictor	Full Model With Adjusted HRs (*c*-Index: 0.802; AIC: 1893; BIC: 1943) Standardized HR (95% CI)	Wald Statistic	p Value
Age (10 yrs)	1.62 (1.26–2.08)	14.44	<0.0001
Male	1.74 (1.38–2.21)	21.37	<0.0001
BMI (10 kg/m^2)	1.26 (1.03–1.55)	4.83	0.028
Diabetes mellitus	1.24 (1.07–1.44)	8.37	0.004
SBP (10 mm Hg)	1.69 (1.33–2.13)	18.97	<0.0001
DBP (10 mm Hg)	0.67 (0.52–0.86)	9.71	0.002
Reflection magnitude (10%)	1.61 (1.32–1.96)	22.03	<0.0001
SBP and DBP together‖	—	—	—

Chirinos J Am Coll Cardiol 2012;60:2170–7

HR for incident heart failure according to hypertension and RM



HTN	High RM	Hazard Ratio (95% CI)	P value
No	No	--------	-------
Yes	No	1.81 (0.85-3.86)	0.12
No	Yes	2.16 (1.06-4.43)	0.03
Yes	Yes	3.98 (1.96-8.05)	<0.0001

P for HTN by RM interaction = 0.97

Chirinos J Am Coll Cardiol 2012;60:2170–7