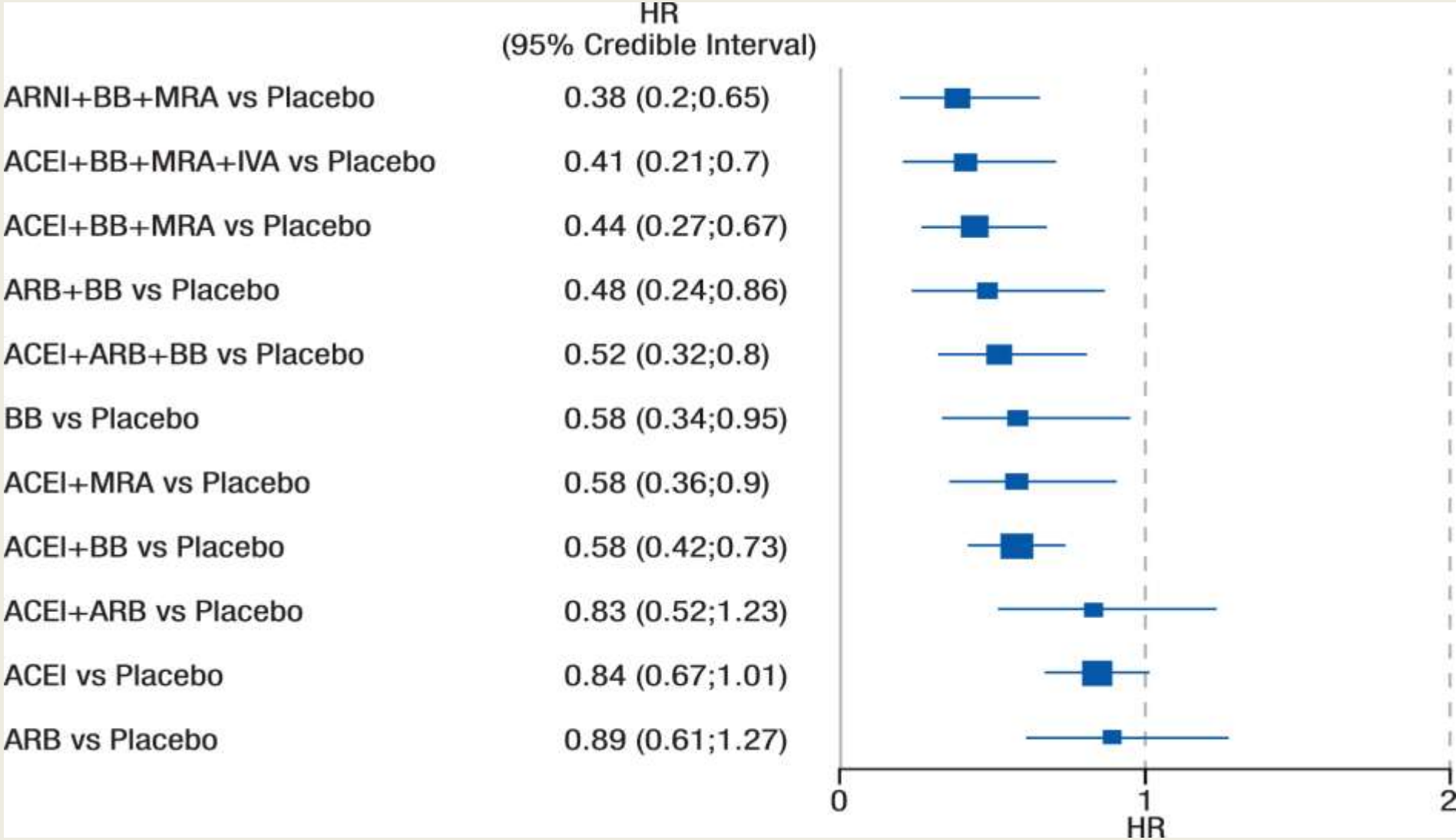
Insuffisance cardiaque en 2019

Pr Ahmed BENNIS

FESC , FACC

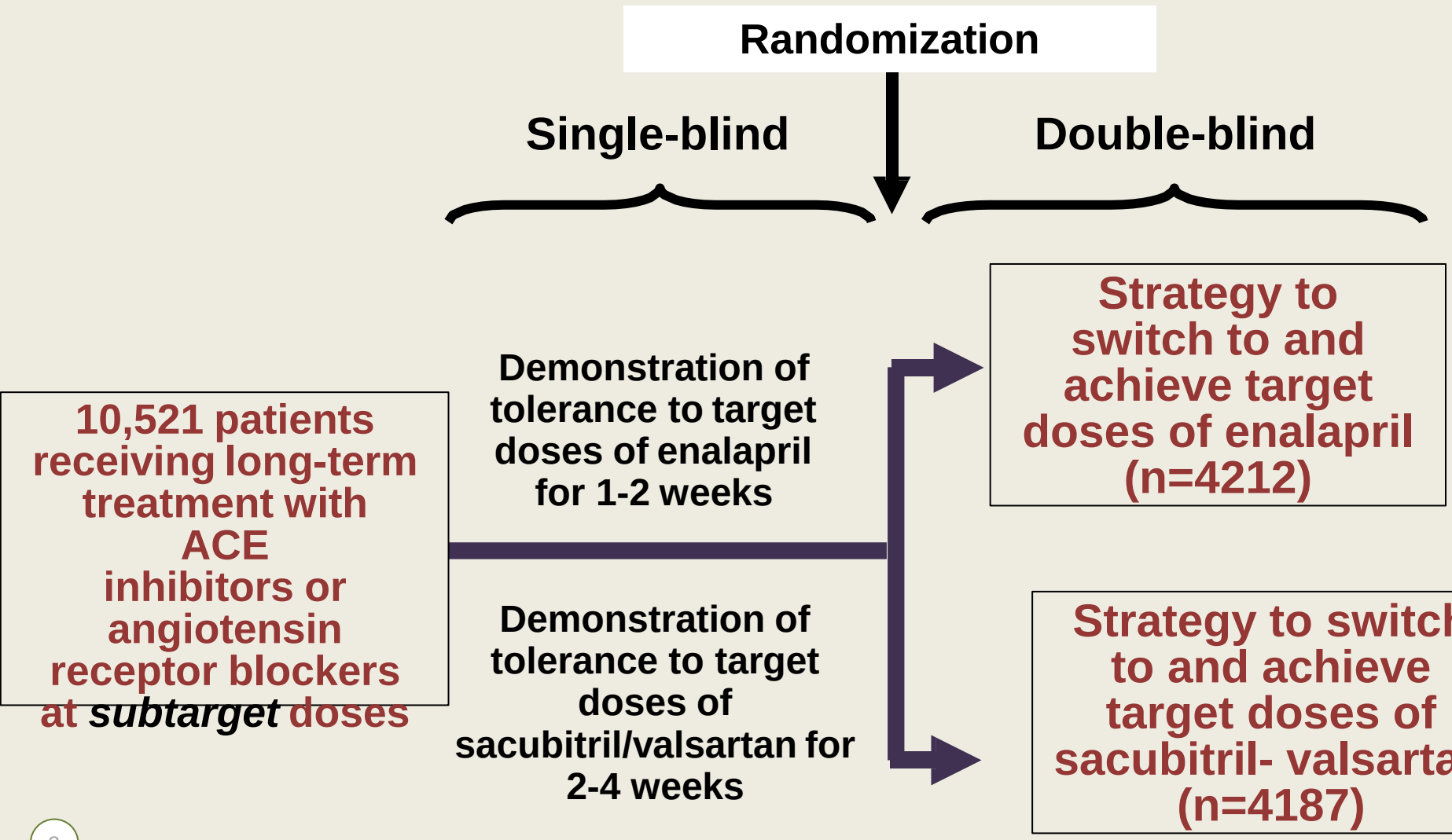
ahmedbennis7@gmail.com

Incremental benefit of drug therapies for chronic heart failure with reduced ejection fraction: a network meta-analysis

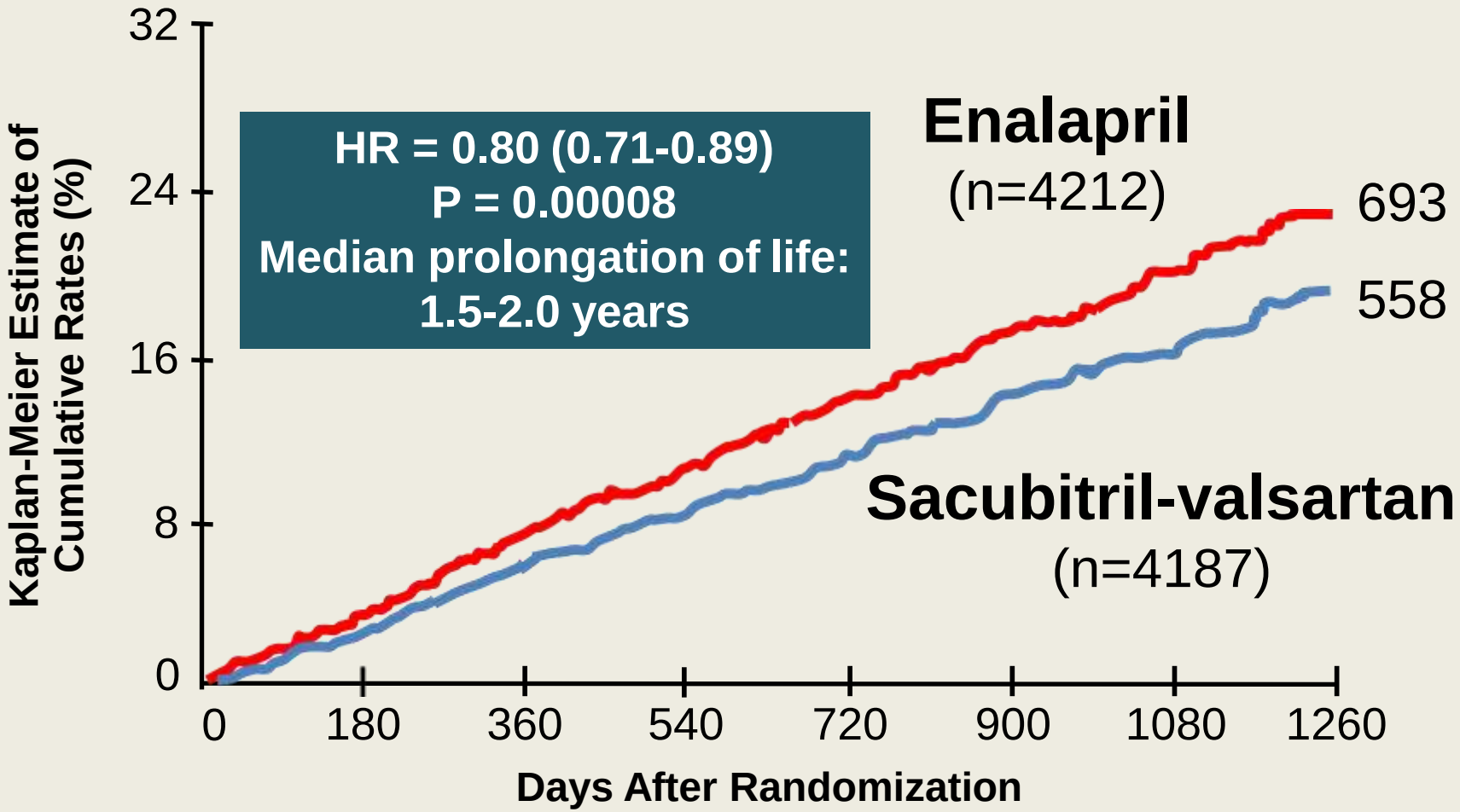


European Journal of Heart Failure, Volume: 20, Issue: 9, Pages: 1315-1322, First published: 27 May 2018, DOI: (10.1002/ejhf.1234)

PARADIGM-HF: Study Design



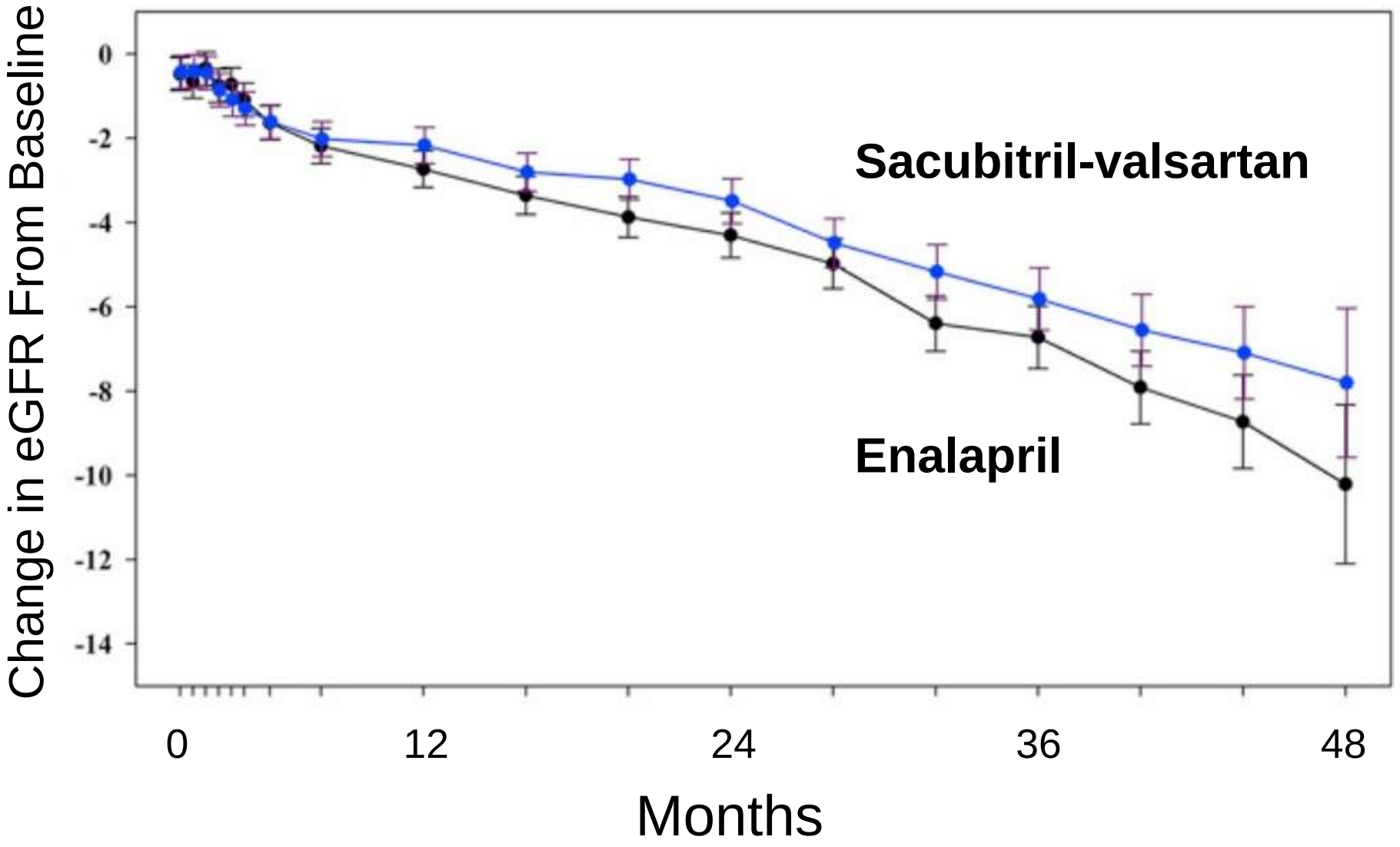
PARADIGM-HF: Cardiovascular Death



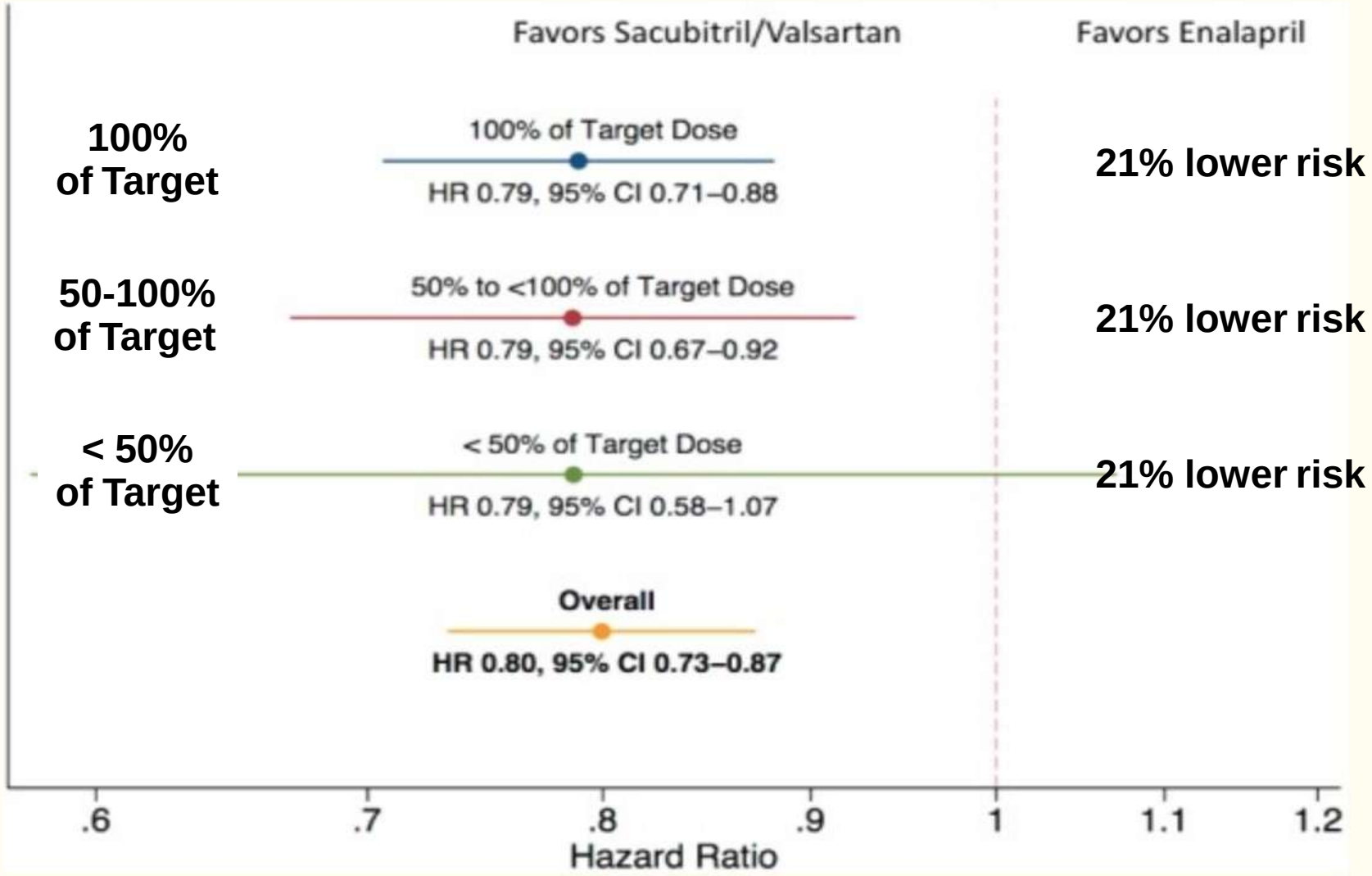
Patients at Risk

LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

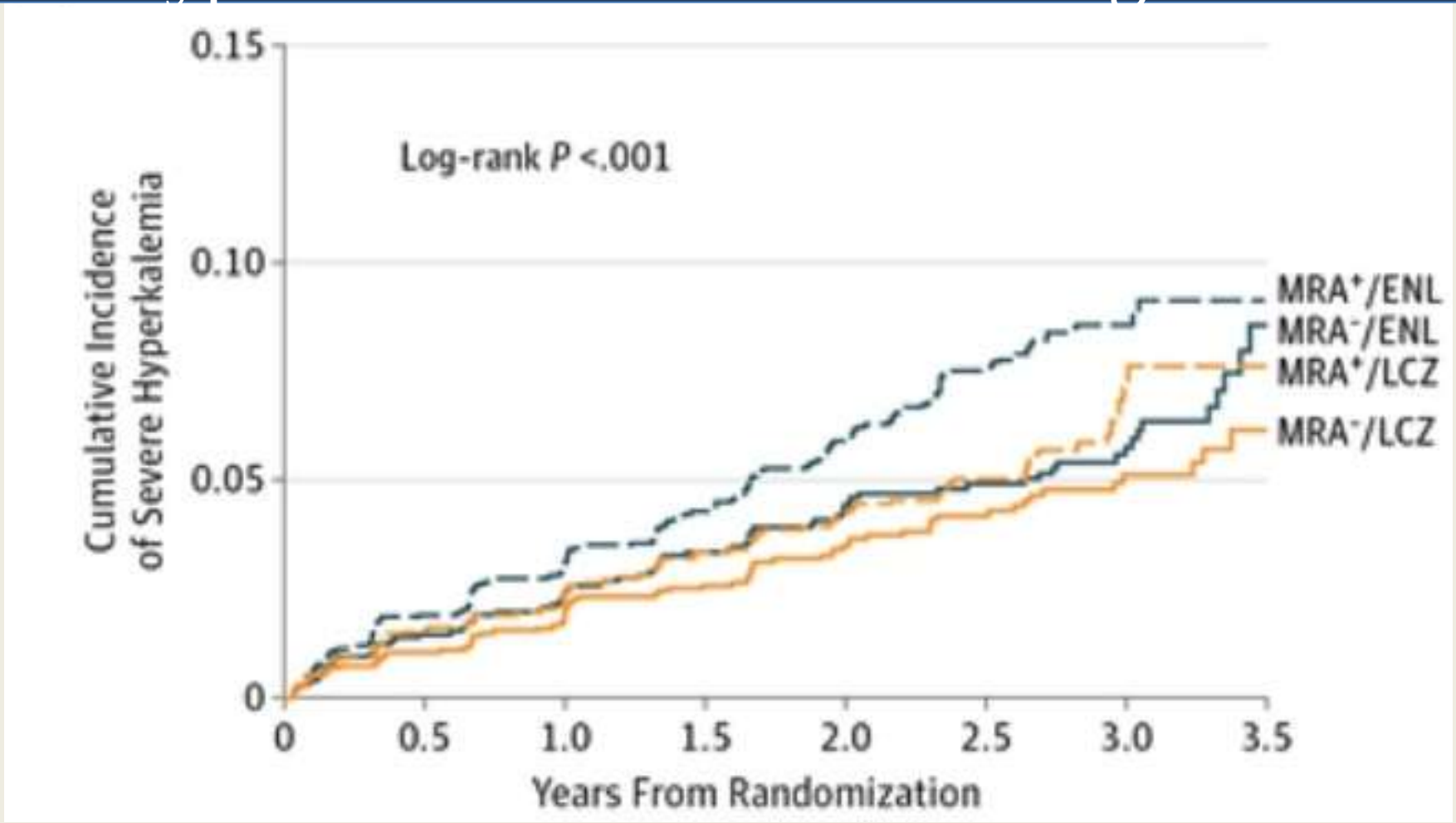
PARADIGM-HF: Less Renal Insufficiency With Sacubitril-Valsartan Than Enalapril



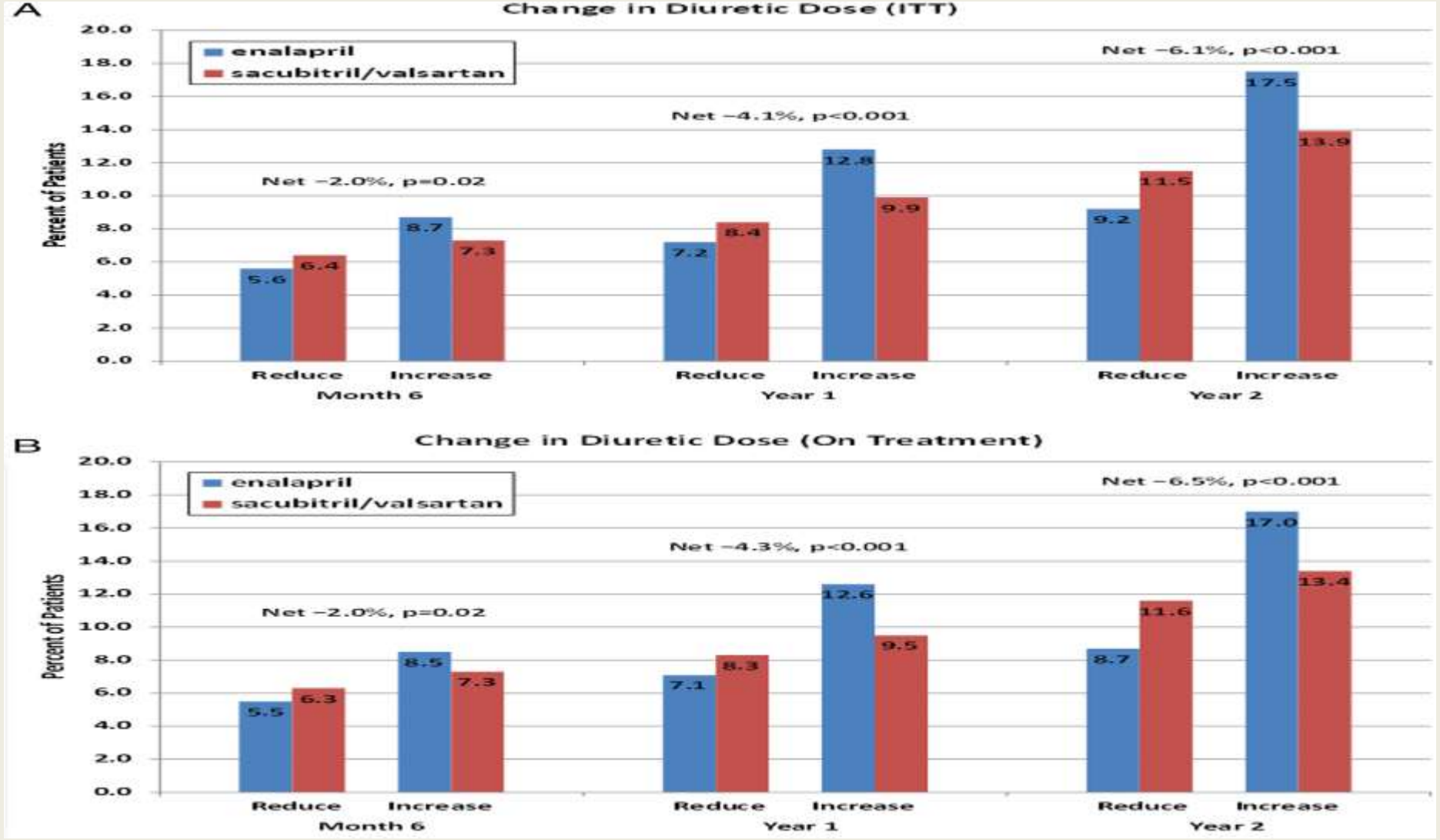
PARADIGM-HF: Superiority of Sacubitril-Valsartan Even in Patients Not Maintained on Target Doses



Sacubitril/Valsartan Prevents Severe Hyperkalemia in Patients Taking MRAs



Reduced loop diuretic use in patients taking sacubitril/valsartan compared with enalapril: the PARADIGM-HF trial



European Journal of Heart Failure, First published: 11 February 2019, DOI: (10.1002/ejhf.1402)

Original Article

Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure

Eric J. Velazquez, M.D., David A. Morrow, M.D., M.P.H., Adam D. DeVore, M.D., M.H.S., Carol I. Duffy, D.O., Andrew P. Ambrosy, M.D., Kevin McCague, M.A., Ricardo Rocha, M.D., Eugene Braunwald, M.D., for the PIONEER-HF Investigators

N Engl J Med
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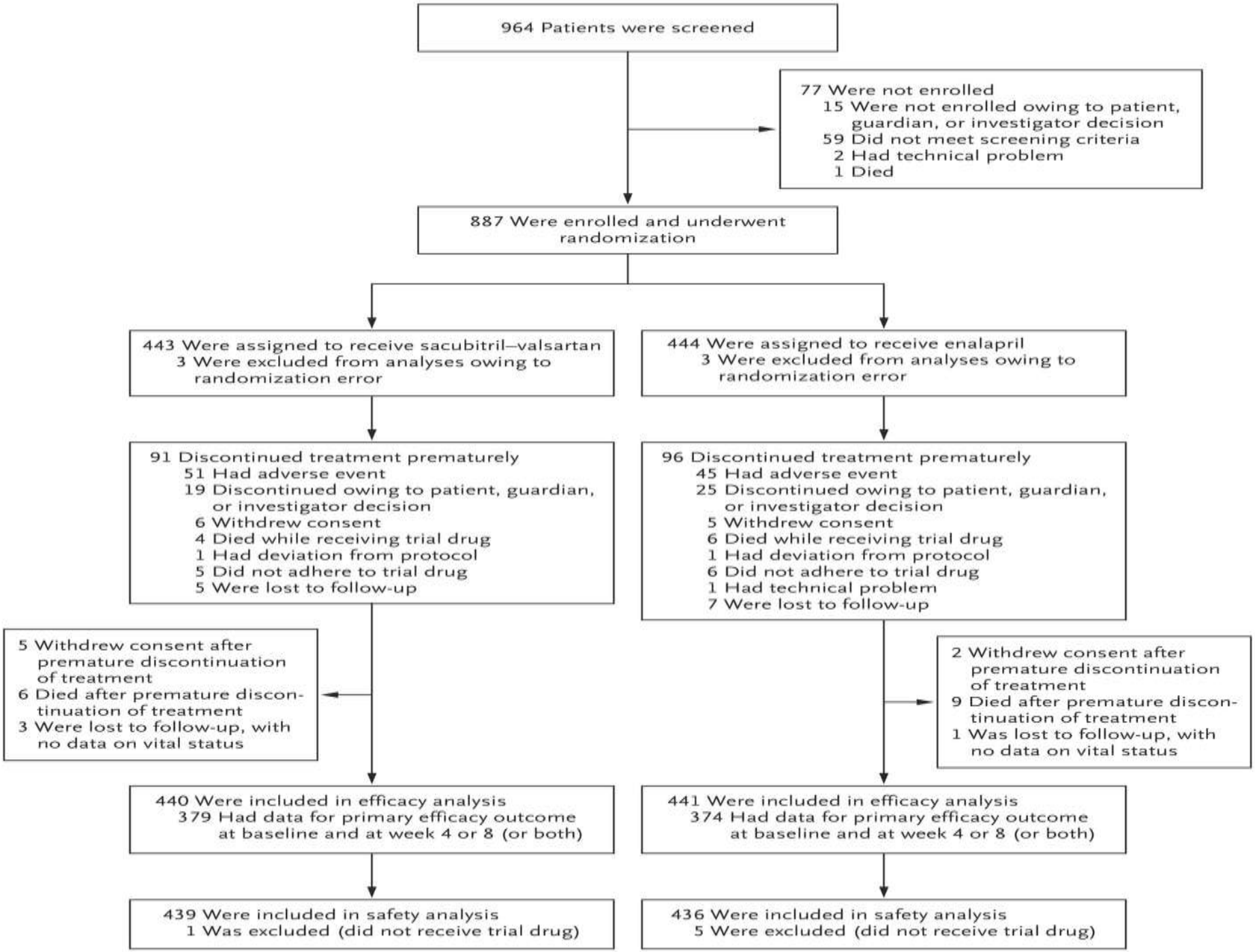
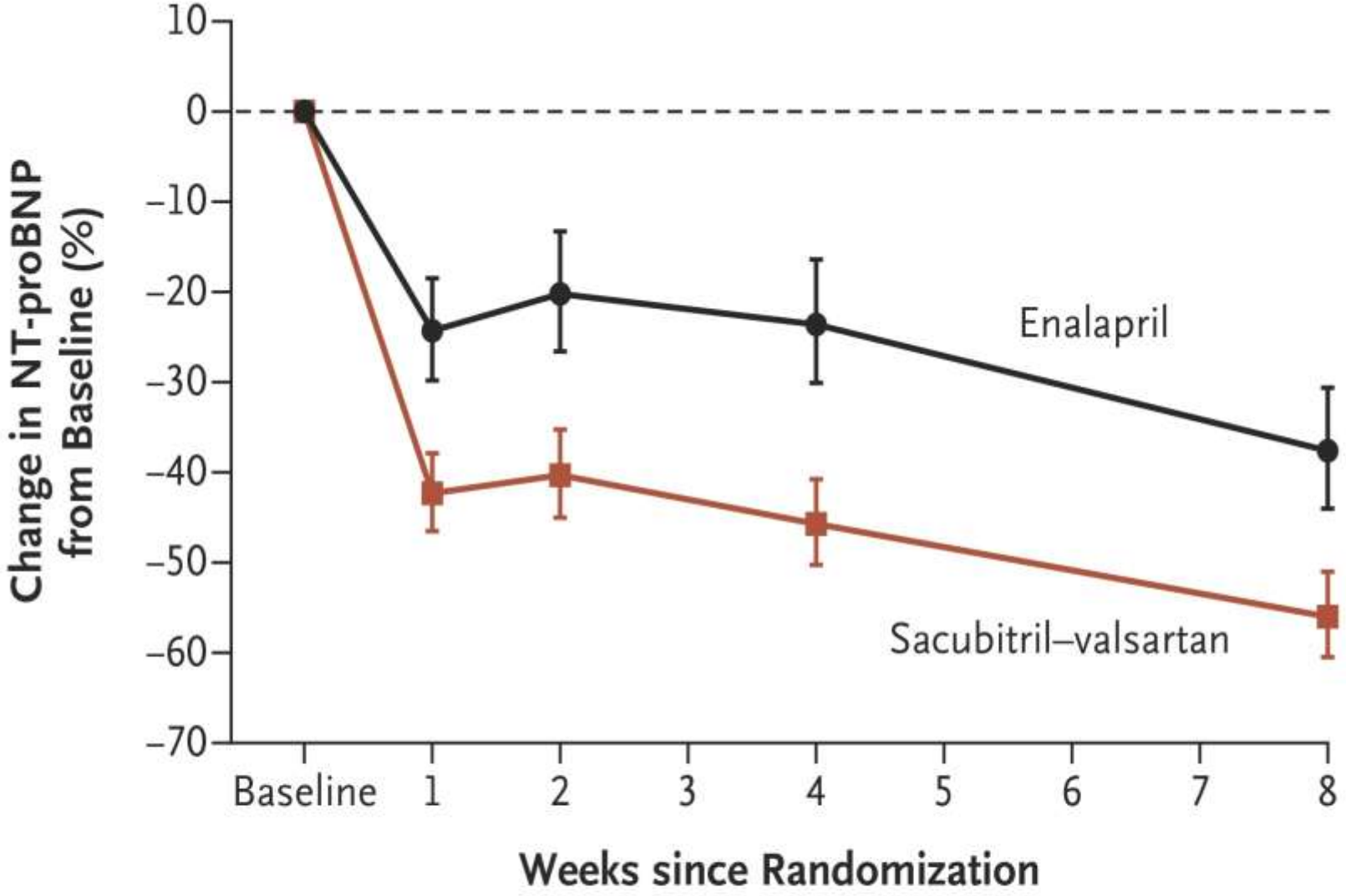
February 7, 2019

The NEW ENGLAND JOURNAL of MEDICINE


964 Patients were screened
77 Were not enrolled
15 Were not enrolled owing to patient, guardian, or investigator decision
59 Did not meet screening criteria
2 Had technical problem
1 Died
887 Were enrolled and underwent randomization
443 Were assigned to receive sacubitril–valsartan
3 Were excluded from analyses owing to randomization error
444 Were assigned to receive enalapril
3 Were excluded from analyses owing to randomization error
91 Discontinued treatment prematurely
51 Had adverse event
19 Discontinued owing to patient, guardian, or investigator decision
6 Withdrew consent
4 Died while receiving trial drug
1 Had deviation from protocol
5 Did not adhere to trial drug
5 Were lost to follow-up
96 Discontinued treatment prematurely
45 Had adverse event
25 Discontinued owing to patient, guardian, or investigator decision
5 Withdrew consent
6 Died while receiving trial drug
1 Had deviation from protocol
6 Did not adhere to trial drug
1 Had technical problem
7 Were lost to follow-up
5 Withdrew consent after premature discontinuation of treatment
6 Died after premature discontinuation of treatment
3 Were lost to follow-up, with no data on vital status
2 Withdrew consent after premature discontinuation of treatment
9 Died after premature discontinuation of treatment
1 Was lost to follow-up, with no data on vital status
440 Were included in efficacy analysis
379 Had data for primary efficacy outcome at baseline and at week 4 or 8 (or both)
441 Were included in efficacy analysis
374 Had data for primary efficacy outcome at baseline and at week 4 or 8 (or both)
439 Were included in safety analysis
1 Was excluded (did not receive trial drug)
436 Were included in safety analysis
5 Were excluded (did not receive trial drug)



No. at Risk

Enalapril	394	359	351	350	348
Sacubitril–valsartan	397	355	363	365	349

Subgroup	Sacubitril–Valsartan (N=440)	Enalapril (N=441)	Ratio of Change in NT-proBNP with Sacubitril–Valsartan vs. Enalapril (95% CI)	P Value for Interaction
	no. of patients (ratio of NT-proBNP at weeks 4 and 8 vs. baseline)			
All patients	379 (0.53)	374 (0.75)	0.71 (0.63–0.81)	
Age				0.76
<65 yr	229 (0.50)	202 (0.68)	0.73 (0.61–0.87)	
≥65 yr	150 (0.61)	172 (0.82)	0.74 (0.63–0.87)	
Sex				0.61
Male	289 (0.55)	265 (0.78)	0.70 (0.60–0.80)	
Female	90 (0.50)	109 (0.66)	0.75 (0.59–0.95)	
Race				0.13
White	226 (0.50)	219 (0.74)	0.68 (0.58–0.80)	
Black	133 (0.56)	129 (0.78)	0.72 (0.57–0.89)	
Other	20 (0.82)	26 (0.70)	1.17 (0.72–1.91)	
Previous heart failure				0.40
No	130 (0.37)	148 (0.56)	0.65 (0.53–0.81)	
Yes	249 (0.65)	225 (0.90)	0.72 (0.63–0.83)	
Previous hypertension				0.62
No	50 (0.42)	64 (0.63)	0.66 (0.49–0.90)	
Yes	329 (0.55)	309 (0.77)	0.72 (0.63–0.82)	
Previous atrial fibrillation				0.32
No	251 (0.49)	230 (0.71)	0.70 (0.60–0.81)	
Yes	127 (0.62)	140 (0.79)	0.79 (0.64–0.96)	
Previous use of ACE inhibitor or ARB				0.98
No	209 (0.48)	196 (0.66)	0.72 (0.60–0.86)	
Yes	170 (0.61)	178 (0.85)	0.72 (0.61–0.85)	
Systolic blood pressure at randomization				0.93
≤118 mm Hg	188 (0.60)	185 (0.84)	0.71 (0.60–0.84)	
>118 mm Hg	191 (0.48)	189 (0.67)	0.72 (0.60–0.86)	
Left ventricular ejection fraction at screening				0.37
≤25%	246 (0.51)	243 (0.74)	0.69 (0.59–0.80)	
>25%	132 (0.59)	131 (0.76)	0.77 (0.63–0.95)	
Estimated GFR at randomization				0.81
<60 ml/min/1.73 m^2	194 (0.55)	192 (0.76)	0.73 (0.61–0.87)	
≥60 ml/min/1.73 m^2	181 (0.51)	177 (0.72)	0.70 (0.59–0.84)	
NT-proBNP concentration at randomization				0.30
≤2701 pg/ml	180 (0.63)	200 (0.93)	0.67 (0.57–0.80)	
>2701 pg/ml	199 (0.45)	174 (0.60)	0.76 (0.63–0.90)	
NYHA class at randomization				0.48
I or II	90 (0.52)	112 (0.78)	0.67 (0.53–0.84)	
III or IV	278 (0.54)	258 (0.73)	0.73 (0.63–0.85)	
Time from presentation to randomization				0.66
≤67.7 hr	192 (0.52)	186 (0.71)	0.74 (0.62–0.87)	
>67.7 hr	186 (0.54)	188 (0.79)	0.69 (0.58–0.83)	

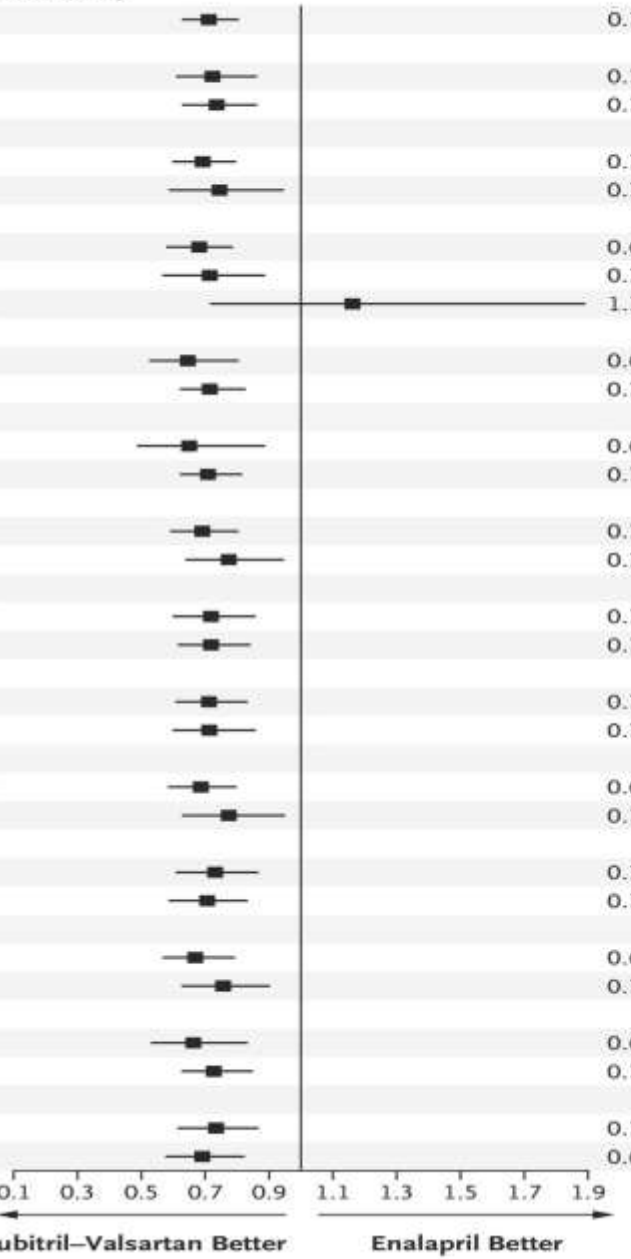


Table 1. Characteristics of the Patients at Baseline.*

Variable	Sacubitril–Valsartan (N = 440)	Enalapril (N = 441)
Age — yr		
Median	61	63
Interquartile range	51–71	54–72
Female sex — no. (%)	113 (25.7)	133 (30.2)
Race — no. (%)†		
Black	158 (35.9)	158 (35.8)
White	261 (59.3)	254 (57.6)
Body-mass index‡		
Median	30.5	30.0
Interquartile range	25.9–37.1	25.8–36.3
Previous heart failure — no. (%)	298 (67.7)	278 (63.0)
Previous use of medication — no. (%)		
ACE inhibitor or ARB	208 (47.3)	214 (48.5)
Beta-blocker	262 (59.5)	263 (59.6)
MRA	48 (10.9)	40 (9.1)
Loop diuretic	262 (59.5)	240 (54.4)
Hydralazine	30 (6.8)	33 (7.5)
Nitrate	43 (9.8)	40 (9.1)
Digoxin	41 (9.3)	35 (7.9)
NYHA class — no. (%)		
I	4 (0.9)	5 (1.1)
II	100 (22.7)	122 (27.7)
III	283 (64.3)	269 (61.0)
IV	39 (8.9)	36 (8.2)
Not assessed	14 (3.2)	9 (2.0)
Systolic blood pressure — mm Hg§		
Median	118	118
Interquartile range	110–133	109–132
Pulse — beats per min§		
Median	81	80
Interquartile range	72–92	72–91
Left ventricular ejection fraction — %¶		
Median	24	25
Interquartile range	18–30	20–30
NT-proBNP at screening — pg/ml¶		
Median	4821	4710
Interquartile range	3109–8767	2966–8280
NT-proBNP at randomization — pg/ml§		
Median	2883	2536
Interquartile range	1610–5403	1363–4917
Serum creatinine — mg/dl§		
Median	1.28	1.27
Interquartile range	1.07–1.51	1.05–1.50
Estimated GFR — ml/min/1.73 m^2§		
Median	58.4	58.9
Interquartile range	47.5–71.5	47.4–70.9
Serum potassium — mmol per liter§		
Median	4.20	4.25
Interquartile range	4.00–4.50	3.90–4.60

Table 2. Secondary Efficacy and Safety Outcomes.*

Outcome	Sacubitril–Valsartan (N=440)	Enalapril (N=441)	Sacubitril–Valsartan vs. Enalapril
Key safety outcomes — no. (%)			**Relative risk (95% CI)**
Worsening renal function†	60 (13.6)	65 (14.7)	0.93 (0.67 to 1.28)
Hyperkalemia	51 (11.6)	41 (9.3)	1.25 (0.84 to 1.84)
Symptomatic hypotension	66 (15.0)	56 (12.7)	1.18 (0.85 to 1.64)
Angioedema	1 (0.2)	6 (1.4)	0.17 (0.02 to 1.38)
Secondary biomarker outcomes — % (95% CI)‡			**Ratio of change (95% CI)**
Change in high-sensitivity troponin T concentration	−36.6 (−40.8 to −32.0)	−25.2 (−30.2 to −19.9)	0.85 (0.77 to 0.94)
Change in B-type natriuretic peptide concentration	−28.7 (−35.5 to −21.3)	−33.1 (−39.5 to −25.9)	1.07 (0.92 to 1.23)
Change in ratio of B-type natriuretic peptide to NT-proBNP	35.2 (28.8 to 42.0)	−8.3 (−3.6 to −12.7)	1.48 (1.38 to 1.58)
Exploratory clinical outcomes — no. (%)			**Hazard ratio (95% CI)§**
Composite of clinical events	249 (56.6)	264 (59.9)	0.93 (0.78 to 1.10)
Death	10 (2.3)	15 (3.4)	0.66 (0.30 to 1.48)
Rehospitalization for heart failure	35 (8.0)	61 (13.8)	0.56 (0.37 to 0.84)
Implantation of left ventricular assist device	1 (0.2)	1 (0.2)	0.99 (0.06 to 15.97)
Inclusion on list for heart transplantation	0	0	NA
Unplanned outpatient visit leading to use of intravenous diuretics	2 (0.5)	2 (0.5)	1.00 (0.14 to 7.07)
Use of additional drug for heart failure	78 (17.7)	84 (19.0)	0.92 (0.67 to 1.25)
Increase in dose of diuretics of >50%	218 (49.5)	222 (50.3)	0.98 (0.81 to 1.18)
Composite of serious clinical events¶	41 (9.3)	74 (16.8)	0.54 (0.37 to 0.79)

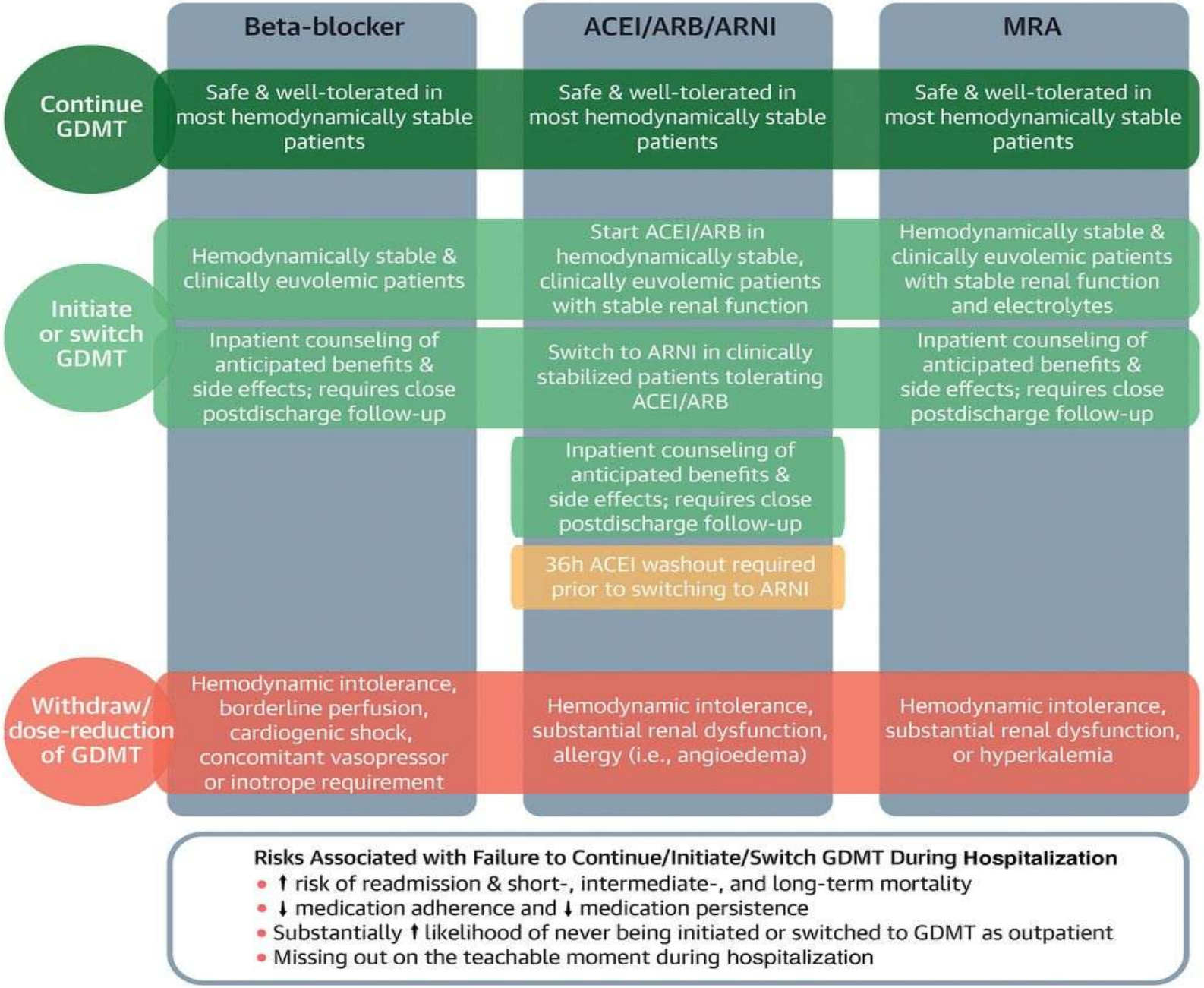
* NA denotes not available.

† Worsening renal function was defined by an increase in the serum creatinine concentration of 0.5 mg per deciliter or more (≥44 μmol per liter) and a decrease in the estimated glomerular filtration rate of 25% or more.

‡ Shown are data on the time-averaged proportional change, from the baseline value to the geometric mean of values obtained at weeks 4 and 8.

§ Hazard ratios and associated 95% confidence intervals were calculated with a Cox proportional-hazards model. Confidence intervals have not been adjusted for multiple comparisons, and therefore, inferences drawn from these intervals may not be reproducible.

¶ The outcome of a composite of serious clinical events was added to the list of exploratory clinical outcomes in May 2018, before the database was locked and unblinding occurred. This end point included death, rehospitalization for heart failure, implantation of a left ventricular device, and inclusion on the list of patients eligible for heart transplantation.



Bhagat, A.A. et al. J Am Coll Cardiol HF. 2019;7(1):1–12.

Angiotensin Receptor Neprilysin Inhibitor for Functional Mitral Regurgitation: The PRIME StudyBackground: The morbidity and mortality of patients with functional mitral regurgitation (MR) remain high, but no pharmacological therapy has been proven effective. The hypothesis of this study was that sacubitril/valsartan would be superior to valsartan alone in improving functional MR via dual inhibition of the renin-angiotensin system and neprilysin.
Methods: In this double-blind trial, we randomly assigned 118 heart failure patients with chronic functional MR secondary to left ventricular (LV) dysfunction to receive either sacubitril/valsartan or valsartan, in addition to standard medical therapy for heart failure. The primary end point was the change in effective regurgitant orifice area (EROA) of functional MR from baseline to the 12-month follow-up. Secondary end points included changes in regurgitant volume, LV end-systolic volume, LV end-diastolic volume and incomplete mitral leaflet closure area. **Results:** The decrease in EROA was significantly greater in the sacubitril/valsartan group compared to the valsartan group (-0.058±0.095 versus -0.018±0.105 cm^2; P=0.032) in an intention-to-treat analysis including 117 (99%) patients. Regurgitant volume was also significantly decreased in the sacubitril/valsartan group compared with the valsartan group (mean difference -7.3 ml, 95% CI -12.6 to -1.9; P=0.009). There were no significant between-group differences regarding the changes in incomplete mitral leaflet closure area and LV volumes except LV end-diastolic volume index (P=0.044). We noted no significant difference in the change of blood pressure between the treatment groups and 7 patients (12%) in the sacubitril/valsartan group and 9 (16%) in the valsartan group had one or more serious adverse events (P=0.54). **Conclusions:** Among patients with secondary functional MR, sacubitril/valsartan reduced MR to a greater extent than did valsartan. Our findings suggest that an angiotensin receptor neprilysin inhibitor might be considered for optimal medical therapy of patients with heart failure and functional MR.

Original Article

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., Ronald Witteles, M.D., Thibaud Damy, M.D., Ph.D., Brian M. Drachman, M.D., Sanjiv J. Shah, M.D., Mazen Hanna, M.D., Daniel P. Judge, M.D., Alexandra I. Barsdorf, Ph.D., Peter Huber, R.Ph., Terrell A. Patterson, Ph.D., Steven Riley, Pharm.D., Ph.D., Jennifer Schumacher, Ph.D., Michelle Stewart, Ph.D., Marla B. Sultan, M.D., M.B.A., Claudio Rapezzi, M.D., for the ATTR-ACT Study Investigators

N Engl J Med
Volume 379(11):1007-1016
September 13, 2018

Study Overview

- In this randomized, controlled, phase 3 trial of tafamidis for transthyretin amyloid cardiomyopathy, tafamidis was associated with lower all-cause mortality and lower rates of cardiovascular-related hospitalizations and decline in functional capacity and quality of life.

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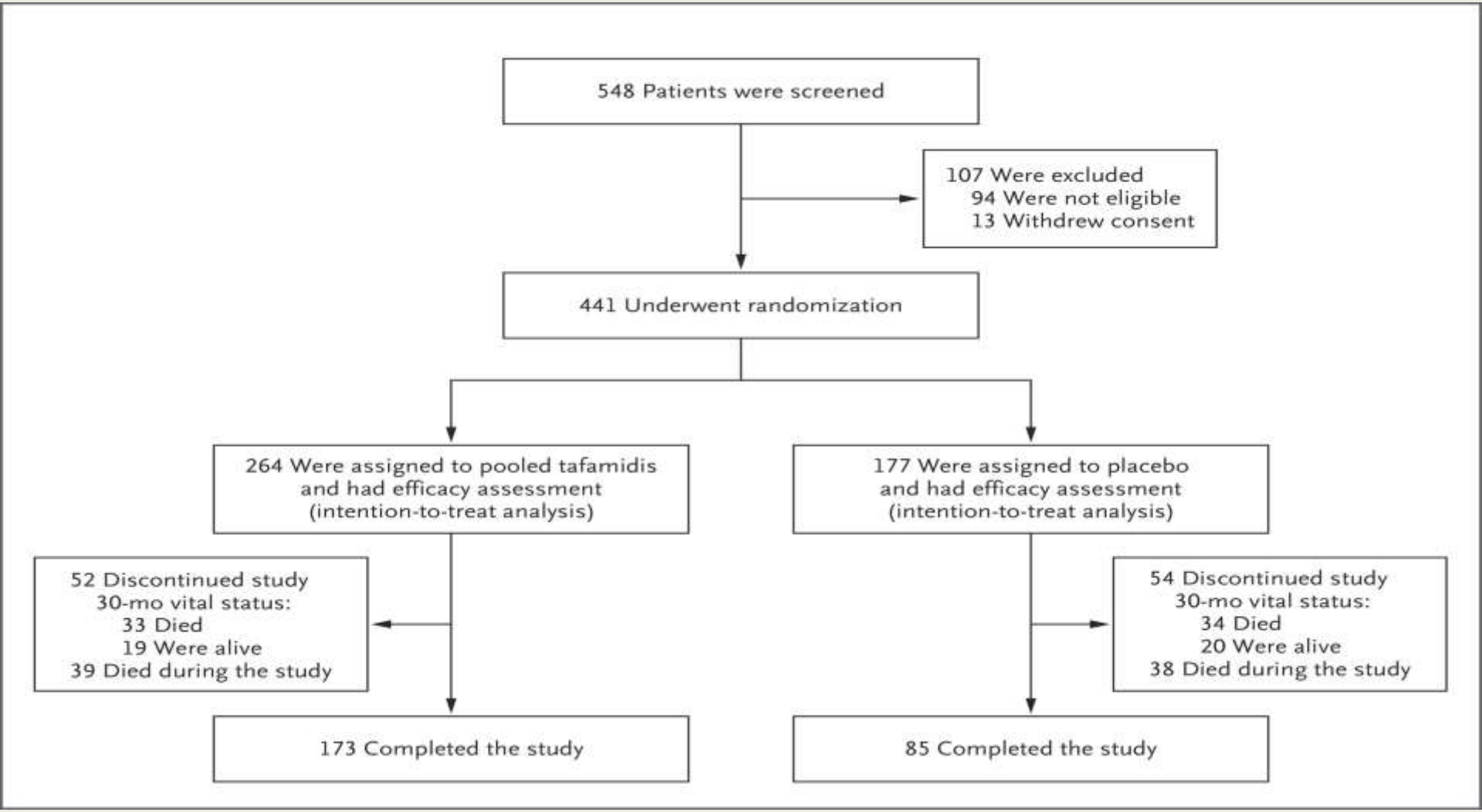
Randomization, Evaluation, and Outcomes.



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

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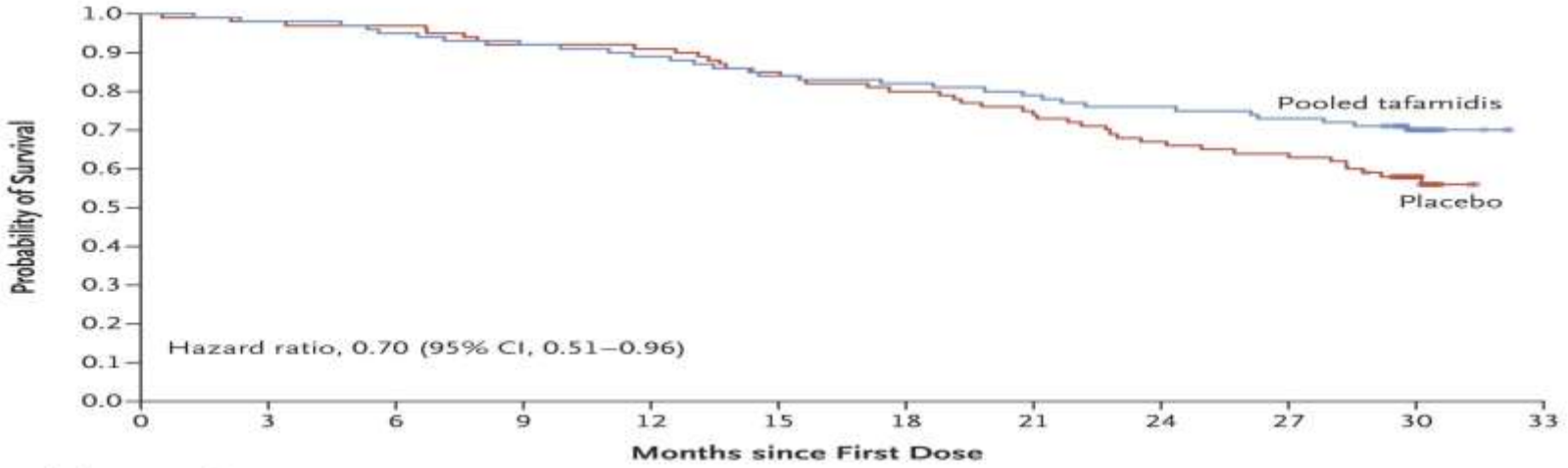
Primary Analysis and Components

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	Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30
				no. (%)	*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



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	Cardiovascular- Related Hospitalizations	Pooled Tafamidis vs. Placebo Treatment Difference
		total no. (%)	*no. per yr*	*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	

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

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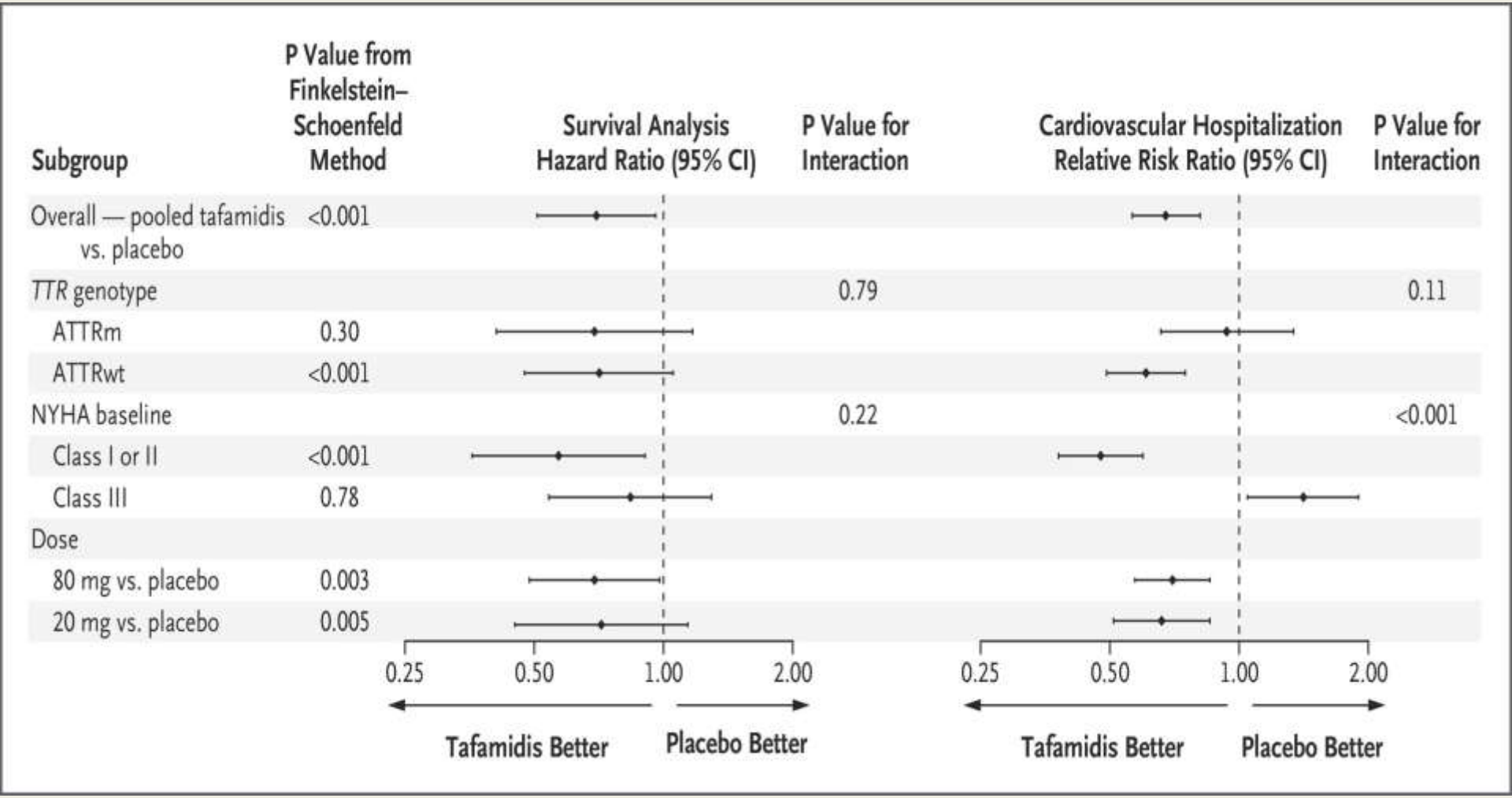
Overall and Subgroup Results as Calculated with the Use of the Finkelstein–Schoenfeld Method, All-Cause Mortality, and Cardiovascular-Related Hospitalizations.



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

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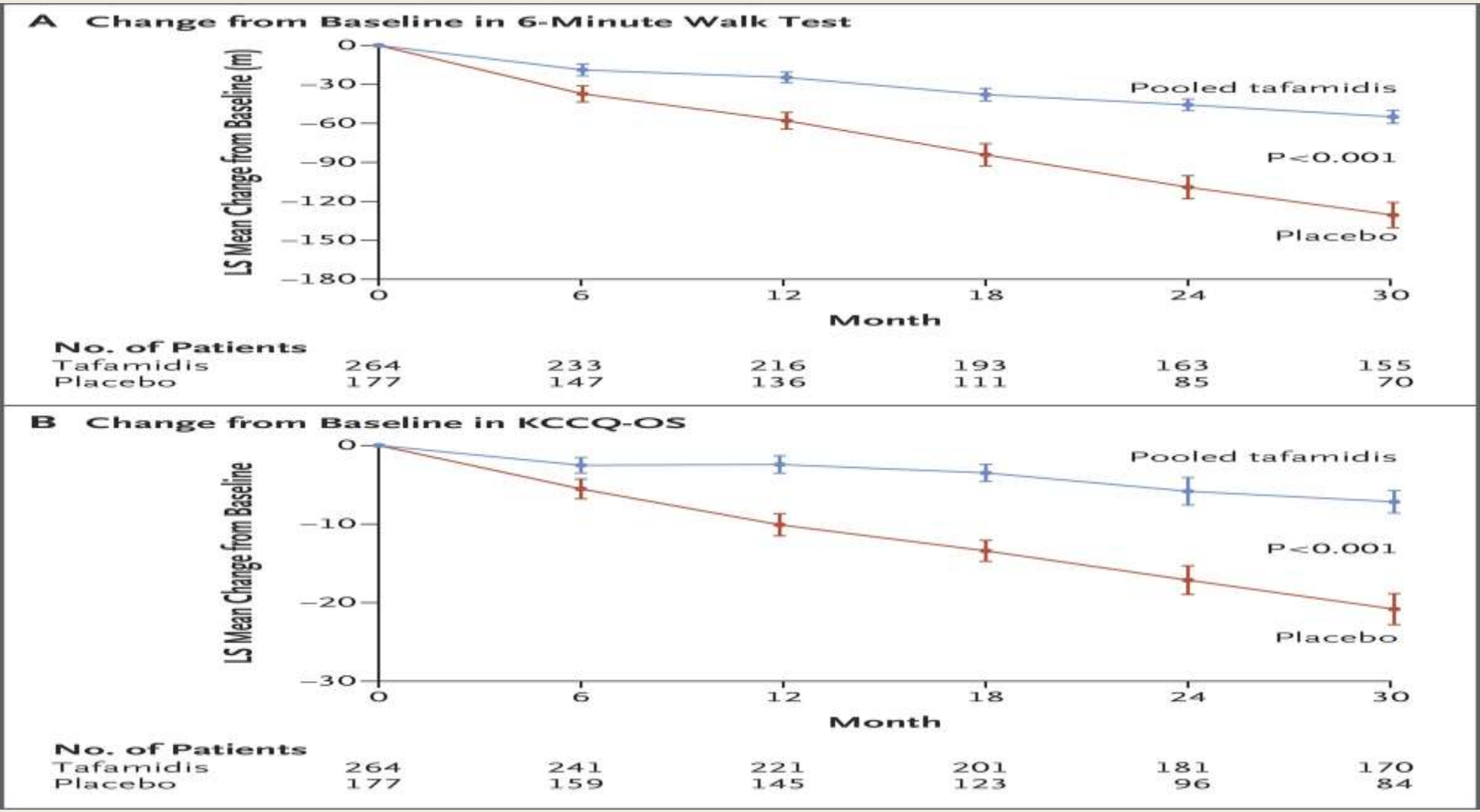
Key Secondary End Points.



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

Demographic and Clinical Characteristics of the Patients at Baseline

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Tafamidis (N=264)	Placebo (N=177)
Age — yr		
Mean	74.5±7.2	74.1±6.7
Median (range)	75 (46–88)	74 (51–89)
Sex — no. (%)		
Male	241 (91.3)	157 (88.7)
Female	23 (8.7)	20 (11.3)
Race — no. (%)		
White	211 (79.9)	146 (82.5)
Black	37 (14.0)	26 (14.7)
Asian	13 (4.9)	5 (2.8)
Other	3 (1.1)	0
TTR genotype — no. (%)		
ATTRm	63 (23.9)	43 (24.3)
ATTRwt	201 (76.1)	134 (75.7)
Blood pressure — mm Hg		
Supine		
Systolic	115.4±15.4	115.1±15.7
Diastolic	70.4±10.3	70.2±9.5
Standing		
Systolic	115.5±15.5	115.9±15.9
Diastolic	70.6±9.9	71.0±10.3
Heart rate, mean — beats per minute		
Supine	70.7±12.3	69.9±11.7
Standing	72.9±12.9	73.8±12.2
NYHA Class — no. (%)		
Class I	24 (9.1)	13 (7.3)
Class II	162 (61.4)	101 (57.1)
Class III	78 (29.5)	63 (35.6)
Modified BMI†	1058.8±173.8	1066.4±194.4
NT-proBNP level — pg/ml		
Median	2995.9	3161.0
Interquartile range	1751.5–4861.5	1864.4–4825.0

* Plus–minus values are means ±SD. There were 264 patients in the tafamidis group and 177 patients in the placebo group in both the intention-to-treat and safety analyses. Percentages may not total 100 because of rounding. NT-proBNP denotes N-terminal pro-B-type natriuretic peptide, and NYHA New York Heart Association.

† The modified body-mass index (BMI) is calculated as the serum albumin level in grams per liter multiplied by the conventional BMI (the weight in kilograms divided by the square of the height in meters).

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

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Conclusions

- In patients with transthyretin amyloid cardiomyopathy, tafamidis was associated with reductions in all-cause mortality and cardiovascular-related hospitalizations and reduced the decline in functional capacity and quality of life as compared with placebo.

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Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial

Brian P Halliday, PhD, Rebecca Wassall, MSc, Amrit S Lota, BMBCh, Zohya Khalique, MBBS, John Gregson, PhD, Simon Newsome, MSc, Robert Jackson, MSc, Tsveta Rahneva, BSc, Rick Wage, DCR, Gillian Smith, PhD, Lucia Venneri, MD, Upasana Tayal, PhD, Dominique Auger, MD, William Midwinter, BSc, Nicola Whiffin, PhD, Ronak Rajani, MD, Jason N Dungu, PhD, Antonis Pantazis, MD, Prof Stuart A Cook, PhD, James S Ware, PhD, A John Baksi, PhD, Prof Dudley J Pennell, MD, Stuart D Rosen, MD, Prof Martin R Cowie, MD, Prof John G F Cleland, MD, Sanjay K Prasad, MD

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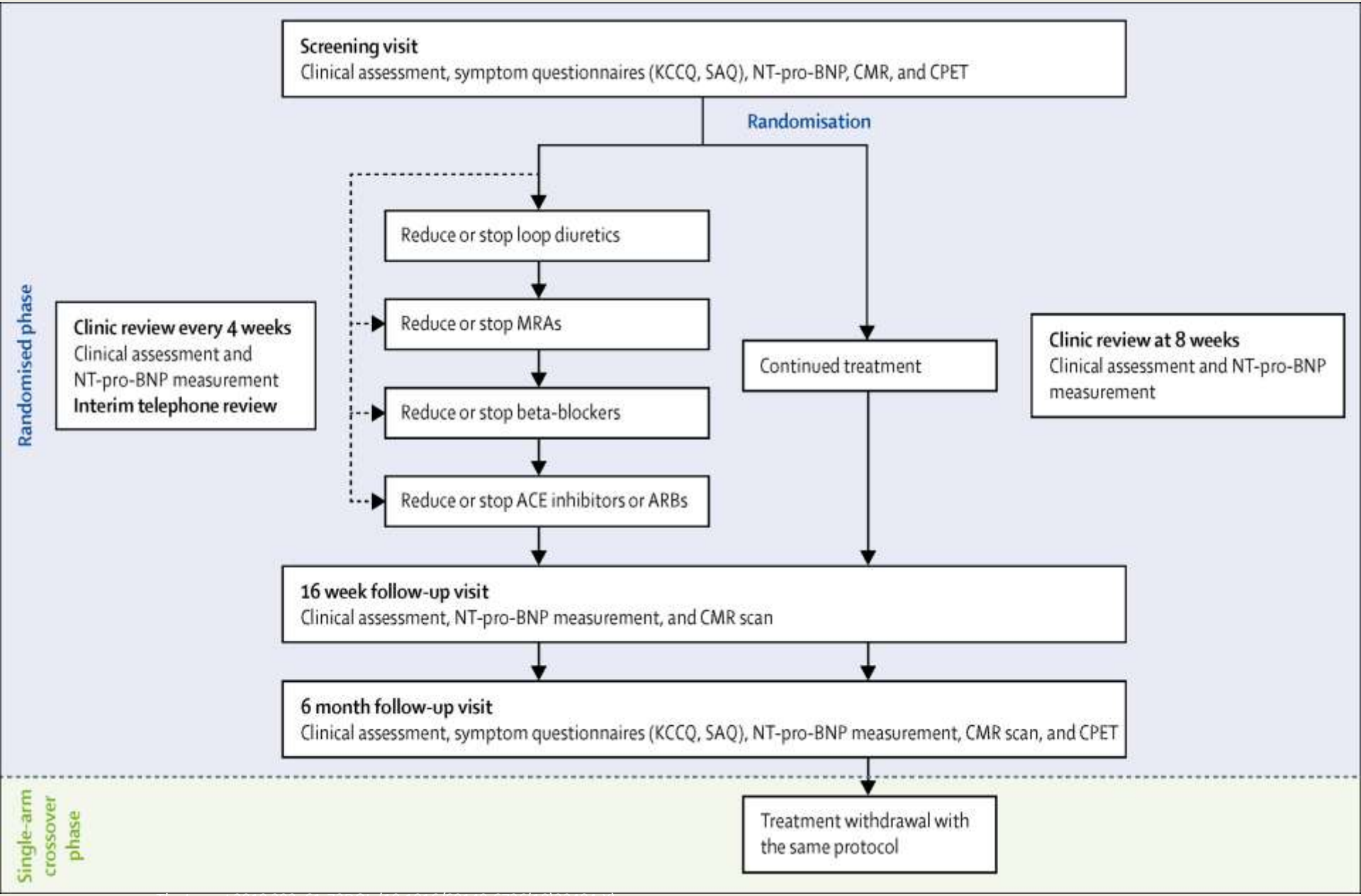
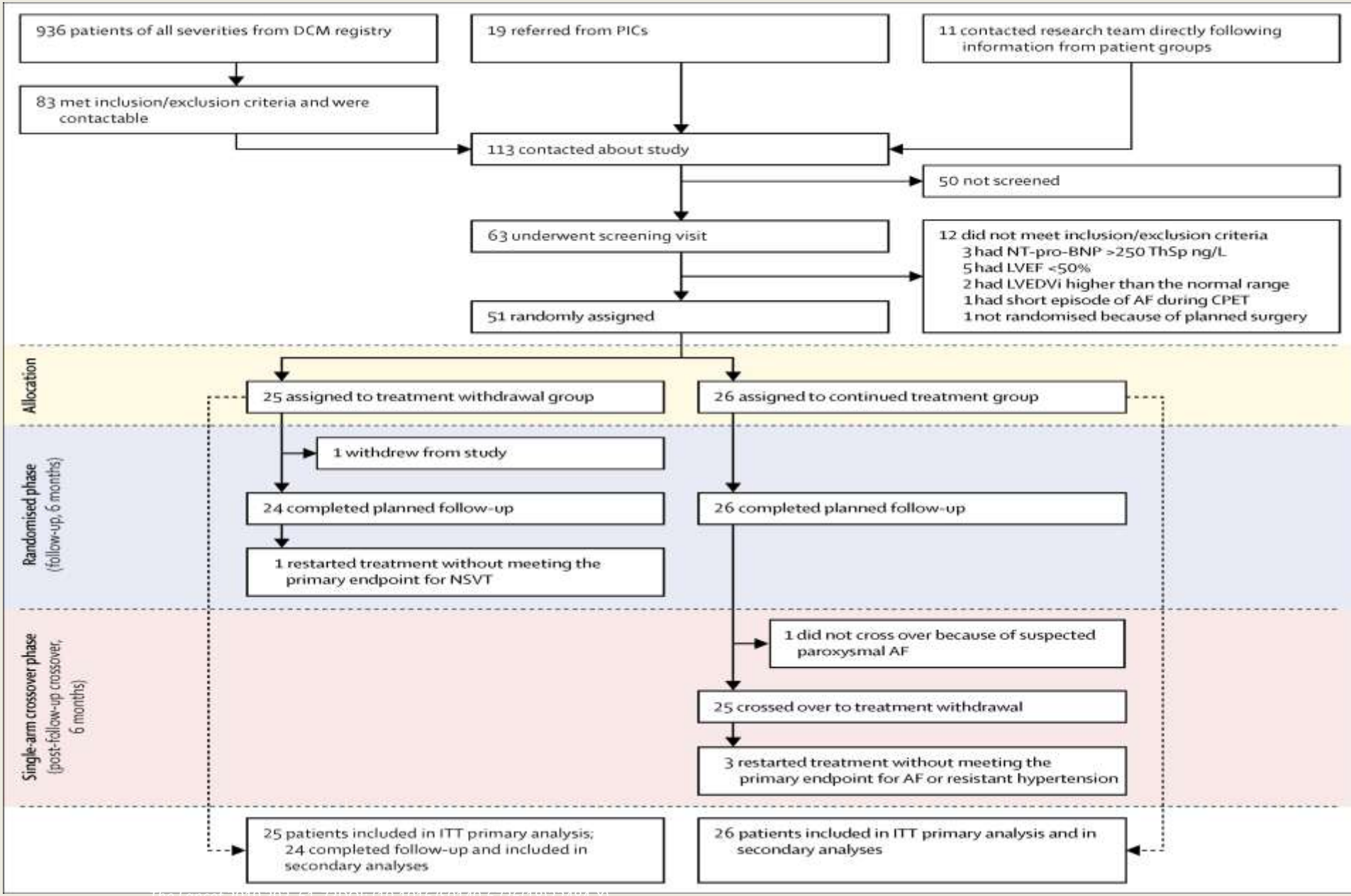
DOI: 10.1016/S0140-6736(18)32484-X

Figure 1



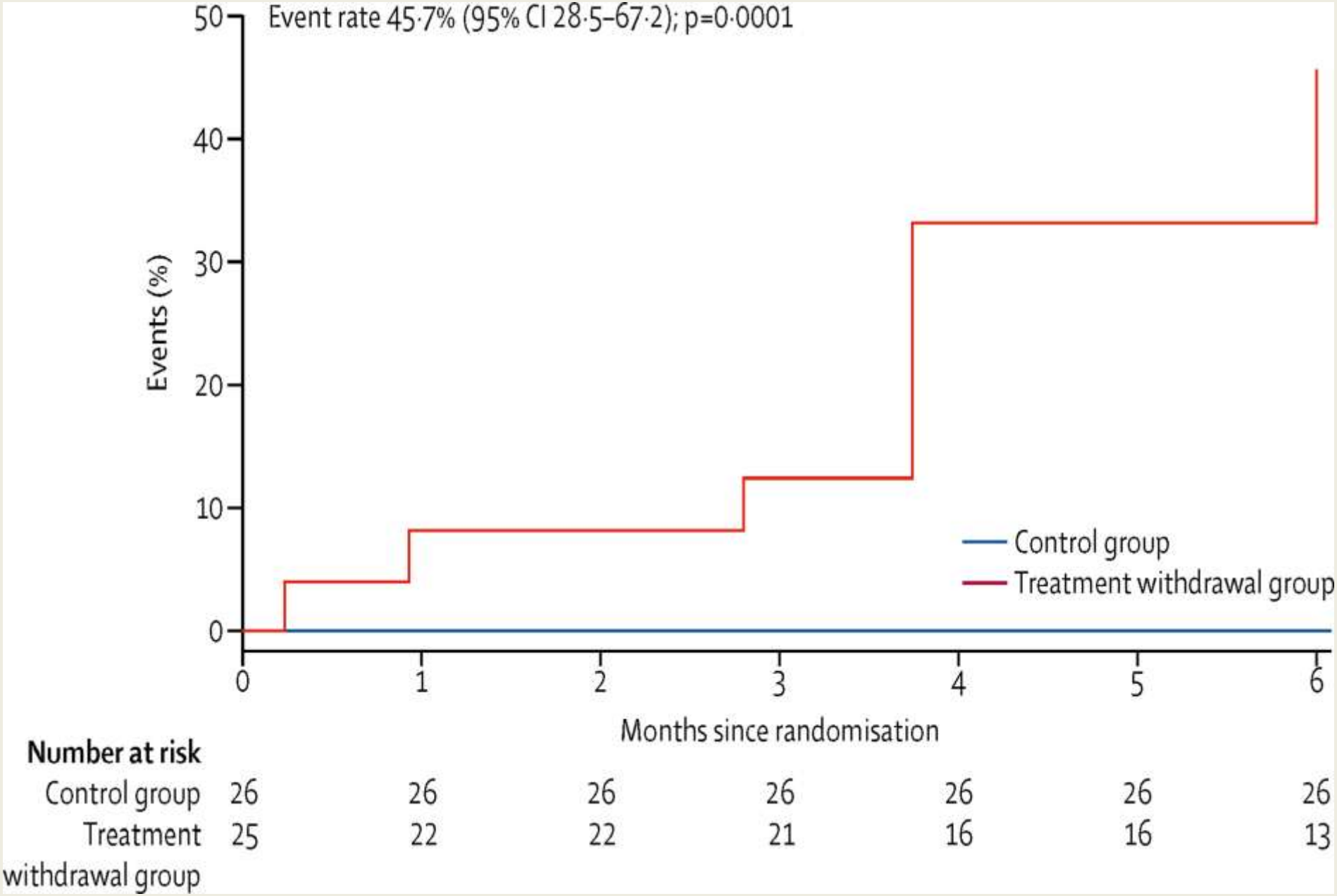
The Lancet 2019 393, 61-73DOI: (10.1016/S0140-6736(18)32484-X)

Figure 2



The Lancet 2019 393, 61-73DOI: (10.1016/S0140-6736(18)32484-X)

Figure 3



The Lancet 2019 393, 61-73DOI: (10.1016/S0140-6736(18)32484-X)

Figure 4

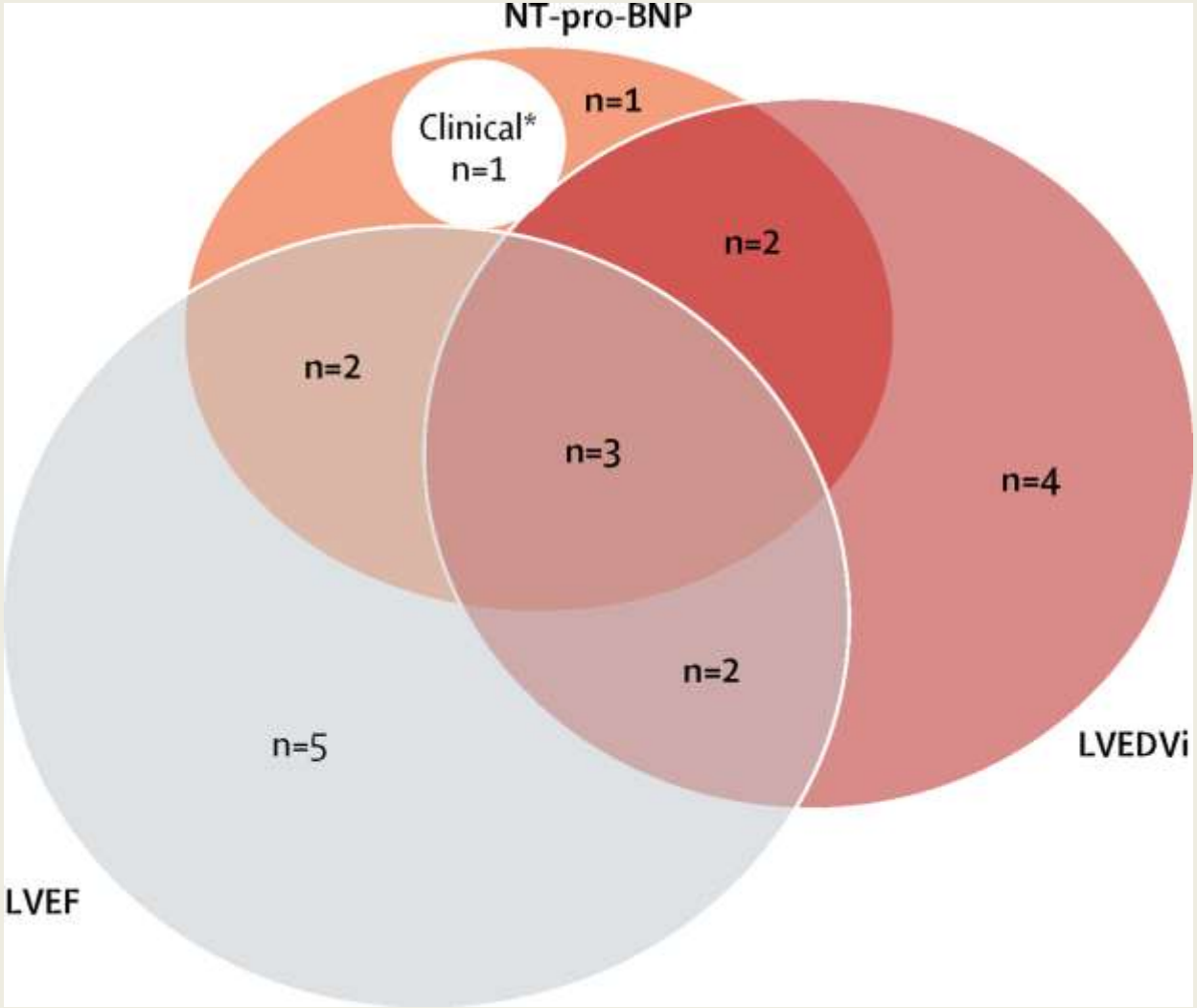
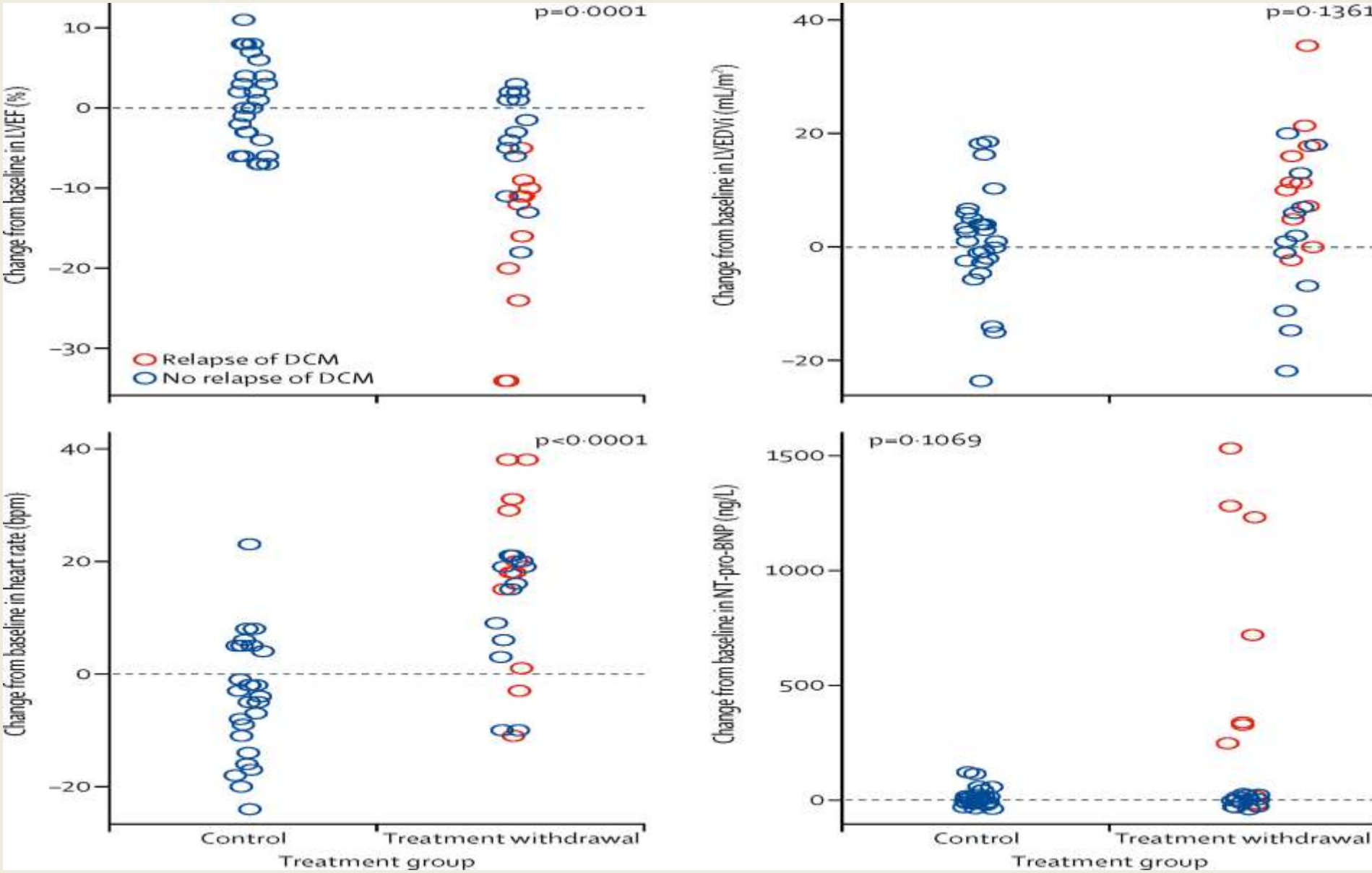


Figure 5



The Lancet 2019 393, 61-73DOI: (10.1016/S0140-6736(18)32484-X)

Original Article

Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease

Faiez Zannad, M.D., Ph.D., Stefan D. Anker, M.D., Ph.D., William M. Byra, M.D., John G.F. Cleland, M.D., Min Fu, Ph.D., Mihai Gheorghiade, M.D., Carolyn S.P. Lam, M.D., Ph.D., Mandeep R. Mehra, M.D., James D. Neaton, Ph.D., Christopher C. Nessel, M.D., Theodore E. Spiro, M.D., Dirk J. van Veldhuisen, M.D., Ph.D., Barry Greenberg, M.D., for the COMMANDER HF Investigators

N Engl J Med
Volume 379(14):1332-1342
October 4, 2018

The NEW ENGLAND JOURNAL of MEDICINE

Study Overview

- Patients with heart failure, coronary artery disease, and no atrial fibrillation were randomly assigned to receive 2.5 mg of rivaroxaban twice daily or placebo.
- Rivaroxaban did not have a significant effect on the composite outcome of death, myocardial infarction, or stroke.

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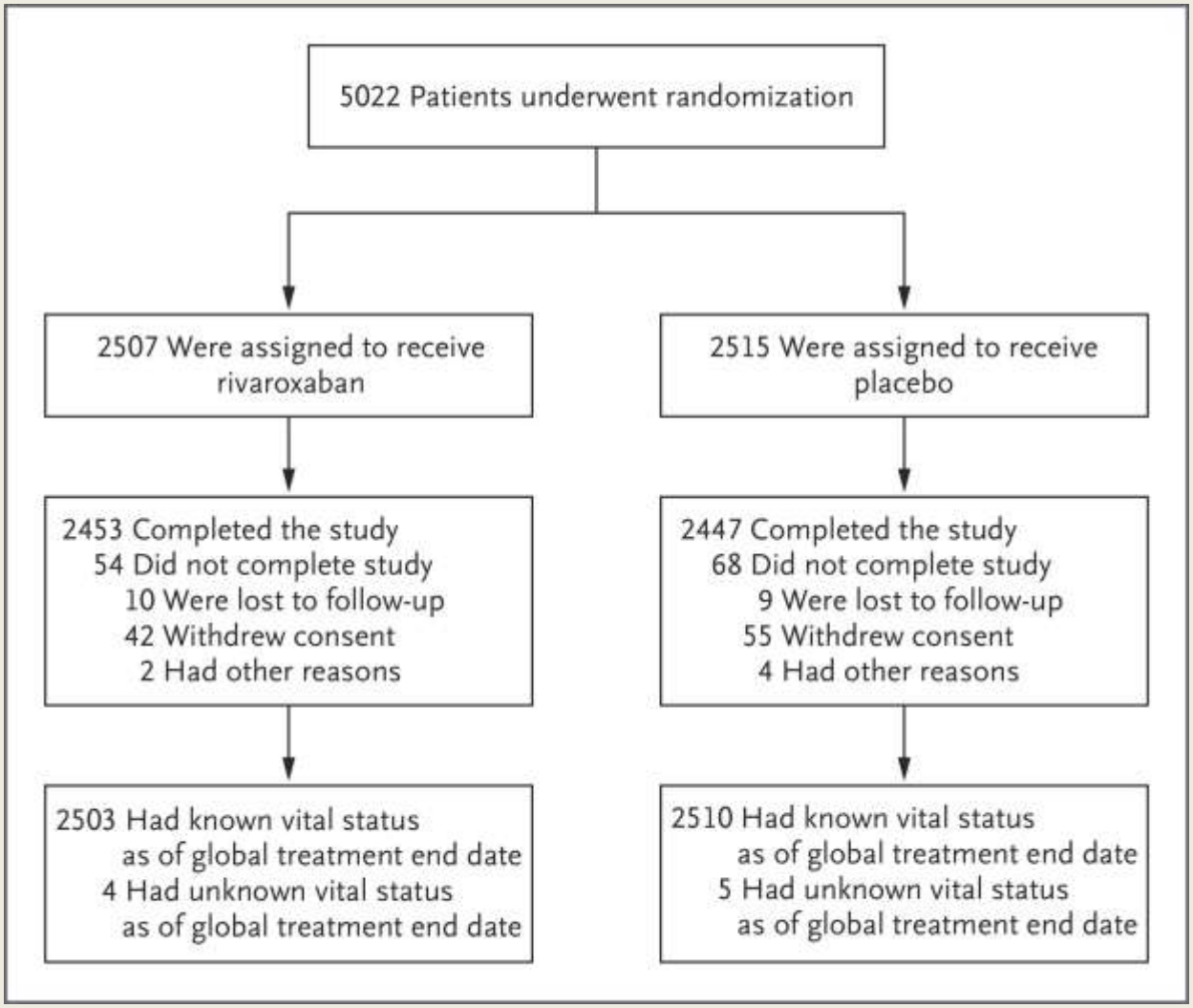
Randomization and Follow-up



Zannad F et al. N Engl J Med 2018;379:1332-1342

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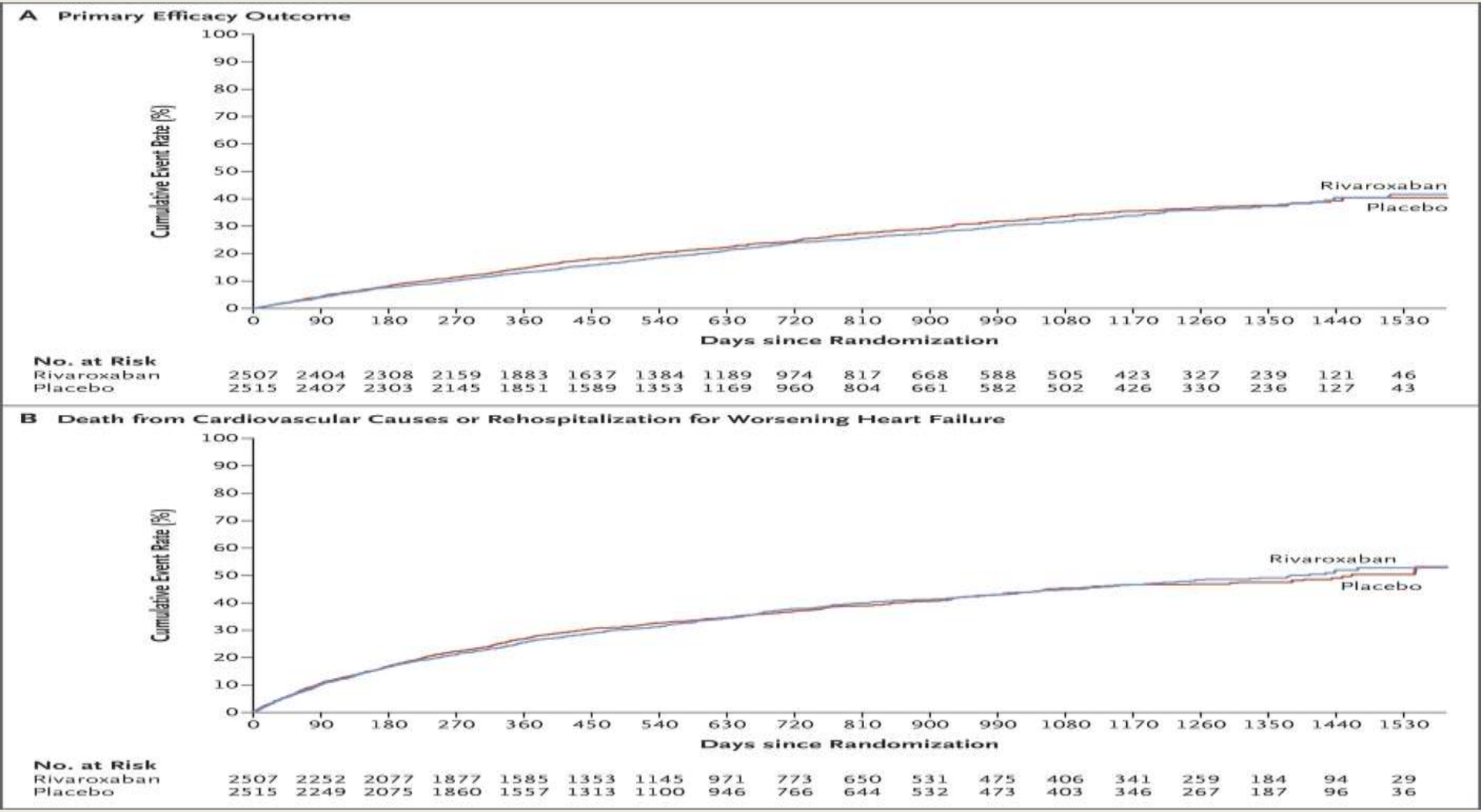
Kaplan–Meier Analysis of the Primary Efficacy Outcome and of Death from Cardiovascular Causes or Rehospitalization for Worsening Heart Failure.



Zannad F et al. N Engl J Med 2018;379:1332-1342

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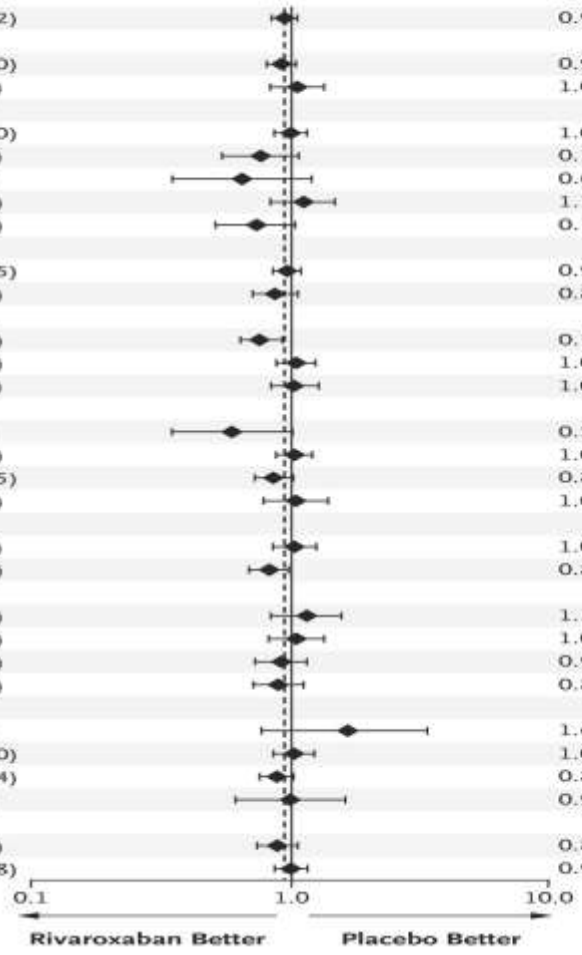
Subgroup Analyses of the Primary Efficacy Outcome

Subgroup	No. of Patients	Rivaroxaban	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
		no. of events/total no. (%)			
Overall	5022	626/2507 (25.0)	658/2515 (26.2)	0.94 (0.84–1.05)	
Sex					0.36
Male	3872	487/1956 (24.9)	517/1916 (27.0)	0.92 (0.81–1.04)	
Female	1150	139/551 (25.2)	141/599 (23.5)	1.05 (0.83–1.33)	
Region					0.14
Eastern Europe	3224	389/1610 (24.2)	388/1614 (24.0)	1.00 (0.87–1.15)	
Western Europe and South Africa	458	61/227 (26.9)	78/231 (33.8)	0.76 (0.54–1.06)	
North America	149	17/74 (23.0)	25/75 (33.3)	0.64 (0.35–1.19)	
Asia-Pacific	733	104/367 (28.3)	94/366 (25.7)	1.11 (0.84–1.46)	
Latin America	458	55/229 (24.0)	73/229 (31.9)	0.73 (0.51–1.04)	
Age					0.43
<75 yr	3831	451/1912 (23.6)	470/1919 (24.5)	0.96 (0.85–1.09)	
≥75 yr	1191	175/595 (29.4)	188/596 (31.5)	0.87 (0.70–1.07)	
BMI					0.03
<25	1602	206/809 (25.5)	253/793 (31.9)	0.76 (0.63–0.92)	
25 to <30	1974	265/1016 (26.1)	236/958 (24.6)	1.05 (0.88–1.25)	
≥30	1442	155/680 (22.8)	167/762 (21.9)	1.03 (0.83–1.28)	
Estimated GFR (ml/min/1.73 m²)					0.18
<30	163	24/81 (29.6)	36/82 (43.9)	0.59 (0.35–1.01)	
30 to <60	1782	274/884 (31.0)	272/898 (30.3)	1.03 (0.87–1.22)	
60 to <90	2238	231/1101 (21.0)	267/1137 (23.5)	0.86 (0.72–1.03)	
≥90	839	97/441 (22.0)	83/398 (20.9)	1.05 (0.78–1.40)	
BNP, NT-proBNP					0.09
≤Median	1950	192/974 (19.7)	185/976 (19.0)	1.03 (0.84–1.26)	
>Median	1949	240/969 (24.8)	289/980 (29.5)	0.82 (0.69–0.97)	
Baseline D-dimer					0.42
≤First quartile	1039	90/516 (17.4)	77/523 (14.7)	1.13 (0.83–1.54)	
>First quartile to ≤median	1027	131/505 (25.9)	125/522 (23.9)	1.03 (0.81–1.32)	
>Median to ≤third quartile	1020	137/491 (27.9)	160/529 (30.2)	0.90 (0.72–1.13)	
>Third quartile	1021	163/525 (31.0)	174/496 (35.1)	0.88 (0.71–1.09)	
Baseline NYHA classification					0.22
I	149	19/80 (23.8)	11/69 (15.9)	1.61 (0.76–3.42)	
II	2218	247/1122 (22.0)	241/1096 (22.0)	1.00 (0.84–1.20)	
III	2462	324/1208 (26.8)	369/1254 (29.4)	0.87 (0.75–1.01)	
IV	192	35/96 (36.5)	37/96 (38.5)	0.98 (0.60–1.59)	
Baseline ejection fraction (%)					0.27
<30	1502	220/717 (30.7)	264/785 (33.6)	0.87 (0.73–1.04)	
≥30	3520	406/1790 (22.7)	394/1730 (22.8)	0.99 (0.86–1.14)	



Zannad F et al. N Engl J Med 2018;379:1332-1342

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Characteristics of the Patients at Baseline

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Rivaroxaban (N = 2507)	Placebo (N = 2515)
Age — yr	66.5±10.1	66.3±10.3
Female sex — no. (%)	551 (22.0)	599 (23.8)
Race — no. (%)†		
White	2063 (82.3)	2065 (82.1)
Black	29 (1.2)	36 (1.4)
Asian	362 (14.4)	365 (14.5)
Other	53 (2.1)	49 (1.9)
Region — no. (%)		
Eastern Europe	1610 (64.2)	1614 (64.2)
North America	74 (3.0)	75 (3.0)
Asia-Pacific	367 (14.6)	366 (14.6)
Latin America	229 (9.1)	229 (9.1)
Western Europe or South Africa	227 (9.1)	231 (9.2)
Body-mass index‡	27.6±5.1	27.8±5.3
eGFR — no. (%)		
<30 ml/min/1.73 m^2	81 (3.2)	82 (3.3)
30 to <60 ml/min/1.73 m^2	884 (35.3)	898 (35.7)
60 to <90 ml/min/1.73 m^2	1101 (43.9)	1137 (45.2)
≥90 ml/min/1.73 m^2	441 (17.6)	398 (15.8)
Clinical features of heart failure		
Median BNP level (IQR) — pg/ml§	702.0 (403.4–1237.0)	695.5 (380.0–1266.3)
Median NT-proBNP level (IQR) — pg/ml§	2840.0 (1537.0–6394.0)	2900.0 (1520.0–6270.5)
Median D-dimer level (IQR) — μg/liter	360 (215–680)	360 (215–650)
Median ejection fraction (IQR) — %	35 (28–38)	34 (27–38)
New York Heart Association classification — no. (%)		
I	80 (3.2)	69 (2.7)
II	1122 (44.8)	1096 (43.6)
III	1208 (48.2)	1254 (49.9)
IV	96 (3.8)	96 (3.8)
Medical history — no. (%)		
Myocardial infarction	1911 (76.2)	1892 (75.2)
Stroke	208 (8.3)	245 (9.7)
Diabetes	1024 (40.8)	1028 (40.9)
Hypertension	1897 (75.7)	1886 (75.0)

* Plus–minus values are means ±SD. There were no significant differences between the groups with regard to any characteristic. More details about the baseline characteristics are provided in Table S1 in the Supplementary Appendix. Percentages may not total 100 because of rounding. BNP denotes brain natriuretic peptide, eGFR estimated glomerular filtration rate, IQR interquartile range, and NT-proBNP N-terminal pro–brain natriuretic peptide.

† Race was reported by the patient.

‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Data on natriuretic peptides were obtained after protocol amendment. Data on BNP were obtained for 965 patients, and data on NT-proBNP were obtained for 2862 patients.

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Efficacy and Safety Outcomes

Table 2. Efficacy and Safety Outcomes.*

Outcome	Rivaroxaban (N=2507)		Placebo (N=2515)		Rivaroxaban vs. Placebo†	
	No. (%)	Events/ 100 Patient-Yr	No. (%)	Events/ 100 Patient-Yr	Hazard Ratio (95% CI)	P Value
Efficacy outcomes‡						
Composite primary efficacy outcome	626 (25.0)	13.44	658 (26.2)	14.27	0.94 (0.84–1.05)	0.27
Death from any cause	546 (21.8)	11.41	556 (22.1)	11.63	0.98 (0.87–1.10)	—
Myocardial infarction	98 (3.9)	2.08	118 (4.7)	2.52	0.83 (0.63–1.08)	—
Stroke	51 (2.0)	1.08	76 (3.0)	1.62	0.66 (0.47–0.95)	—
Secondary and exploratory efficacy outcomes						
Death from a cardiovascular cause or rehospitalization for worsening of heart failure	932 (37.2)	23.32	929 (36.9)	23.46	0.99 (0.91–1.09)	—
Death from a cardiovascular cause	453 (18.1)	9.46	476 (18.9)	9.96	0.95 (0.84–1.08)	—
Rehospitalization for worsening of heart failure	689 (27.5)	17.24	691 (27.5)	17.45	0.98 (0.89–1.09)	—
Rehospitalization for cardiovascular event other than worsening of heart failure	543 (21.7)	13.30	572 (22.7)	14.04	0.95 (0.84–1.07)	—
Death from any cause or rehospitalization for worsening of heart failure	993 (39.6)	24.84	973 (38.7)	24.57	1.01 (0.92–1.10)	—
Symptomatic deep-vein thrombosis	5 (0.2)	0.10	7 (0.3)	0.15	0.71 (0.23–2.24)	—
Symptomatic pulmonary embolism	11 (0.4)	0.23	9 (0.4)	0.19	1.23 (0.51–2.96)	—
	Rivaroxaban (N=2499)		**Placebo (N=2509)**		**Rivaroxaban vs. Placebo†**	
	No. (%)	Events/ 100 Patient-Yr	No. (%)	Events/ 100 Patient-Yr	Hazard Ratio (95% CI)	P Value
Safety outcomes§						
Composite principal safety outcome	18 (0.7)	0.44	23 (0.9)	0.55	0.80 (0.43–1.49)	0.48
Fatal bleeding	9 (0.4)	0.22	9 (0.4)	0.22	1.03 (0.41–2.59)	0.95
Bleeding into a critical space with potential for causing permanent disability	13 (0.5)	0.32	20 (0.8)	0.48	0.67 (0.33–1.34)	0.25
ISTH-defined major bleeding¶	82 (3.3)	2.04	50 (2.0)	1.21	1.68 (1.18–2.39)	0.003
Hemoglobin decrease of ≥2 g/dl	55 (2.2)	1.37	30 (1.2)	0.73	1.87 (1.20–2.91)	0.005
Transfusion of ≥2 units of packed red cells or whole blood	31 (1.2)	0.77	18 (0.7)	0.43	1.74 (0.98–3.12)	0.06
Bleeding at a critical site	25 (1.0)	0.62	23 (0.9)	0.56	1.12 (0.63–1.97)	0.70
Fatal bleeding	3 (0.1)	0.07	7 (0.3)	0.17	0.45 (0.12–1.72)	0.23
Bleeding requiring hospitalization	61 (2.4)	1.52	48 (1.9)	1.16	1.30 (0.89–1.90)	0.17

* For each composite outcome, only the first event in a given patient was included; for the individual components of that outcome, all first events of that component outcome were included.
† Hazard ratios and 95% confidence intervals are from a Cox proportional-hazards model stratified according to region, with trial-group assignment as the only effect. P values (two-sided) are from the log-rank test stratified according to region. The 95% confidence intervals have not been adjusted for multiplicity, and inferences drawn from these intervals may not be reproducible.
‡ The primary efficacy outcome was a composite of death from any cause, myocardial infarction, or stroke. Data are from the intention-to-treat population during the observation period from randomization through the global treatment end date (March 5, 2018).
§ The principal safety outcome was a composite of fatal bleeding or bleeding into a critical space with a potential for causing permanent disability. Safety outcome comparisons included only the patients who took at least one dose of rivaroxaban or placebo. Events are those that occurred during the observation period from the first dose of rivaroxaban or placebo through 2 days after the last dose.
¶ Major bleeding is defined by the International Society on Thrombosis and Haemostasis (ISTH) as overt bleeding associated with a decrease in hemoglobin level of at least 2 g per deciliter, transfusion of two or more units of packed red cells or whole blood, a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or a fatal outcome.

Zannad F et al. N Engl J Med 2018;379:1332-1342

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Conclusions

- Rivaroxaban at a dose of 2.5 mg twice daily was not associated with a significantly lower rate of death, myocardial infarction, or stroke than placebo among patients with worsening chronic heart failure, reduced left ventricular ejection fraction, coronary artery disease, and no atrial fibrillation.

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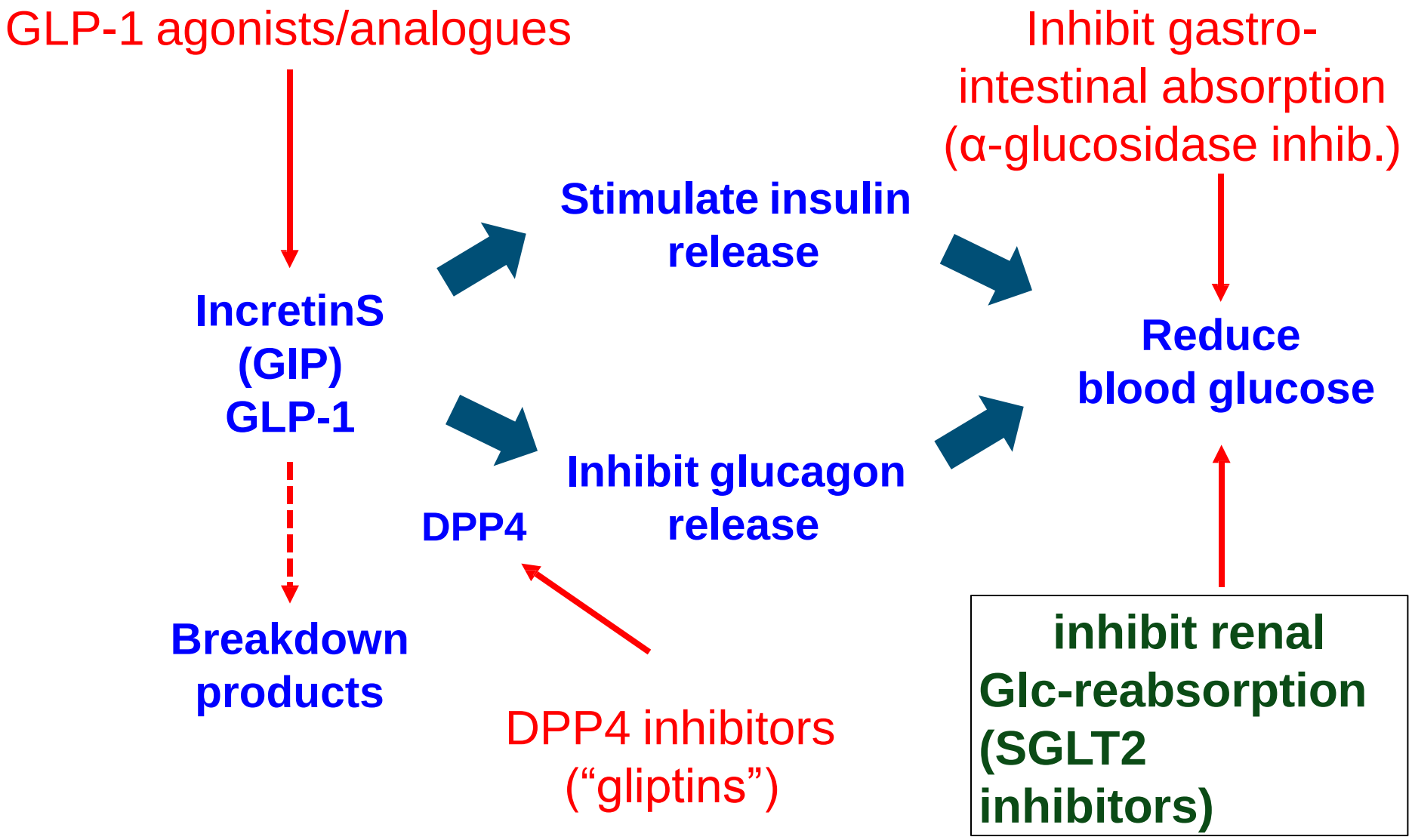
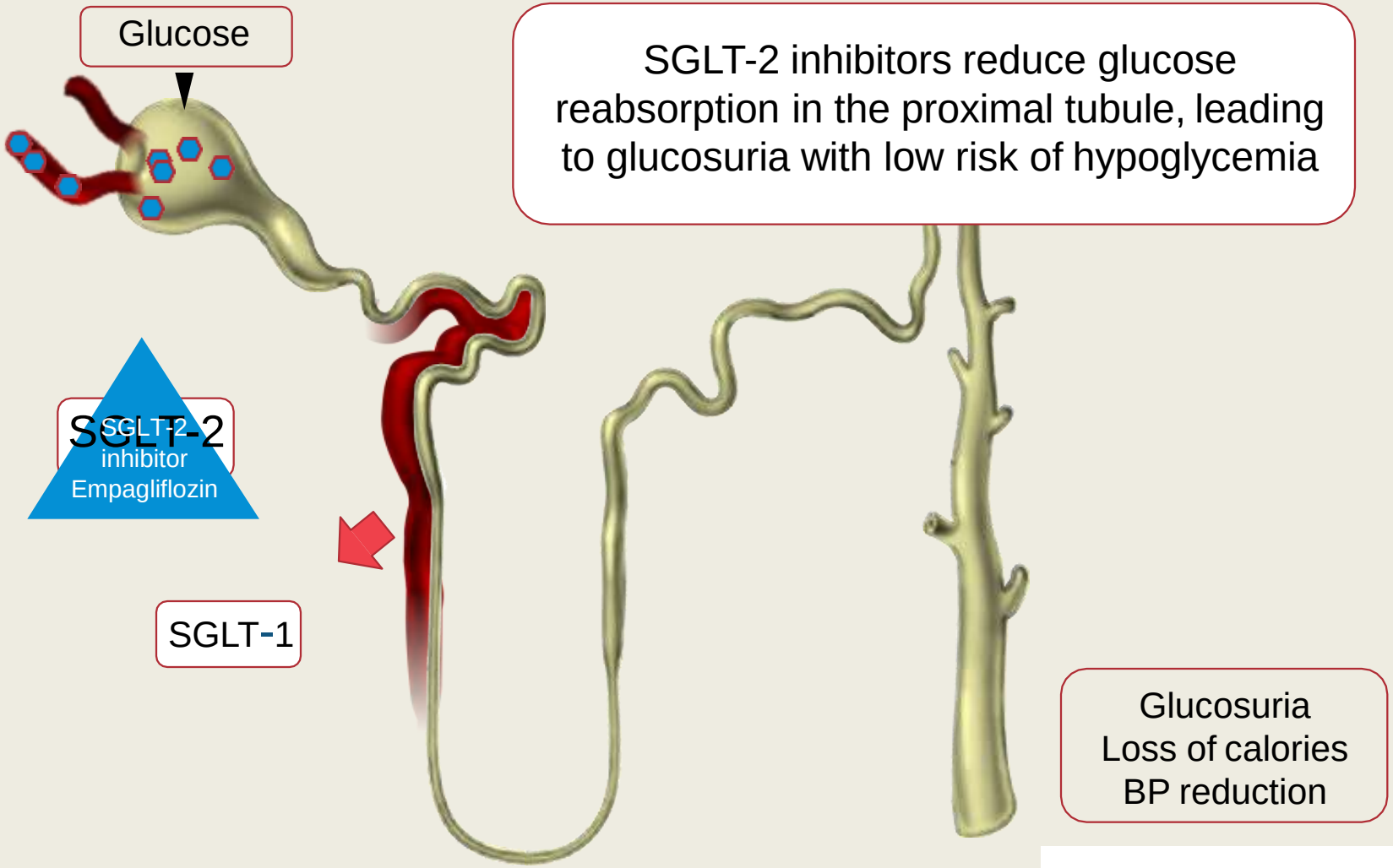
New Approaches To Reducing Blood Glucose



Mode of action



Randomised controlled trials of SGLT2 inhibitors in HF

	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;
4. ClinicalTrials.gov NCT03521934; 5. EU Clinical Trials Register 2017-003510-16. Available at: https://www.clinicaltrialsregister.eu

Boehringer Ingelheim and Lilly announce the CAROLINA® cardiovascular outcome trial of Tradjenta® met its primary endpoint of non-inferiority compared with glimepiride

Tradjenta (linagliptin) demonstrated no increased cardiovascular risk compared with glimepiride in adults with type 2 diabetes and cardiovascular risk

With a median follow-up of more than 6 years, CAROLINA adds evidence to the long-term safety profile of Tradjenta

Ridgefield, Conn. and Indianapolis, February 14, 2019 – Boehringer Ingelheim and Eli Lilly and Company (NYSE: LLY) announced CAROLINA® (CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes) met its primary endpoint, defined as non-inferiority for Tradjenta® (linagliptin) versus glimepiride in time to first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (3P-MACE). CAROLINA is the only active-comparator cardiovascular outcome trial for a dipeptidyl peptidase-4 (DPP-4) inhibitor. The trial evaluated the cardiovascular safety of Tradjenta (5 mg once daily) compared with the sulfonylurea glimepiride, on top of standard of care, in 6,033 adults with type 2 diabetes and increased cardiovascular risk or established cardiovascular disease. The study assessed Tradjenta safety over the longest period ever studied in a DPP-4 inhibitor cardiovascular outcome trial, with a median follow-up of more than 6 years. The overall safety profile of Tradjenta in CAROLINA was consistent with previous data, and no new safety signals were observed.

CENTRAL ILLUSTRATION: Stepwise Approach to Prescription of SGLT2 inhibitors by Cardiologists

Patients with T2DM with or at High Risk for CV Disease, Already on Metformin

Below Individualized HbA1c Target:

Switch non-metformin oral therapies (e.g. sulfonylureas) to a SGLT2i

Above Individualized HbA1c Target:

Consider SGLT2i initiation

Drug Type

Canagliflozin, dapagliflozin, & empagliflozin with similar efficacy profile in reducing HF events

Starting Dose (once daily in AM)

- Canagliflozin (100mg)
- Dapagliflozin (5mg)
- Empagliflozin (10mg)
- Ertugliflozin (5mg)

Metformin+SGLT2i Combination Therapies

Consider to limit non-adherence and pill burden

Stable Hemodynamic and Clinical Status

Pre-Initiation eGFR must be above:

- 60 mL/min/1.73 m^2 (dapagliflozin, ertugliflozin)
- 45 mL/min/1.73 m^2 (canagliflozin, empagliflozin)

Anticipatory Guidance

Consider diuretic dose reduction

Patient Counseling

- Genital/perineal hygiene
- Orthostatic hypotension
- Regular foot exams
- Symptoms of DKA
- Avoid excessive alcohol

Multidisciplinary Care

Close communication with other providers, including PCPs and endocrinologists

Follow-up and Monitoring

- Serial assessment of ren function, body weights, b pressure, and symptoms
- Dose uptitration guided b need for glycemic contro
- Ensure adherence to SG other therapies, and therapeutic lifestyle
- Multidisciplinary care tea follow-up

Vardeny, O. et al. J Am Coll Cardiol HF. 2019;7(2):169-72.

Original Article

Two-Year Outcomes with a Magnetically Levitated Cardiac Pump in Heart Failure

Mandeep R. Mehra, M.D., Daniel J. Goldstein, M.D., Nir Uriel, M.D., Joseph C. Cleveland, Jr., M.D., Melana Yuzefpolskaya, M.D., Christopher Salerno, M.D., Mary N. Walsh, M.D., Carmelo A. Milano, M.D., Chetan B. Patel, M.D., Gregory A. Ewald, M.D., Akinobu Itoh, M.D., David Dean, M.D., Arun Krishnamoorthy, M.D., William G. Cotts, M.D., Antone J. Tatooles, M.D., Ulrich P. Jorde, M.D., Brian A. Bruckner, M.D., Jerry D. Estep, M.D., Valluvan Jeevanandam, M.D., Gabriel Sayer, M.D., Douglas Horstmanshof, M.D., James W. Long, M.D., Sanjeev Gulati, M.D., Eric R. Skipper, M.D., John B. O'Connell, M.D., Gerald Heatley, M.S., Poornima Sood, M.D., Yoshifumi Naka, M.D., for the MOMENTUM 3 Investigators

N Engl J Med
Volume 378(15):1386-1395
April 12, 2018

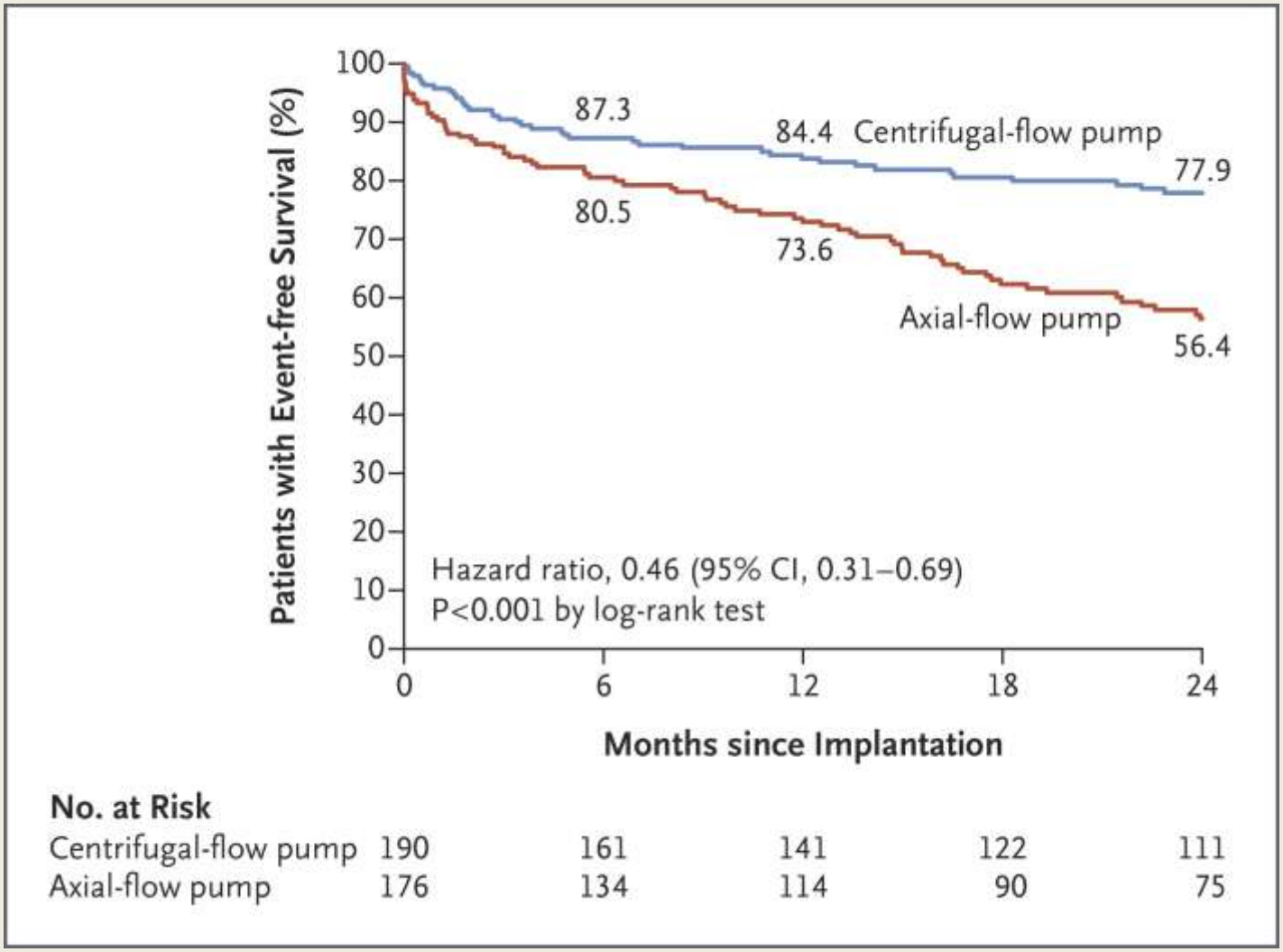
The NEW ENGLAND JOURNAL of MEDICINE

Study Overview

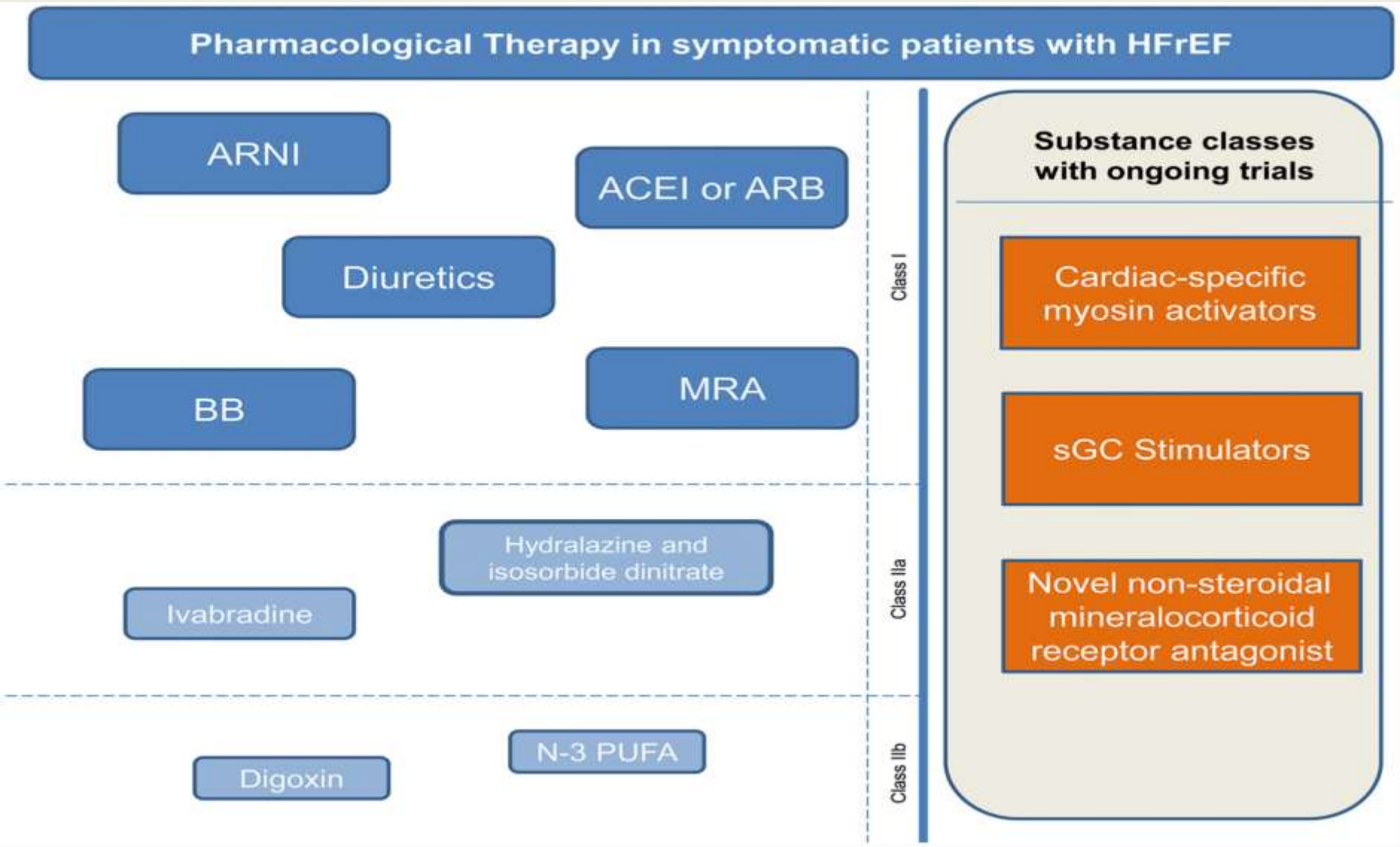
- In a randomized trial, 366 patients with advanced heart failure received a centrifugal- or axial-flow LVAD.
- At 2 years, the centrifugal-flow LVAD was superior with regard to survival free of disabling stroke or reoperation to replace or remove a malfunctioning device.

The NEW ENGLAND JOURNAL of MEDICINE

Kaplan–Meier Estimates of the Primary End Point in the Intention-to-Treat Population



Mehra MR et al. N Engl J Med 2018;378:1386-1395



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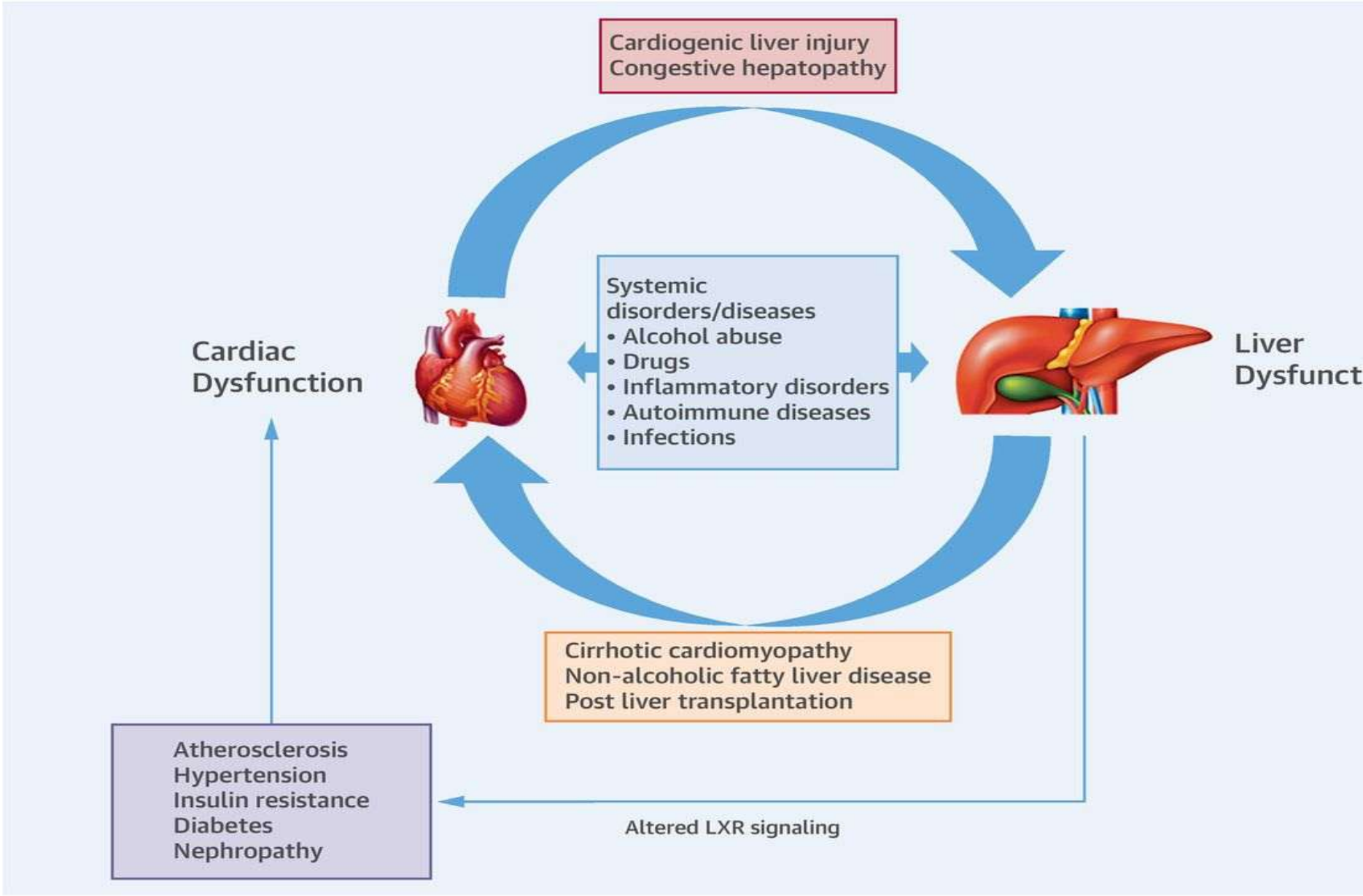
CENTRAL ILLUSTRATION: Cardiac and Liver Dysfunction Often Co-



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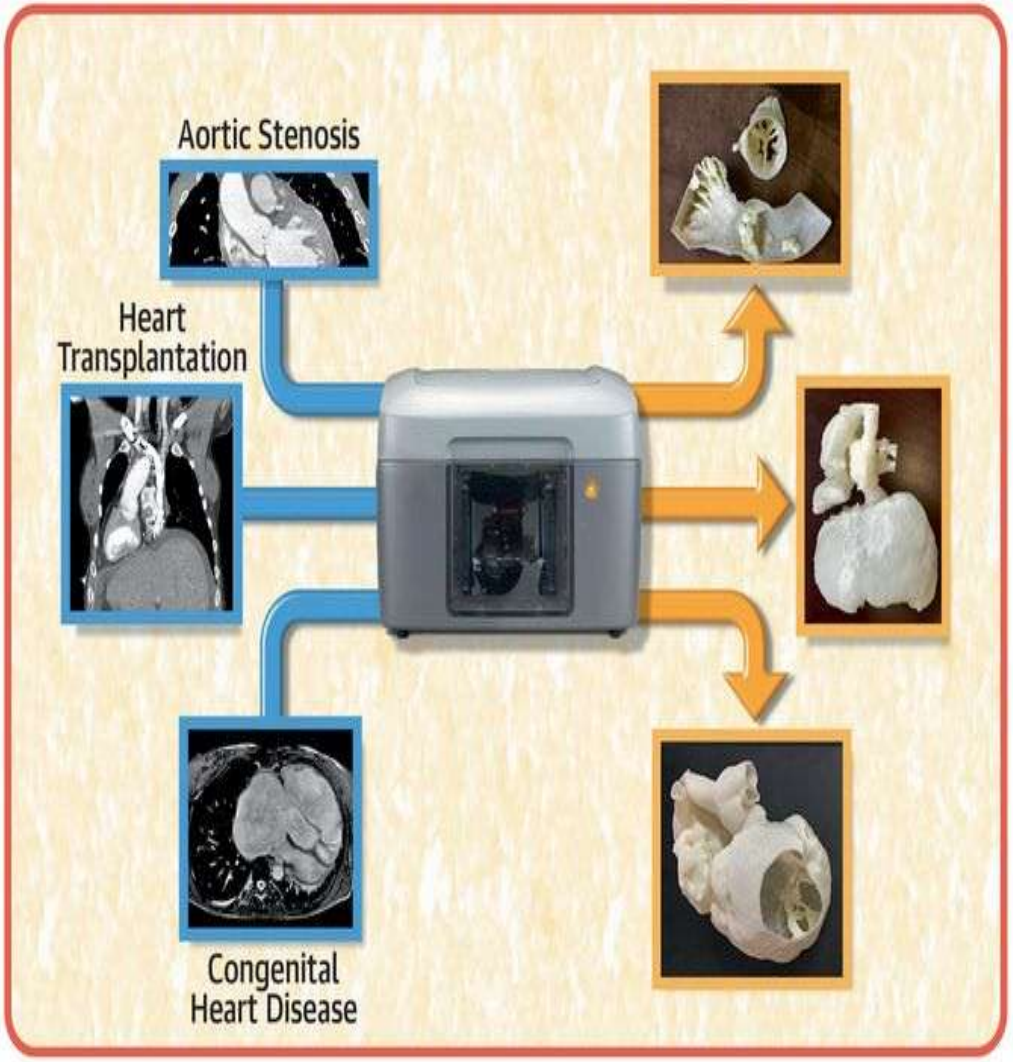
CENTRAL ILLUSTRATION: Causes of Heart Failure



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