ACC Middle East Conference 2018

In partnership with:

جمعية القلب السعودية
Saudi Heart Association

State of the Art Management of HFpEF

Biykem Bozkurt, MD, FACC
The Mary and Gordon Cain Chair & Professor of Medicine
Medical Care Line Executive, DeBakey VA Medical Center,
Director, Winters Center for HF Research,
Associate Director, CV Research Institute
Baylor College of Medicine, Houston, TX

GWTG-HF data linked to Medicare data, ~ 40 k pts,

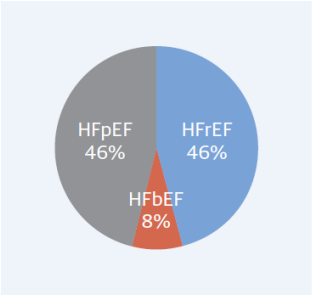
Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction

5-Year Outcomes

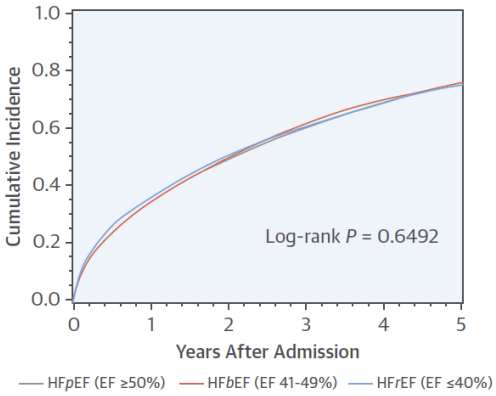
Kevin S. Shah, MD,[a] Haolin Xu, MS,[b,c] Roland A. Matsouaka, PhD,[b,c] Deepak L. Bhatt, MD, MPH,[d] Paul A. Heidenreich, MD, MS,[e] Adrian F. Hernandez, MD, MHS,[b,c] Adam D. Devore, MD,[b,c] Clyde W. Yancy, MD, MSc,[f]

CENTRAL ILLUSTRATION 5-Year Outcomes in Patients Hospitalized With HF With Preserved, Borderline, and Reduced EF

Heart Failure

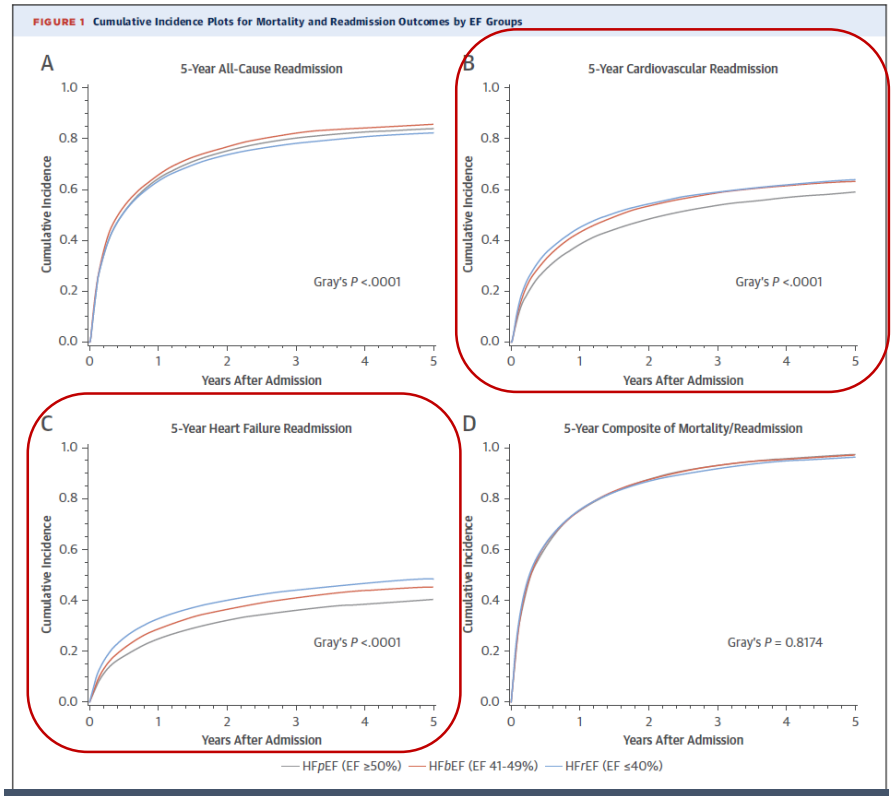


5-Year Mortality



Outcomes – 5-Year Event Rates (%)					
	Mortality	Readmission	CV Readmission	HF Readmission	Mortality/Readmission
HFrEF	75.3	82.2	63.9	48.5	96.4
HFbEF	75.7	85.7	63.3	45.2	97.2
HFpEF	75.7	84.0	58.9	40.5	97.3

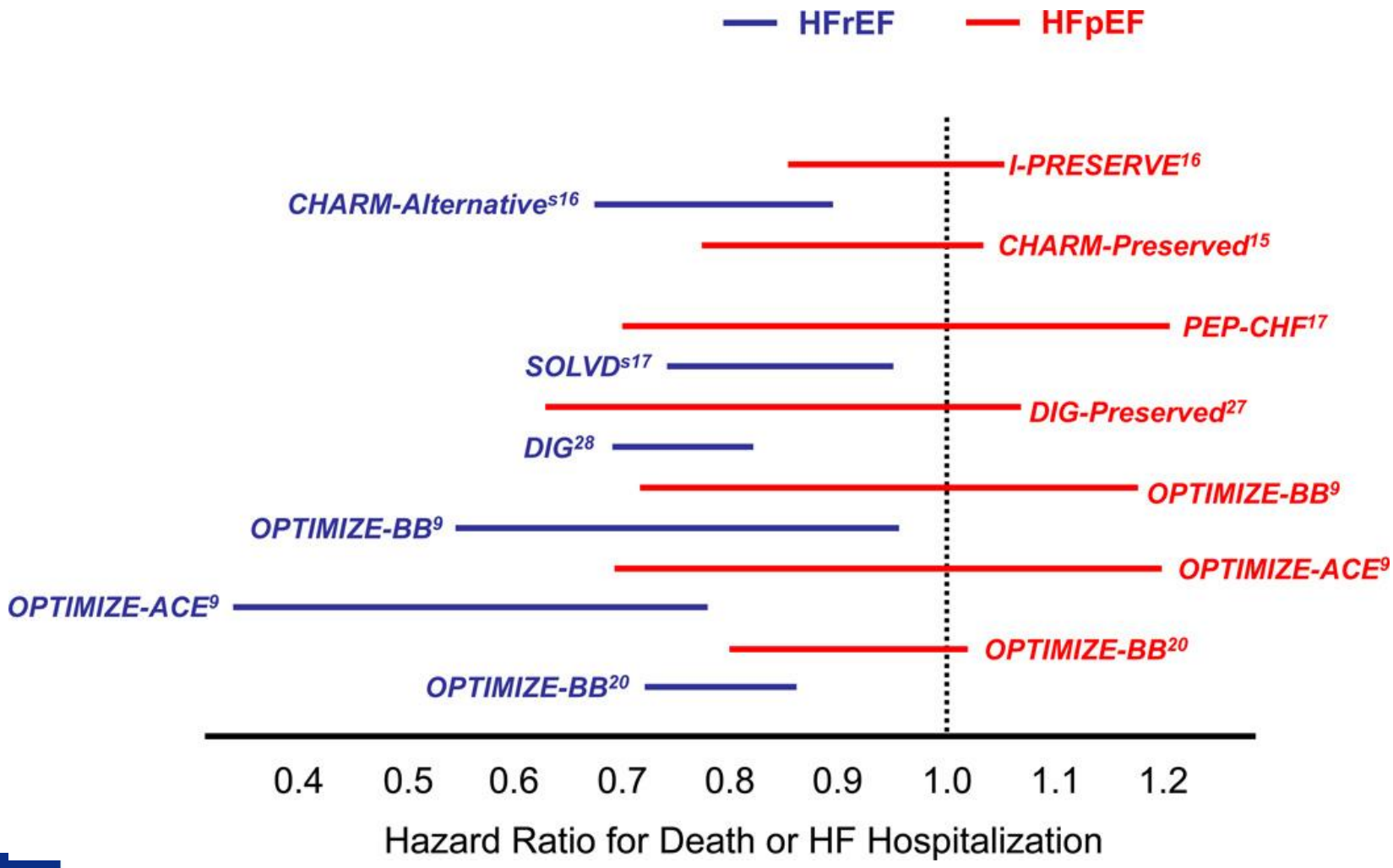
Mortality



Hospitalization

All 3 groups had **similar 5-year mortality rates** (HFrEF 75.3% vs. HFpEF 75.7%; HFbEF 75.7%)
CVH and HFH higher in HFrEF and HFbEF compared with those with HFpEF

Randomized Trials in HFpEF



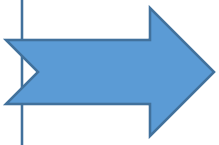
Baylor College of Medicine

MARGARET M. & ALBERT B. ALKEK DEPARTMENT OF MEDICINE

Circulation. 2011 May 10; 123(18): 2006–2014.

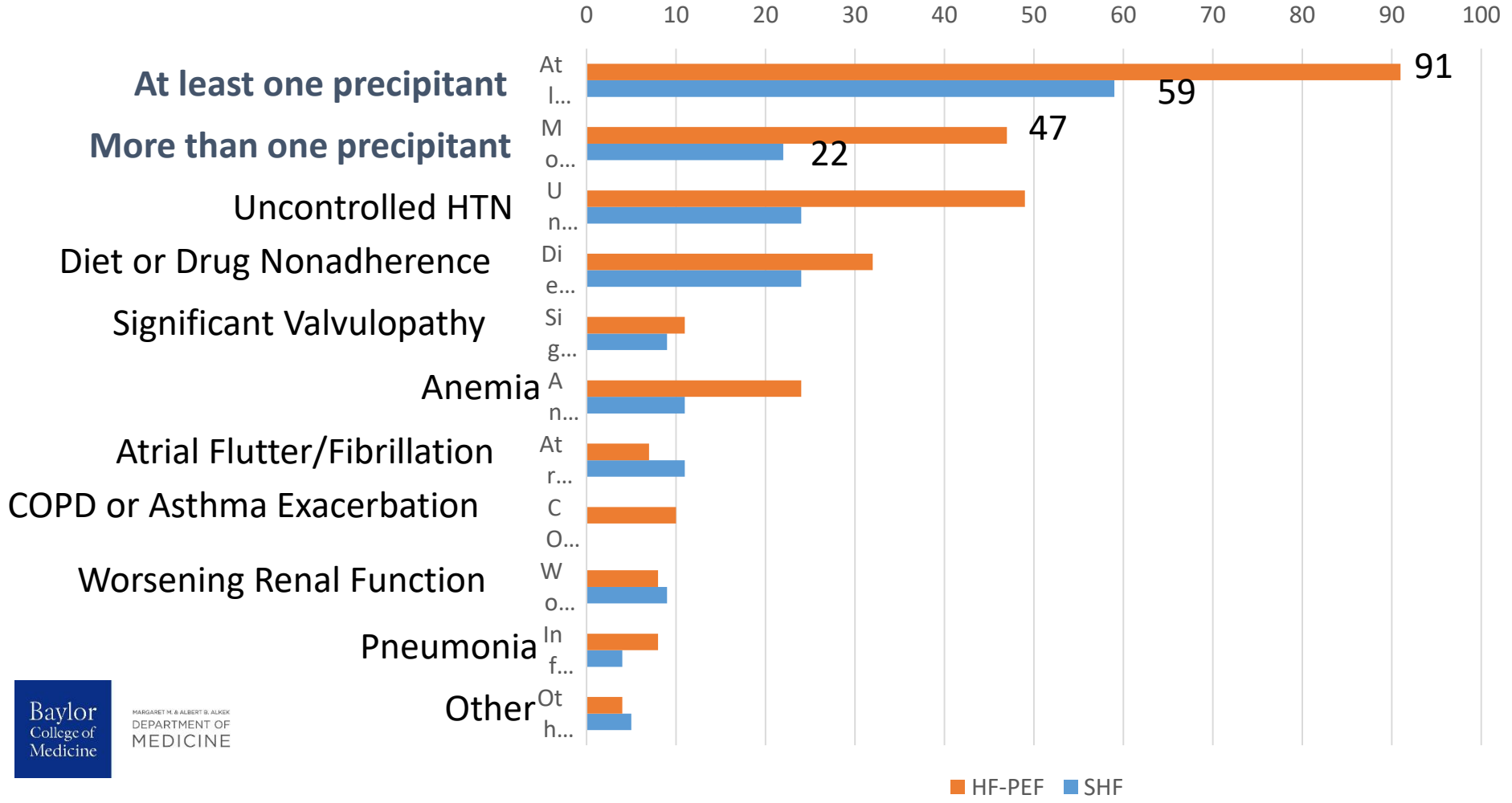
Risk Factors for HF-PEF

- Older age
- Women
- Systolic hypertension
- Diabetes
- Increased pulse pressure
- Left ventricular hypertrophy
- Diastolic filling abnormalities
- Obesity



Treatable

Precipitants of Heart Failure Exacerbations in Patients with HF-PEF



Baylor College of Medicine
MARGARET M. & ALBERT B. ALKEK DEPARTMENT OF MEDICINE

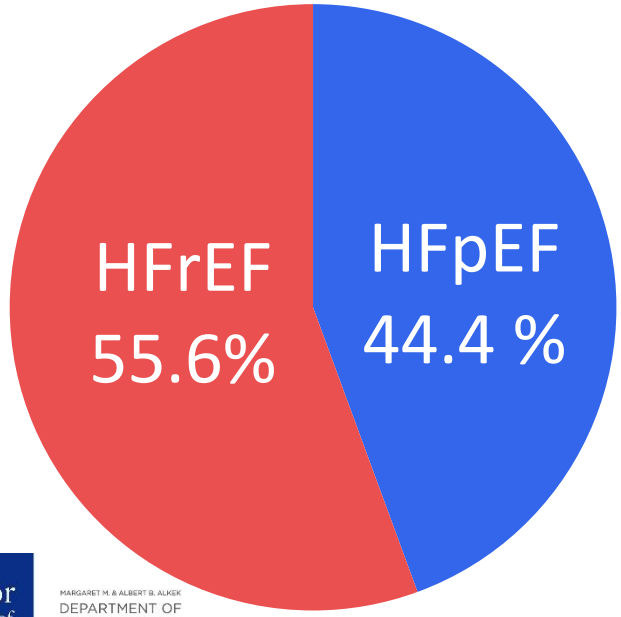
J Am Coll Cardiol. 2012 Mar 13;59(11):998-1005.

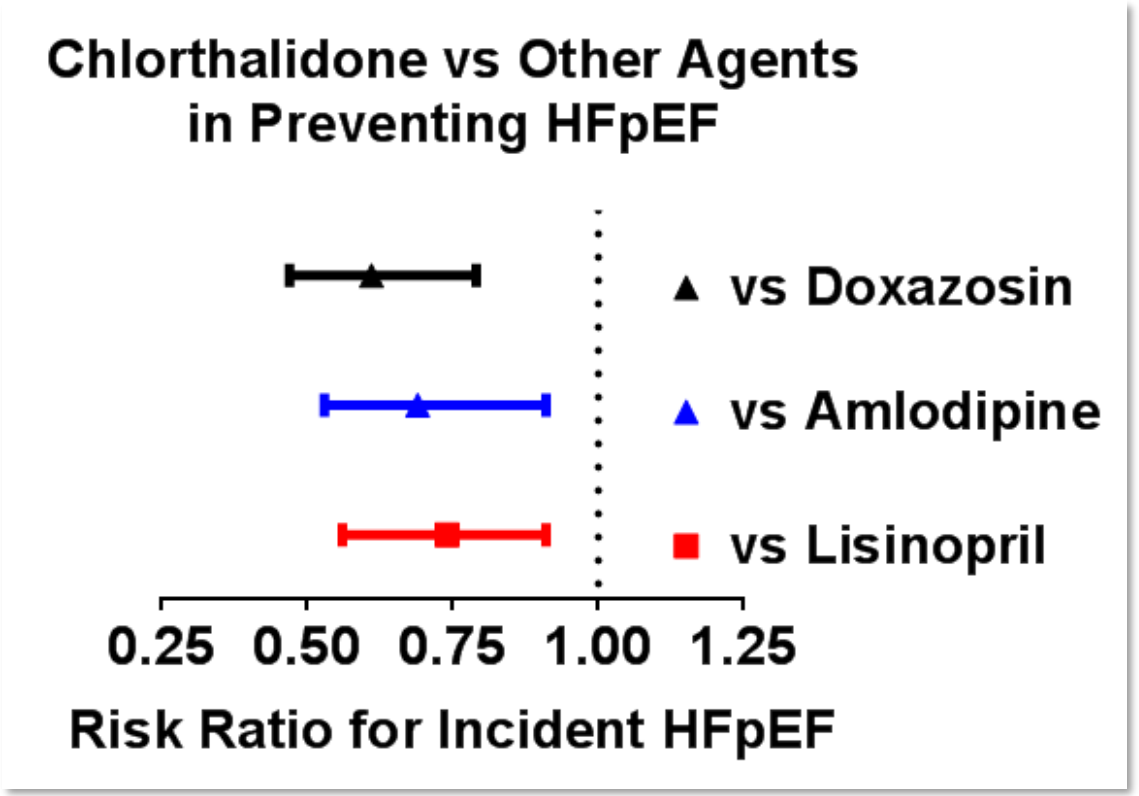
Stage A – Prevention of HFpEF

ALLHAT
42,418 High Risk HTN
> 55 yrs old

4.9 years

910 HF+EF





Lower Systolic BP with Chlorthalidone

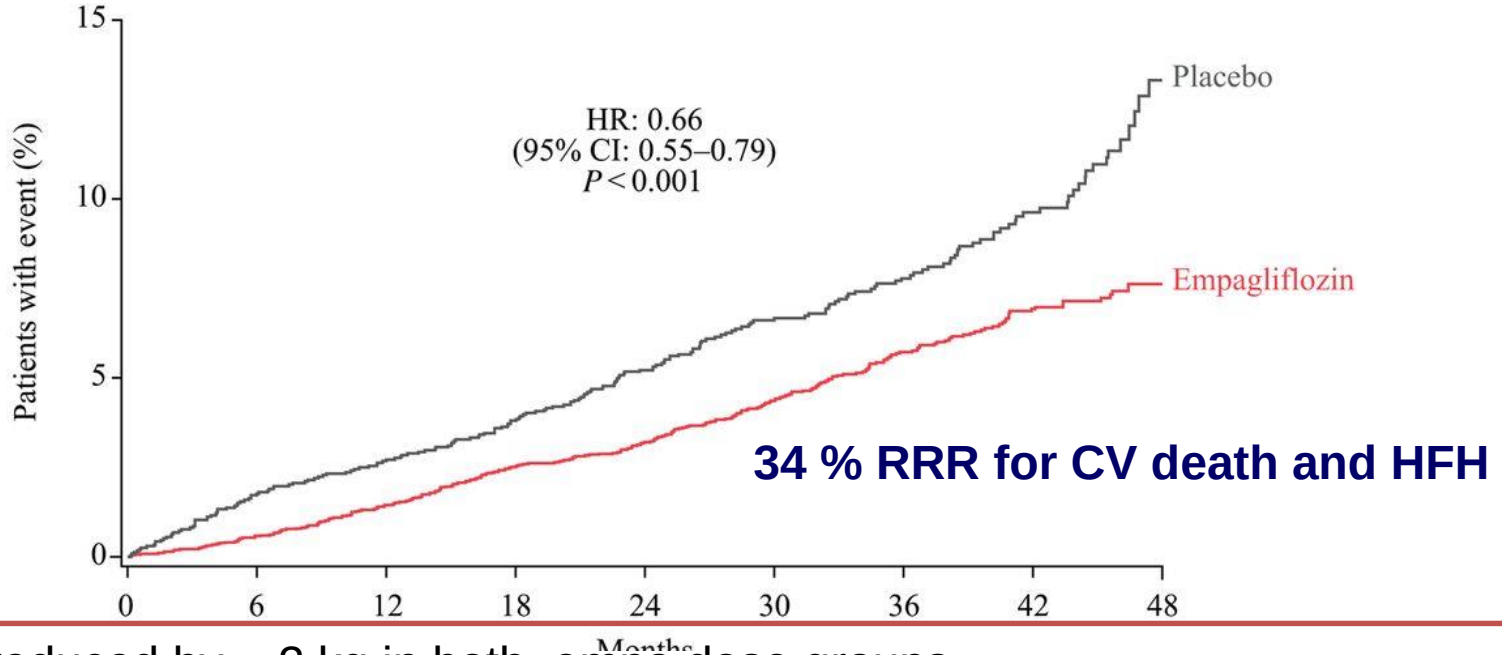
Baylor College of Medicine
MARGARET M. & ALBERT B. ALKEK DEPARTMENT OF MEDICINE

Davis DR, Circ, 2008

HF Events Reduced with SGLT2i in high risk CVD -EMPA-REG OUTCOME TRIAL

- **~ 10% had pre- existing HF, 43% on loop diuretics at baseline**

Time to first HFH or CVD



34 % RRR for CV death and HFH

- Weight reduced by ~2 kg in both empa dose groups
- **No measure of LVEF, no data on HFrEF vs HFpEF, or BNP**
- **Reduction in HFH could be due to HFpEF**

Fitchett et al. European Heart Journal 37, 1526–1534

Ongoing SGLT2i Trials in HF – some HFpEF

	EMPEROR-Preserved[1]	EMPEROR-Reduced[2]	Dapa-HF[3]	SOLOIST-WHF[4,5]
Sample size	4126	2850*	4500	4000[4] (6667 ?)[5]
Key inclusion criteria	• Chronic HF† • Elevated NT-proBNP • eGFR ≥20 ml/min/1.73 m²		• Symptomatic HFrEF† • Elevated NT-proBNP • eGFR ≥30 ml/min/1.73 m²	• Type 2 diabetes • Chronic HF • Elevated NT-proBNP • Hospital admission for worsening HF and haemodynamically stable
	HFpEF (LVEF >40%)	HFrEF (LVEF ≤40%)	HFrEF (LVEF ≤40%)	
Primary endpoint	• Time to first event of adjudicated CV death or adjudicated HHF		• Time to first occurrence of CV death, HHF or urgent HF visit	• Time to first event of CV death or HHF (both EF<50% and II)
Key secondary endpoints	• Individual components of primary endpoint • All-cause mortality • All-cause hospitalisation • Time to first occurrence of sustained reduction of eGFR • Change from baseline in KCCQ		• Total number of CV death or HHF • All-cause mortality • Composite of ≥50% sustained eGFR decline, ESRD or renal death • Change from baseline in KCCQ	• Total number of CV death, HHF or urgent HF visit • Composite of ≥50% sustained eGFR decline, chronic dialysis, renal transplant or sustained eGFR <15 ml/min/1.73 m²
Start date	March 2017	March 2017	February 2017	June 2018
Expected completion date	June 2020	June 2020	December 2019	January 2021

*NT-proBNP-based enrichment of the population with patients at higher severity of HF; †NYHA class II–IV

ESRD, end-stage renal disease; HHF, hospitalisation for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide

1. ClinicalTrials.gov NCT03057951; 2. ClinicalTrials.gov NCT03057977; 3. ClinicalTrials.gov NCT03036124; sotagliflozin
4. ClinicalTrials.gov NCT03521934; 5. EU Clinical Trials Register 2017-003510-16. Available at: https://www.clinicaltrialsregister.eu

Stage C – Treatment of HFpEF

Pharmacological Treatment for Stage C HFpEF (remains same)

COR	LOE	Recommendations	Comment/ Rationale
I	B	Systolic and diastolic blood pressure should be controlled in patients with HF*p*EF in accordance with published clinical practice guidelines to prevent morbidity	2013 recommendation remains current.
I	C	Diuretics should be used for relief of symptoms due to volume overload in patients with HF*p*EF.	2013 recommendation remains current.

Yancy CW, et al. *J Am Coll Cardiol.* 2016;22:659-669.

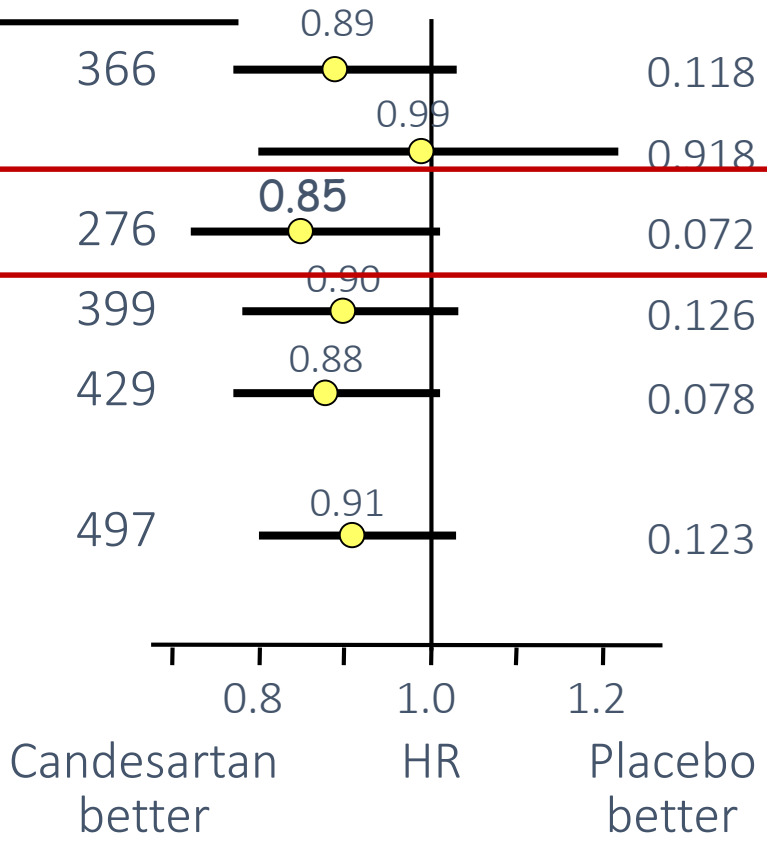
Pharmacological Treatment for Stage C HFpEF (remains same)

COR	LOE	Recommendations	Comment/ Rationale
IIa	C	Coronary revascularization is reasonable in patients with CAD in whom symptoms (angina) or demonstrable myocardial ischemia is judged to be having an adverse effect on symptomatic HF*p*EF despite GDMT.	2013 recommendation remains current.
IIa	C	Management of AF according to published clinical practice guidelines in patients with HF*p*EF is reasonable to improve symptomatic HF.	2013 recommendation remains current.
IIa	C	The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HF*p*EF.	2013 recommendation remains current.

Yancy CW, et al. *J Am Coll Cardiol.* 2016;22:659-669.

CHARM-PRESERVED: Primary and secondary outcomes

	Candesartan	Placebo	*P*-value	Covariate adjusted *P*-value
CV death, HF hosp	333	366	0.118	0.051
CV death 170	170		0.918	0.635
HF hospitalization	241	276	0.072	0.047
CV death, HF hosp, MI,	365	399	0.126	0.051
CV death, HF hosp, MI, stroke	388	429	0.078	0.037
CV death, HF hosp, MI, stroke, revascularization	460	497	0.123	0.13



Baylor College of Medicine
MARGARET M. & ALBERT B. ALKEK DEPARTMENT OF MEDICINE

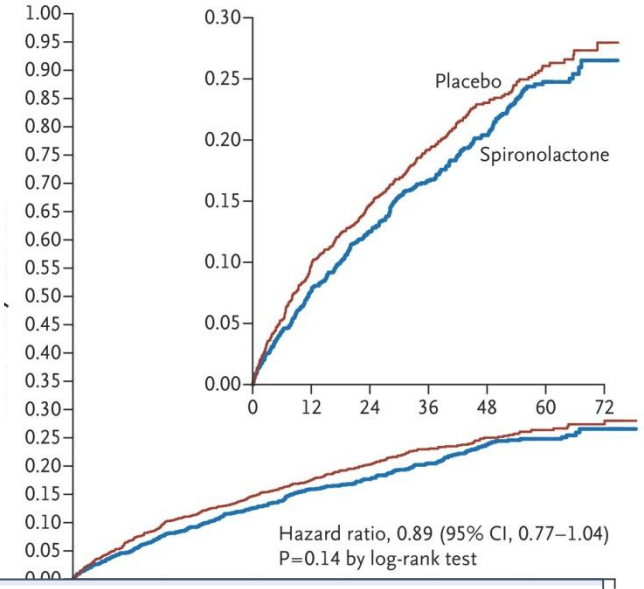
Yusuf S et al. Lancet. 2003;362:777-781.

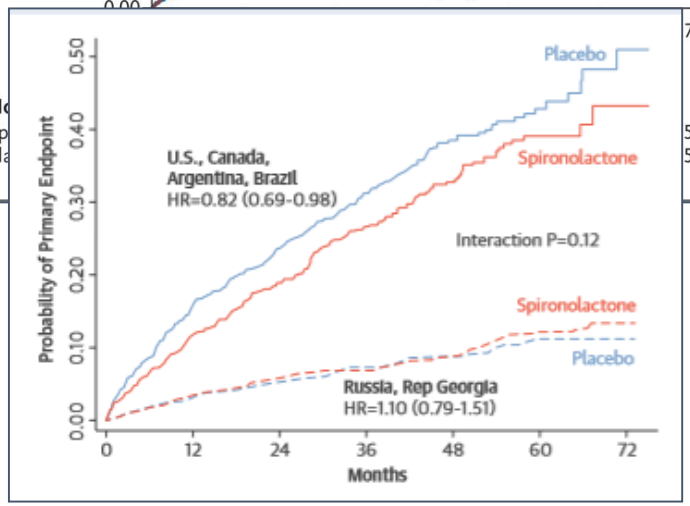
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 APRIL 10, 2014 VOL. 370 NO. 15

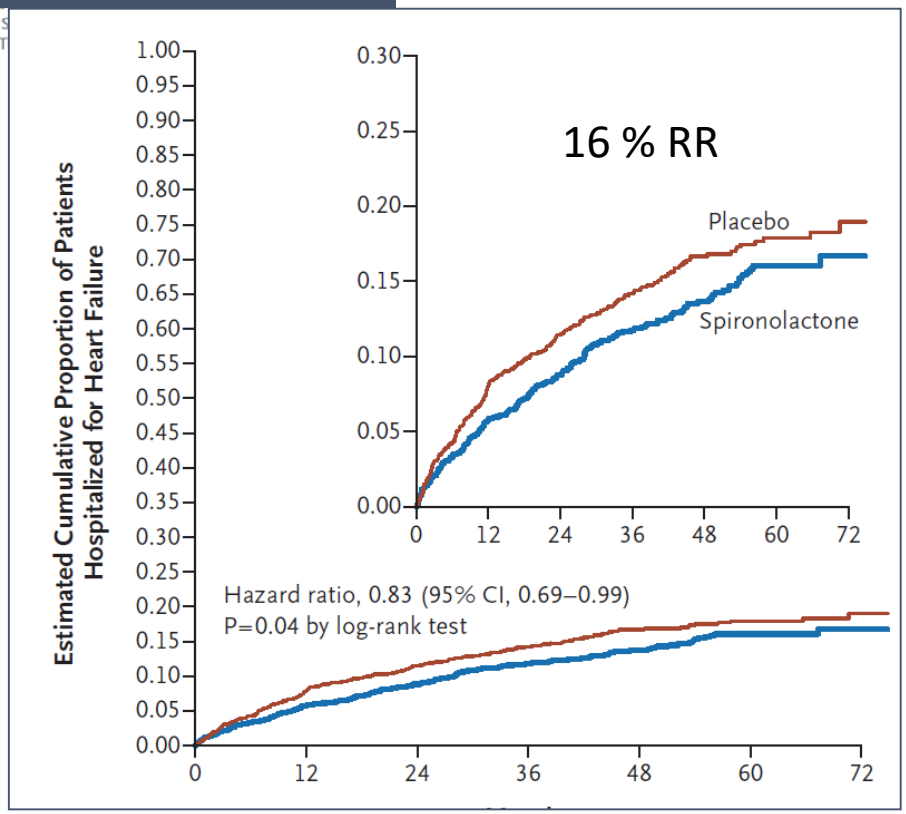
Spironolactone for Heart Failure with Preserved Ejection Fraction

TOPCAT

combined endpoint of death, aborted cardiac death







JACC; Volume 66, Issue 24, December 2015

Pharmacological Treatment for Stage C HFpEF

COR	LOE	Recommendations	Comment/ Rationale
IIb	**B-R**	In appropriately selected patients with HF*p*EF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations.	NEW: Current recommendation reflects new RCT data.
IIb	**B**	The use of ARBs might be considered to decrease hospitalizations for patients with HF*p*EF.	2013 recommendation remains current.

EF = ejection fraction

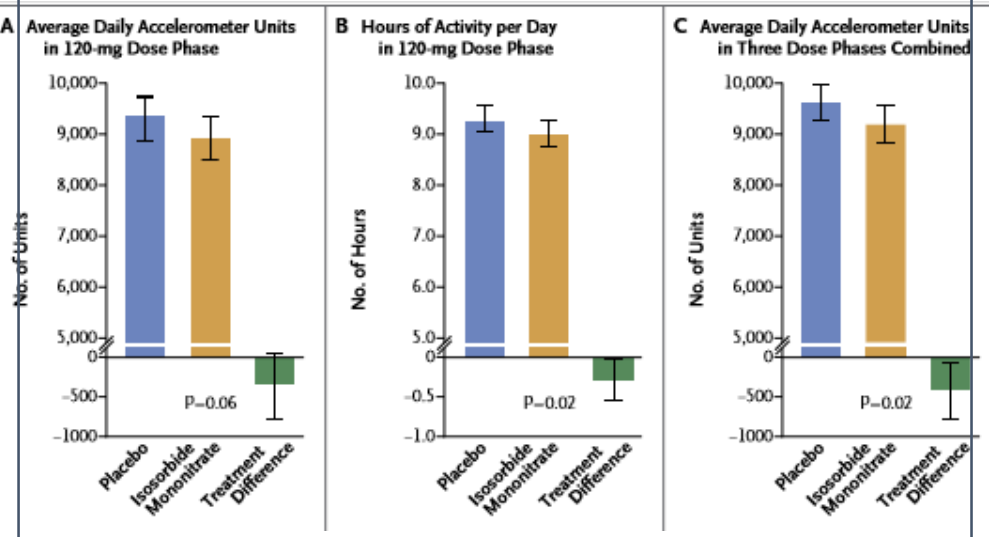
Yancy CW, et al. *J Am Coll Cardiol.* 2016;22:659-669.

ORIGINAL ARTICLE

Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction

Margaret M. Redfield, M.D., Kevin J. Anstrom, Ph.D., James A. Levine, M.D.,

NEAT-HF



- 110 patients with HFEF ≥50% randomized to either isosorbide mononitrate or placebo
- no beneficial effects on activity levels, QoL, exercise tolerance, or NT-proBNP levels.

ONLINE FIRST

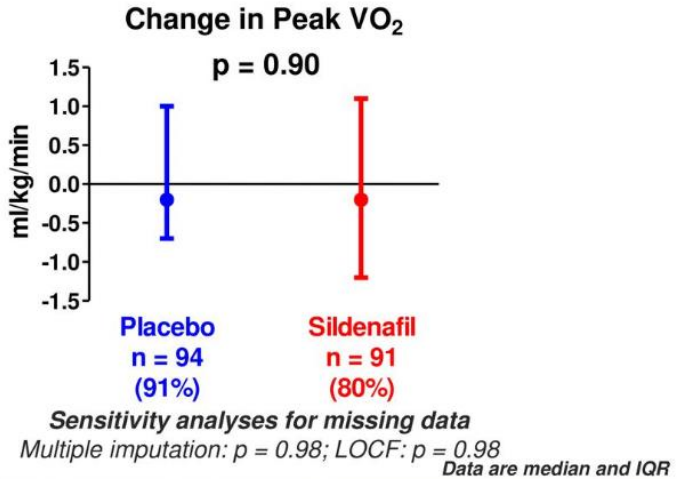
Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure With Preserved Ejection Fraction

A Randomized Clinical Trial

RELAX-HF

Results: Primary Endpoint

HEART FAILURE NETWORK



- PDE-5 inh augments the NO by upregulating cGMP
- Randomized 216 patients with HFEF ≥50% on and pVo2 <60% to sildenafil or placebo.
- No improvement in O2 consumption or exercise tolerance

Pharmacological Treatment for Stage C HFpEF

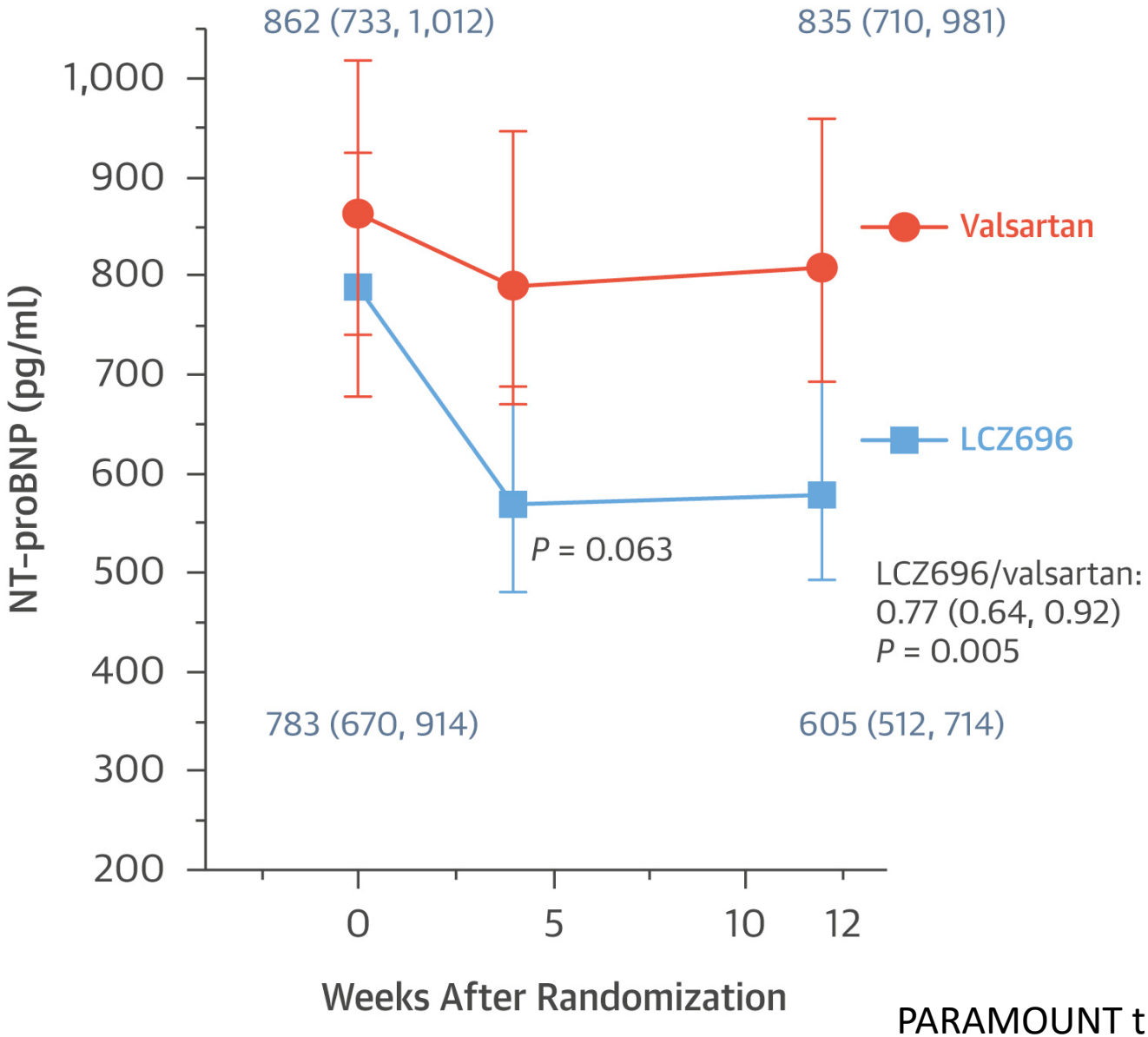
COR	LOE	Recommendations	Comment/ Rationale
III: No Benefit	**B-R**	Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL in patients with HF*p*EF is ineffective.	NEW: Current recommendation reflects new data from RCTs.
III: No Benefit	**C**	Routine use of nutritional supplements is not recommended for patients with HF*p*EF.	2013 recommendation remains current.

Yancy CW, et al. *J Am Coll Cardiol.* 2016;22:659-669.

HFpEF

Evolving New Approaches

Effects of LCZ696 in HFpEF (Paramount Pilot Trial)



PARAMOUNT trial

New Studies with ARNI

NAME	TITLE	Primary End Point
PARAGON-HF	Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in **HFpEF**	CV death and HF hospitalizations
TITRATION	Safety and Tolerability of Initiating LCZ696 in Heart Failure Patients 200 mg twice daily (bid) over 3 weeks vs 6 weeks)	Hypotension, Renal Dysfunction, Hyperkalemia and Angioedema
PARABLE	ARNI in **Asymptomatic Patients** With Elevated Natriuretic Peptide and Elevated Left Atrial Volume	impact on LV diastolic function
PIONEER	comParIson Of Sacubitril/valsartaN Versus Enalapril on Effect on ntpRo-bnp in Patients Stabilized From an **Acute Heart Failure Episode**	Change from baseline in NT-proBNP (hypotension, hyperkalemia, angioedema)
PARASAIL	Description of Tolerability of LCZ696 (Sacubitril / Valsartan) in Heart Failure With Reduced Ejection Fraction (HFrEF) Treated in Real Life Setting (PARASAIL) in CANADA	% Pts tolerated LCZ696 at the dose of 97.2 mg sacubitril / 102.8 mg valsartan bid at month 6

Source: ClinicalTrials.gov

European Heart Journal (2017) **38**, 1119–1127
doi:10.1093/eurheartj/ehw593

FASTTRACK CLINICAL RESEARCH
Heart failure/cardiomyopathy

Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: results of the SOluble guanylate Cyclase stimulatoR in heArT failurE patientS with PRESERVED EF (SOCRATES-PRESERVED) study

⬆ cGMP by soluble guanylate cyclase stimulator

Table 2 Primary endpoints [per protocol analysis (PPS-NT-proBNP and PPS-LAV)]

Primary analysis[a]		n	Baseline Mean (SD)	12 weeks (Visit 5) Mean change from baseline (SD)	Treatment comparison Difference (Treat-Plac) [Back-transformed[b]]	90% Confidence interval [Back-transformed[b]]	P-value[c] One-sided	P-value[c] Two-sided
LAV (mL)	Placebo	67	89.075 (51.059)	-3.361 (12.654)				
	Pooled 2.5/5/10 mg	194	87.083 (30.204)	-1.732 (12.808)	1.6291	-1.36 to 4.62	0.8156	0.3688
log(NT-proBNP) [log(pg/mL)]	Placebo	73	6.897 (1.203)	-0.098 (0.778)				
	Pooled 2.5/5/10 mg	195	6.945 (1.297)	0.038 (0.782)	0.1372 [1.147]	-0.04 to 0.31 [0.96–1.37]	0.8991	0.2017

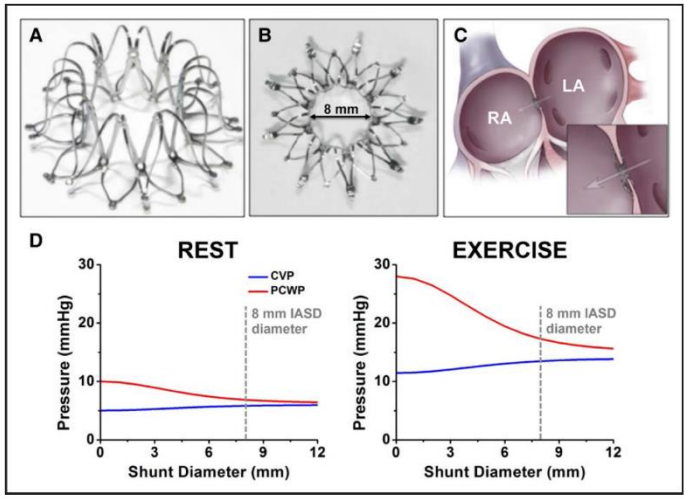
- Phase II Study, Vericiguat once daily at different doses was well tolerated
- did not change NT-proBNP and LAV at 12 weeks
- but was associated with improvements in QOL in HFpEF

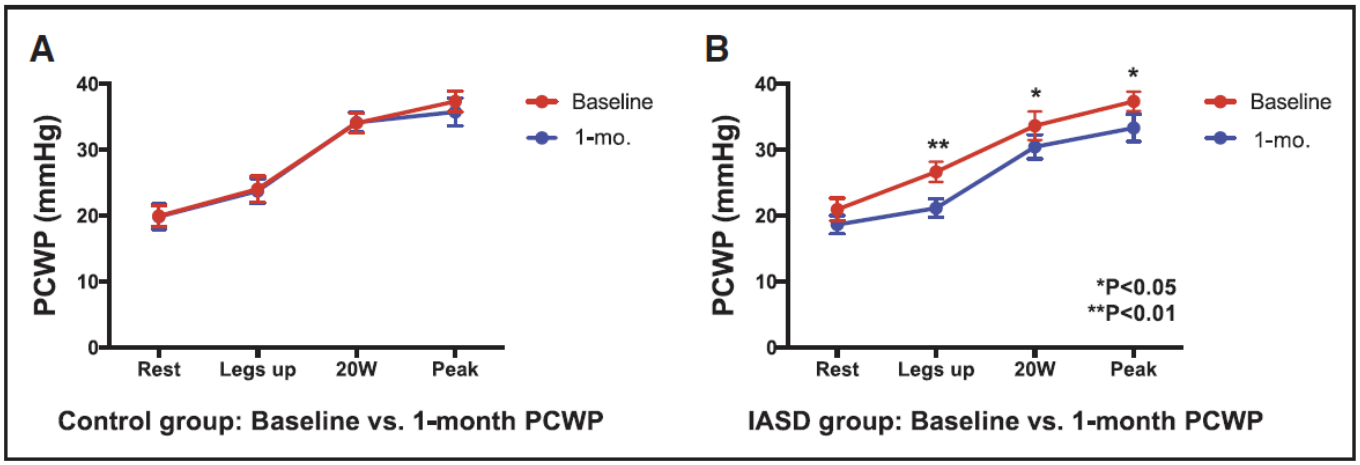
Baylor College of Medicine
MARGARET M. & ALBERT B. ALKEK DEPARTMENT OF MEDICINE

Circulation

Transcatheter Interatrial Shunt Device for the Treatment of Heart Failure With Preserved Ejection Fraction (REDUCE LAP-HF I [Reduce Elevated Left Atrial Pressure in Patients With Heart Failure])

A Phase 2, Randomized, Sham-Controlled Trial





- patients with NYHA-III-IV EF≥40%HF, exercise PCWP≥25
- creation of an 8-mm interatrial communication to unload LA
- implantation of an **interatrial shunt device** reduced PCWP during exercise,

Heart Failure

Mid-Range LVEF

Baylor College of Medicine

MARGARET M. & ALBERT B. ALKEK DEPARTMENT OF MEDICINE

ESC European Society of Cardiology
European Heart Journal (2018) 39, 26–35
doi:10.1093/eurheartj/ehx564

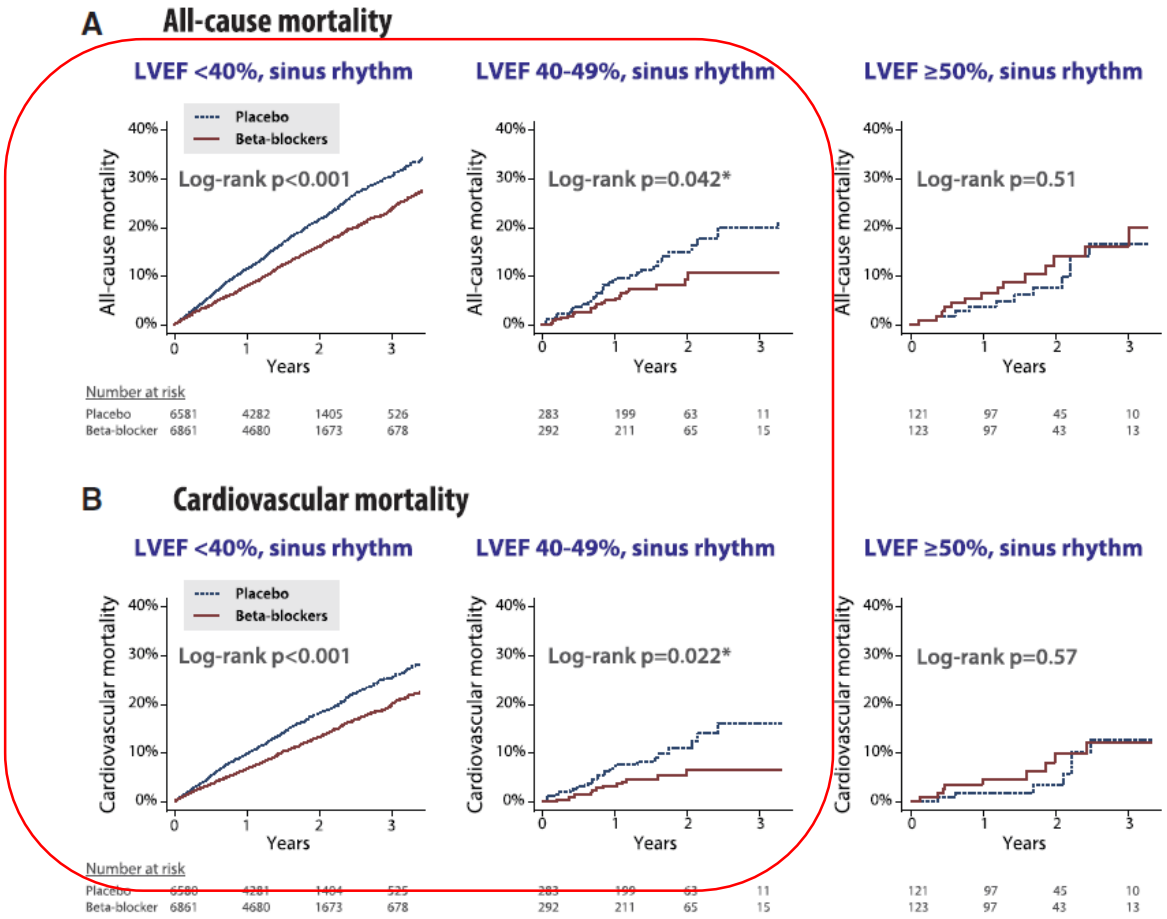
FASTTRACK CLINICAL RESEARCH
Heart failure/cardiomyopathy

Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials

John G.F. Cleland[1], Karina V. Bunting[2], Marcus D. Flather[3], Douglas G. Altman[4], Jane Holmes[4], Andrew J.S. Coats[5], Luis Manzano[6], John J.V. McMurray[7], Frank Ruschitzka[8], Dirk J. van Veldhuisen[9], Thomas G. von Lueder[10,11], Michael Böhm[12], Bert Andersson[13], John Kjekshus[14], Milton Packer[15], Alan S. Rigby[16], Giuseppe Rosano[17,18], Hans Wedel[19], Åke Hjalmarson[13], John Wikstrand[20], and Dipak Kotecha[2,11]*; on behalf of the Beta-blockers in Heart Failure Collaborative Group

- The Beta-blockers in Heart Failure Collaborative Group (BBmeta-HF) pool individual patient data from 11 major HF RCTs : :Australia/New Zealand Heart Failure Study (ANZ), BEST, CAPRICORN, CHRISTMAS, CIBIC I , CIBIS II, COPERNICUS, MDC, MERIT-HF, SENIORS, U.S.Carvedilol HF Program (US-HF)
- to determine efficacy of beta blockers in mid range and preserved EF and also atrial fibrillation patients
- Though guidelines suggest to treat mid-range EF as HF-PEF, in practice most of these patients are treated as HFrEF
- 14262 patients in sinus rhythm, 3050 patients in atrial fibrillation
- Pts with **baseline LVEF** and ECG that showing either sinus rhythm or AF/atrial flutter included

Treat HFmEF like HFrEF



Recommendations for treatment of patients w failure with preserved ejection fraction and hea with mid-range ejection fraction

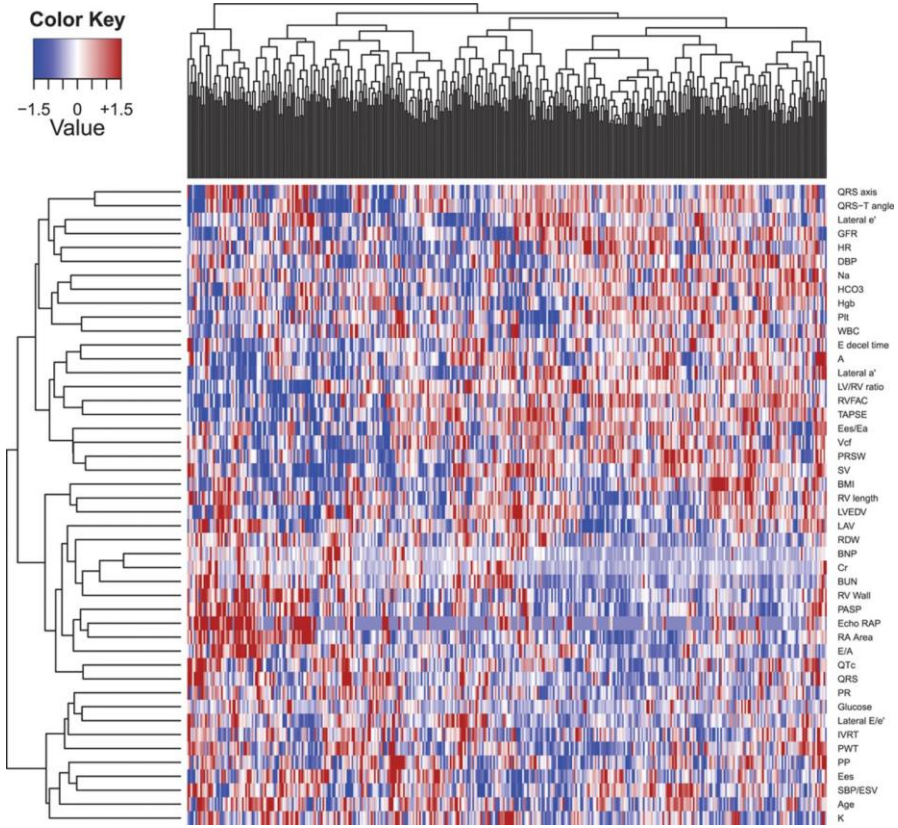
Recommendations	Class [a]	Level [b]
it is recommended to screen patients with HFpEF or HFmrEF for both cardiovascular and non-cardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis.	I	C
Diuretics are recommended in congested patients with HFpEF or HFmrEF in order to alleviate symptoms and signs.	I	B

β-blockers improve outcomes for all pts with HF any reduced EF and in SR.
Most robust for LVEF<40%, but similar benefit in LVEF 40–49 %

HFpEF

Targeted Therapies for Phenomapping / Subgrouping

Phenomapping Novel Classification of HFpEF



Clinical Characteristic	Group 1 (n=128)	Group 2 (n=120)	Group 3 (n=149)	*P* Value
Age, y	60.7±13.6	65.7±11.3	67.3±13.1	<0.001
Female, n (%)	86 (67)	81 (68)	82 (55)	0.049
Race, n (%)				0.32
White	72 (56)	58 (48)	77 (52)	
Black	42 (33)	54 (45)	56 (37)	
Other	14 (11)	8 (7)	16 (11)	
NYHA functional class, n (%)				0.17
I	25 (20)	11 (9)	13 (9)	
II	61 (48)	40 (33)	56 (38)	
III	38 (30)	64 (53)	78 (52)	
IV	3 (2)	5 (4)	2 (1)	
Comorbidities, n (%)				
Coronary artery disease	54 (42)	58 (48)	75 (50)	0.38
Hypertension	84 (66)	108 (90)	112 (75)	<0.001
Hyperlipidemia	65 (51)	75 (62)	73 (49)	0.06
Diabetes mellitus	12 (9)	63 (52)	50 (34)	<0.001
Obesity	65 (51)	84 (70)	55 (37)	<0.001
Chronic kidney disease	8 (6)	41 (34)	79 (53)	<0.001
Atrial fibrillation	17 (13)	26 (22)	64 (43)	<0.001
Chronic obstructive pulmonary disease	43 (34)	46 (38)	56 (38)	0.70
Obstructive sleep apnea	35 (27)	60 (50)	46 (31)	<0.001

Phenogroup 1 younger, lower BNP

Phenogroup 2 obesity, DM and OSA

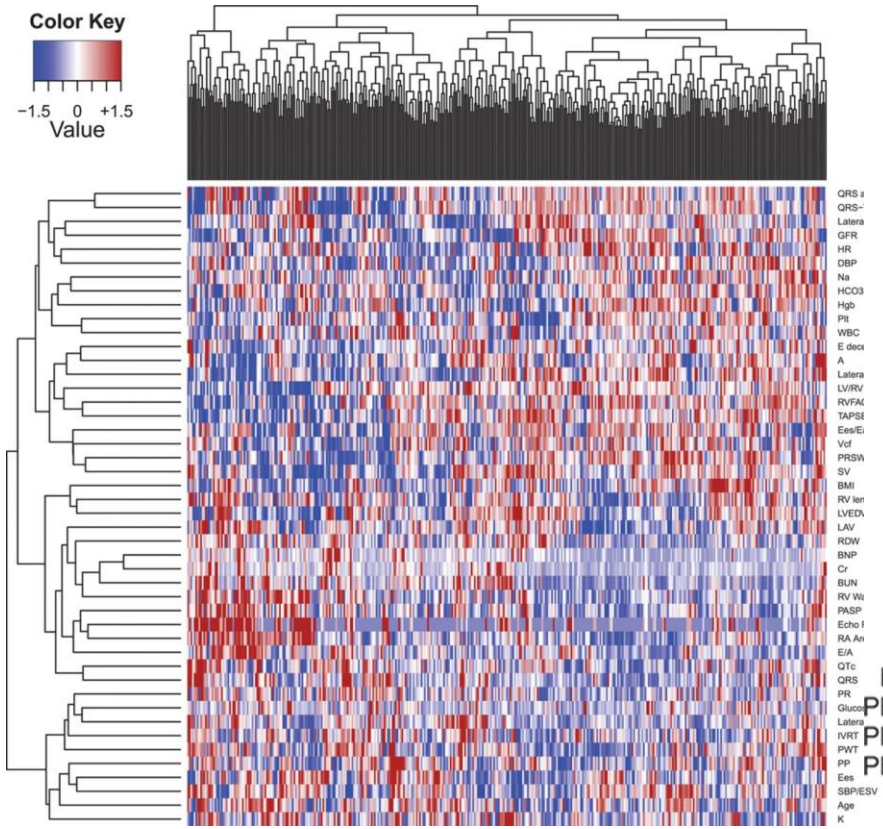
Phenogroup 3 oldest, with CKD , highest BNP and MAGGIC score

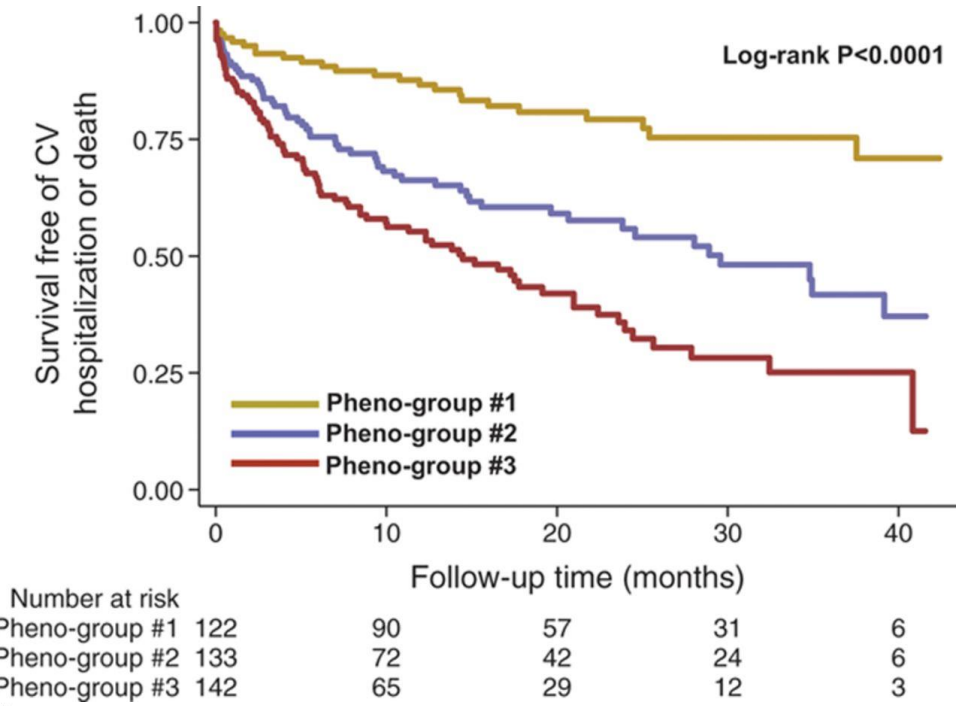
Baylor College of Medicine

MARGARET M. & ALBERT B. ALKEK DEPARTMENT OF MEDICINE

Phenomapping for Novel Classification of Heart Failure With Preserved Ejection Fraction, Volume: 131, Issue: 3, Pages: 269-279, DOI: (10.1161/CIRCULATIONAHA.114.010637)

Phenomapping for Novel Classification of HFpEF





Baylor College of Medicine
MARGARET M. & ALBERT B. ALKEK DEPARTMENT OF MEDICINE

HFpEF Predisposition Phenotypes	HFpEF Clinical Presentation Phenotypes					
	Lung Congestion	+Chronotropic Incompetence	+Pulmonary Hypertension (CpcPH)	+Skeletal muscle weakness	+Atrial Fibrillation
Overweight/obesity/ metabolic syndrome/ type 2 DM	• **Diuretics (loop diuretic in DM)** • **Caloric restriction** • Statins • Inorganic nitrite/nitrate • Sacubitril • Spironolactone	+Rate adaptive atrial pacing	+Pulmonary vasodilators (e.g. PDE5I)	**+Exercise training program**	+Cardioversion + Rate Control **+Anticoagulation**
+Arterial hypertension	+ACEI/ARB	+ACEI/ARB +Rate adaptive atrial pacing	+ACEI/ARB +Pulmonary vasodilators (e.g. PDE5I)	+ACEI/ARB **+Exercise training program**	+ACEI/ARB +Cardioversion + Rate Control **+Anticoagulation**
+Renal dysfunction	+Ultrafiltration if needed	+Ultrafiltration if needed +Rate adaptive atrial pacing	+Ultrafiltration if needed +Pulmonary vasodilators (e.g. PDE5I)	+Ultrafiltration if needed **+Exercise training program**	+Ultrafiltration if needed +Cardioversion + Rate Control **+Anticoagulation**
+CAD	+ACEI +Revascularization	+ACEI +Revascularization +Rate adaptive atrial pacing	+ACEI +Revascularization +Pulmonary vasodilators (e.g. PDE5I)	+ACEI +Revascularization **+Exercise training program**	+ACEI +Revascularization +Cardioversion + Rate Control **+Anticoagulation**

Baylor College of Medicine

MARGARET M. & ALBERT B. ALKEK DEPARTMENT OF MEDICINE

Shah S. et al Circulation. 2016;134:73-90.

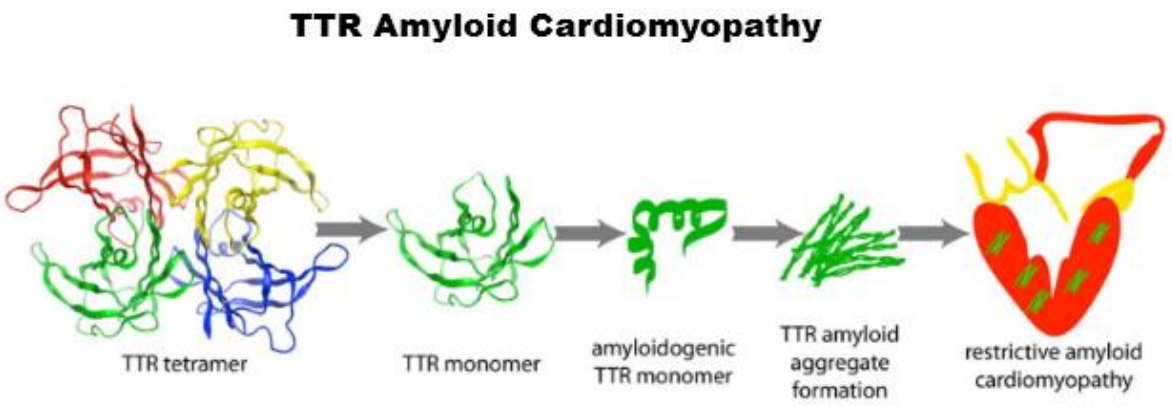
HFpEF

Targeted Therapies for Genotyping

Amyloidosis-TTR

- TTR is a carrier for thyroxine and retinol binding protein, made in liver
- originally called prealbumin
- dissociated transthyretin (TTR) monomers misfold and assemble into amyloid fibrils
- mutation in the TTR gene or aging facilitates dissociation of tetramer into monomers

- 2 distinct types of ATTR:
  - ❖ hereditary or mutated (mt-ATTR) : Autosomal Dominant
    - familial amyloid poly-neuropathy (FAP),
    - familial amyloid cardiomyopathy (FAC)
  - ❖ wild-type(wt-ATTR; senile systemic amyloidosis (SSA)



Baylor College of Medicine

MARGARET M. & ALBERT DEPARTMEN MEDICI

Circulation. 2016 Dec 6;134(23):e579-e646

ATTR-ACT Study: Tafamidis: binds to transthyretin, preventing tetramer dissociation

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

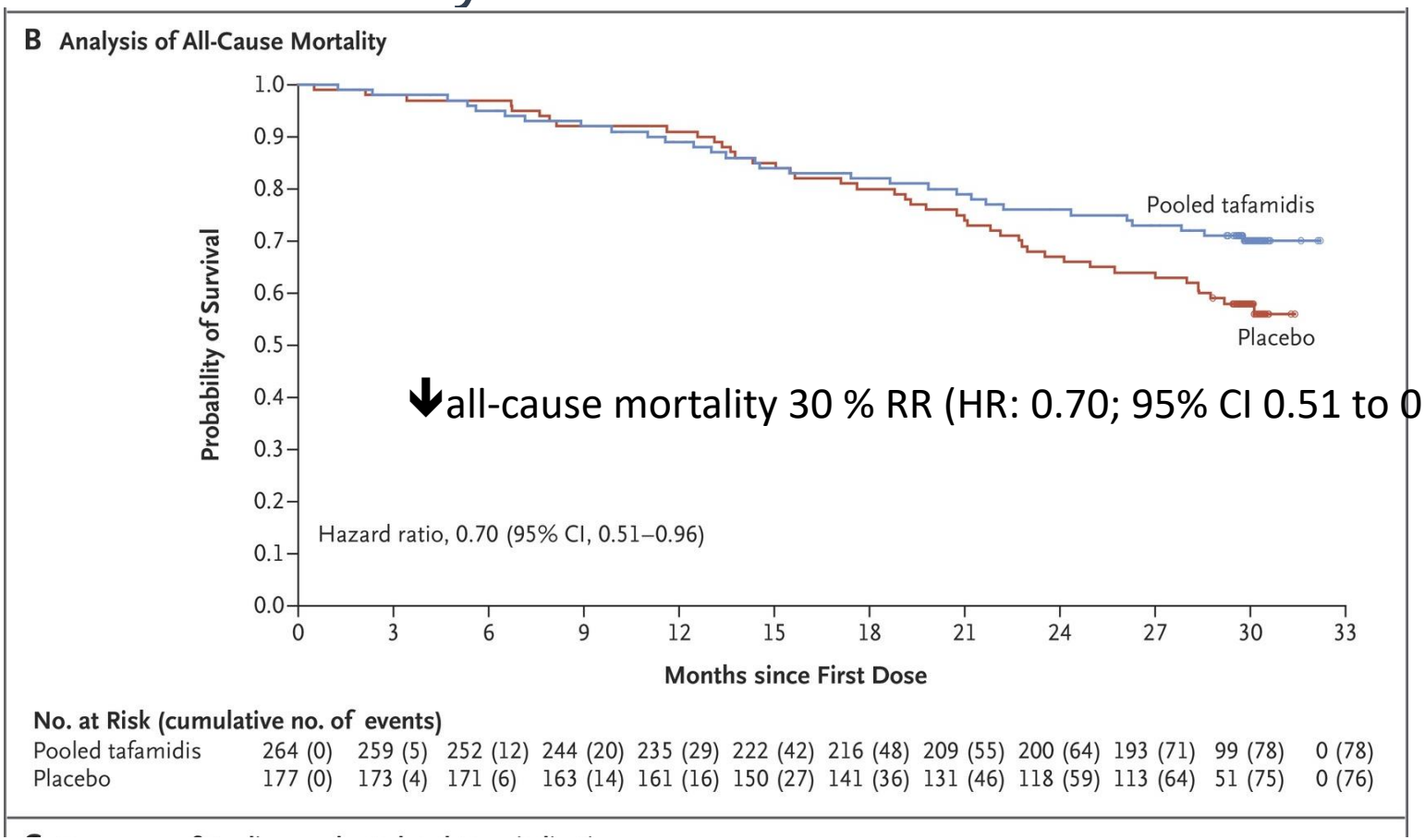
Mathew S. Maurer, M.D., Jeffrey H. Schwartz, Ph.D., Balarama Gundapaneni, M.S., Perry M. Elliott, M.D., Giampaolo Merlini, M.D., Ph.D., Marcia Waddington-Cruz, M.D., Arnt V. Kristen, M.D., Martha Grogan, M.D.,

- 441 patients with transthyretin amyloid CMP
- 80 mg or 20 mg of tafamidis, or placebo for 30 months.
- hierarchical assessment of all-cause mortality, followed by CVH

Baylor College of Medicine
MARGARET M. & ALBERT B. ALKEK DEPARTMENT OF MEDICINE

Maurer MS et al. N Engl J Med 2018;379:1007-1016

ATTR-ACT Study: Tafamidis



↓all-cause mortality 30 % RR (HR: 0.70; 95% CI 0.51 to 0.96

Baylor College of Medicine
MARGARET M. & ALBERT B. ALKEK DEPARTMENT OF MEDICINE

Maurer MS et al. N Engl J Med 2018;379:1007-1016

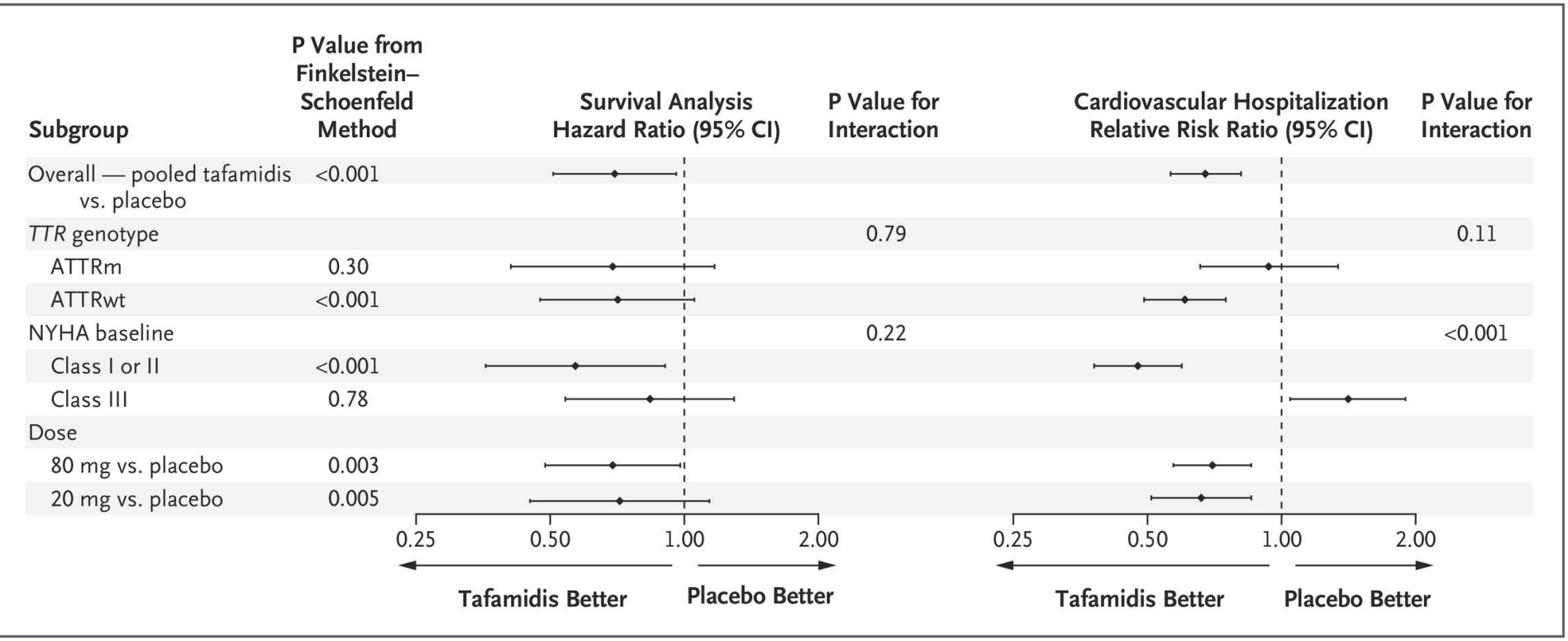
ATTR-ACT Study: Tafamidis Secondary End-Points

- ↓ CV hospitalizations 32 % RR (RRR 0.68, 95% CI, 0.56 to 0.81)
- lower rate of decline in 6-minute walk test (P<0.001)
- lower rate of decline in QOL by KCCQ-OS score (P<0.001)

In patients with transthyretin amyloid cardiomyopathy, tafamidis was associated with reductions in all-cause mortality and CV hospitalizations and reduced the decline in functional capacity and QOL

Maurer MS et al. N Engl J Med 2018;379:1007-1016

Tafamidis: Subgroup analysis



Baylor College of Medicine
MARGARET M. & ALBERT B. ALKEK DEPARTMENT OF MEDICINE

Maurer MS et al. N Engl J Med 2018;379:1007-1016

PATISIRAN: interfering RNAs (siRNAs) control gene expression by mediating the cleavage mRNAs.

- IV infusion every 3 weeks.
- APOLLO clinical trial, patisiran (n=148) showed significantly improved scores on the Neuropathy Impairment Score+7 and Norfolk Quality of Life Questionnaire–Diabetic Neuropathy (QOL-DN) at 18 months, compared with those taking placebo (n=77) ($P < 0.001$).
- FDA approved for FAP

INOTERSEN:

Antisense oligonucleotide that causes degradation of mutant and wild-type transthyretin mRNA by binding TTR mRNA ➔reduced TTR protein levels

- Sq inj once/week
- NEURO-TTR Trial : Stage 1 or 2 hATTR with polyneuropathy (n=172) randomized to weekly inotersen or placebo. Scores on the mNIS+7 and the QOL-DN showed improvement ($P < 0.001$).
- FDA approved for FAP Oct 2018

Baylor College of Medicine

MARGARET M. & ALBERT B. ALKEK DEPARTMENT OF MEDICINE

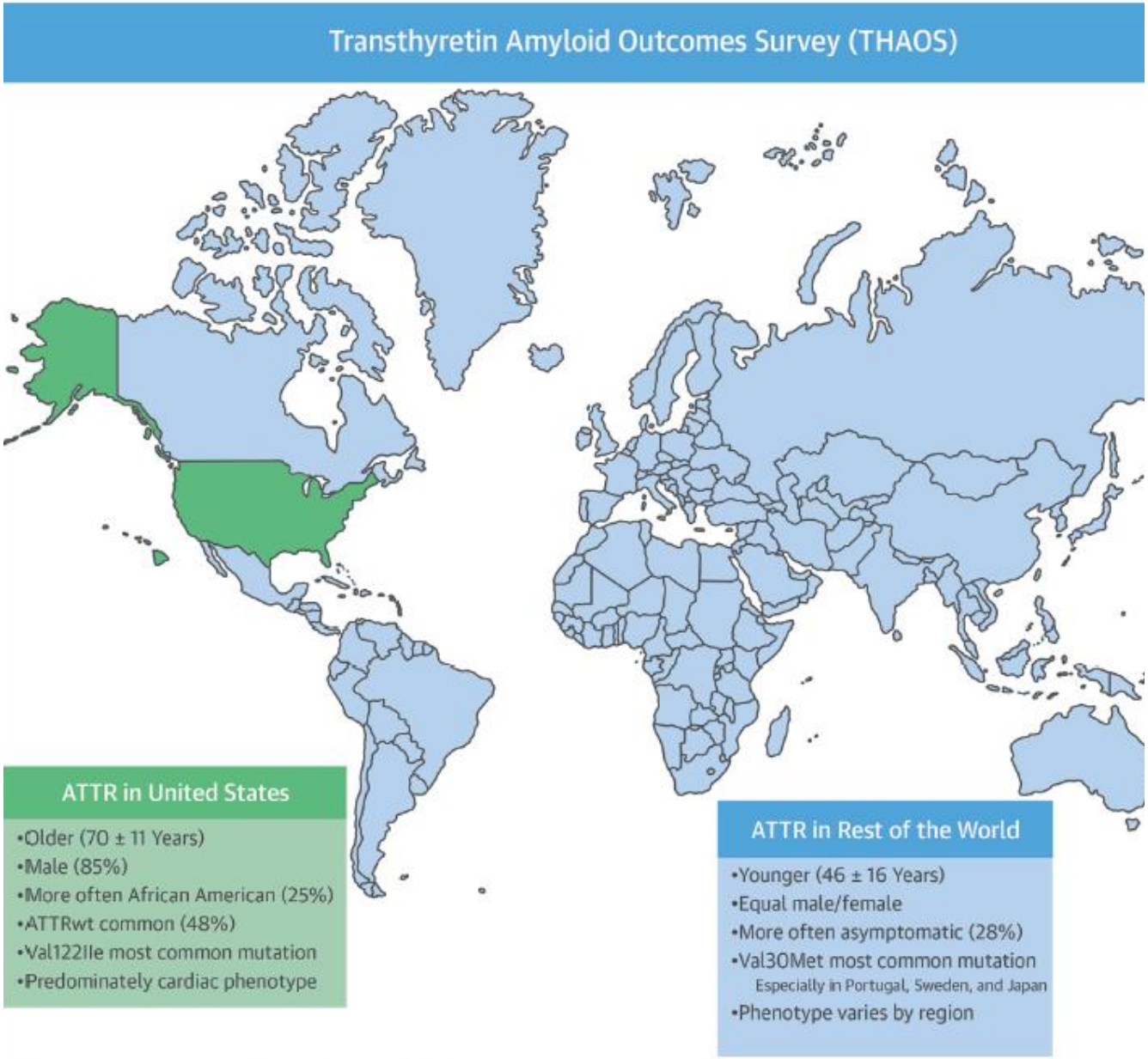
Adams D, et al Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018 Jul 5. 379 (1):11-21.
Benson MD, et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018 Jul 5;. 379(1):22-31.

Tafamidis binds and stabilizes TTR	Diflunisal: NSAID drug approved for treatment of arthritis.	Tolcapone FDA approved for Parkinson disease (Orphan Drug designation –ATTR)
• Halt TTR tetramer dissociation, monomer misfolding • Early intervention: minimal disease progression > 5yrs years in FAP. • decreased rate of progression(European Medical Agency in 2011 for stage I of neuropathic ATTR)	• complexes to the thyroxine binding site , stabilizes circulating TTR tetramers, inh release of monomer • RCT stage I-II ATTR-FAP, improved QOL s and reduced neurological impairment .(off-label)	• Occupies the T_4-binding sites, stabilizing the tetramer • docks better than tafamidis in wt-TTR.

Baylor College of Medicine

MARGARET M. & ALBERT B. ALKEK DEPARTMENT OF MEDICINE

Neurol Ther. 2015. 4:61-79. Amyloid. 05 Aug 2016. Vol. 23 , Iss. 3:178-183. Transplantation. 2015. 00:1-9. JAMA. 2013 Dec 25. 310(24):2658-67. Nature Communications. 2016 Feb 23.



Among U.S. subjects

- **wild-type:**
  - **older and white**
  - **more males**
- **Val122Ile mutations**
  - **more African descent%**
  - **worse NYHA, faster HR, and lower QOL**

Maurer MS et al. J Am Coll Cardiol 68 (2): 161-72

College of Medicine

MEDICINE

J Am Coll Cardiol 2016;68:161–72)

Heart Failure

Stage C/D Treatment Strategies Need to be Individualized for

- Patient's severity of illness and trajectory
- Responsiveness to therapy
- Goals of care
- Comorbidities and side effect profile
- Tolerability
- Phenogroups

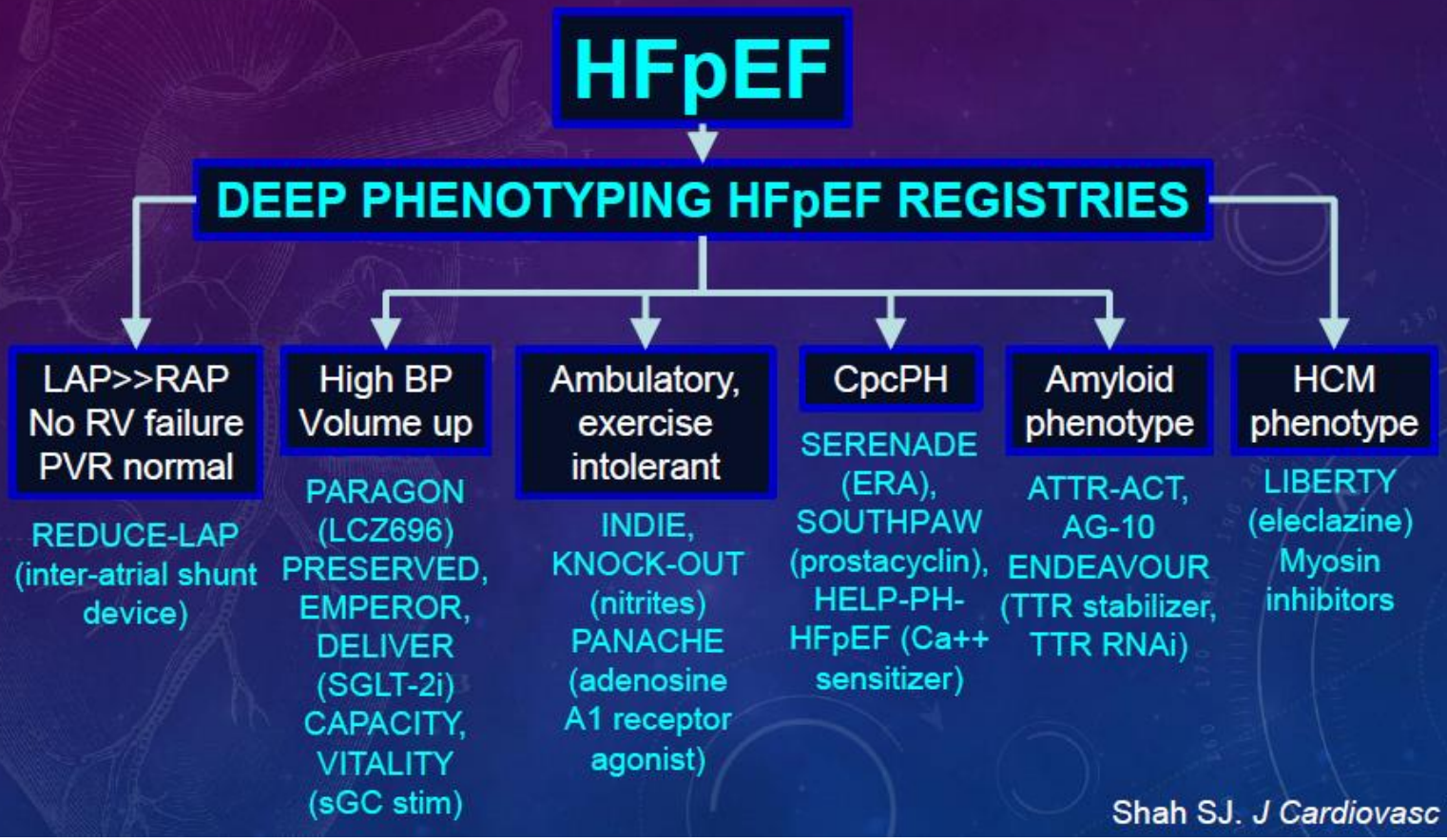
Baylor College of Medicine

MARGARET M. & ALBERT B. ALKEK DEPARTMENT OF MEDICINE

Summary

- Confirm diagnosis of HF-PEF
- Consider different etiologies and precipitating factors
- Treatments may differ based on etiology
- Treat volume overload carefully
- Treatment of HTN is key
- In appropriately selected patients with HFpEF (elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations
- Routine use of nitrates or PDE5 inhibitors in patients with HFpEF is ineffective
- New targeted and individualized treatment strategies are evolving

Ongoing HFpEF clinical trials



Shah SJ. *J Cardiovasc Transl Res* 2017