Updates in Heart Failure: From Drugs to Devices

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Disclosures

Speaker's Bureau: Novartis, Pfizer/BMS, BI/Lilly
Advisory Board: Novartis, BMS

Eras of Heart Failure Management Timeline

Palliative Drugs

Neurohormonal Drugs

Devices

ARNI

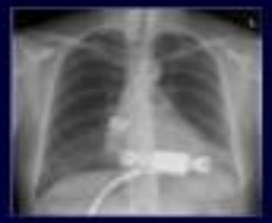
Pre-1980 | 1980s | 1990s | 2000s | 2010s | 2015

Digitalis
Diuretics

ACE-I

b-Blockers

ICDs



CRT, CRT-D
MR-Antagonists
Ivabradine

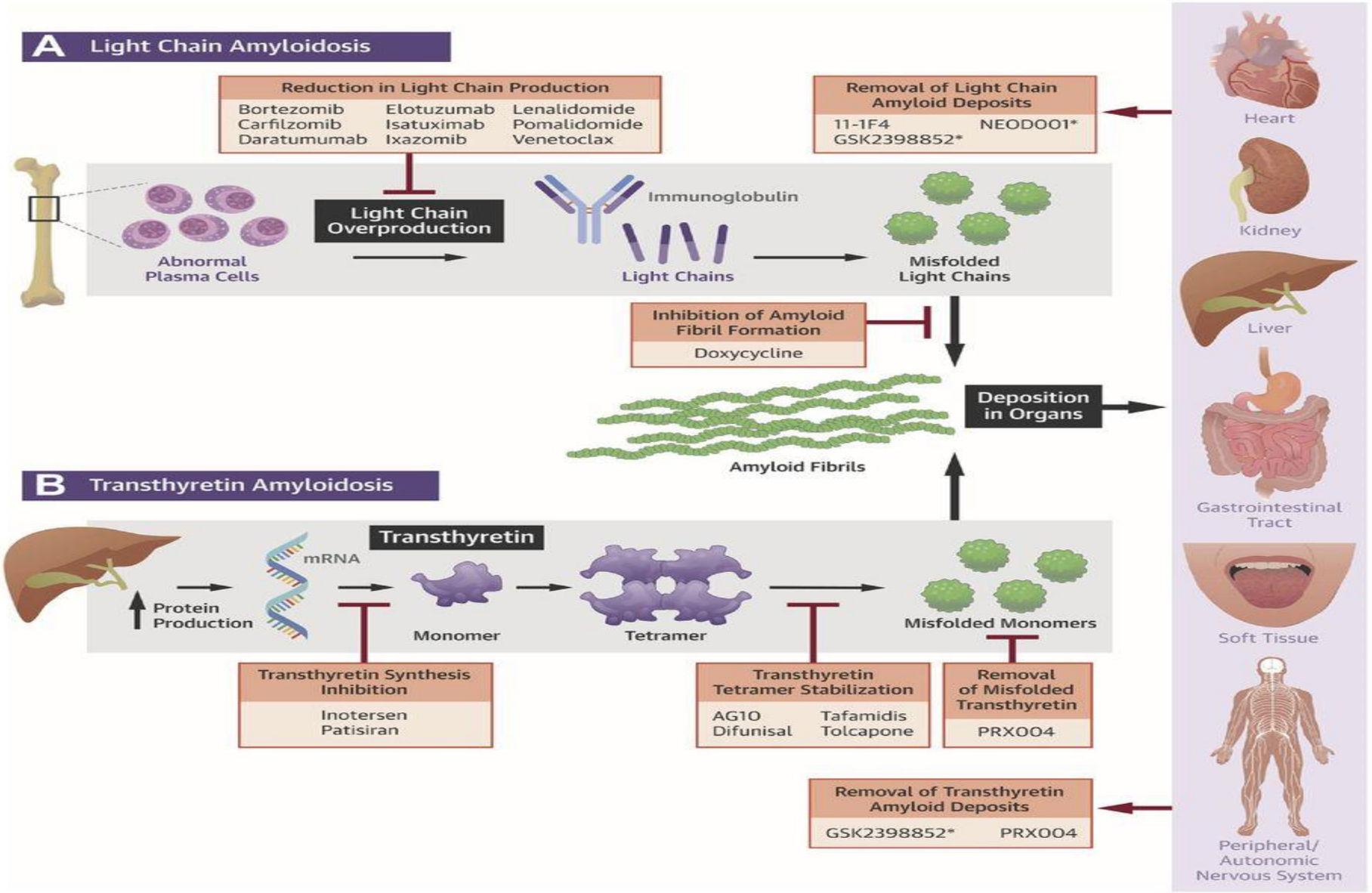
Sensing Devices

ARNI

Outline

- Amyloidosis: TTR (tafamadis)
- Sacubitril/Valsartan in HFpEF (PARAGON-HF)
- SGLT-2 Inhibitors
  - EMPA-REG, CANVAS
  - DAPA-HF

CENTRAL ILLUSTRATION: Pathophysiology of Light Chain and Transthyretin Amyloidosis and Mechanism of Action of Novel Therapeutics



Zhang, K.W. et al. J Am Coll Cardiol Basic Trans Science. 2019;4(3):438-48.

Amyloid Type	Systemic Amyloidosis		Transthyretin (TTR) Amyloidosis	
ubtype	AL	AA	ATTRm	ATTRwt
rotein eposited	Light chain	Amyloid A	Mutated TTR protein	wt TTR monomers
isease tiology	Plasma cell dyscrasia with ↑ light chains	Systemic autoimmune or infections	Familial mutation of TTR	Common in elderly aged > 75 years
pecific eatures	Kidney, heart and liver affected	Renal dysfunction	V122I common in African Americans	Carpal tunnel; Male dominance
ledian urvival	1-3 years	11 years	2 years	4-6 years

Prevalence of ATTR-Cardiac Amyloidosis (not based upon biopsy)

- 101 patients scheduled for TAVR underwent bone scintigraphy for the detection of cardiac transthyretin amyloidosis (Siontis GC et al. JACC 2015; 65(3): 313.
- In total, 13.9% of patients (mean age 86 years) were diagnosed with occult cardiac amyloidosis
- Patients with amyloid were older, had slightly lower aortic valve gradients and stroke volume
- 13% of patients with HFpEF (Gonzalez-Lopez, E et al, Eur Heart J 2015)
- 5% in patients with presumed HCM (Damy T el al, E Heart J 2016)

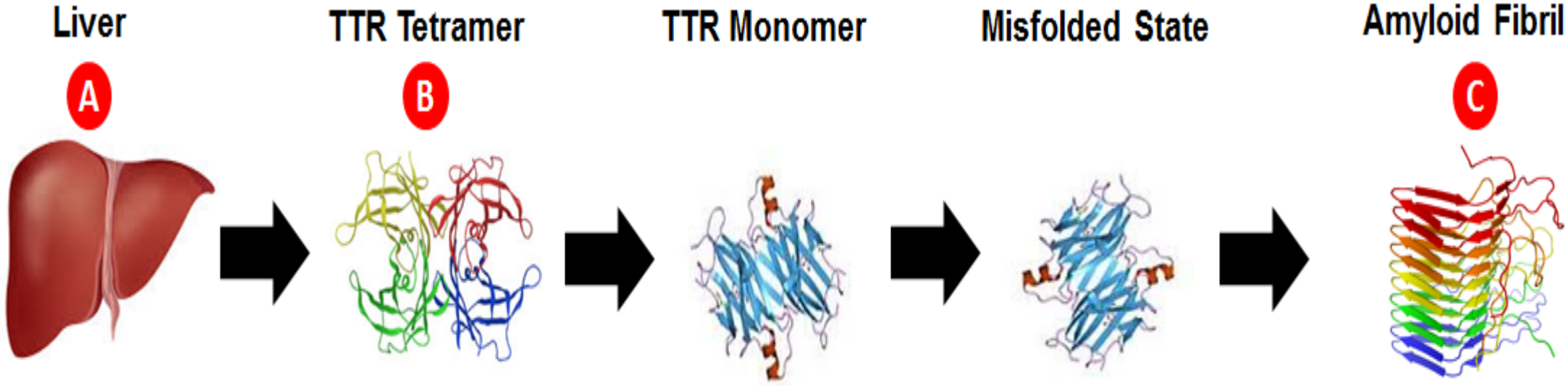
TABLE 1

Symptoms that raise suspicion of cardiac amyloidosis

Red Flags for Cardiac Amyloidosis	
Echocardiography: ▪ Low voltage on ECG and thickening of the septum/posterior wall > 1.2 cm ▪ Thickening of right ventricle free wall, valves	
Intolerance to beta-blockers or ACE inhibitors	
Low normal blood pressure in patients with a previous history of hypertension	
History of bilateral carpal tunnel syndrome, often requiring surgery	
AL	**ATTR**
HFpEF + nephrotic syndrome	White male age ≥ 60 with HFpEF + history of carpal tunnel syndrome and/or spinal stenosis
Macroglossia and/or periorbital purpura	African American age ≥ 60 with HFpEF without a history of hypertension
Orthostatic hypotension	New diagnosis of hypertrophic cardiomyopathy in an elderly patient
Peripheral neuropathy	New diagnosis of low flow, low gradient aortic stenosis in an elderly patient
MGUS	Family history of ATTRm amyloidosis

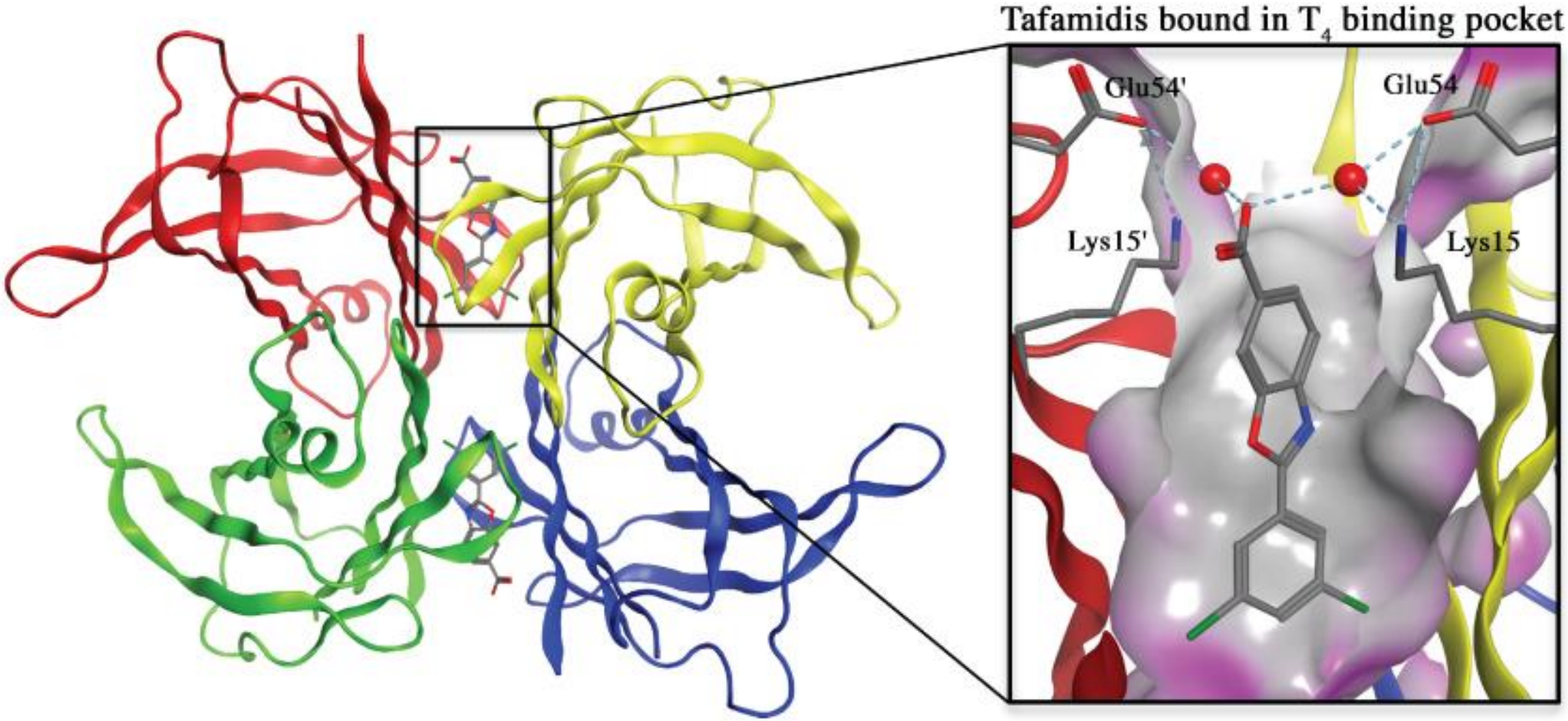
ACE = angiotensin-converting enzyme; AL = immunoglobulin light chain amyloidosis; ATTR = transthyretin amyloidosis; ECG = electrocardiogram; ATTRm = hereditary mutant variant ATTR; HFpEF = heart failure with preserved ejection fraction ("diastolic heart failure"); MGUS = monclonal gammopathy of undetermined significance

Amyloidogenic TTR Cascade



- **A** Suppression of Amyloidogenic TTR
- **B** TTR Stabilization
- **C** Fibril Degradation

- Diastolic dysfunction
- Restrictive cardiomyopathy
- Heart failure

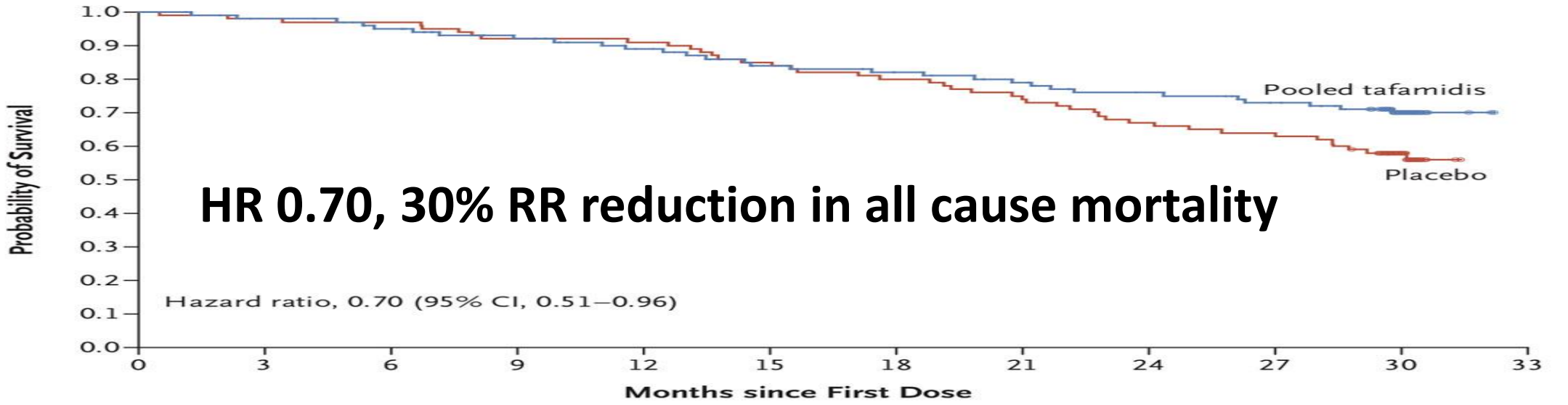


The current *Proceedings of the National Academy of Sciences* study provides new molecular and structural data showing how tafamidis works. (Image courtesy of the Wilson and Kelly labs, The Scripps Research Institute.)

A Primary Analysis, with Finkelstein–Schoenfeld Method

	No. of Patients	P Value from Finkelstein–Schoenfeld Method	Win Ratio (95% CI)	Patients Alive at Mo 30 *no. (%)*	Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30 *per patient per yr*
Pooled Tafamidis	264	<0.001	1.70 (1.26–2.29)	186 (70.5)	0.30
Placebo	177			101 (57.1)	0.46

B Analysis of All-Cause Mortality



HR 0.70, 30% RR reduction in all cause mortality

No. at Risk (cumulative no. of events)

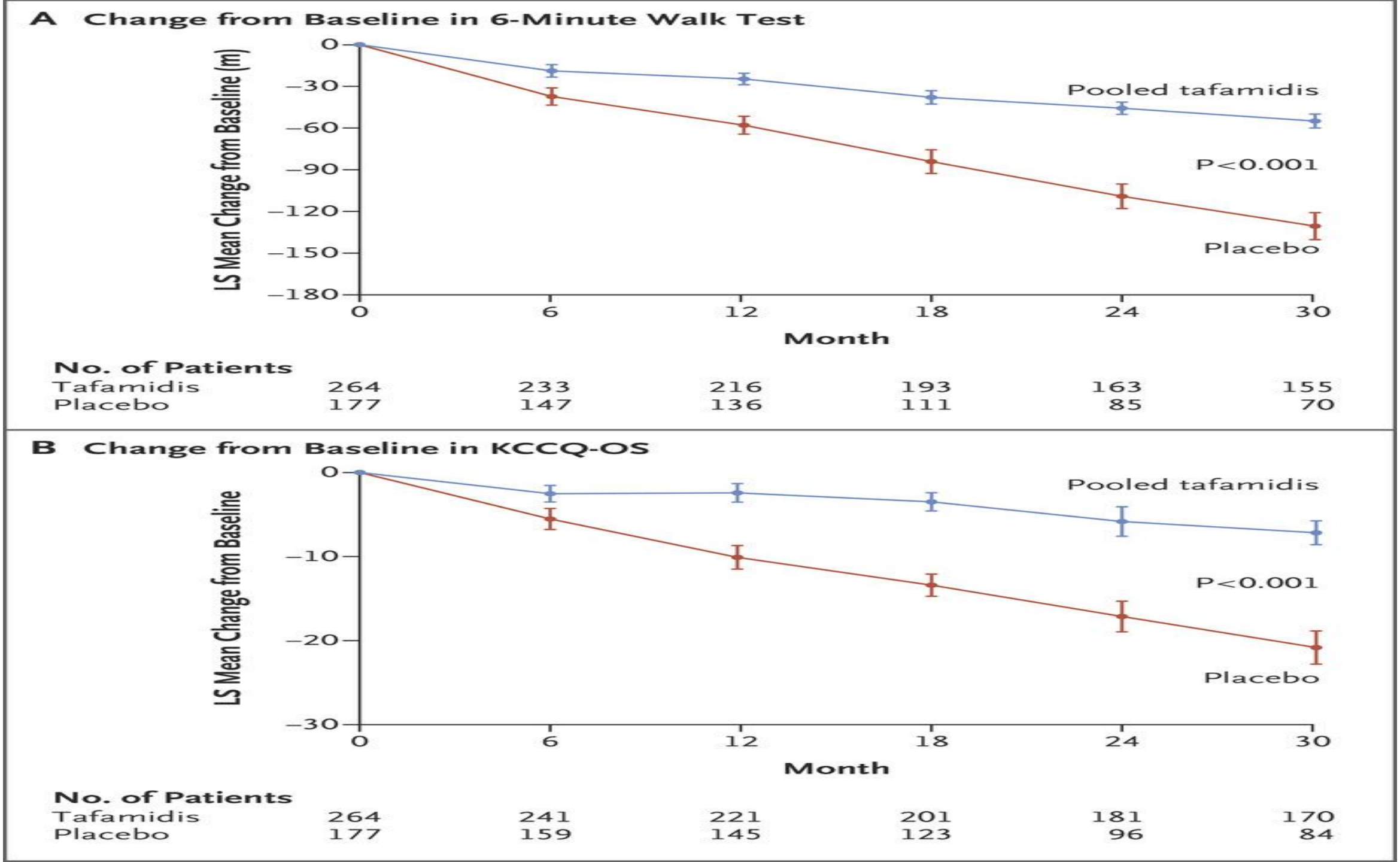
Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)

C Frequency of Cardiovascular-Related Hospitalizations

	No. of Patients	No. of Patients with Cardiovascular- Related Hospitalizations *total no. (%)*	Cardiovascular- Related Hospitalizations *no. per yr*	Pooled Tafamidis vs. Placebo Treatment Difference *relative risk ratio (95% CI)*
Pooled Tafamidis	264	138 (52.3)	0.48	0.68 (0.56–0.81)
Placebo	177	107 (60.5)	0.70	

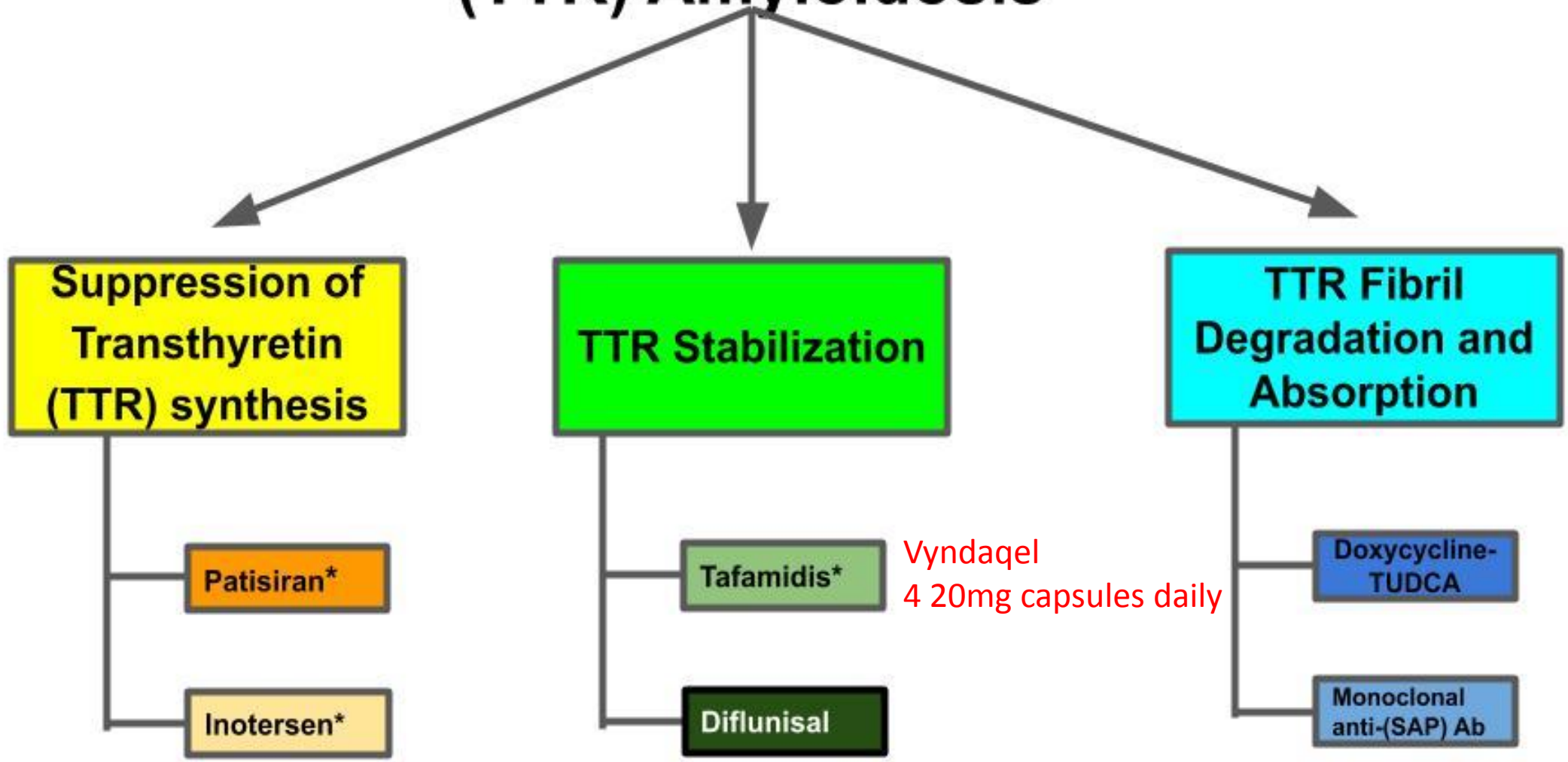
Figure 2. Primary Analysis and Components.

Panel A shows the results of the primary analysis as determined with the use of the Finkelstein–Schoenfeld method. Panel B shows an analysis of all-cause mortality for pooled tafamidis and for placebo, a secondary end point. Panel C shows the frequency of cardiovascular-related hospitalizations, also a secondary end point.


A Change from Baseline in 6-Minute Walk Test
LS Mean Change from Baseline (m)
0
−30
−60
−90
−120
−150
−180
Pooled tafamidis
P<0.001
Placebo
0
6
12
18
24
30
Month
No. of Patients
Tafamidis 264 233 216 193 163 155
Placebo 177 147 136 111 85 70
B Change from Baseline in KCCQ-OS
LS Mean Change from Baseline
0
−10
−20
−30
Pooled tafamidis
P<0.001
Placebo
0
6
12
18
24
30
Month
No. of Patients
Tafamidis 264 241 221 201 181 170
Placebo 177 159 145 123 96 84

Bullock-Palmer, RP

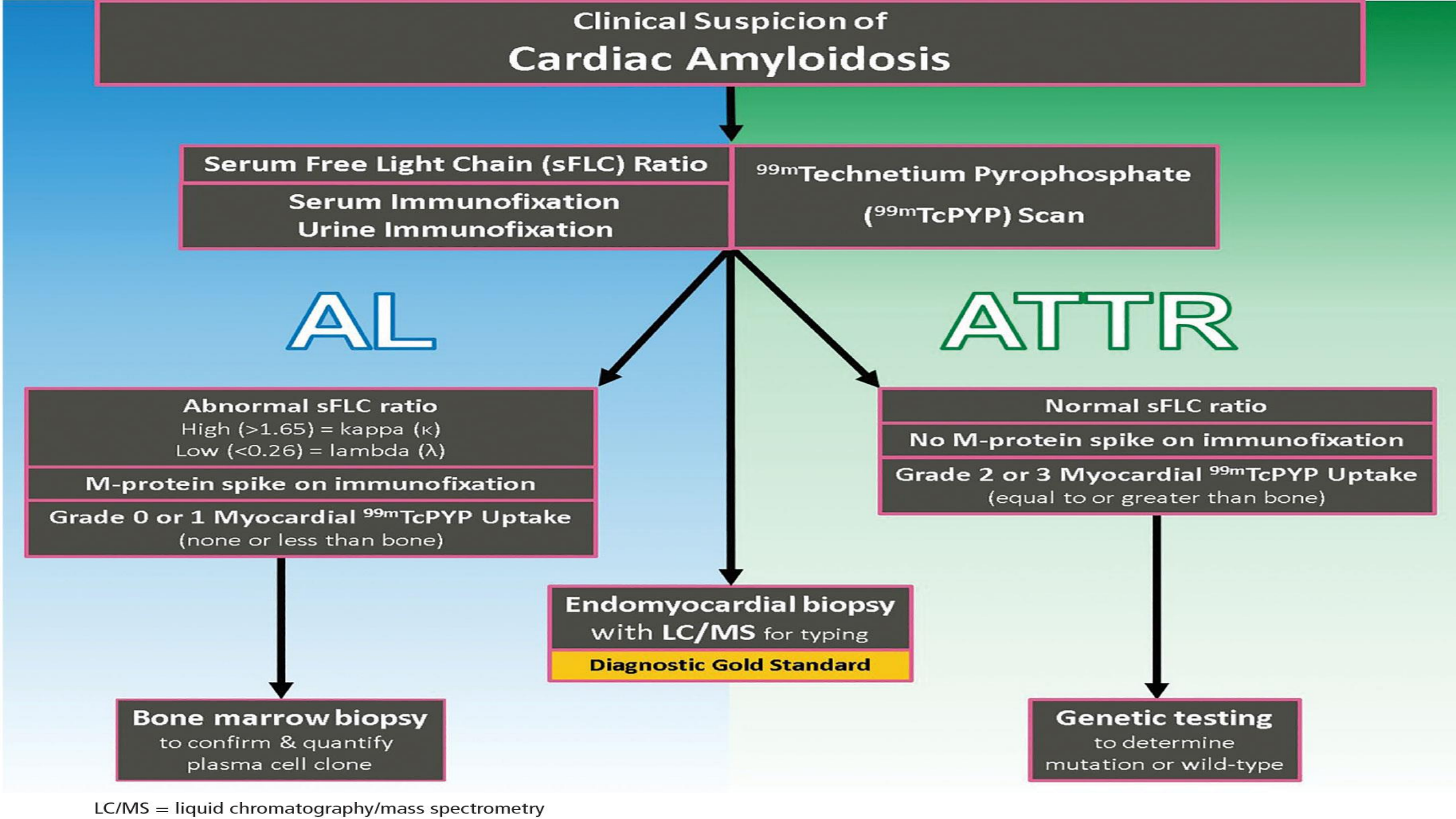
Emerging Treatment Options for Transthyretin (TTR) Amyloidosis



Vyndaqel
4 20mg capsules daily

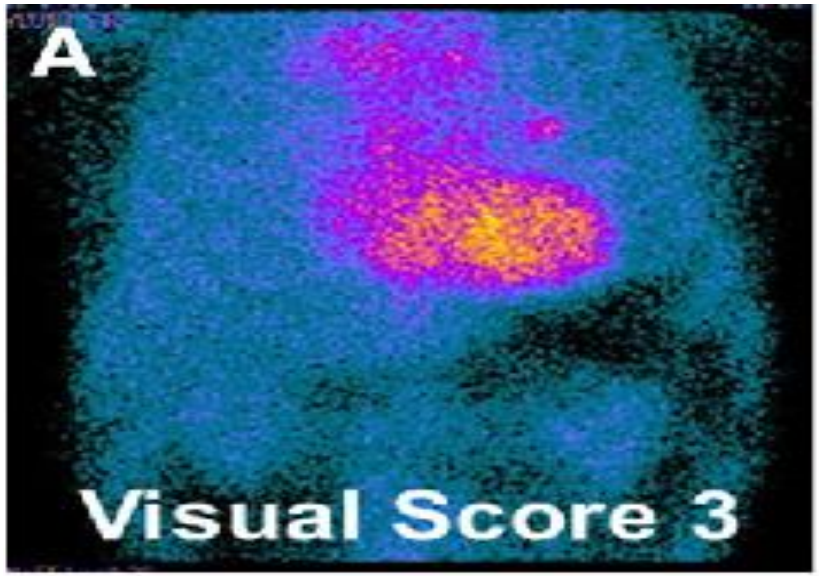
TUDCA-Tauroursodeoxycholic Acid. **SAP**-serum amyloid protein

* Approved by the Food and Drug Administration



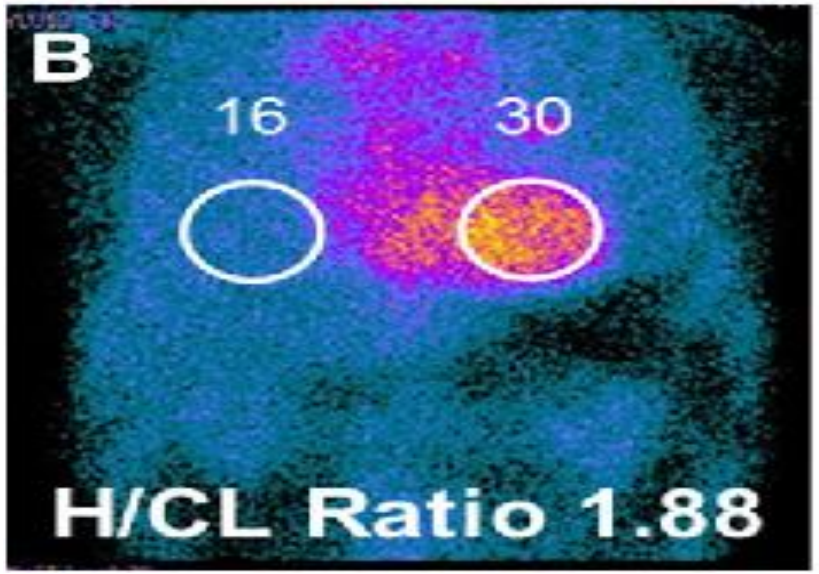
LC/MS = liquid chromatography/mass spectrometry

Technetium-99m Pyrophosphate Scan



Visual Cardiac Score

0 Absent Myocardial Uptake
1 Myocardial Uptake < Bone
2 Myocardial Uptake = Bone
3 Myocardial Uptake > Bone

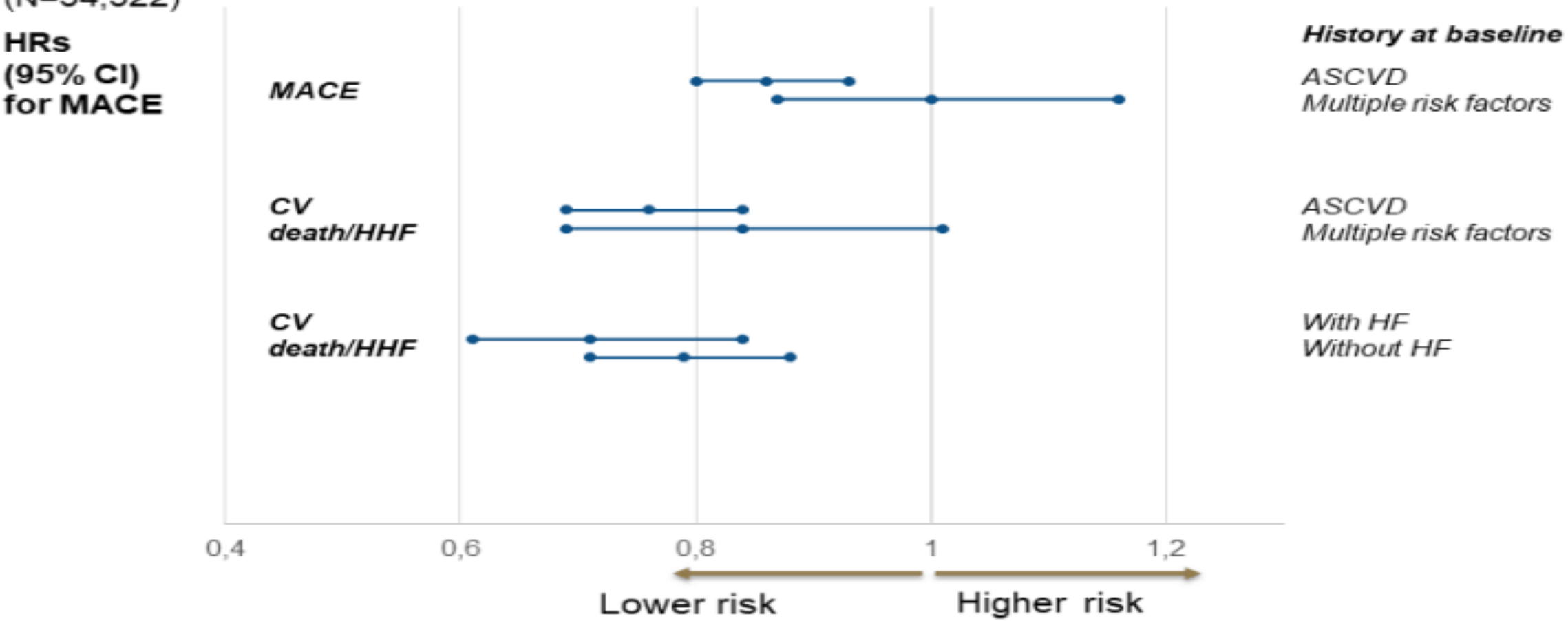


Heart-to-Contralateral Ratio

$$\text{H/CL Ratio} = \frac{\textit{Heart ROI Mean Counts Per Pixel}}{\textit{Contralateral ROI Mean Counts Per Pixel}}$$

Type of existing CVD at baseline affects CV benefits of SGLT2 inhibition

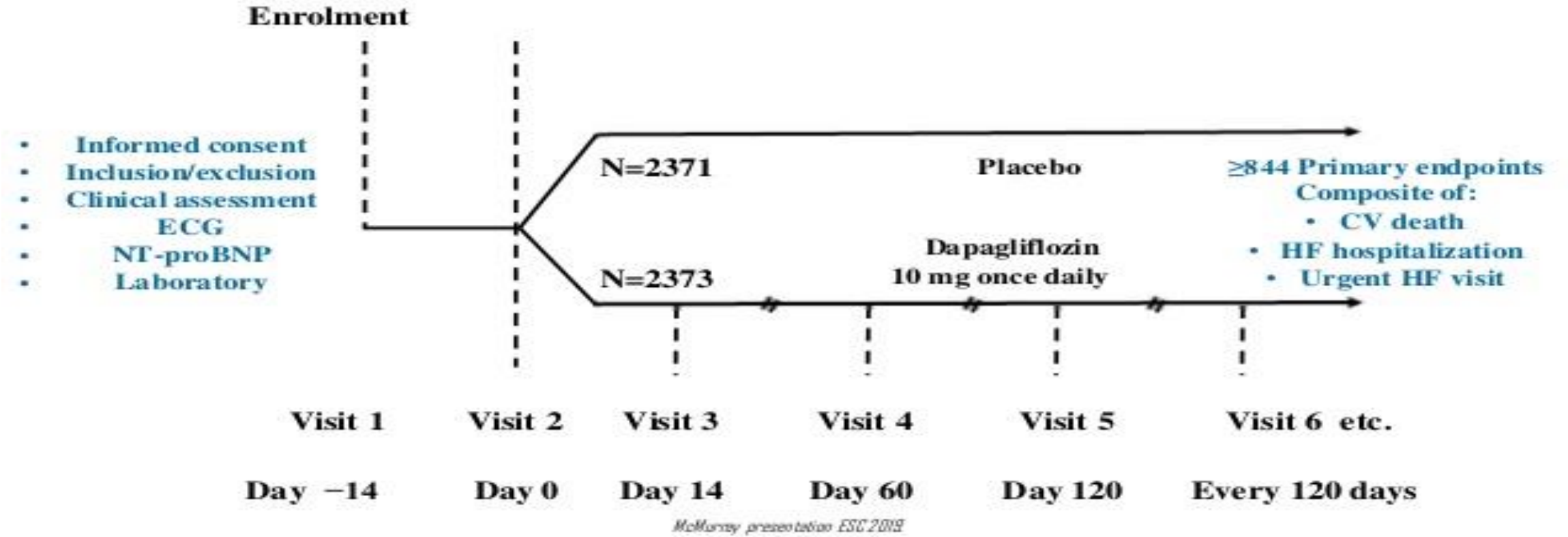
A meta-analysis of the **EMPA-REG OUTCOME**, **CANVAS Program** and **DECLARE-TIMI 58** trials (N=34,322)



MACE: major adverse cardiovascular events; CI: confidence interval; SGLT2: sodium-glucose cotransporter-2; HHF: hospitalization for heart failure; HF: heart failure; ASCVD: atherosclerotic cardiovascular disease

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction.

McMurray JJV[1] et al. DAPA-HF Trial Committees and Investigators.
N Engl J Med. 2019 Sep 19. doi: 10.1056/NEJMoa1911303. [Epub ahead of print]



Characteristic	Dapagliflozin (n=2373)	Placebo (n=2371)
Mean age (yr)	66	67
Male (%)	76	77
NYHA class II/III/IV (%)	68/31/1	67/32/1
Mean LVEF (%)	31	31
Median NT pro BNP (pg/ml)	1428	1446
Mean systolic BP (mmHg)	122	122
Ischaemic aetiology (%)	55	57
Mean eGFR (ml/min/1.73m2)	66	66
Prior diagnosis T2D (%)	42	42
Any baseline T2D (%)*	45	45

McMurray presentation ESC 2019

Treatment (%)	Dapagliflozin (n=2373)	Placebo (n=2371)
Diuretic	93	94
ACE-inhibitor/ARB/ARNI+	94	93
ACE inhibitor	56	56
ARB	28	27
Sacubitril/valsartan	11	11
Beta-blocker	96	96
MRA	71	71
ICD*	26	26
CRT**	8	7

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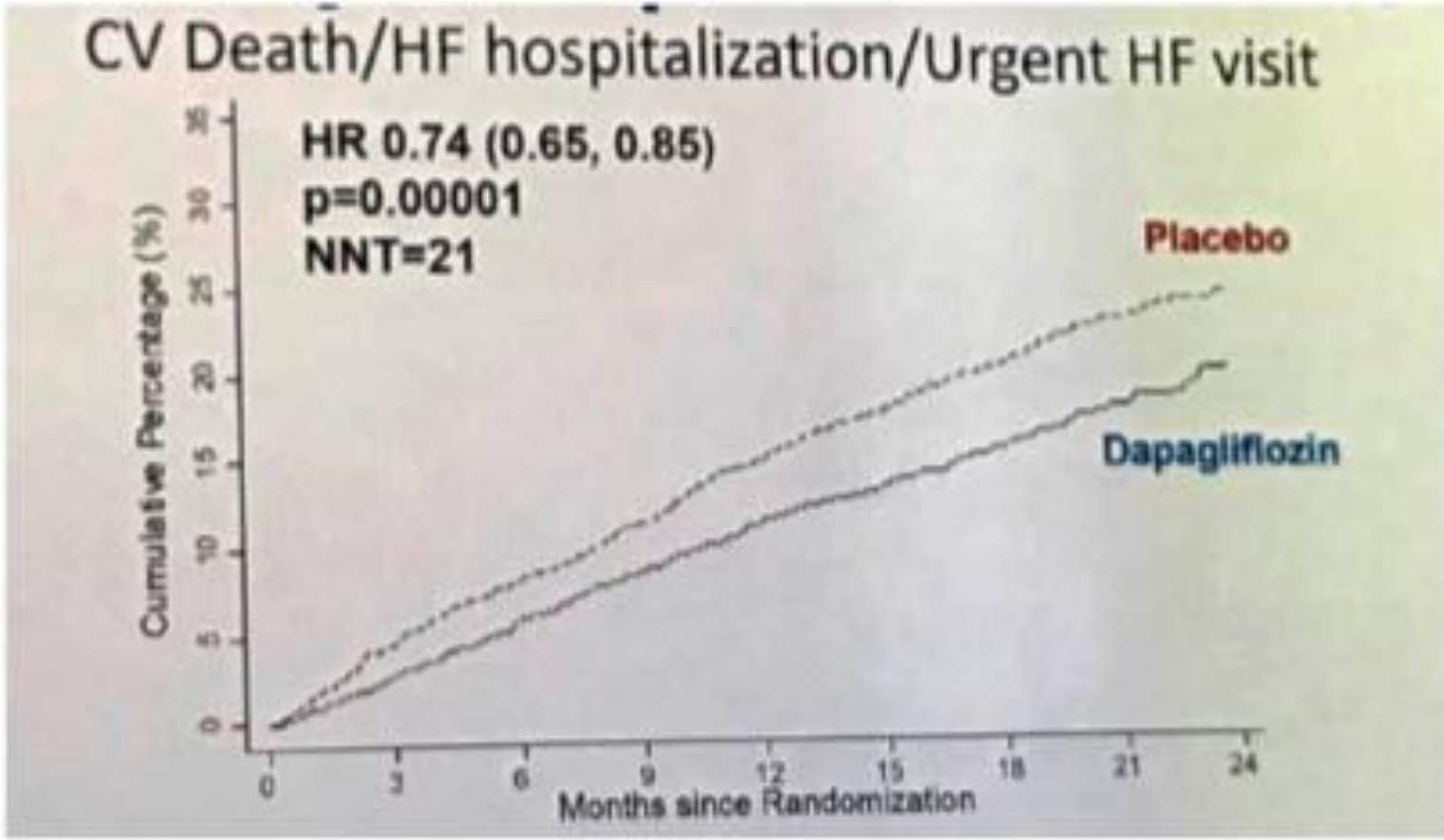
Primary composite outcome



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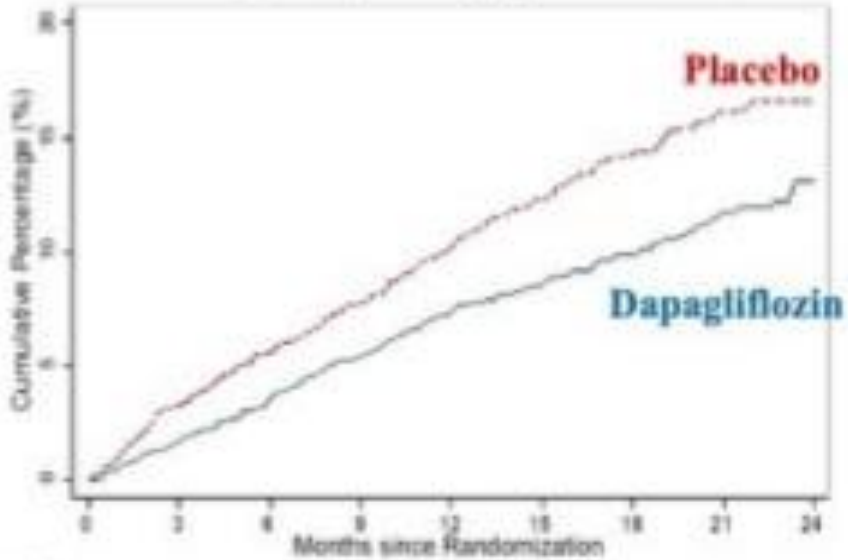
Primary composite outcome

Worsening HF event

HR 0.70 (0.59, 0.83); p=0.00003

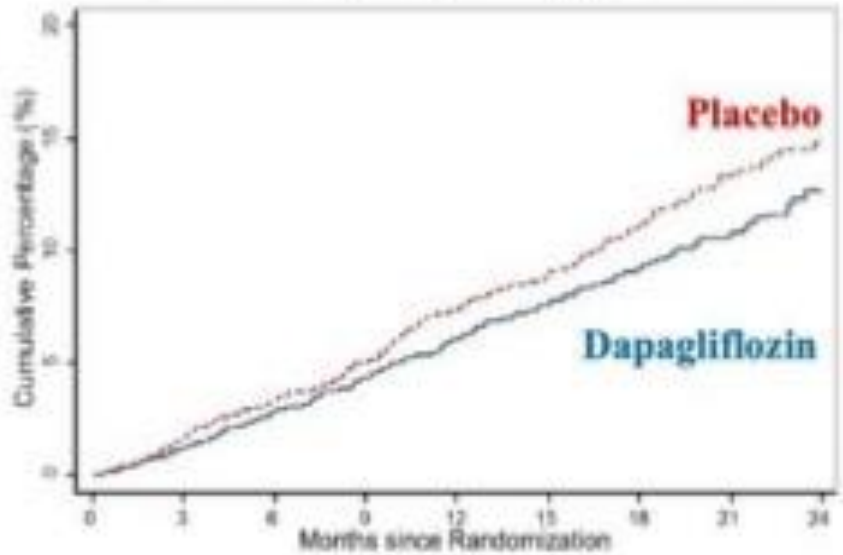


Number at Risk

Dapagliflozin	2373	2306	2221	2147	2002	1880	1148	612	210
Placebo	2371	2258	2183	2078	1917	1478	1086	583	210

Cardiovascular death

HR 0.82 (0.69, 0.98); p=0.029



	2373	2309	2293	2248	2127	1664	1242	671	232
	2371	2330	2279	2230	2091	1638	1219	664	234

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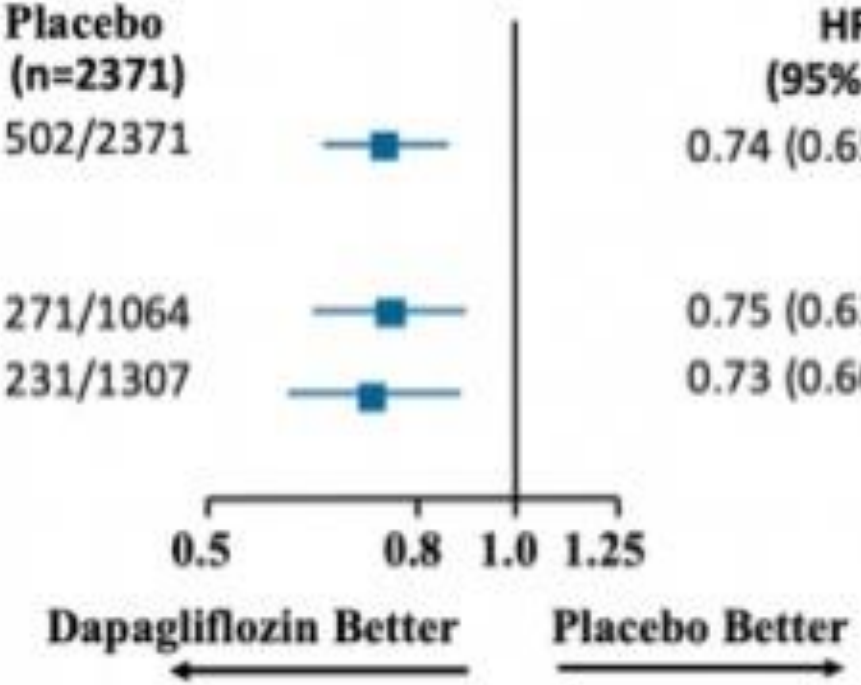
No diabetes/diabetes subgroup: Primary endpoint

	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Type 2 diabetes at baseline*			
Yes	215/1075	271/1064	0.75 (0.63, 0.90)
No	171/1298	231/1307	0.73 (0.60, 0.88)



*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.

Kansas City Cardiomyopathy Questionnaire (KCCQ)

Total Symptom Score: Proportion with ≥5 point change from baseline to 8 months*

Total Symptom Score: Proportion with ≥5 point change from baseline to 8 months*

Treatment	Dapagliflozin	Placebo	Oddsratio(95%CI)
≥5point improvement	58%	51%	1.15 (1.08, 1.23) p<0.001
≥5point deterioration	25%	33%	0.84 (0.78, 0.90) p<0.001

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Safety/adverse events

Patients exposed to at least one dose of study drug	Dapagliflozin (n=2368)	Placebo (n=2368)	p-value
Adverse events (AE) of interest (%)			
Volume depletion+	7.5	6.8	0.40
Renal AE‡	6.5	7.2	0.36
Fracture	2.1	2.1	1.00
Amputation	0.5	0.5	1.00
Major hypoglycaemia	0.2	0.2	-
Diabetic ketoacidosis	0.1	0.0	-
AE leading to treatment discontinuation (%)	4.7	4.9	0.79
Any serious adverse event (incl. death) (%)	38	42	<0.01

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Putative mechanisms underlying SGLT2 inhibitor-associated cardiovascular benefits

1. Improvement in ventricular loading conditions through a reduction in preload (secondary to natriuresis, osmotic diuresis) and afterload (reduction in blood pressure and improvement in vascular function) [7, 20, 21, 30–38]

2. Improvement in cardiac metabolism and bioenergetics [39, 40, 44, 45]

3. Myocardial Na^+/H^+ exchange inhibition [46–48]

4. Reduction of necrosis and cardiac fibrosis [51, 52, 60]

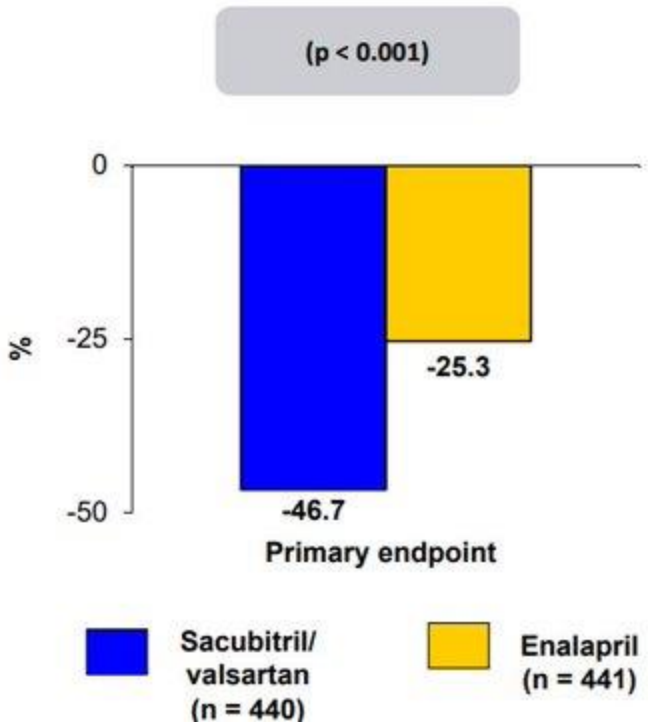
5. Alteration in adipokines, cytokine production and epicardial adipose tissue mass [55–57]

PIONEER-HF

#AHA18

AMERICAN COLLEGE of CARDIOLOGY

Trial description: Patients hospitalized with acute decompensated heart failure (ADHF) were randomized in a 1:1 fashion to either sacubitril/valsartan or enalapril. Patients were followed for 8 weeks.



RESULTS

- Primary endpoint, time-averaged reduction in NT-proBNP: sacubitril/valsartan vs. enalapril: -46.7% vs. -25.3%, $p < 0.001$
- Worsening renal function: 13.6% vs. 14.7%, $p > 0.05$, symptomatic hypotension: 15.0% vs. 12.7%, $p > 0.05$
- Rehospitalization for HF: 8.0% vs. 13.8%, $p < 0.05$

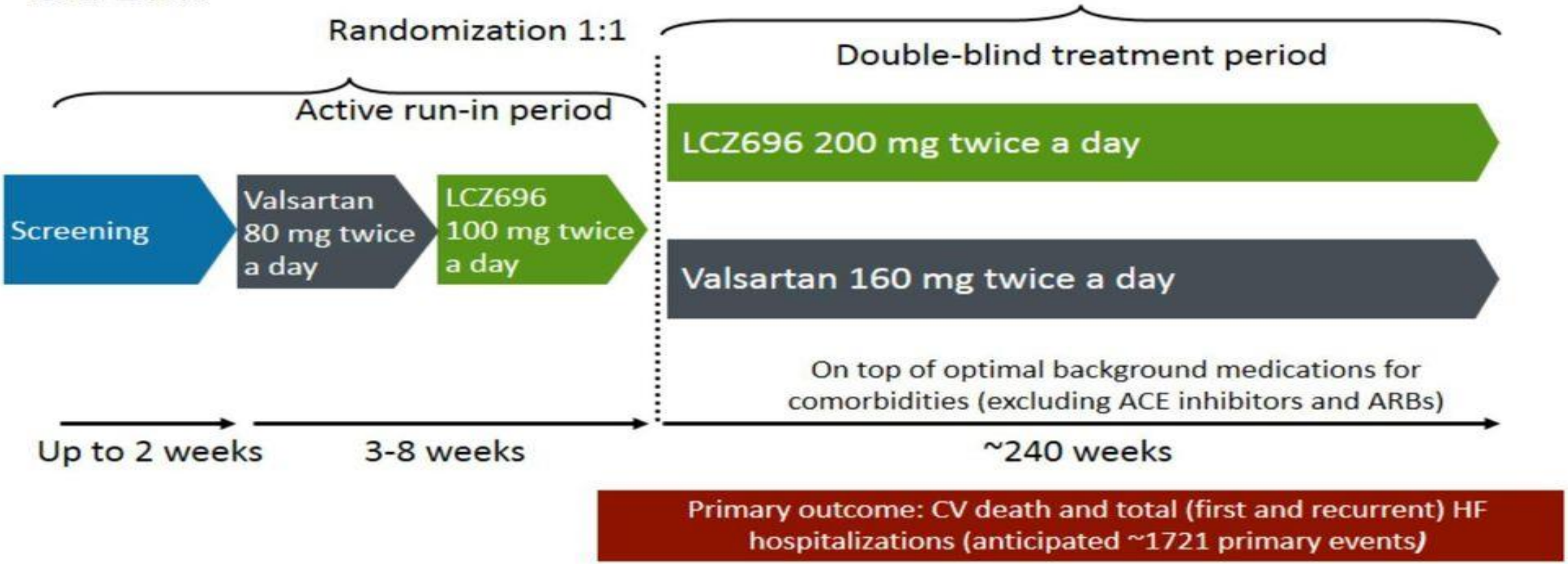
CONCLUSIONS

- Sacubitril/valsartan reduced NT-proBNP more than enalapril among patients with ADHF; noted as early as 1 week after drug initiation
- Although not powered for clinical endpoints, a reduction in rehospitalization for HF was noted

Velazquez EJ, et al. N Engl J Med 2018;Nov 11:[Epub]

PARAGON-HF: Trial Design

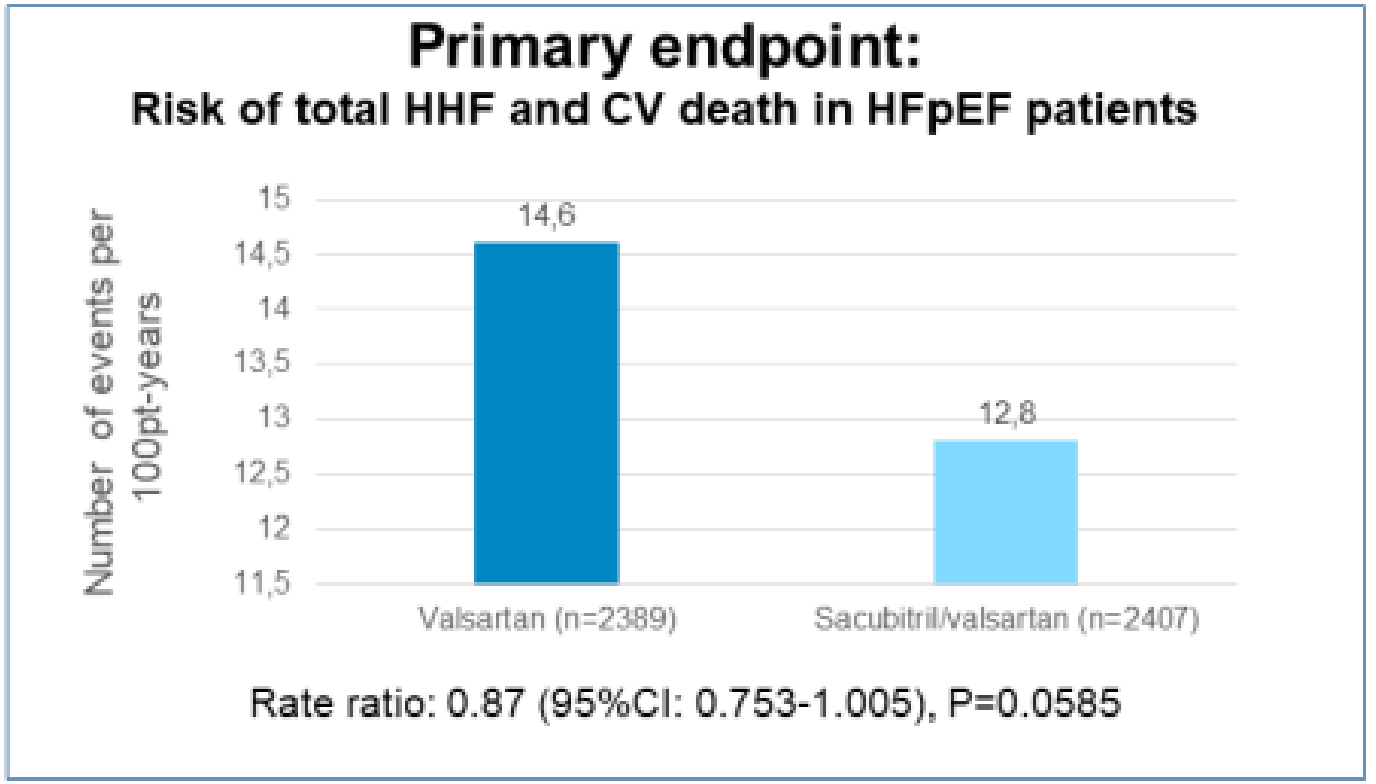
Target patient population: ~4600 patients with symptomatic HF (NYHA Class II-IV) and LVEF ≥45%



ClinicalTrials.gov. NCT01920711

Primary endpoint just missed significance in trial evaluating ARNI in HFpEF patients

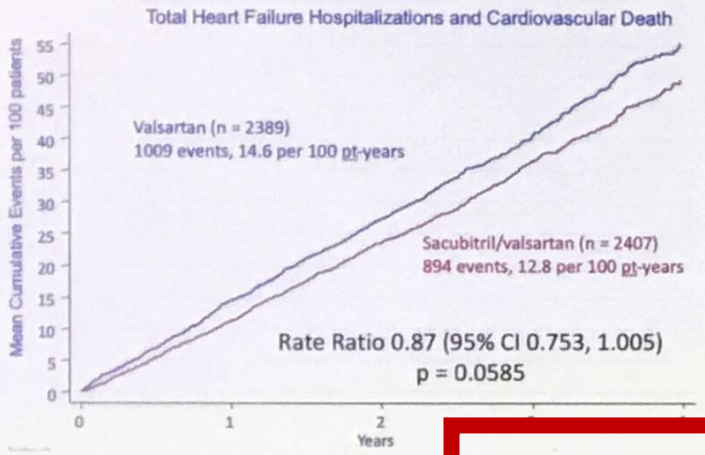
Randomized, double-blind, active comparator PARAGON-HF trial, in HF patients with LVEF ≥45%



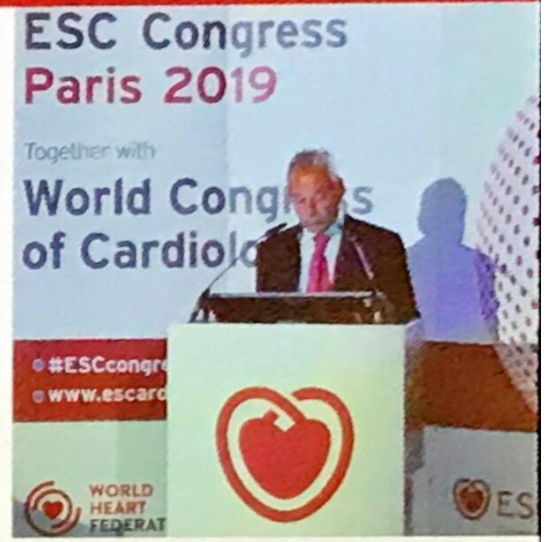
ARNI: angiotensin neprilysin inhibitor; HFpEF: heart failure with preserved ejection fraction; LVEF: left ventricular ejection fraction; HHF: hospitalization for heart failure

Results: Primary Endpoint just misses, benefit observed in several secondary endpoints, Lower EF patients and women benefit the greatest

Recurrent Event Analysis of Total HF Hospitalizations and CV death*



	Sacubitril/Valsartan N = 2316	Valsartan N = 2302	Effect Size (95% CI)	Nominal P-Value
NYHA functional classification at 8 months - Change from baseline (%)				
Improved	15.0%	12.6%	Odds ratio for improvement 1.45 (1.13, 1.86)	0.0035
Unchanged	76.3%	77.9%		
worsened	8.7%	9.6%		
KCCQ clinical summary score at 8 months – LSM of change from baseline (SE)	-1.6 (0.4)	-2.6 (0.4)	LSM of difference = 1.03 (0.00, 2.1)	0.051
KCCQ responder (greater than 5-point improvement)	33.0%	29.6%	OR = 1.30 (1.04, 1.61)	0.019
Worsening renal function (%) defined as renal death, reaching end stage renal disease (ESRD), or ≥50% decline in estimated glomerular filtration rate (eGFR) relative to baseline	1.4%	2.7%	HR = 0.50 (0.33, 0.77)	0.002
All-cause mortality (%)	14.2%	14.6%	HR = 0.97 (0.84, 1.13)	0.68



Scott SOLOMON
@scottdsolomon

Gender		
Male	980/2317	1.03 (0.85–1.25)
Female	923/2479	0.73 (0.59–0.90)
LVEF		
at or below median (57%)	1048/2495	0.78 (0.64–0.95)
above median (57%)	855/2301	1.00 (0.81–1.23)

Summary 2019 What's new in HF (drugs)

- TTR (wt and mutant) cardiac amyloidosis
  - FDA approved tafamadis (Vyndaqel), 30% RR reduction in all cause mortality, reduction in HF hospitalization, and improved quality of life
- SGLT-2 inhibitors (Dapaglifozin, Canagliflozin, Empaglifozin)
  - Reduction in HF hospitalization (all agents)
  - DAPA-HF, significant reductions in CV mortality and HF hospitalization in patients with HFrEF (fast track FDA)
  - Await DELIVER (Dapa in HFpEF), SOLOIST (Sota SGLT1/2) and EMPEROR-HFpEF/HFrEF
- ARNI for HFpEF: (PARAGON-HF), did not meet primary endpoint (p=0.059), key secondary endpoints: women with significant benefit and patients with EF below mean of 57% with significant benefit

Ongoing studies

- GALACTIC-HF (omecamtil mecarbil, myosin sensitizing agent, HFrEF)
- TRANSFORM-HF (torsemide vs furosemide in HFrEF/HFpEF)
- SPIRRIT-HF (pragmatic registry trial with spironolactone in HFpEF)
- HEART-FID (iron infusions in patient with low iron and HFrEF)

Kathleen Morris