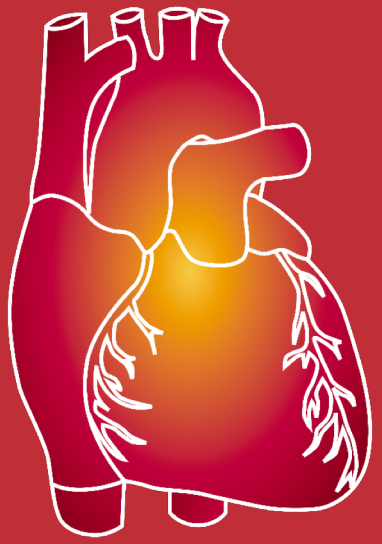
FÜR ALLE ÄRZTE AUS PRAXIS UND KLINIK!



20 Jahre Consensus Meeting

DER AG HERZINSUFFIZIENZ

DFP

Diese Veranstaltung entspricht 5 DFP-Punkten der österreichischen Ärztekammer

med Congress

Therapie der kardialen ATTR Amyloidose

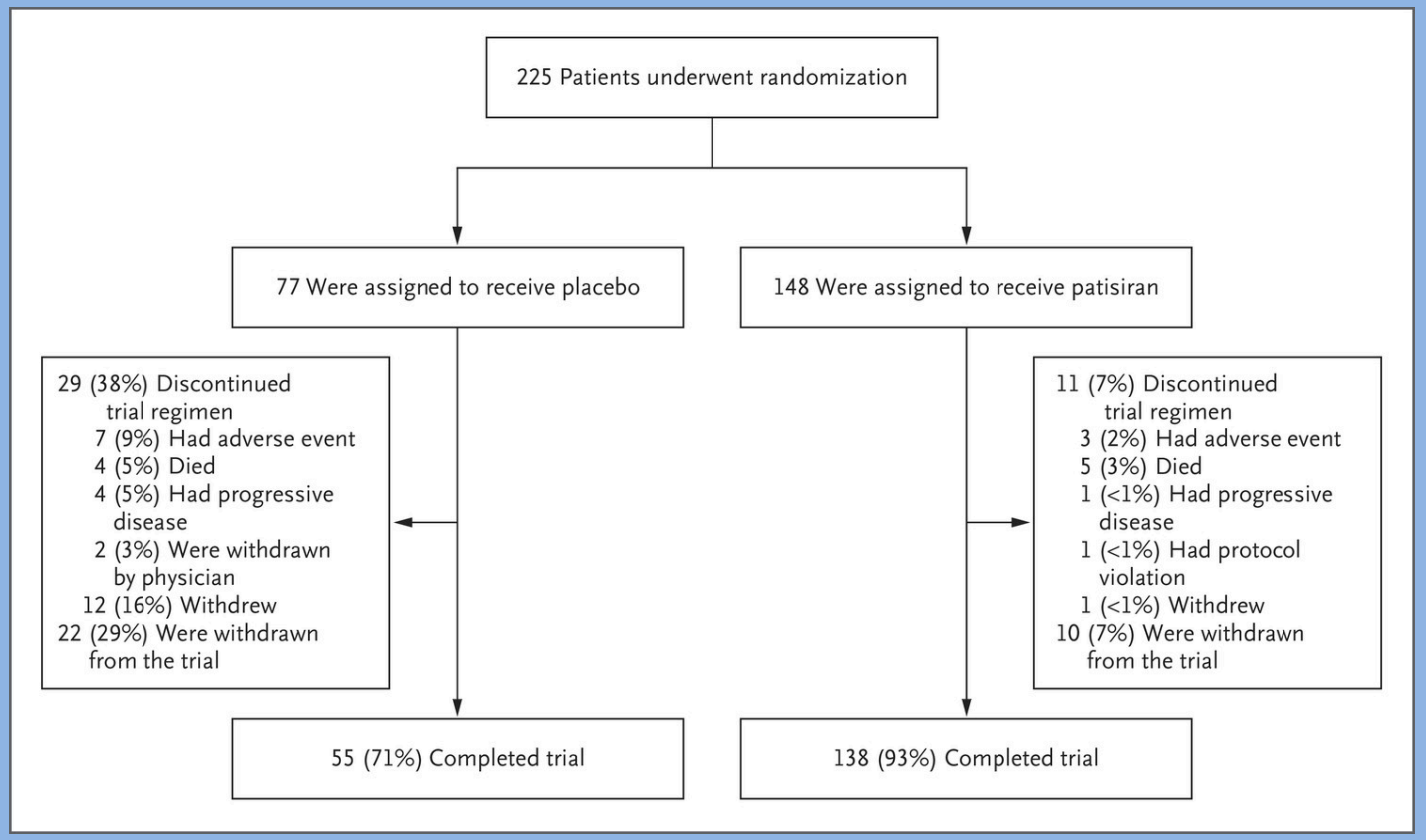
Circulation

ORIGINAL RESEARCH ARTICLE

Effects of Patisiran, an RNA Interference Therapeutic, on Cardiac Parameters in Patients With Hereditary Transthyretin-Mediated Amyloidosis

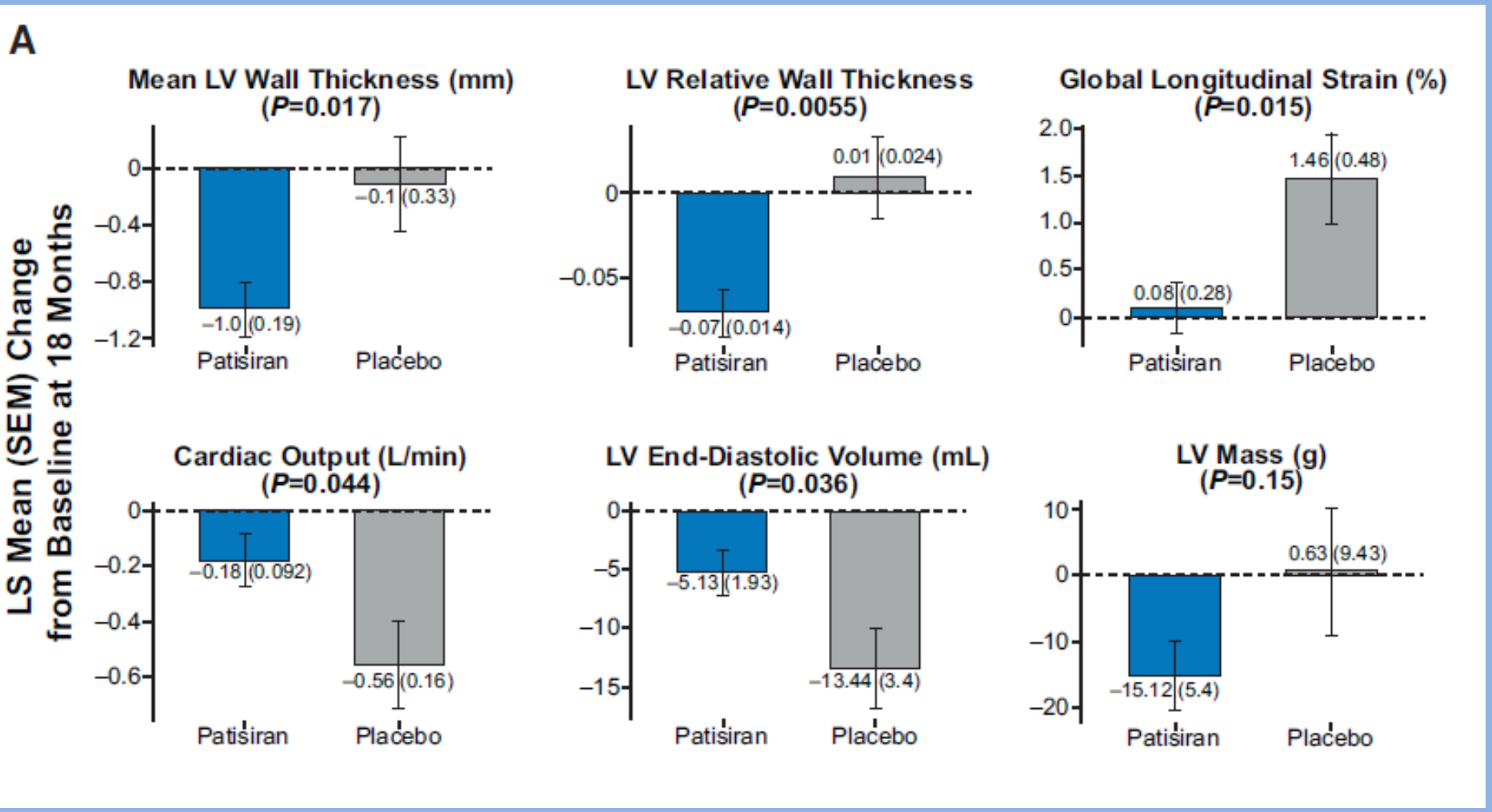
Analysis of the APOLLO Study

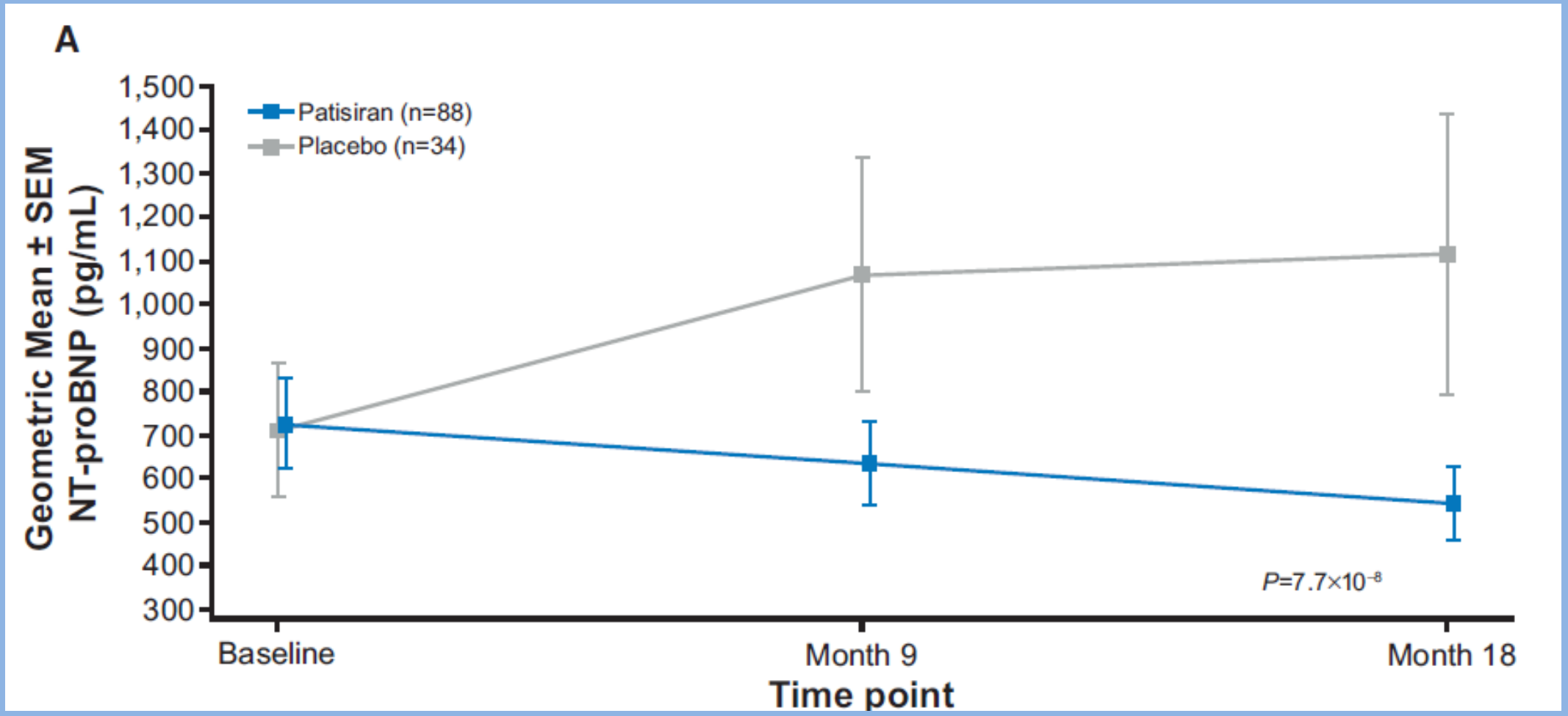
Randomization and Follow-up.

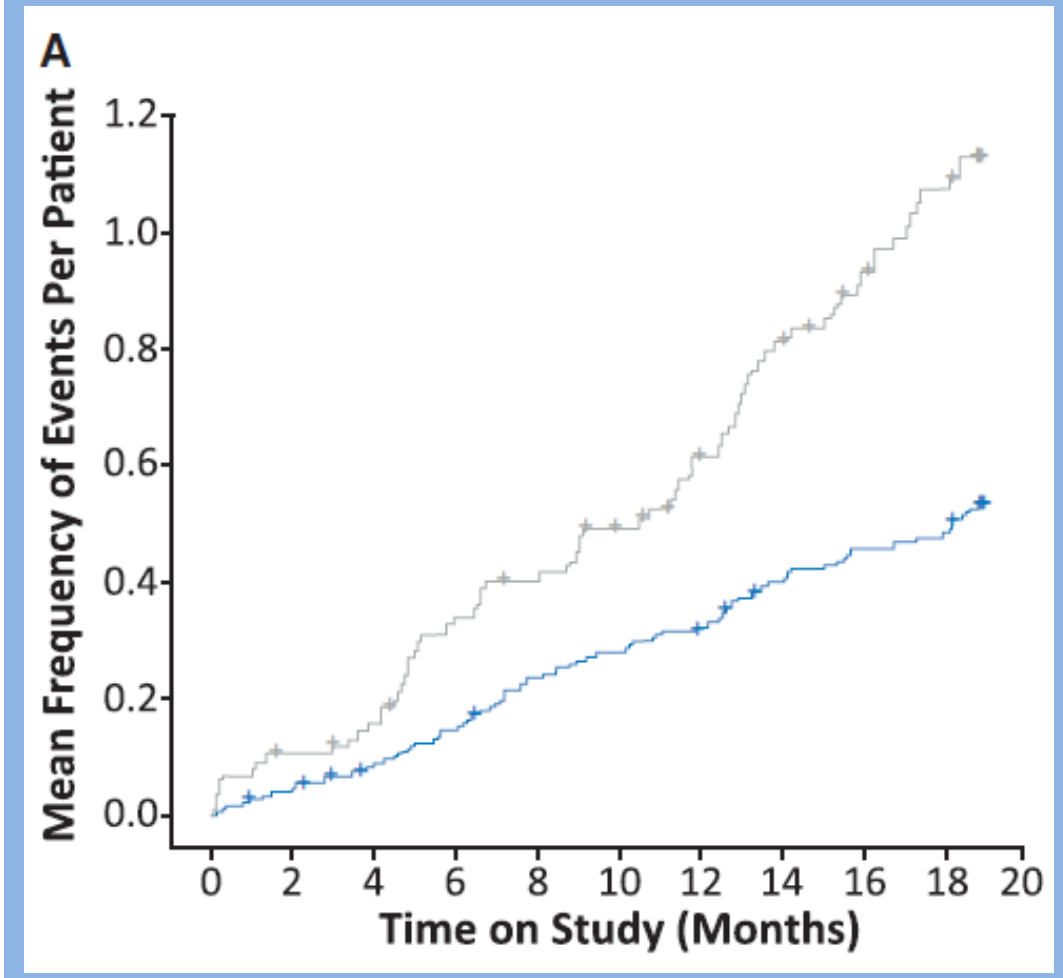


D Adams et al. N Engl J Med 2018;379:11-21.

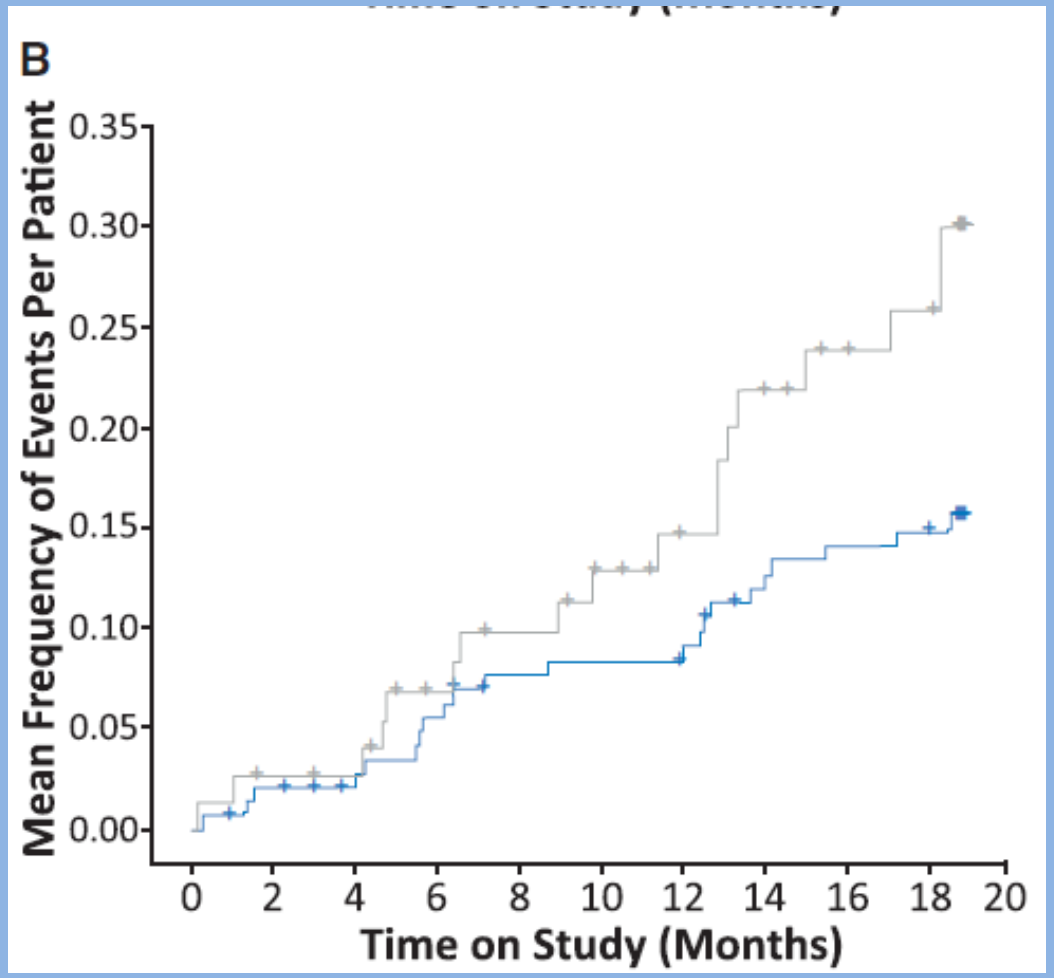
The NEW ENGLAND JOURNAL of MEDICINE


A
LS Mean (SEM) Change from Baseline at 18 Months
Mean LV Wall Thickness (mm) (P=0.017)
0
−0.4
−0.8
−1.2
−1.0 (0.19)
−0.1 (0.33)
Patisiran
Placebo
LV Relative Wall Thickness (P=0.0055)
0
−0.05
−0.07 (0.014)
0.01 (0.024)
Patisiran
Placebo
Global Longitudinal Strain (%) (P=0.015)
2.0
1.5
1.0
0.5
0
0.08 (0.28)
1.46 (0.48)
Patisiran
Placebo
Cardiac Output (L/min) (P=0.044)
0
−0.2
−0.4
−0.6
−0.18 (0.092)
−0.56 (0.16)
Patisiran
Placebo
LV End-Diastolic Volume (mL) (P=0.036)
0
−5
−10
−15
−5.13 (1.93)
−13.44 (3.4)
Patisiran
Placebo
LV Mass (g) (P=0.15)
10
0
−10
−20
−15.12 (5.4)
0.63 (9.43)
Patisiran
Placebo


A
Patisiran (n=88)
Placebo (n=34)
Geometric Mean ± SEM
NT-proBNP (pg/mL)
1,500
1,400
1,300
1,200
1,100
1,000
900
800
700
600
500
400
300
P=7.7×10-8
Baseline
Month 9
Month 18
Time point



All cause hospitalisation and all cause mortality



Cardiac hospitalisation and all cause mortality

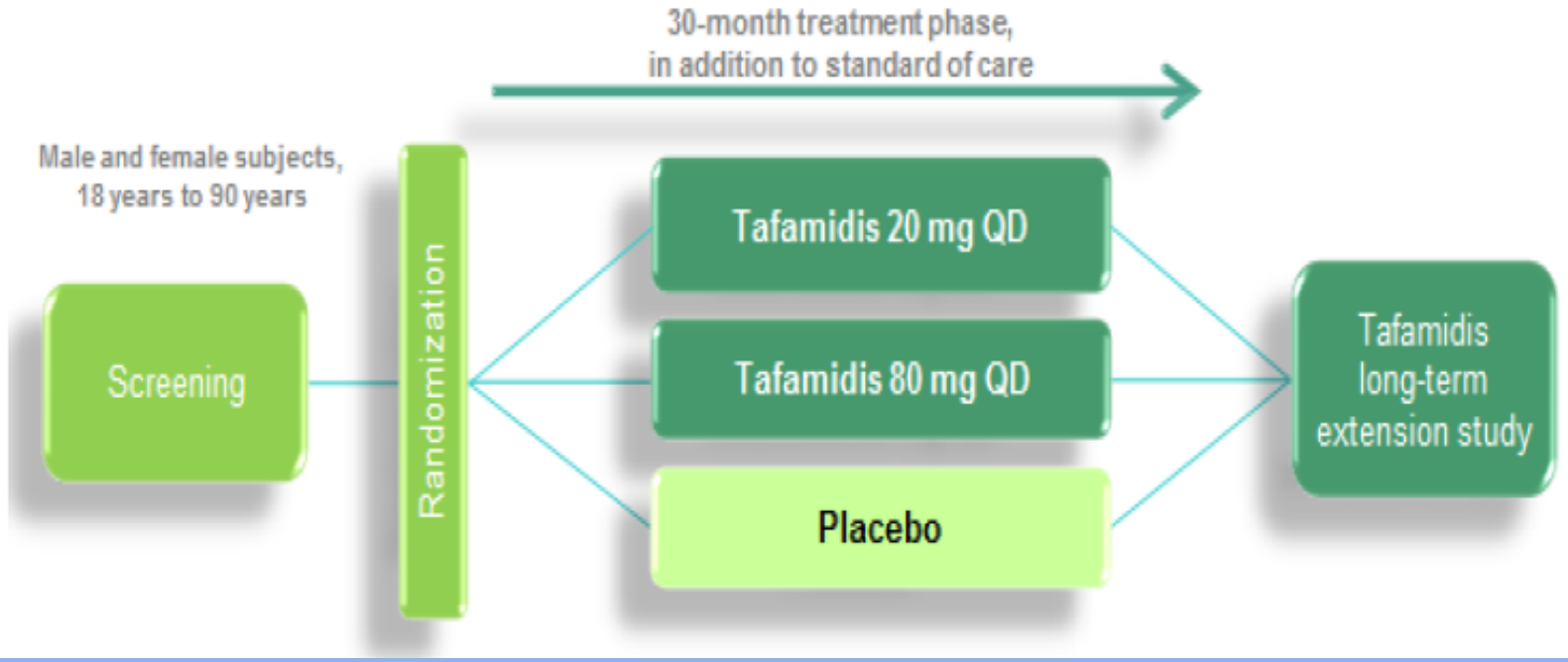
ATTR-ACT

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., and Claudio Rapezzi, M.D., for the ATTR-ACT Study Investigators*

ATTR-ACT Study Design



2:1:2 Tafamidis 80mg : Tafamidis 20mg : Placebo

Maurer MS NEJM 2018

Ein- und Ausschlusskriterien

Einschlusskriterien

- **Biopsie** (auch nicht-kardial) mit **Amyloid**ablagerungen und **TTR** Precursor Protein (Massenspektrometrisch, immunhistochemisch oder szintigrapisch)
- **Herzbeteiligung** (Enddiast. Septumdicke >12mm)
- Mind. 1 frühere **HI-Hospitalisierung**
- **NT-proBNP ≥600pg/mL**

Ausschlusskriterien

- **NYHA IV**
- **eGFR <25mL/min/1.73m2**
- **NSAR**
- **mBMI <600 kg/m^2*g/L**

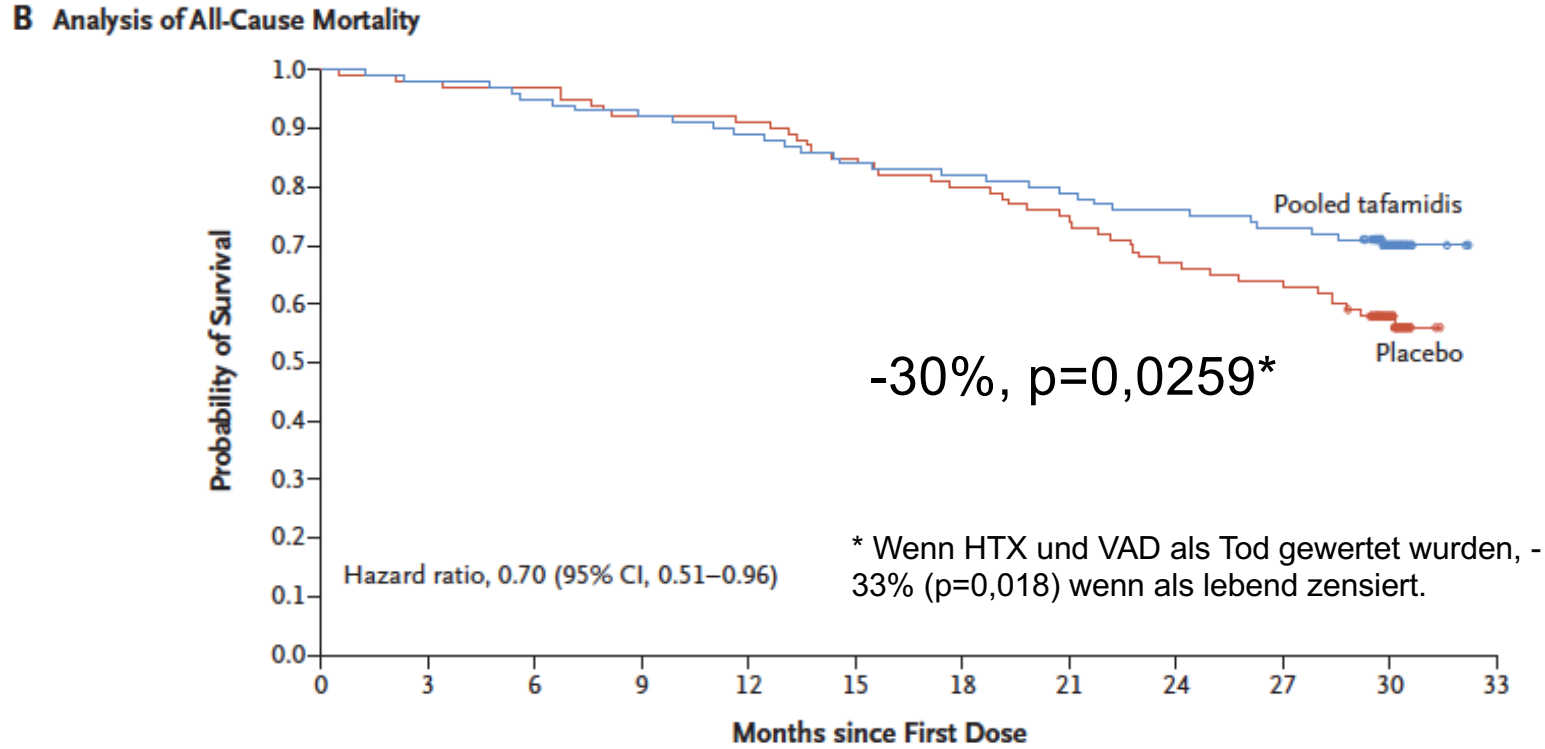
Maurer MS NEJM 2018

CV Hospitalisierungen -32% mit Tafamidis

	Pooled Tafamidis n=264	Placebo n=177
Total (%) number of patients with CV-related hospitalizations	138 (52.3)	107 (60.5)
CV-related hospitalizations per yr	0.4750	0.7025
Pooled tafamidis vs placebo treatment difference (relative risk ratio)	0.6761	
P-value	**<0.0001**	

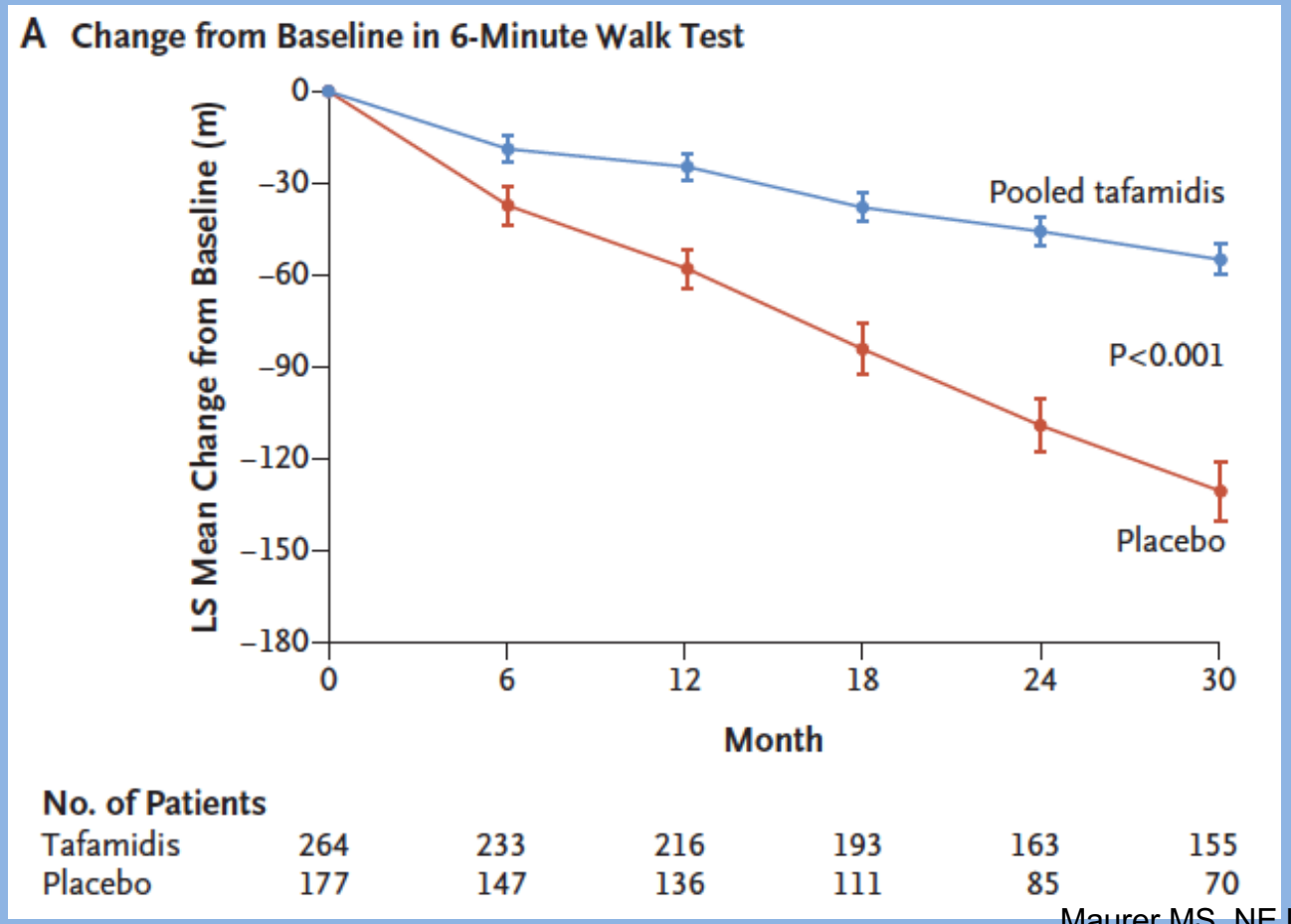
Maurer MS NEJM 2018

Sterberate



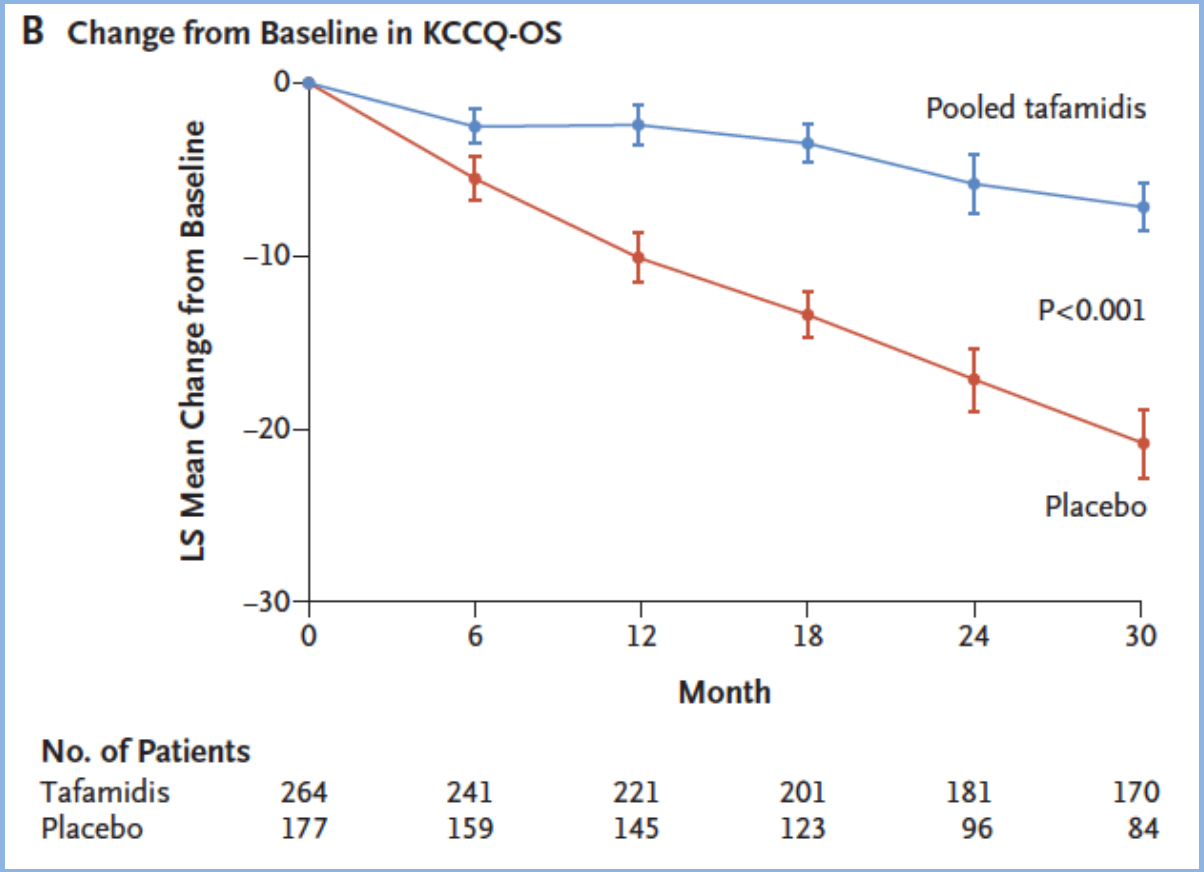
Maurer MS NEJM 2018

Leistungsfähigkeit: 6 Minuten Gehtest



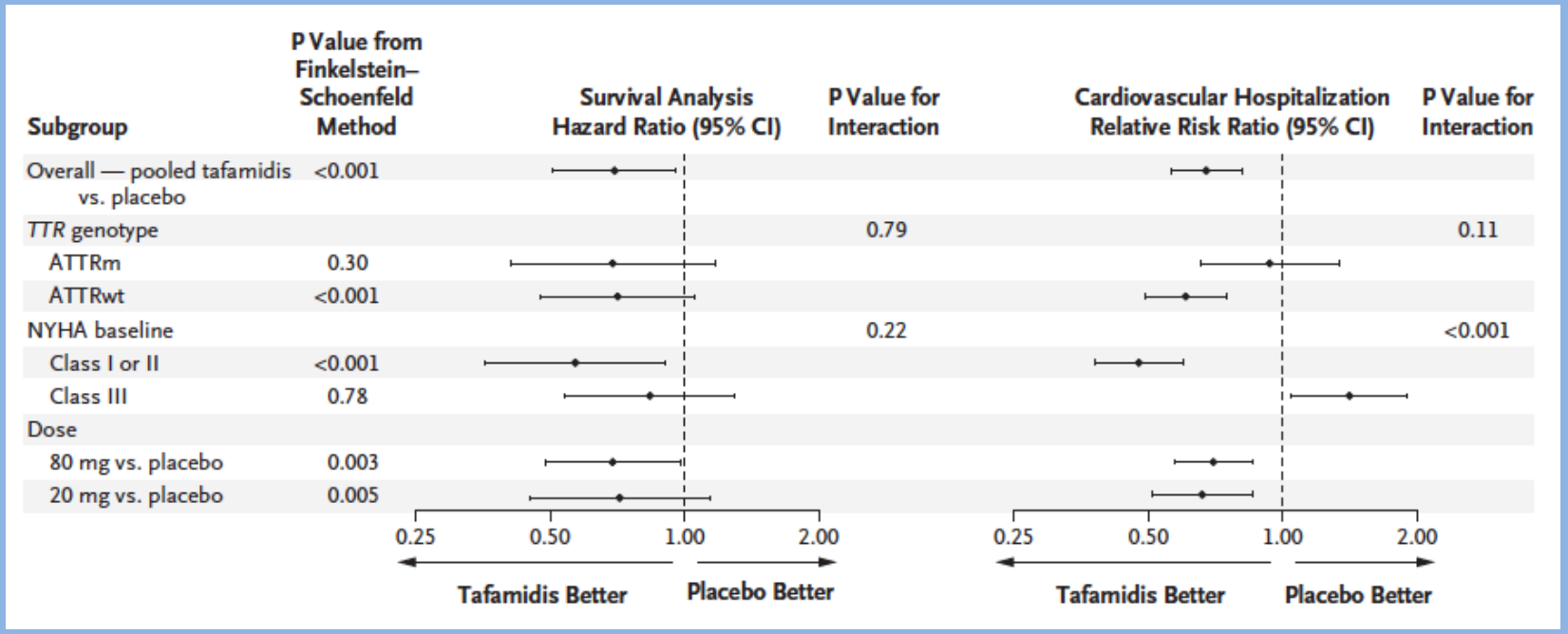
Maurer MS NEJM 2018

Lebensqualität:
Kansas City Cardiomyopathy Questionaire



Maurer MS NEJM 2018

Subgruppenanalysen



Maurer MS NEJM 2018

Kommentar

Tafamidis

- reduzierte die Sterberate und die CV-Hospitalisierungen
- verzögerte die Verschlechterung der Lebensqualität und Leistungsfähigkeit
- wurde gut toleriert und hatte ein Sicherheitsprofil vergleichbar mit Placebo

→ ist offenbar eine effektive Therapie für Patienten mit ATTR-CM - Kosten?

→ **Patisiran und Inotersen**

weisen in kleinen Studien in die gleiche Richtung.

Hier erhoffen wir noch eine Indiationserweiterung.

Immer Neues von Entresto

Original Article

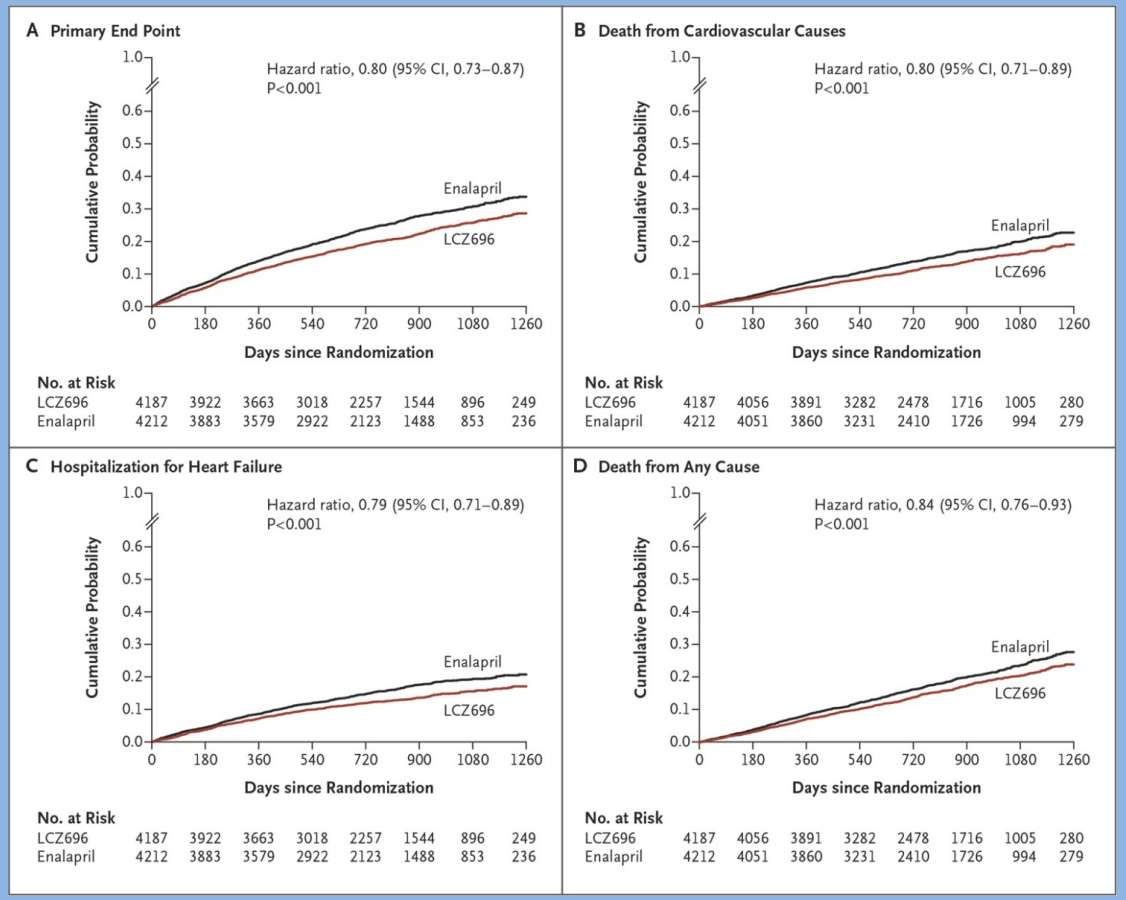
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees

N Engl J Med
Volume 371(11):993-1004
September 11, 2014

The NEW ENGLAND JOURNAL of MEDICINE

Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.



McMurray JJV et al. N Engl J Med 2014;371:993-1004

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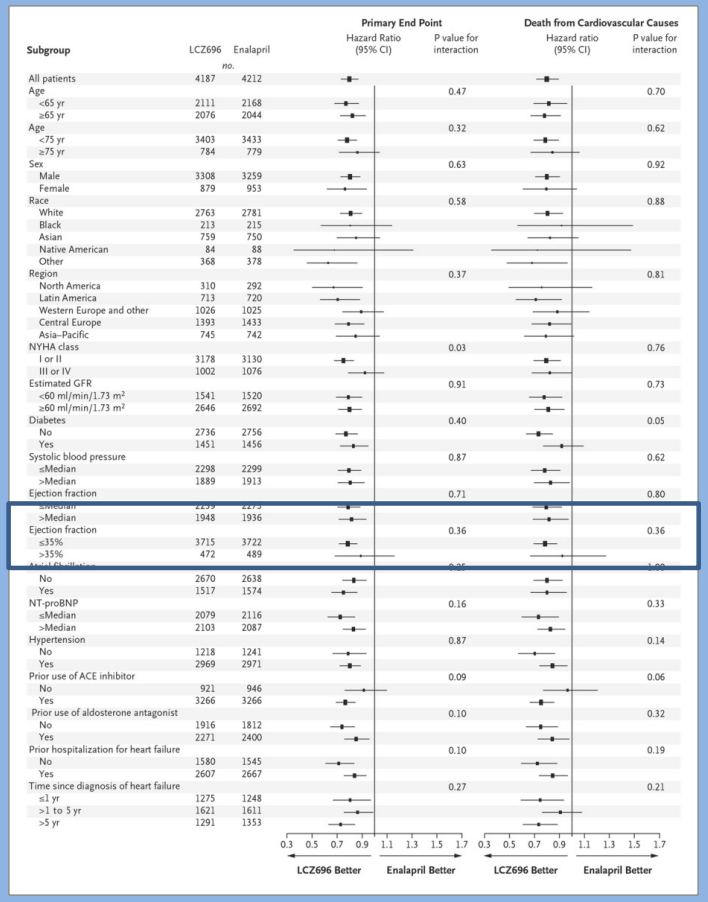
Prespecified Subgroup Analyses.



McMurray JJV et al. N Engl J Med 2014;371:993-1004

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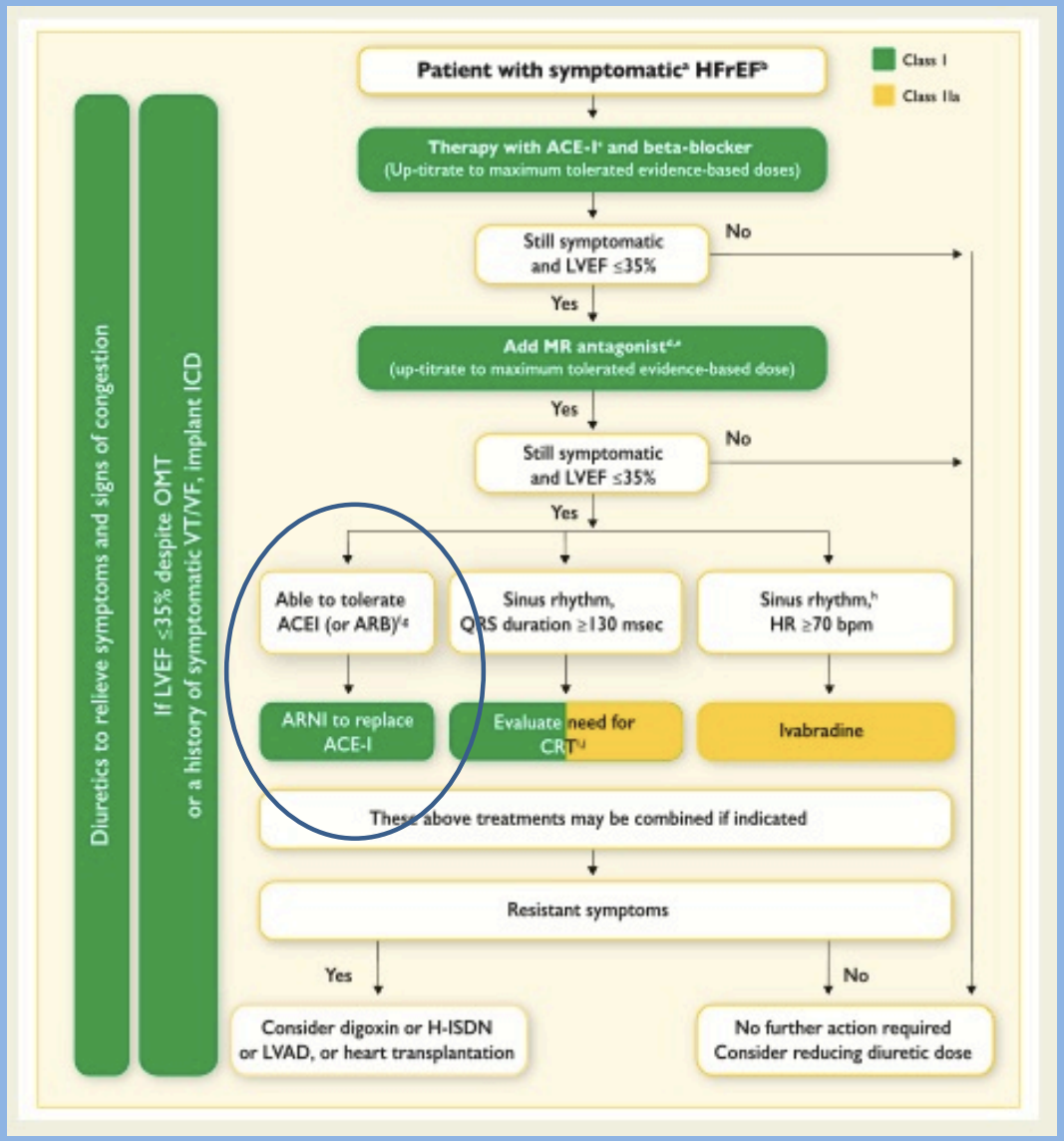
Patient with symptomatic[a] HFrEF[b]
Class I
Class IIa
Therapy with ACE-I[c] and beta-blocker
(Up-titrate to maximum tolerated evidence-based doses)
Still symptomatic and LVEF ≤35%
No
Yes
Add MR antagonist[d,e]
(up-titrate to maximum tolerated evidence-based dose)
Yes
Still symptomatic and LVEF ≤35%
No
Yes
Able to tolerate ACEI (or ARB)[f,g]
Sinus rhythm, QRS duration ≥130 msec
Sinus rhythm,[h] HR ≥70 bpm
ARNI to replace ACE-I
Evaluate need for CRT[i,j]
Ivabradine
These above treatments may be combined if indicated
Resistant symptoms
Yes
No
Consider digoxin or H-ISDN or LVAD, or heart transplantation
No further action required
Consider reducing diuretic dose
Diuretics to relieve symptoms and signs of congestion
If LVEF ≤35% despite OMT or a history of symptomatic VT/VF, implant ICD

Table 3.1 **Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)**

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.

[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

[b]BNP >35 pg/ml and/or NT-proBNP> 125 pg/mL.

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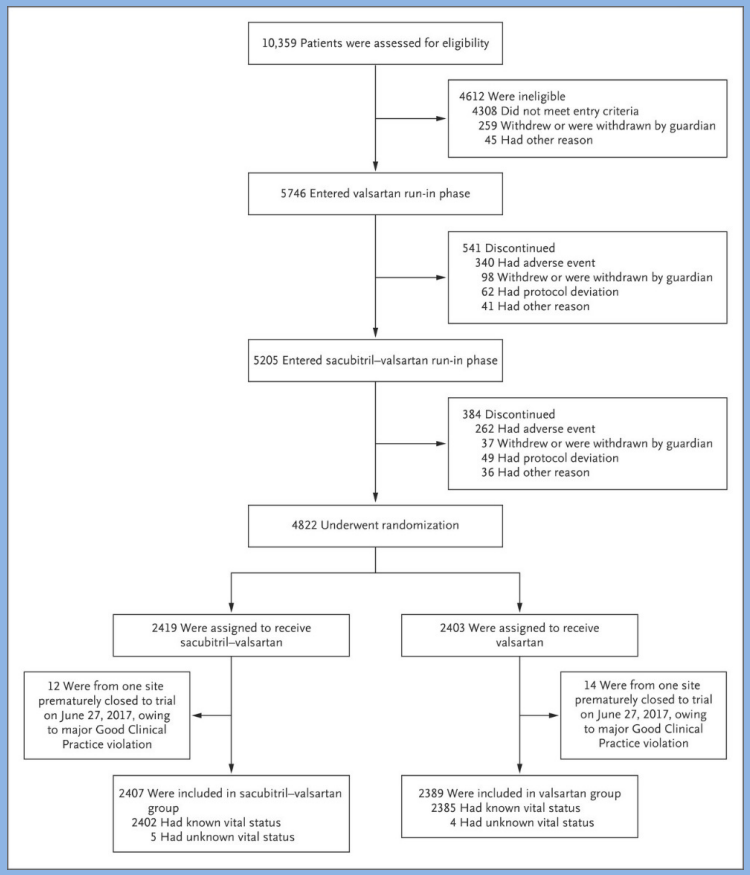
ESTABLISHED IN 1812 OCTOBER 24, 2019 VOL. 381 NO. 17

Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, I.S. Anand, J. Ge, C.S.P. Lam, A.P. Maggioni, F. Martinez, M. Packer, M.A. Pfeffer, B. Pieske, M.M. Redfield, J.L. Rouleau, D.J. van Veldhuisen, F. Zannad, M.R. Zile, A.S. Desai, B. Claggett, P.S. Jhund, S.A. Boytsov, J. Comin-Colet, J. Cleland, H.-D. Düngen, E. Goncalvesova, T. Katova, J.F. Kerr Saraiva, M. Lelonek, B. Merkely, M. Senni, S.J. Shah, J. Zhou, A.R. Rizkala, J. Gong, V.C. Shi, and M.P. Lefkowitz, for the PARAGON-HF Investigators and Committees*

Screening, Randomization, and Follow-up.



SD Solomon et al. N Engl J Med 2019;381:1609-1620.

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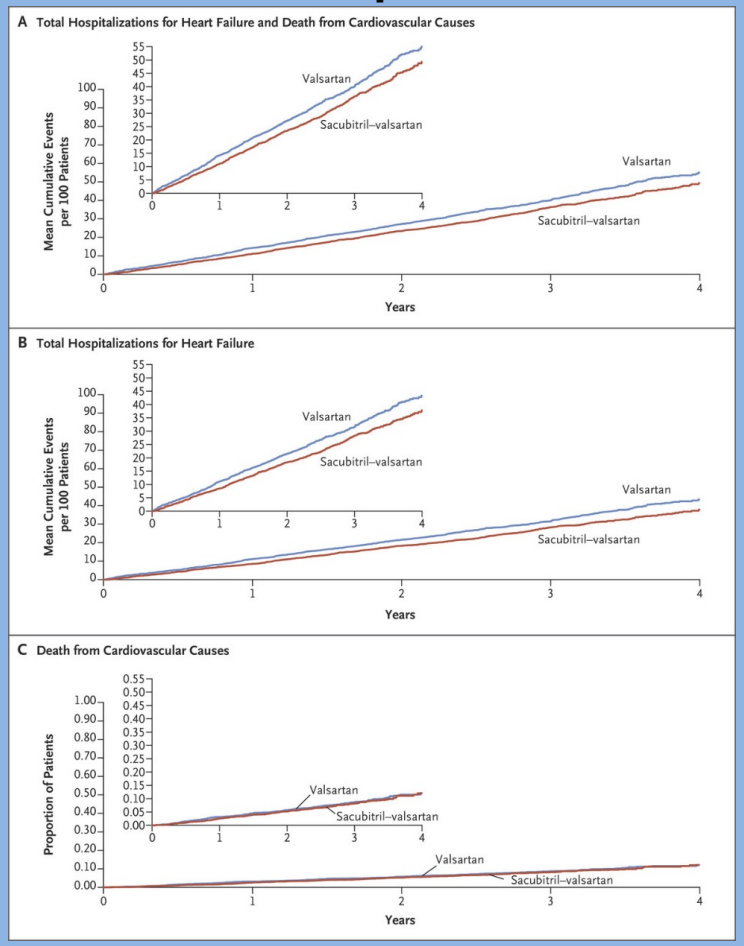
Wichtigste Einschlusskriterien

- LVEF 45% oder größer
- NYHA II-IV
- Erhöhtes NT-proBNP
- Diuretikabedarf

Time-to-Event Curves for Primary Composite Outcome and Its Components.



SD Solomon et al. N Engl J Med 2019;381:1609-1620.

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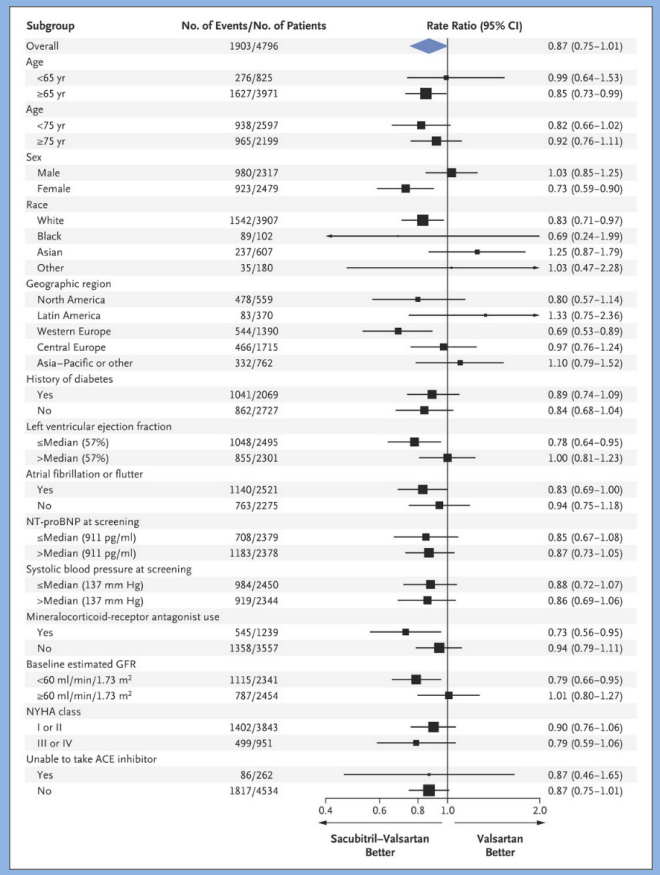
Table 2. Primary and Secondary Outcomes.*

Outcome	Sacubitril–Valsartan (N=2407)	Valsartan (N=2389)	Ratio or Difference (95% CI)
Primary composite outcome and components			
Total hospitalizations for heart failure and death from cardiovascular causes†			RR, 0.87 (0.75–1.01)
Total no. of events	894	1009	
Rate per 100 patient-yr	12.8	14.6	
Total no. of hospitalizations for heart failure	690	797	RR, 0.85 (0.72–1.00)
Death from cardiovascular causes — no. (%)	204 (8.5)	212 (8.9)	HR, 0.95 (0.79–1.16)
Secondary outcomes			
Change in NYHA class from baseline to 8 mo — no./total no. (%)			OR, 1.45 (1.13–1.86)
Improved	347/2316 (15.0)	289/2302 (12.6)	
Unchanged	1767/2316 (76.3)	1792/2302 (77.8)	
Worsened	202/2316 (8.7)	221/2302 (9.6)	
Change in KCCQ clinical summary score at 8 mo‡	−1.6±0.4	−2.6±0.4	Difference, 1.0 (0.0–2.1)
Renal composite outcome — no. (%)§	33 (1.4)	64 (2.7)	HR, 0.50 (0.33–0.77)
Death from any cause — no. (%)	342 (14.2)	349 (14.6)	HR, 0.97 (0.84–1.13)

Primary Outcome in Prespecified Subgroups.



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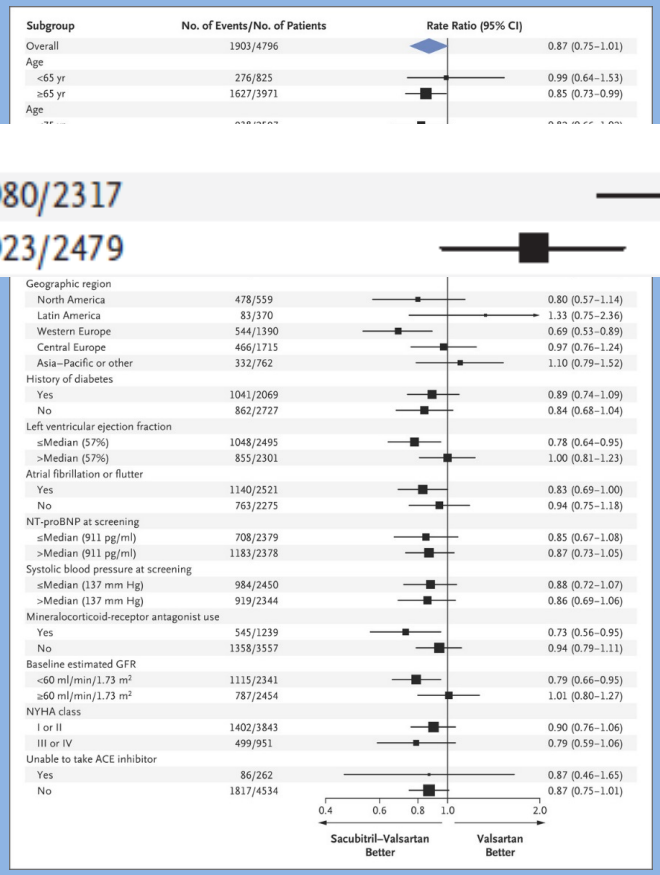
Primary Outcome in Prespecified Subgroups.



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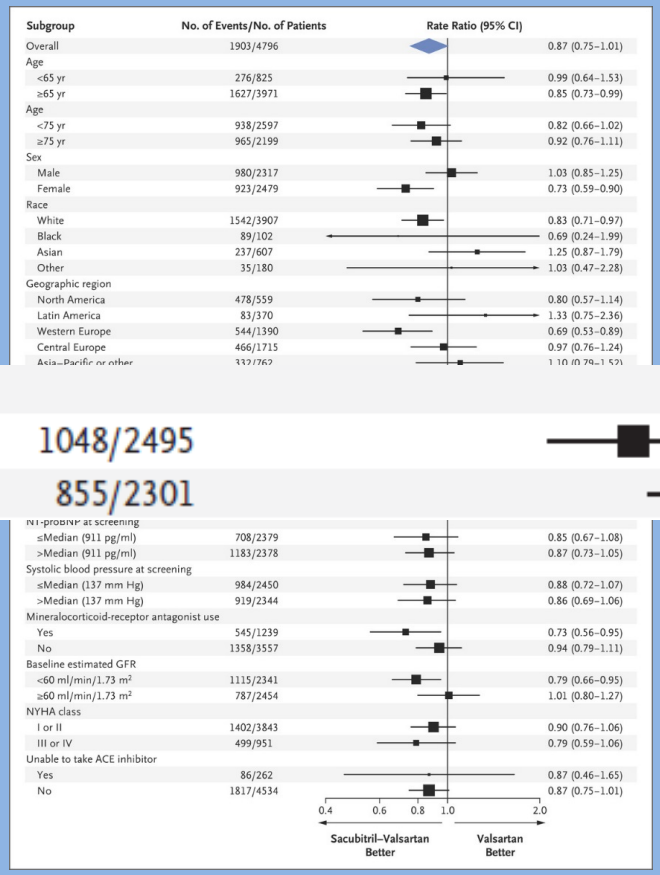
Primary Outcome in Prespecified Subgroups.



SD Solomon et al. N Engl J Med 2019;381:1609-1620.

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LVEF

- >55% Normal
- 45-55 % leichtgradig reduziert
- 44-30 % mittelgradig reduziert
- <30% hochgradig reduziert

HFpEF

HFmREF

HFrEF

Zusammenfassung Entresto

- **Dzt weiterhin unveränderte Indikation bei HFrEF**
- **Dzt weiterhin keine Indikation für HFpEF**

- **Möglicherweise Erweiterung der Indikation für HFmREF**

Indication hopping
SGLT2i
vom Diabetes zur Herzinsuffizienz
Herzinsuffizienz

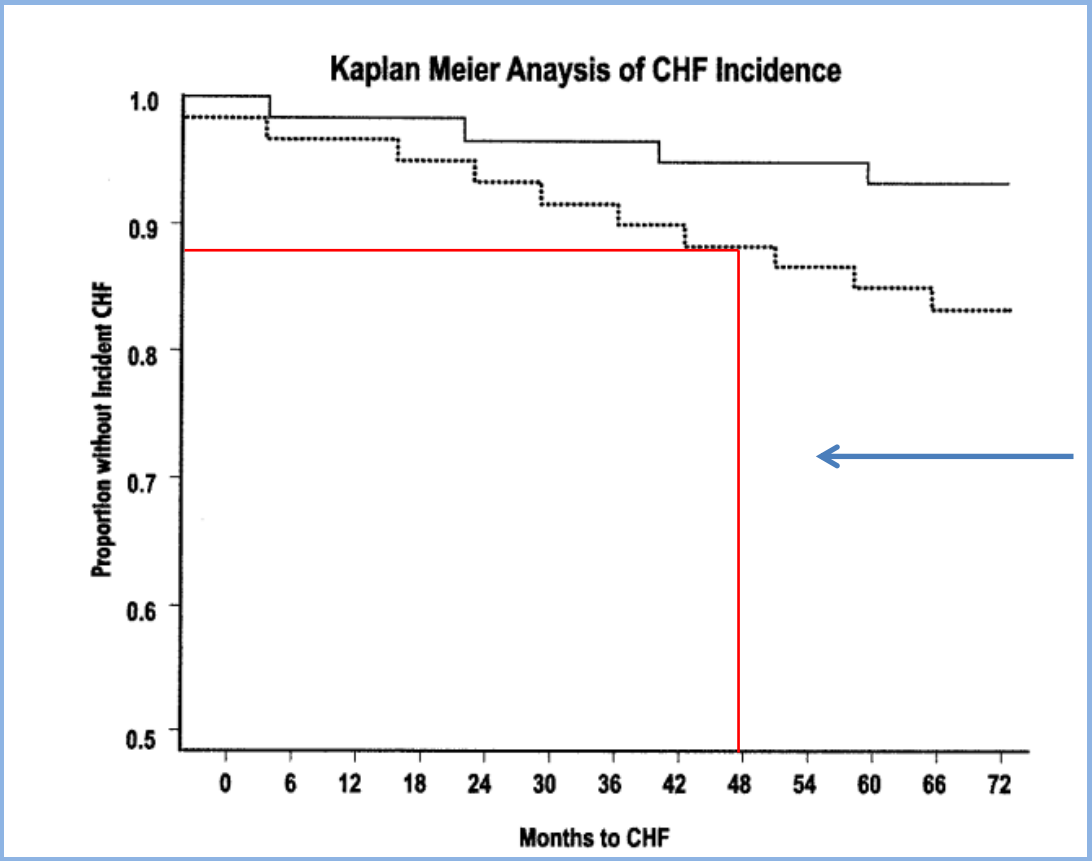
Epidemiology/Health Services/Psychosocial Research
ORIGINAL ARTICLE

The Incidence of Congestive Heart Failure in Type 2 Diabetes

An update

Gregory A. Nichols, phd[1]
Christina M. Gullion, phd[1]
Carol E. Koro, phd[2]
Sara A. Ephross, phd[2]
Jonathan B. Brown, phd, mpp[1]

Unselected cohort, but prior diagnosis of heart failure excluded



Observation period of TECOS

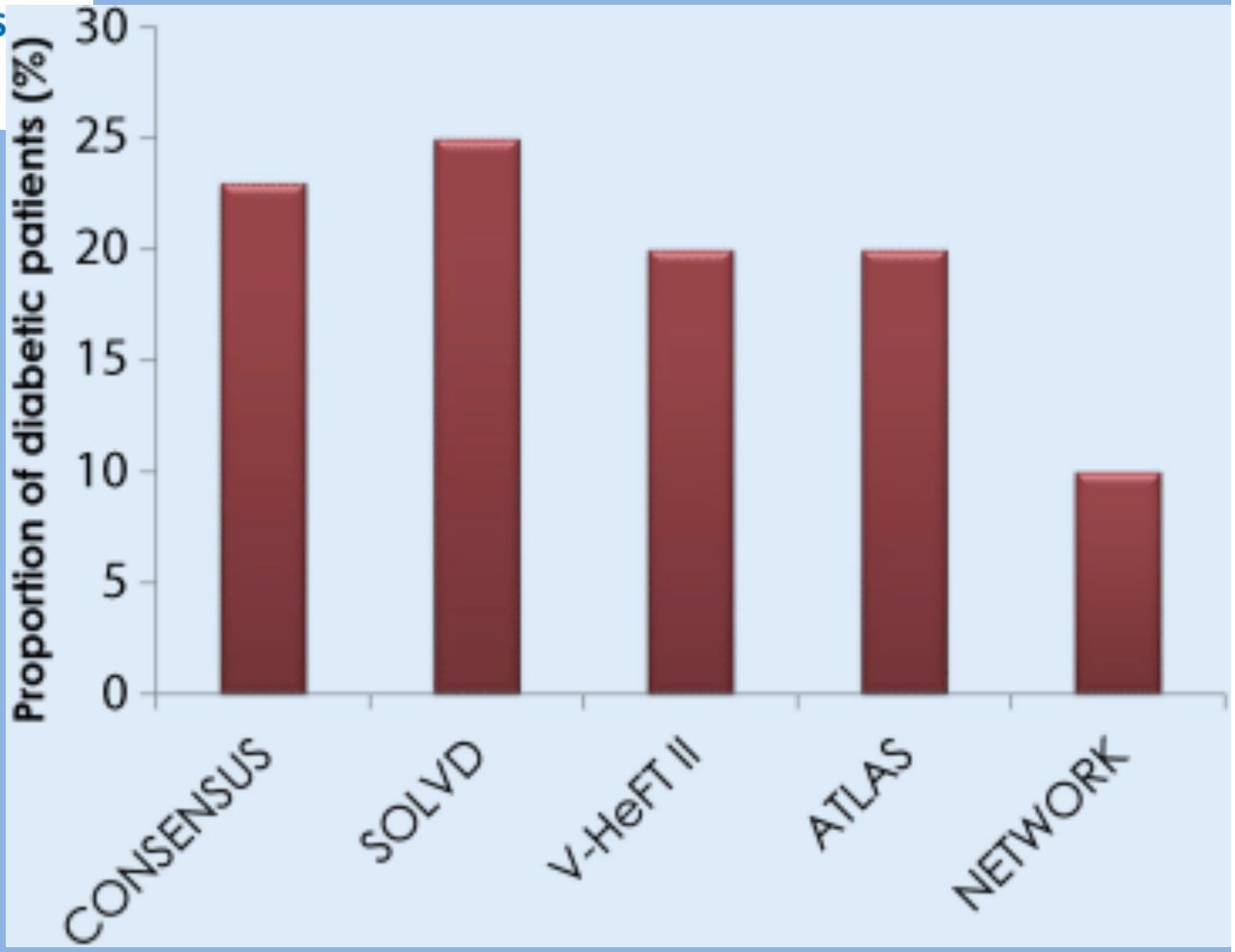
Herz 2016 · 41:201–207
DOI 10.1007/s00059-016-4415-7
Published online: 12 April 2016

C. Lombardi[1] · V. Spigoni[2] · E. Gorga[1] · A. Dei Cas[2]

[1] Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, Cardiology, University of Brescia, Brescia, Italy

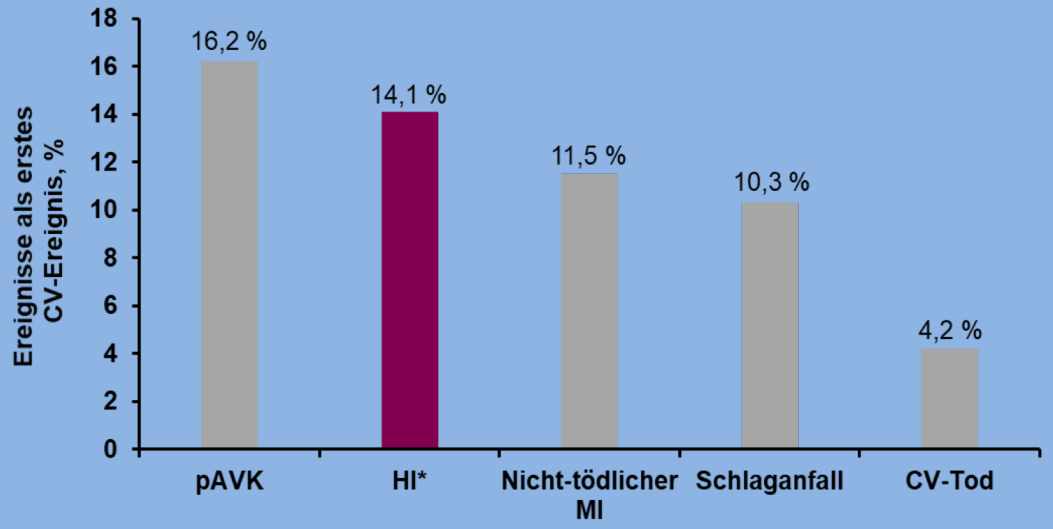
[2] Endocrinology Unit, Department of Clinical and Experimental Medicine, University of Parma and AOU of Parma, Parma, Italy

Novel insight into the dangerous connection between diabetes and heart failure



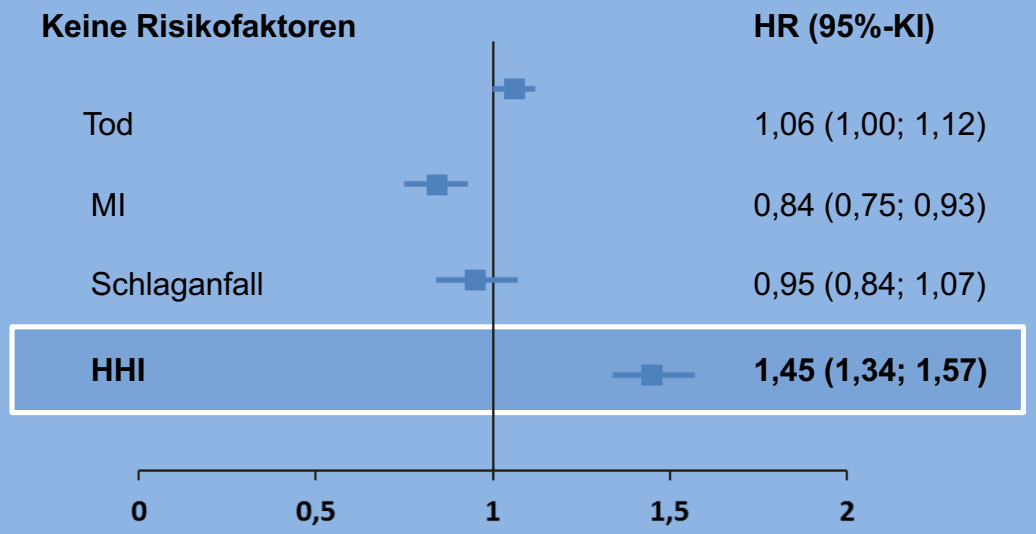
Herzinsuffizienz tritt bei T2D früh und häufig auf, trotz Kontrolle von CV-Risikofaktoren

HI trat als erste Manifestation einer T2D-bedingten CV-Erkrankung häufiger auf als MI oder Schlaganfall



Kohortenstudie bei Patienten mit T2DM und Inzidenz einer CV-Erkrankung (n=1,9 Mio.)

Trotz der Kontrolle bekannter CV-Risikofaktoren weisen T2D-Patienten ein erhöhtes Risiko für Herzinsuffizienz auf



Risiko für ein Ereignis bei T2DM-Patienten (n=271.174) ohne weitere Risikofaktoren außerhalb des Zielbereichs im Vergleich zu Personen ohne Diabetes (n=1.355.870)

*HI nach MI wurde in dieser HI-Definition nicht eingeschlossen

CV, kardiovaskulär; HI, Herzinsuffizienz; MACE; schwerwiegendes unerwünschtes kardiovaskuläres Ereignis (*major adverse cardiovascular event*); MI, Myokardinfarkt; pAVK, periphere arterielle Verschlusskrankheit; T2DM, Typ 2 Diabetes mellitus.

Modifiziert nach: Shah AD, et al. Lancet Diabetes Endocrinol. 2015;3:105-113, Appendix. Modifiziert nach: Rawshani A, et al. N Engl J Med. 2018;379:633-644..

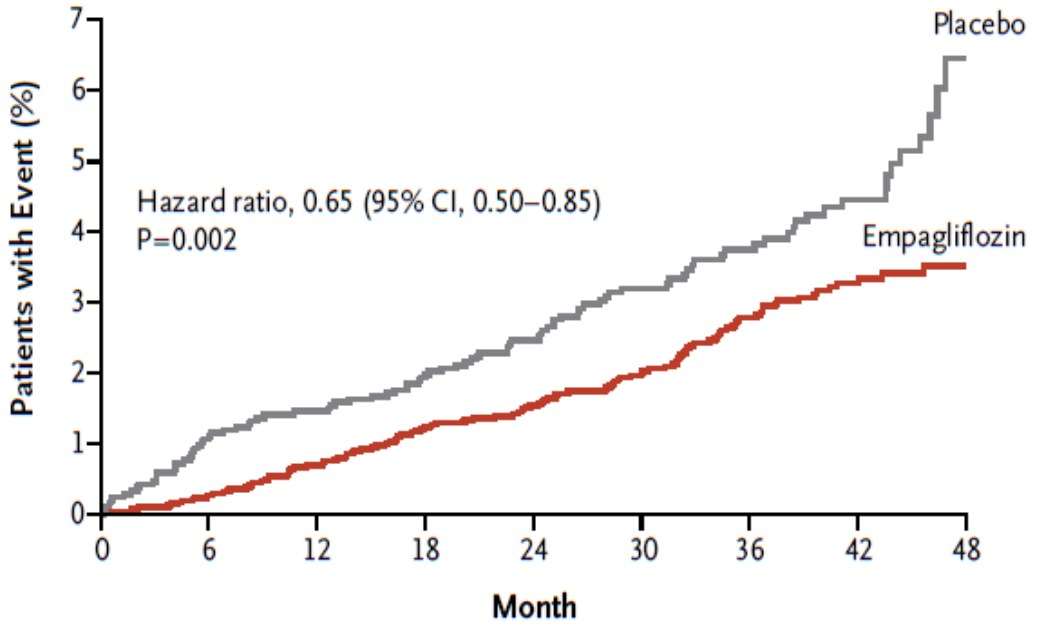
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG O

D Hospitalization for Heart Failure



No. at Risk

Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

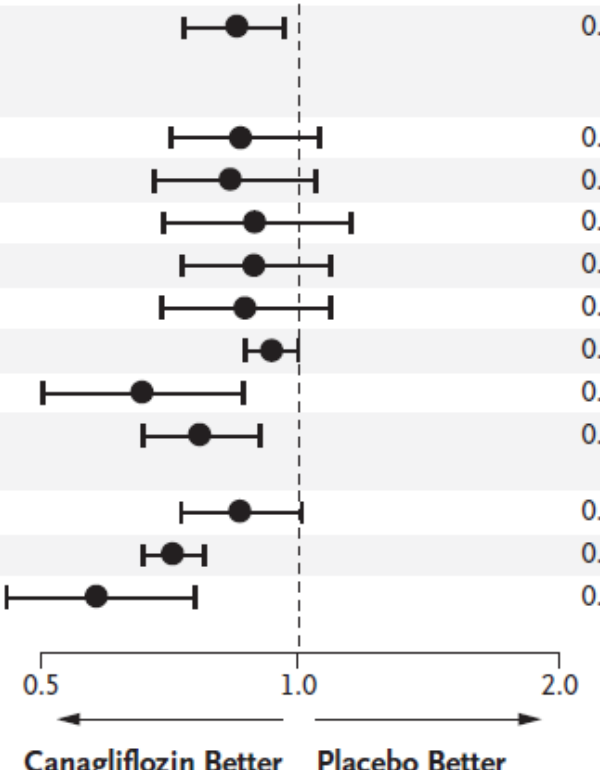
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal

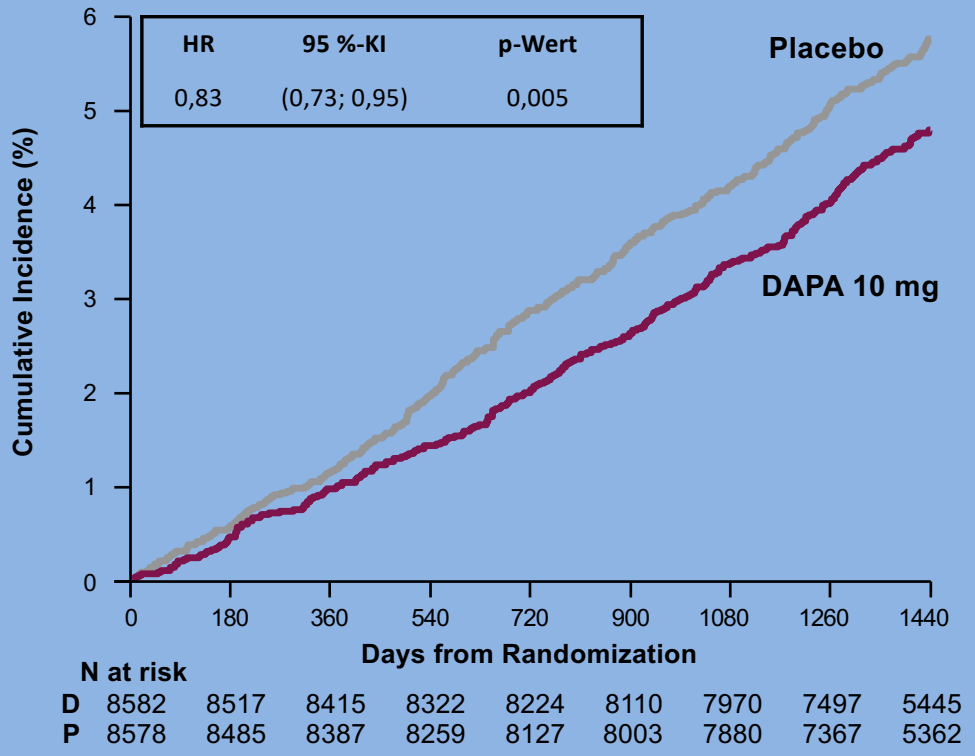
Bruce N
Kenneth W. M
Ngozi Ero
Mehul D

Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)

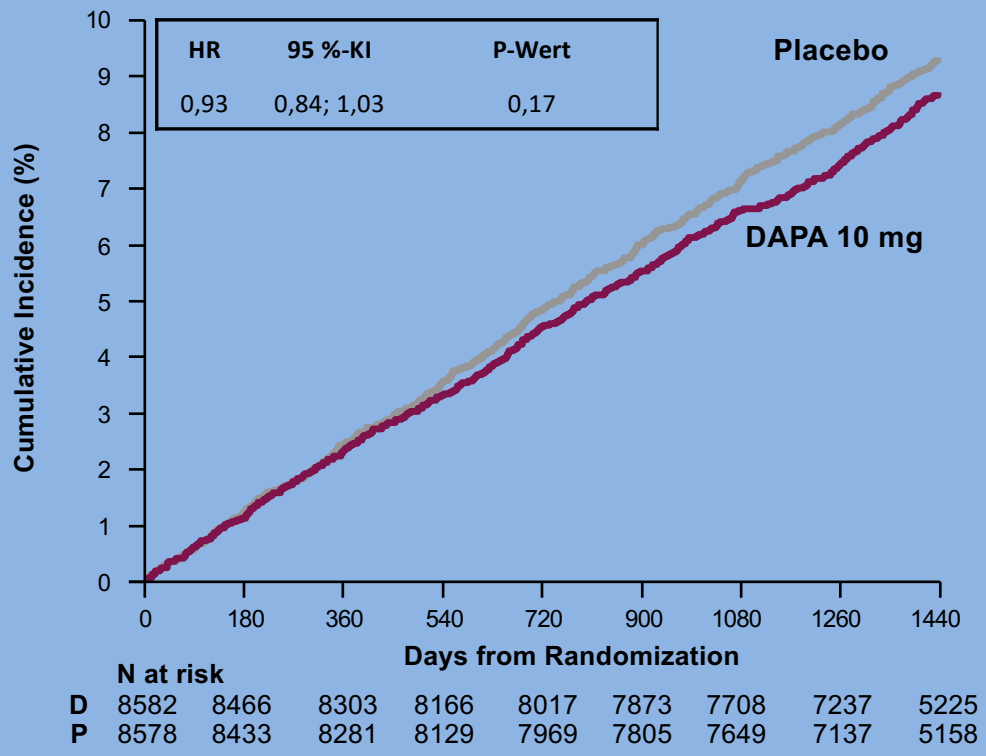


Dapagliflozin senkte den primären Endpunkt CV-Tod/HHI signifikant und reduzierte die Anzahl an MACE Events

Ko-Primärer zusammengesetzter Endpunkt: CV Tod & Hospitalisierung f. Herzinsuffizienz (HHI)



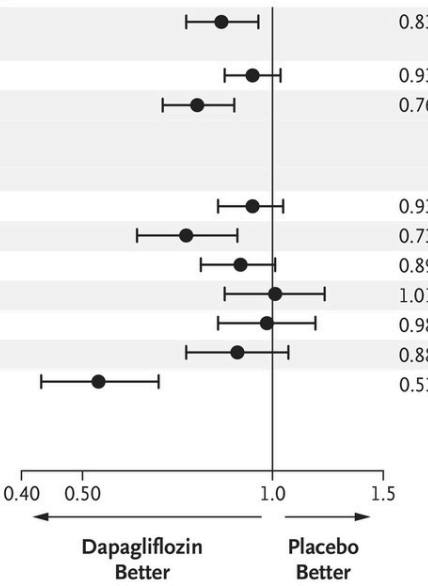
Ko-Primärer zusammengesetzter Endpunkt: MACE



Modifiziert nach: Wiviott SD, et al. N Engl J Med 2019; 380:347-57.

Key Efficacy Outcomes and Their Components.

Outcome	Dapagliflozin (N=8582) no. (%)	Dapagliflozin (N=8582) rate/1000 patient-yr	Placebo (N=8578) no. (%)	Placebo (N=8578) rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Cardiovascular death or hospitalization for heart failure	417 (4.9)	12.2	496 (5.8)	14.7	0.83 (0.73–0.95)	0.005
MACE	756 (8.8)	22.6	803 (9.4)	24.2	0.93 (0.84–1.03)	0.17
≥40% decrease in eGFR to <60 ml/min/1.73 m^2, ESRD, or death from renal or cardiovascular cause	370 (4.3)	10.8	480 (5.6)	14.1	0.76 (0.67–0.87)	
Death from any cause	529 (6.2)	15.1	570 (6.6)	16.4	0.93 (0.82–1.04)	
Hospitalization for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61–0.88)	
Myocardial infarction	393 (4.6)	11.7	441 (5.1)	13.2	0.89 (0.77–1.01)	
Ischemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	1.01 (0.84–1.21)	
Death from cardiovascular cause	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82–1.17)	
Death from noncardiovascular cause	211 (2.5)	6.0	238 (2.8)	6.8	0.88 (0.73–1.06)	
≥40% decrease in eGFR to <60 ml/min/1.73 m^2, ESRD, or death from renal cause	127 (1.5)	3.7	238 (2.8)	7.0	0.53 (0.43–0.66)	



SD Wiviott et al. N Engl J Med 2019;380:347-357.

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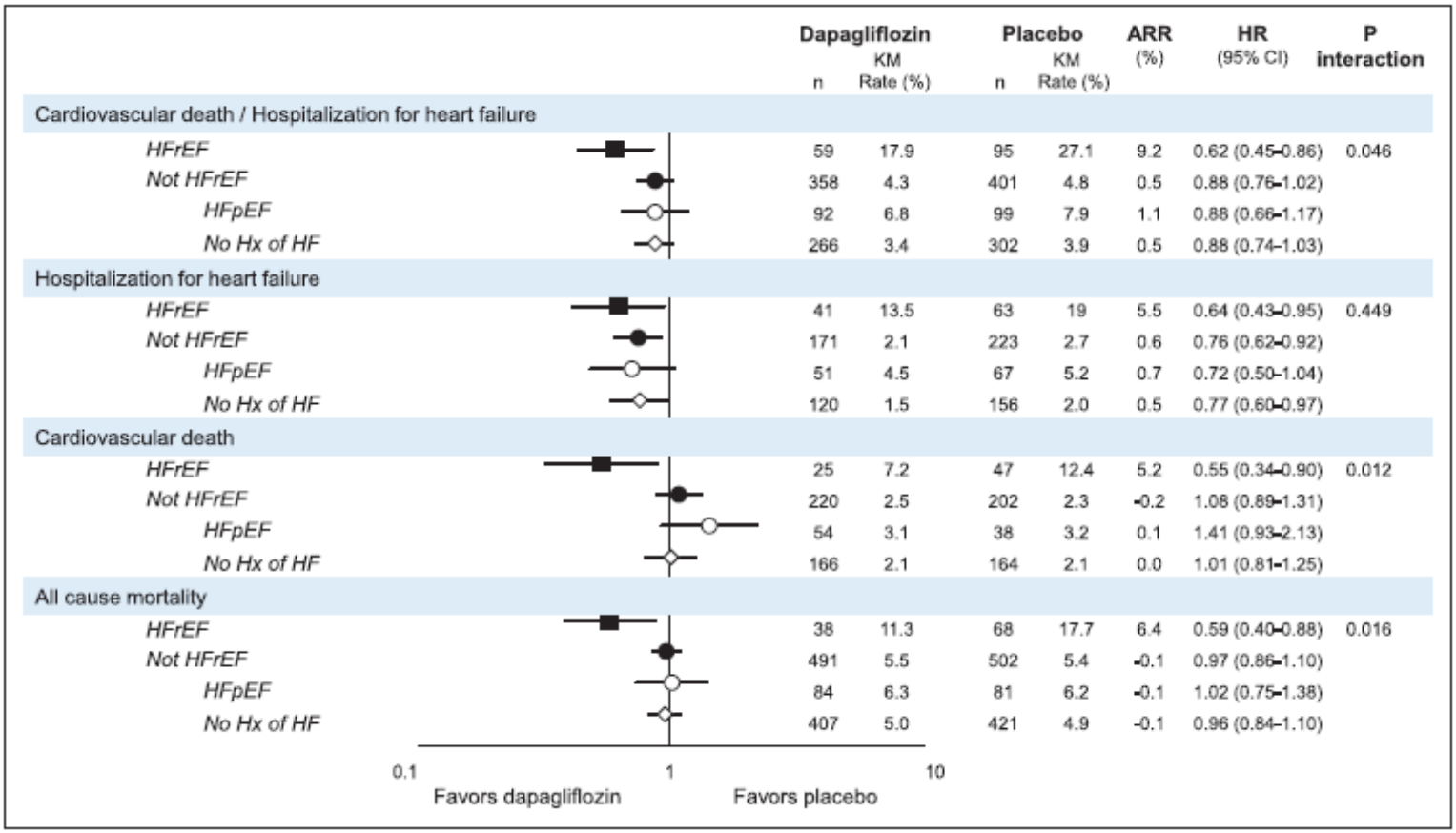
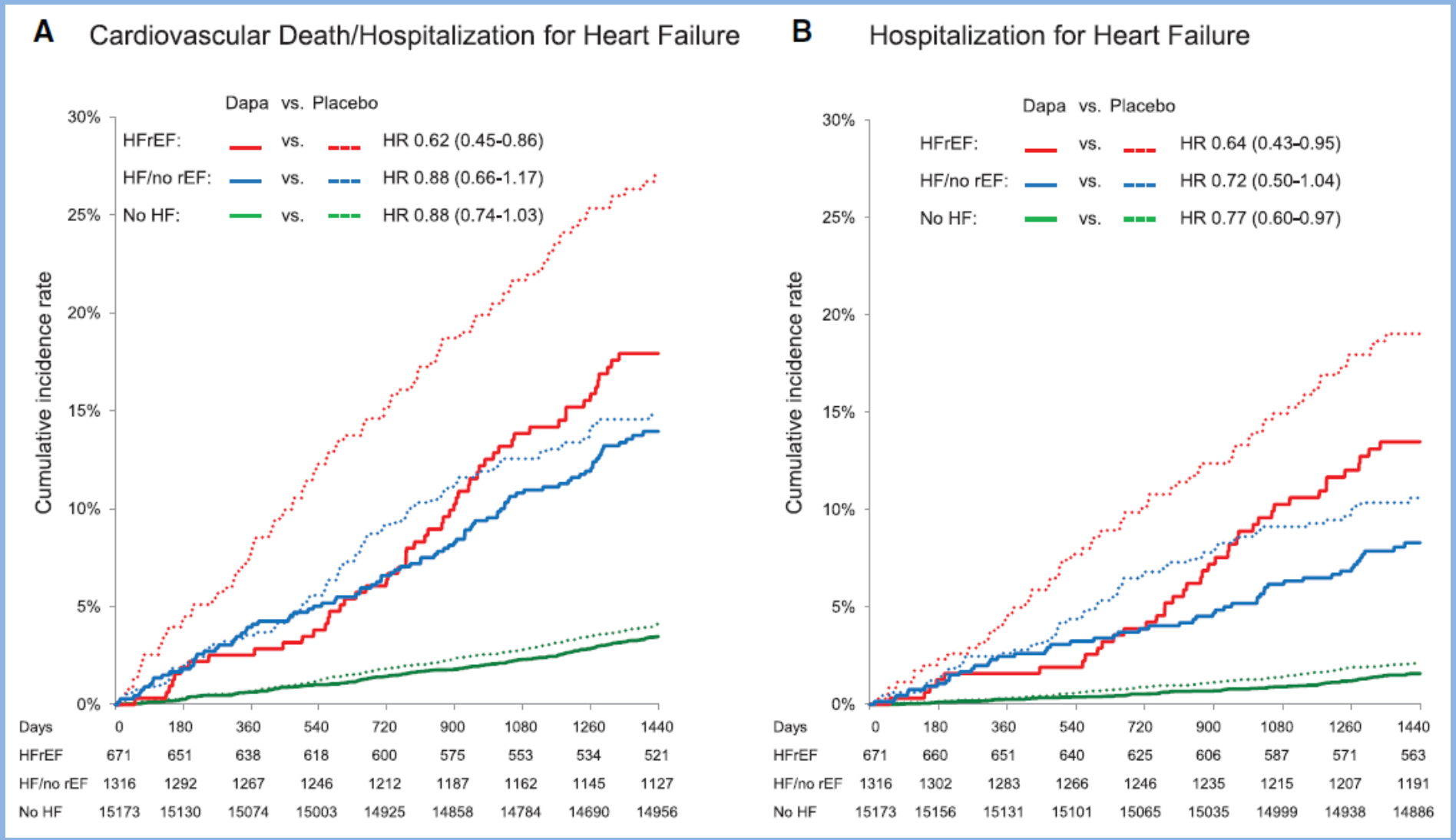
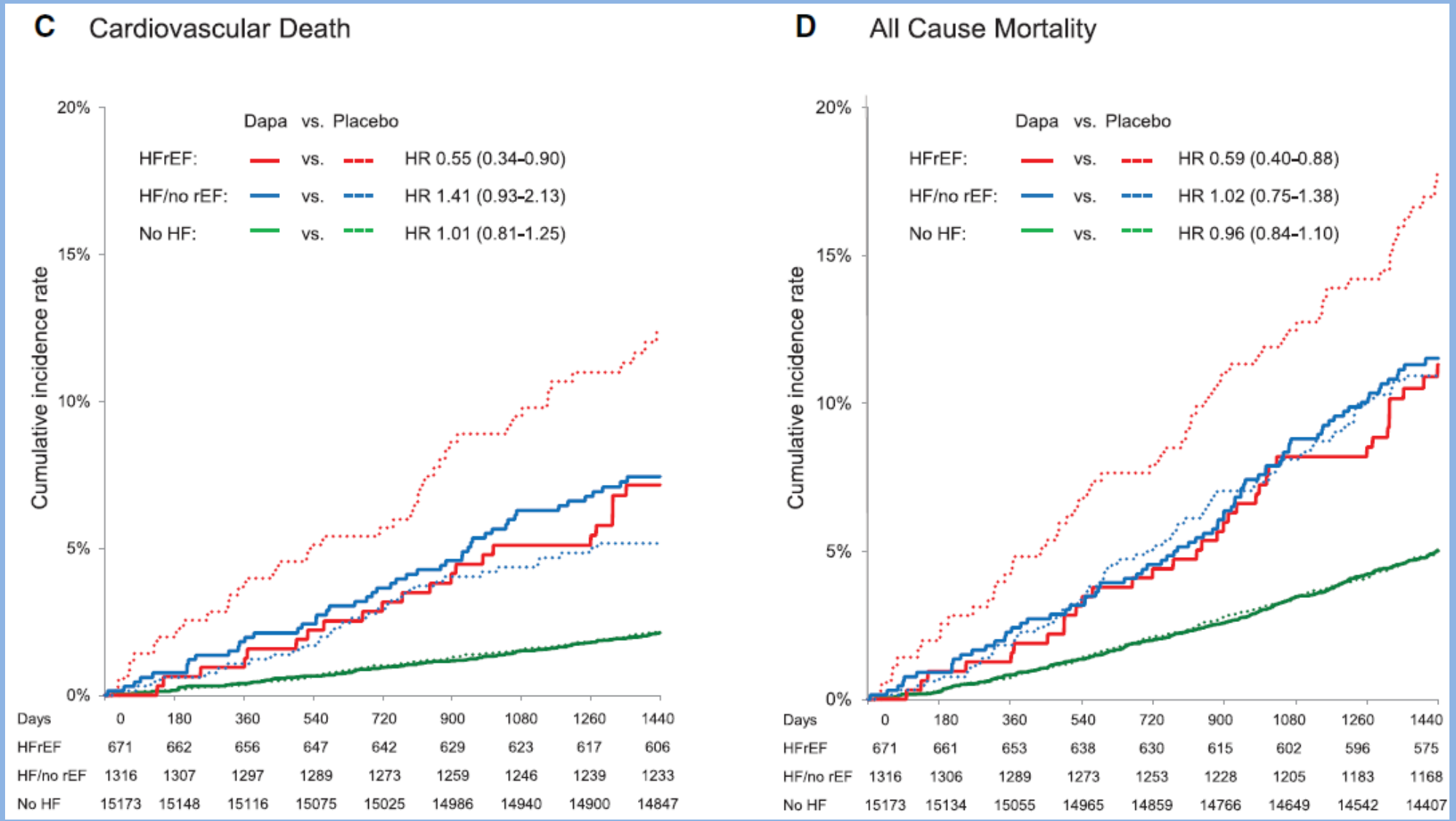
DECLARE-TIMI 58



Kato et al.


A
Cardiovascular Death/Hospitalization for Heart Failure
Dapa vs. Placebo
HFrEF: vs. HR 0.62 (0.45-0.86)
HF/no rEF: vs. HR 0.88 (0.66-1.17)
No HF: vs. HR 0.88 (0.74-1.03)
Cumulative incidence rate
30%
25%
20%
15%
10%
5%
0%
Days 0 180 360 540 720 900 1080 1260 1440
HFrEF 671 651 638 618 600 575 553 534 521
HF/no rEF 1316 1292 1267 1246 1212 1187 1162 1145 1127
No HF 15173 15130 15074 15003 14925 14858 14784 14690 14956
B
Hospitalization for Heart Failure
Dapa vs. Placebo
HFrEF: vs. HR 0.64 (0.43-0.95)
HF/no rEF: vs. HR 0.72 (0.50-1.04)
No HF: vs. HR 0.77 (0.60-0.97)
Cumulative incidence rate
30%
25%
20%
15%
10%
5%
0%
Days 0 180 360 540 720 900 1080 1260 1440
HFrEF 671 660 651 640 625 606 587 571 563
HF/no rEF 1316 1302 1283 1266 1246 1235 1215 1207 1191
No HF 15173 15156 15131 15101 15065 15035 14999 14938 14886

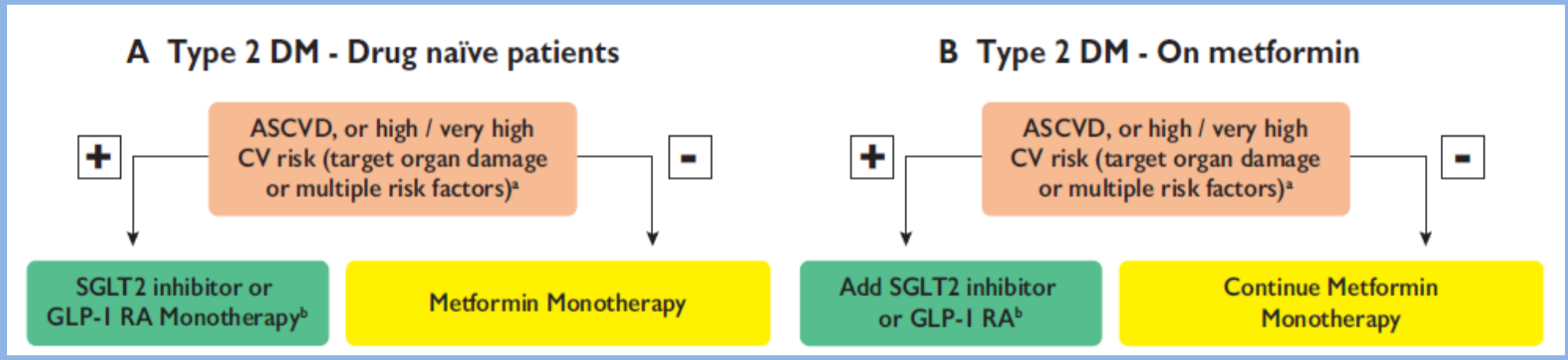

C
Cardiovascular Death
Dapa vs. Placebo
HFrEF: vs. HR 0.55 (0.34-0.90)
HF/no rEF: vs. HR 1.41 (0.93-2.13)
No HF: vs. HR 1.01 (0.81-1.25)
Cumulative incidence rate
20%
15%
10%
5%
0%
Days 0 180 360 540 720 900 1080 1260 1440
HFrEF 671 662 656 647 642 629 623 617 606
HF/no rEF 1316 1307 1297 1289 1273 1259 1246 1239 1233
No HF 15173 15148 15116 15075 15025 14986 14940 14900 14847
D
All Cause Mortality
Dapa vs. Placebo
HFrEF: vs. HR 0.59 (0.40-0.88)
HF/no rEF: vs. HR 1.02 (0.75-1.38)
No HF: vs. HR 0.96 (0.84-1.10)
Cumulative incidence rate
20%
15%
10%
5%
0%
Days 0 180 360 540 720 900 1080 1260 1440
HFrEF 671 661 653 638 630 615 602 596 575
HF/no rEF 1316 1306 1289 1273 1253 1228 1205 1183 1168
No HF 15173 15134 15055 14965 14859 14766 14649 14542 14407

ESC
European Society of Cardiology

European Heart Journal (2019) **00**, 1–69
doi:10.1093/eurheartj/ehz486

ESC GUIDELINES

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD


A Type 2 DM - Drug naïve patients
ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)[a]
+
-
SGLT2 inhibitor or GLP-1 RA Monotherapy[b]
Metformin Monotherapy
B Type 2 DM - On metformin
ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)[a]
+
-
Add SGLT2 inhibitor or GLP-1 RA[b]
Continue Metformin Monotherapy

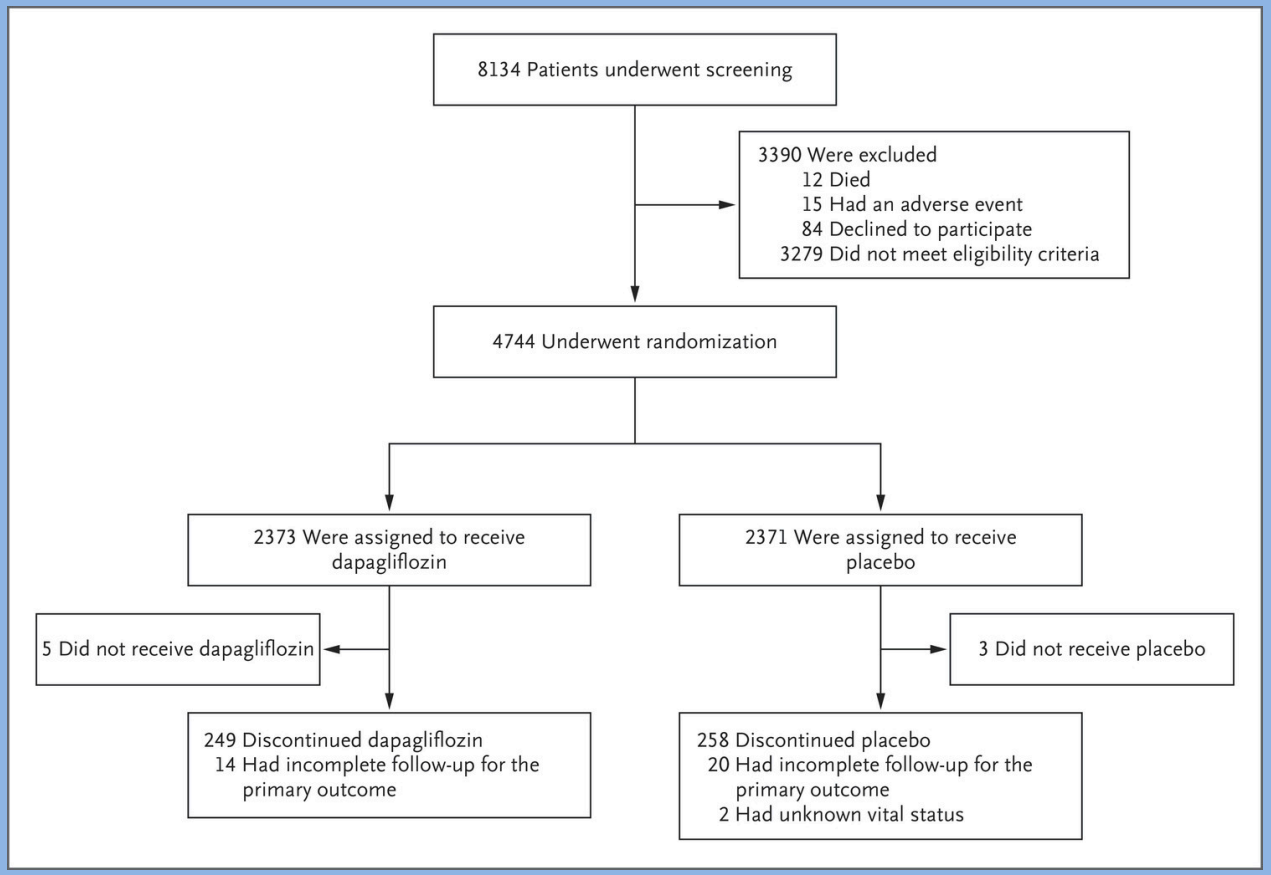
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 21, 2019 VOL. 381 NO. 21

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

Enrollment and Follow-up.



JJ McMurray et al. N Engl J Med 2019;381:1995-2008.

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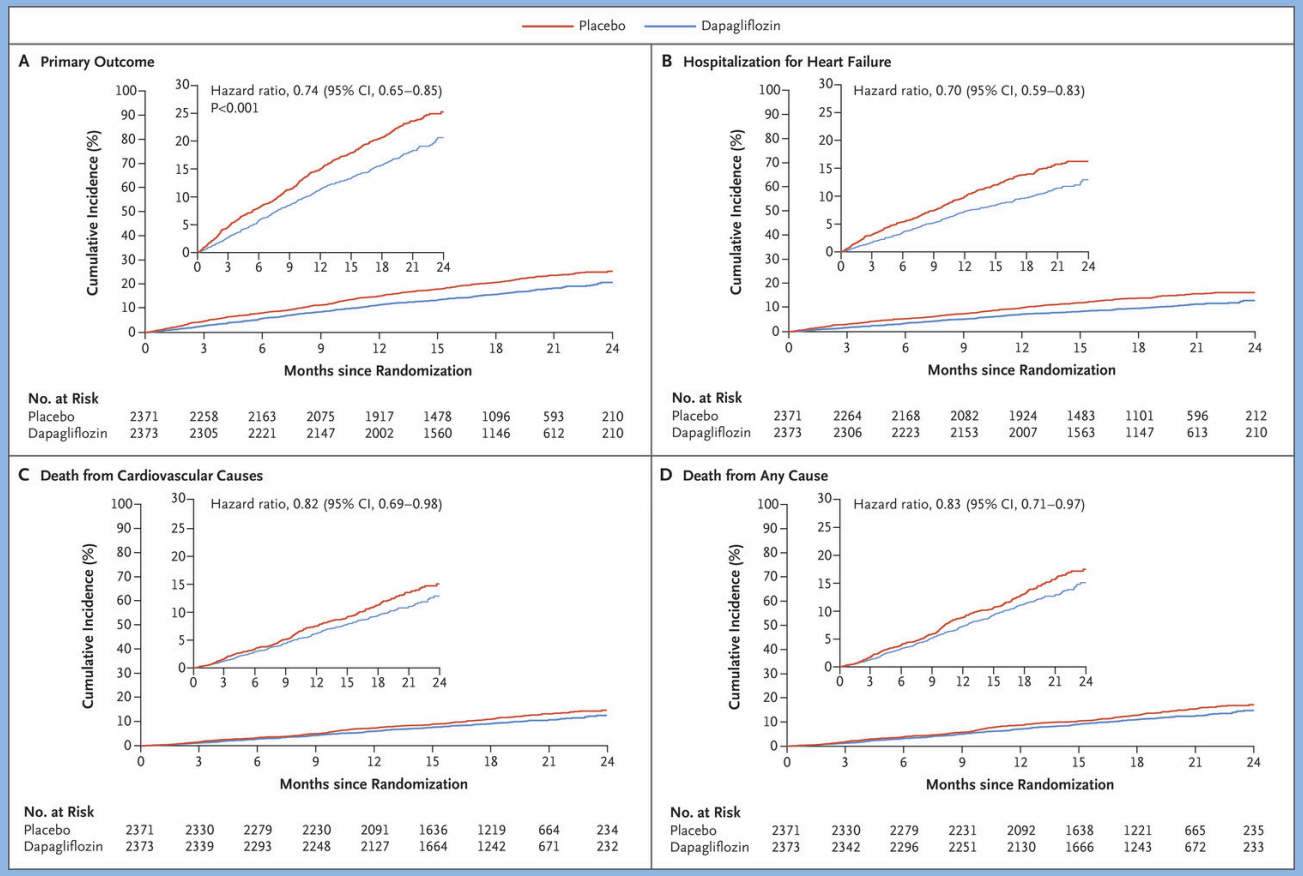
Cardiovascular Outcomes.



JJ McMurray et al. N Engl J Med 2019;381:1995-2008.

The NEW ENGLAND JOURNAL of MEDICINE

Primary and Secondary Cardiovascular Outcomes and Adverse Events of Special Interest.

Primary composite outcome — no. (%)† 386 (16.3) 11.6 502 (21.2) 15.6 0.74 (0.65 to 0.85) <0.001

Table 2. Primary and Secondary Cardiovascular Outcomes and Adverse Events of Special Interest.*

Variable	Dapagliflozin (N=2373)		Placebo (N=2371)		Hazard or Rate Ratio or Difference (95% CI)	P Value
	values	*events/100 patient-yr*	*values*	*events/100 patient-yr*		
Efficacy outcomes						
Hospitalization for heart failure	231 (9.7)	6.9	318 (13.4)	9.8	0.70 (0.59 to 0.83)	NA
Urgent heart-failure visit	10 (0.4)	0.3	23 (1.0)	0.7	0.43 (0.20 to 0.90)	NA
Cardiovascular death	227 (9.6)	6.5	273 (11.5)	7.9	0.82 (0.69 to 0.98)	NA
Secondary outcomes						
Cardiovascular death or heart-failure hospitalization — no. (%)	382 (16.1)	11.4	495 (20.9)	15.3	0.75 (0.65 to 0.85)	<0.001
Total no. of hospitalizations for heart failure and cardiovascular deaths‡	567	—	742	—	0.75 (0.65 to 0.88)	<0.001
Change in KCCQ total symptom score at 8 mo§	6.1±18.6	—	3.3±19.2	—	1.18 (1.11 to 1.26)	<0.001
Worsening renal function — no. (%)¶	28 (1.2)	0.8	39 (1.6)	1.2	0.71 (0.44 to 1.16)	NA
Death from any cause — no. (%)	276 (11.6)	7.9	329 (13.9)	9.5	0.83 (0.71 to 0.97)	NA
Safety outcomes‖						
Discontinuation due to adverse event — no./total no. (%)	111/2368 (4.7)	—	116/2368 (4.9)	—	—	0.79
Adverse events of interest — no./total no. (%)						
Volume depletion	178/2368 (7.5)	—	162/2368 (6.8)	—	—	0.40
Renal adverse event	153/2368 (6.5)	—	170/2368 (7.2)	—	—	0.36
Fracture	49/2368 (2.1)		50/2368 (2.1)	—	—	1.00
Amputation	13/2368 (0.5)	—	12/2368 (0.5)	—	—	1.00
Major hypoglycemia**	4/2368 (0.2)	—	4/2368 (0.2)	—	—	NA
Diabetic ketoacidosis††	3/2368 (0.1)	—	0	—	—	NA
Fournier's gangrene	0	—	1/2368 (<0.1)	—	—	NA
Laboratory and other measures						
Change from baseline to 8 mo‡‡						
Glycated hemoglobin — %§§	−0.21±1.14	—	0.04±1.29	—	−0.24 (−0.34 to −0.13)	<0.001
Creatinine — mg/dl	0.07±0.24	—	0.04±0.25	—	0.02 (0.01 to 0.03)	<0.007
Hematocrit — %	2.31±3.90	—	−0.19±3.81	—	2.41 (2.21 to 2.62)	<0.001
NT-proBNP — pg/ml	−196±2387	—	101±2944	—	−303 (−457 to −150)	<0.001
Weight — kg	−0.88±3.86	—	0.10±4.09	—	−0.87 (−1.11 to −0.62)	<0.001
Systolic blood pressure — mm Hg	−1.92±14.92	—	−0.38±15.27	—	−1.27 (−2.09 to −0.45)	0.002

* Plus–minus values are means ±SD. NA denotes not applicable because P values for efficacy outcomes are reported only for outcomes that were included in the hierarchical-testing strategy.

† The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or death from cardiovascular causes.

‡ The total number of hospitalizations for heart failure and cardiovascular deaths was analyzed by means of the semiparametric proportional-rates model, in which the treatment effect is reported as a rate ratio.

§ The total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. The treatment effect is shown as a win ratio, in which a value greater than 1 indicates superiority.

¶ Worsening renal function is a composite outcome of a reduction of 50% or more in the estimated GFR sustained for at least 28 days, end-stage renal disease, or death from renal causes. End-stage renal disease was defined as an estimated GFR of less than 15 ml per minute per 1.73 m^2 that was sustained for at least 28 days, long-term dialysis treatment (sustained for ≥28 days), or kidney transplantation. Serious adverse events of acute kidney injury were reported in 23 patients (1.0%) in the dapagliflozin group and in 46 (1.9%) in the placebo group (P=0.007).

‖ The safety population included all the patients who had undergone randomization and received at least one dose of dapagliflozin or placebo.

** Major hypoglycemia was defined as hypoglycemia requiring the assistance of another person to actively administer carbohydrates or glucagon or to take other corrective action. All cases occurred in patients with diabetes at baseline.

†† All cases of diabetic ketoacidosis occurred in patients with diabetes at baseline.

‡‡ The between-group difference in laboratory and other measures is reported as the treatment effect.

§§ Glycated hemoglobin values are listed only for the patients with diabetes.

JJ McMurray et al. N Engl J Med 2019;381:1995-2008.

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Primary and Secondary Cardiovascular Outcomes and Adverse Events of Special Interest.*

Table 2. Primary and Secondary Cardiovascular Outcomes and Adverse Events of Special Interest.*

Variable	Dapagliflozin (N=2373)		Placebo (N=2371)		Hazard or Rate Ratio or Difference (95% CI)	P Value
	values	*events/100 patient-yr*	*values*	*events/100 patient-yr*		
Efficacy outcomes						
Primary composite outcome — no. (%)†	386 (16.3)	11.6	502 (21.2)	15.6	0.74 (0.65 to 0.85)	<0.001
Hospitalization or an urgent visit for heart failure	237 (10.0)	7.1	326 (13.7)	10.1	0.70 (0.59 to 0.83)	NA
Hospitalization for heart failure	231 (9.7)	6.9	318 (13.4)	9.8	0.70 (0.59 to 0.83)	NA
Urgent heart-failure visit	10 (0.4)	0.3	23 (1.0)	0.7	0.43 (0.20 to 0.90)	NA
Cardiovascular death	227 (9.6)	6.5	273 (11.5)	7.9	0.82 (0.69 to 0.98)	NA
Secondary outcomes						
Cardiovascular death or heart-failure hospitalization — no. (%)	382 (16.1)	11.4	495 (20.9)	15.3	0.75 (0.65 to 0.85)	<0.001
Total no. of hospitalizations for heart failure and cardiovascular deaths‡	567	—	742	—	0.75 (0.65 to 0.88)	<0.001
Change in KCCQ total symptom score at 8 mo§	6.1±18.6	—	3.3±19.2	—	1.18 (1.11 to 1.26)	<0.001
Worsening renal function — no. (%)¶	28 (1.2)	0.8	39 (1.6)	1.2	0.71 (0.44 to 1.16)	NA
Laboratory and other measures						
Change from baseline to 8 mo‡‡						
Glycated hemoglobin — %§§	−0.21±1.14	—	0.04±1.29	—	−0.24 (−0.34 to −0.13)	<0.001
Creatinine — mg/dl	0.07±0.24	—	0.04±0.25	—	0.02 (0.01 to 0.03)	<0.007
Hematocrit — %	2.31±3.90	—	−0.19±3.81	—	2.41 (2.21 to 2.62)	<0.001
NT-proBNP — pg/ml	−196±2387	—	101±2944	—	−303 (−457 to −150)	<0.001
Weight — kg	−0.88±3.86	—	0.10±4.09	—	−0.87 (−1.11 to −0.62)	<0.001
Systolic blood pressure — mm Hg	−1.92±14.92	—	−0.38±15.27	—	−1.27 (−2.09 to −0.45)	0.002

* Plus–minus values are means ±SD. NA denotes not applicable because P values for efficacy outcomes are reported only for outcomes that were included in the hierarchical-testing strategy.

† The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or death from cardiovascular causes.

‡ The total number of hospitalizations for heart failure and cardiovascular deaths was analyzed by means of the semiparametric proportional-rates model, in which the treatment effect is reported as a rate ratio.

§ The total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. The treatment effect is shown as a win ratio, in which a value greater than 1 indicates superiority.

¶ Worsening renal function is a composite outcome of a reduction of 50% or more in the estimated GFR sustained for at least 28 days, end-stage renal disease, or death from renal causes. End-stage renal disease was defined as an estimated GFR of less than 15 ml per minute per 1.73 m^2 that was sustained for at least 28 days, long-term dialysis treatment (sustained for ≥28 days), or kidney transplantation. Serious adverse events of acute kidney injury were reported in 23 patients (1.0%) in the dapagliflozin group and in 46 (1.9%) in the placebo group (P=0.007).

‖ The safety population included all the patients who had undergone randomization and received at least one dose of dapagliflozin or placebo.

** Major hypoglycemia was defined as hypoglycemia requiring the assistance of another person to actively administer carbohydrates or glucagon or to take other corrective action. All cases occurred in patients with diabetes at baseline.

†† All cases of diabetic ketoacidosis occurred in patients with diabetes at baseline.

‡‡ The between-group difference in laboratory and other measures is reported as the treatment effect.

§§ Glycated hemoglobin values are listed only for the patients with diabetes.

Cardiovascular death or heart-failure hospitalization — no. (%)	382 (16.1)	11.4	495 (20.9)	15.3	0.75 (0.65 to 0.85)	<0.001
Total no. of hospitalizations for heart failure and cardiovascular deaths‡	567	—	742	—	0.75 (0.65 to 0.88)	<0.001
Change in KCCQ total symptom score at 8 mo§	6.1±18.6	—	3.3±19.2	—	1.18 (1.11 to 1.26)	<0.001

JJ McMurray et al. N Engl J Med 2019;381:1995-2008.

The NEW ENGLAND JOURNAL of MEDICINE

Primary and Secondary Cardiovascular Outcomes and Adverse Events of Special Interest.*

Table 2. Primary and Secondary Cardiovascular Outcomes and Adverse Events of Special Interest.*

Variable	Dapagliflozin (N=2373)		Placebo (N=2371)		Hazard or Rate Ratio or Difference (95% CI)	P Value
	values	*events/100 patient-yr*	*values*	*events/100 patient-yr*		
Efficacy outcomes						
Primary composite outcome — no. (%)†	386 (16.3)	11.6	502 (21.2)	15.6	0.74 (0.65 to 0.85)	<0.001
Hospitalization or an urgent visit for heart failure	237 (10.0)	7.1	326 (13.7)	10.1	0.70 (0.59 to 0.83)	NA
Hospitalization for heart failure	231 (9.7)	6.9	318 (13.4)	9.8	0.70 (0.59 to 0.83)	NA
Urgent heart-failure visit	10 (0.4)	0.3	23 (1.0)	0.7	0.43 (0.20 to 0.90)	NA
Cardiovascular death	227 (9.6)	6.5	273 (11.5)	7.9	0.82 (0.69 to 0.98)	NA
Secondary outcomes						
Cardiovascular death or heart-failure hospitalization — no. (%)	382 (16.1)	11.4	495 (20.9)	15.3	0.75 (0.65 to 0.85)	<0.001
Total no. of hospitalizations for heart failure and cardiovascular deaths‡	567	—	742	—	0.75 (0.65 to 0.88)	<0.001
Change in KCCQ total symptom score at 8 mo§	6.1±18.6	—	3.3±19.2	—	1.18 (1.11 to 1.26)	<0.001
Worsening renal function — no. (%)¶	28 (1.2)	0.8	39 (1.6)	1.2	0.71 (0.44 to 1.16)	NA
Change from baseline to 8 mo‡‡						
Glycated hemoglobin — %§§	−0.21±1.14	—	0.04±1.29	—	−0.24 (−0.34 to −0.13)	<0.001
Creatinine — mg/dl	0.07±0.24	—	0.04±0.25	—	0.02 (0.01 to 0.03)	<0.007
Hematocrit — %	2.31±3.90	—	−0.19±3.81	—	2.41 (2.21 to 2.62)	<0.001
NT-proBNP — pg/ml	−196±2387	—	101±2944	—	−303 (−457 to −150)	<0.001
Weight — kg	−0.88±3.86	—	0.10±4.09	—	−0.87 (−1.11 to −0.62)	<0.001
Systolic blood pressure — mm Hg	−1.92±14.92	—	−0.38±15.27	—	−1.27 (−2.09 to −0.45)	0.002

* Plus–minus values are means ±SD. NA denotes not applicable because P values for efficacy outcomes are reported only for outcomes that were included in the hierarchical-testing strategy.

† The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or death from cardiovascular causes.

‡ The total number of hospitalizations for heart failure and cardiovascular deaths was analyzed by means of the semiparametric proportional-rates model, in which the treatment effect is reported as a rate ratio.

§ The total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. The treatment effect is shown as a win ratio, in which a value greater than 1 indicates superiority.

¶ Worsening renal function is a composite outcome of a reduction of 50% or more in the estimated GFR sustained for at least 28 days, end-stage renal disease, or death from renal causes. End-stage renal disease was defined as an estimated GFR of less than 15 ml per minute per 1.73 m^2 that was sustained for at least 28 days, long-term dialysis treatment (sustained for ≥28 days), or kidney transplantation. Serious adverse events of acute kidney injury were reported in 23 patients (1.0%) in the dapagliflozin group and in 46 (1.9%) in the placebo group (P=0.007).

‖ The safety population included all the patients who had undergone randomization and received at least one dose of dapagliflozin or placebo.

** Major hypoglycemia was defined as hypoglycemia requiring the assistance of another person to actively administer carbohydrates or glucagon or to take other corrective action. All cases occurred in patients with diabetes at baseline.

†† All cases of diabetic ketoacidosis occurred in patients with diabetes at baseline.

‡‡ The between-group difference in laboratory and other measures is reported as the treatment effect.

§§ Glycated hemoglobin values are listed only for the patients with diabetes.

JJ McMurray et al. N Engl J Med 2019;381:1995-2008.

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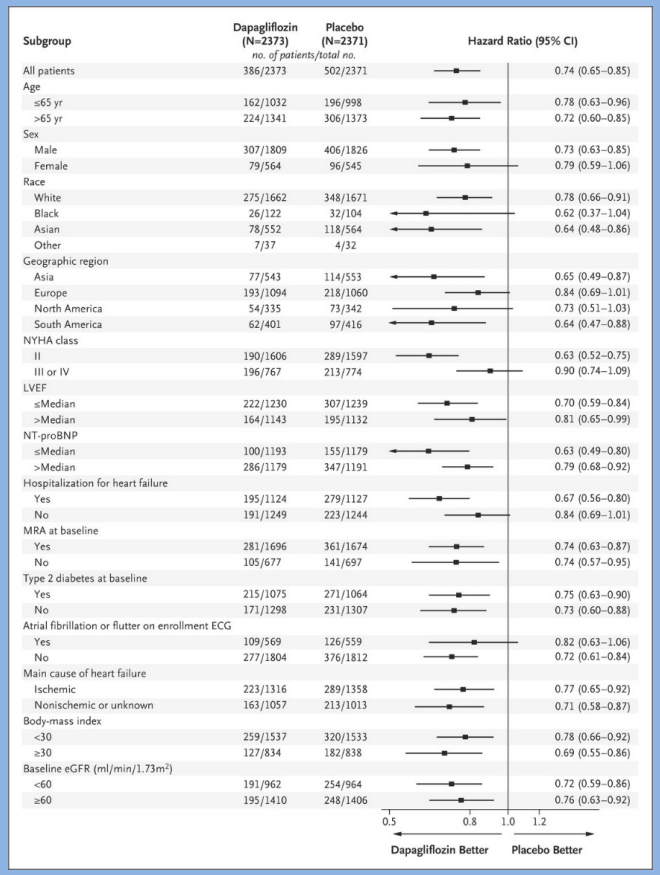
Primary Composite Outcome, According to Prespecified Subgroup.



Subgroup	Dapagliflozin (N=2373)	Placebo (N=2371)	Hazard Ratio (95% CI)
	no. of patients/total no.		
All patients	386/2373	502/2371	0.74 (0.65–0.85)
Age			
≤65 yr	162/1032	196/998	0.78 (0.63–0.96)
>65 yr	224/1341	306/1373	0.72 (0.60–0.85)
Sex			
Male	307/1809	406/1826	0.73 (0.63–0.85)
Female	79/564	96/545	0.79 (0.59–1.06)
Race			
White	275/1662	348/1671	0.78 (0.66–0.91)
Black	26/122	32/104	0.62 (0.37–1.04)
Asian	78/552	118/564	0.64 (0.48–0.86)
Other	7/37	4/32	
Geographic region			
Asia	77/543	114/553	0.65 (0.49–0.87)
Europe	193/1094	218/1060	0.84 (0.69–1.01)
North America	54/335	73/342	0.73 (0.51–1.03)
South America	62/401	97/416	0.64 (0.47–0.88)
NYHA class			
II	190/1606	289/1597	0.63 (0.52–0.75)
III or IV	196/767	213/774	0.90 (0.74–1.09)
LVEF			
≤Median	222/1230	307/1239	0.70 (0.59–0.84)
>Median	164/1143	195/1132	0.81 (0.65–0.99)
NT-proBNP			
≤Median	100/1193	155/1179	0.63 (0.49–0.80)
>Median	286/1179	347/1191	0.79 (0.68–0.92)
Hospitalization for heart failure			
Yes	195/1124	279/1127	0.67 (0.56–0.80)
No	191/1249	223/1244	0.84 (0.69–1.01)
MRA at baseline			
Yes	281/1696	361/1674	0.74 (0.63–0.87)
No	105/677	141/697	0.74 (0.57–0.95)
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)
Atrial fibrillation or flutter on enrollment ECG			
Yes	109/569	126/559	0.82 (0.63–1.06)
No	277/1804	376/1812	0.72 (0.61–0.84)
Main cause of heart failure			
Ischemic	223/1316	289/1358	0.77 (0.65–0.92)
Nonischemic or unknown	163/1057	213/1013	0.71 (0.58–0.87)
Body-mass index			
<30	259/1537	320/1533	0.78 (0.66–0.92)
≥30	127/834	182/838	0.69 (0.55–0.86)
Baseline eGFR (ml/min/1.73m^2)			
<60	191/962	254/964	0.72 (0.59–0.86)
≥60	195/1410	248/1406	0.76 (0.63–0.92)

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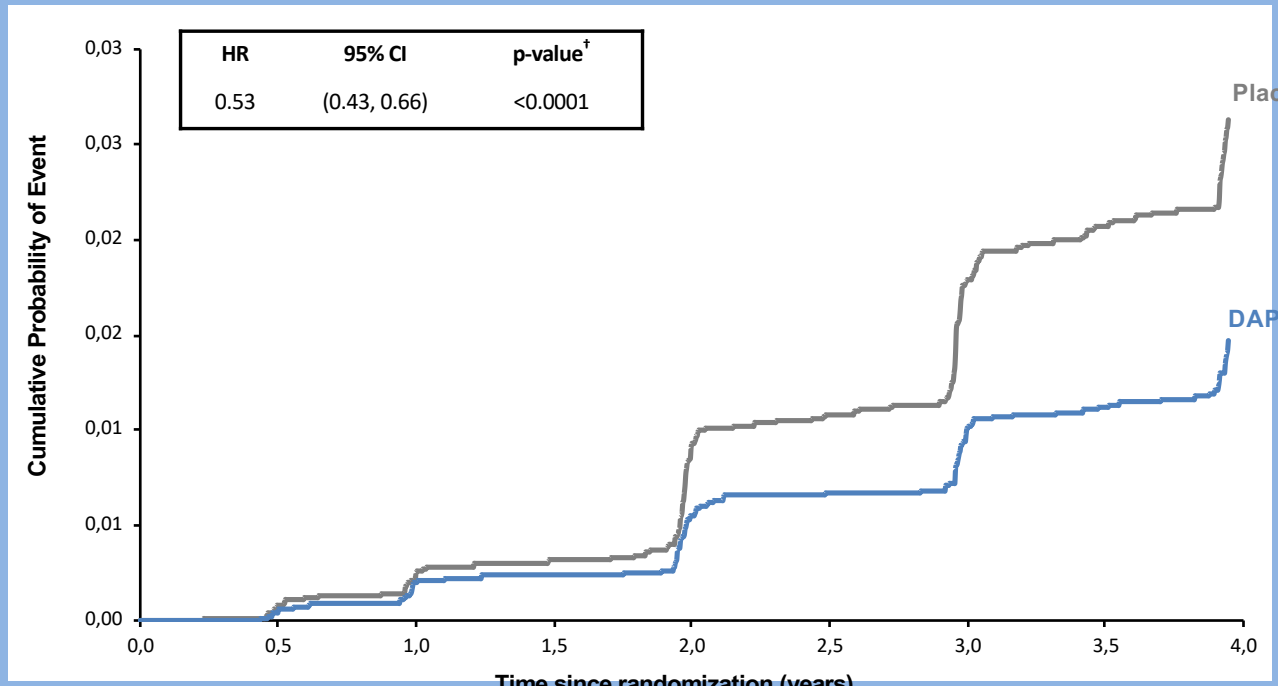
Renal-specific Outcome*
Decrease eGFR ≥40%, ESRD or Renal Death



No. at risk									
DAPA 10 mg	8582	8523	8422	8338	8242	8127	8004	7522	5464
Placebo	8578	8504	8415	8321	8193	8056	7925	7403	5382

*Prespecified exploratory endpoint †Because the trial met only one of its dual primary outcomes for superiority (CV death or hospital admission for heart failure), all other analyses of additional outcomes should be considered hypothesis generating only. No. at risk is the number of subjects at risk at the beginning of the period.
DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HR = hazard ratio.
Mosenzon O et al. Online ahead of print. *Lancet Diabetes Endocrinol*. 2019.

Zusammenfassung SGLT2-Hemmer

- Gut für den Diabetes (Gruppeneffekt)
- Gut für die Herzinsuffizienz (dzt nur für Dapagliflozin belegt)
- Gut für die Niere (Gruppeneffekt)

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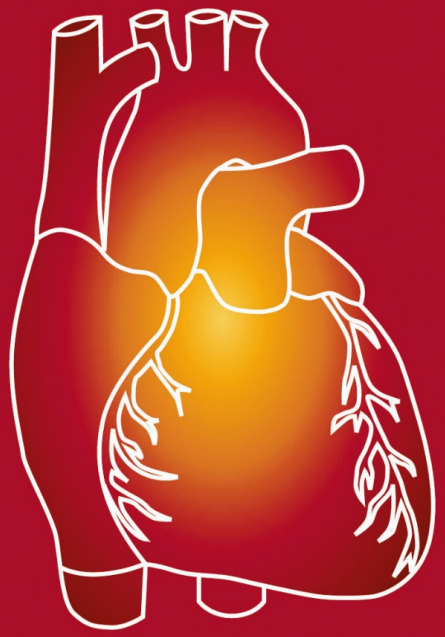
Herzinsuffizienz



Diagnostik - Devices - Therapie
Multimorbide Patienten
anhand aktueller Fallbeispiele

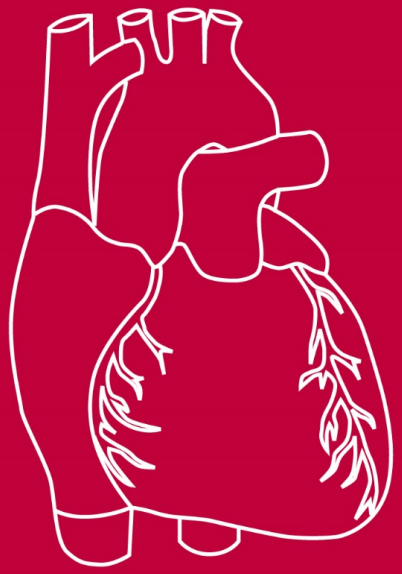
Klagenfurt, Sa 17. Oktober 2020

9.00 bis 13.00 Uhr

med Congress

21. Consensus Meeting

DER AG HERZINSUFFIZIENZ



Herzinsuffizienz

Sa 23. Jänner 2021
9.00–13.00 Uhr

Hofstallung des MuseumsQuartiers Wien