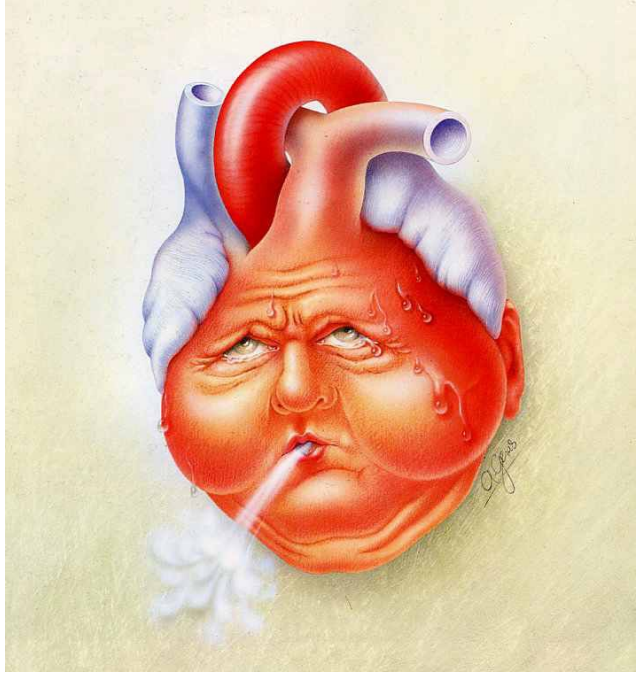
HARTCENTRUM GENT

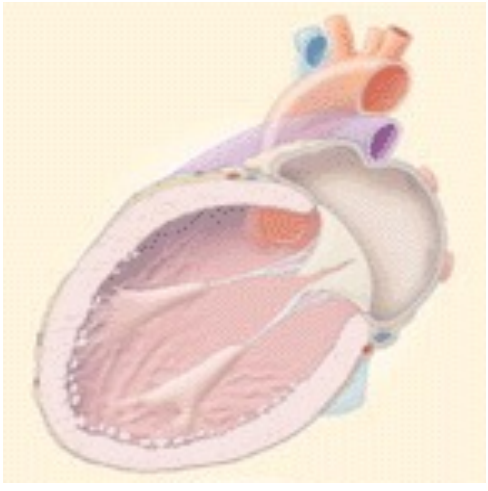
E17 ziekenhuis netwerk

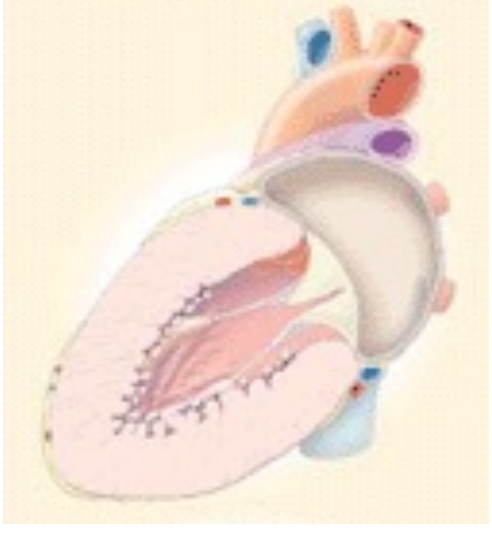
MARIA MIDDELARES

Hartfalen in het tijdperk van SGLT2-remmers en ARNI's

Johan De Sutter





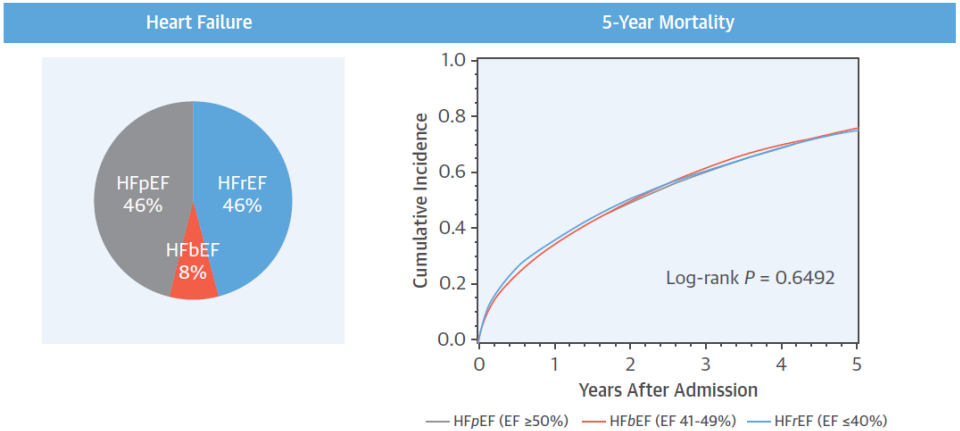


LVEF < 40 % : HFREF

LVEF 40-50 % : HFMREF

LVEF > 50 % : HFPEF

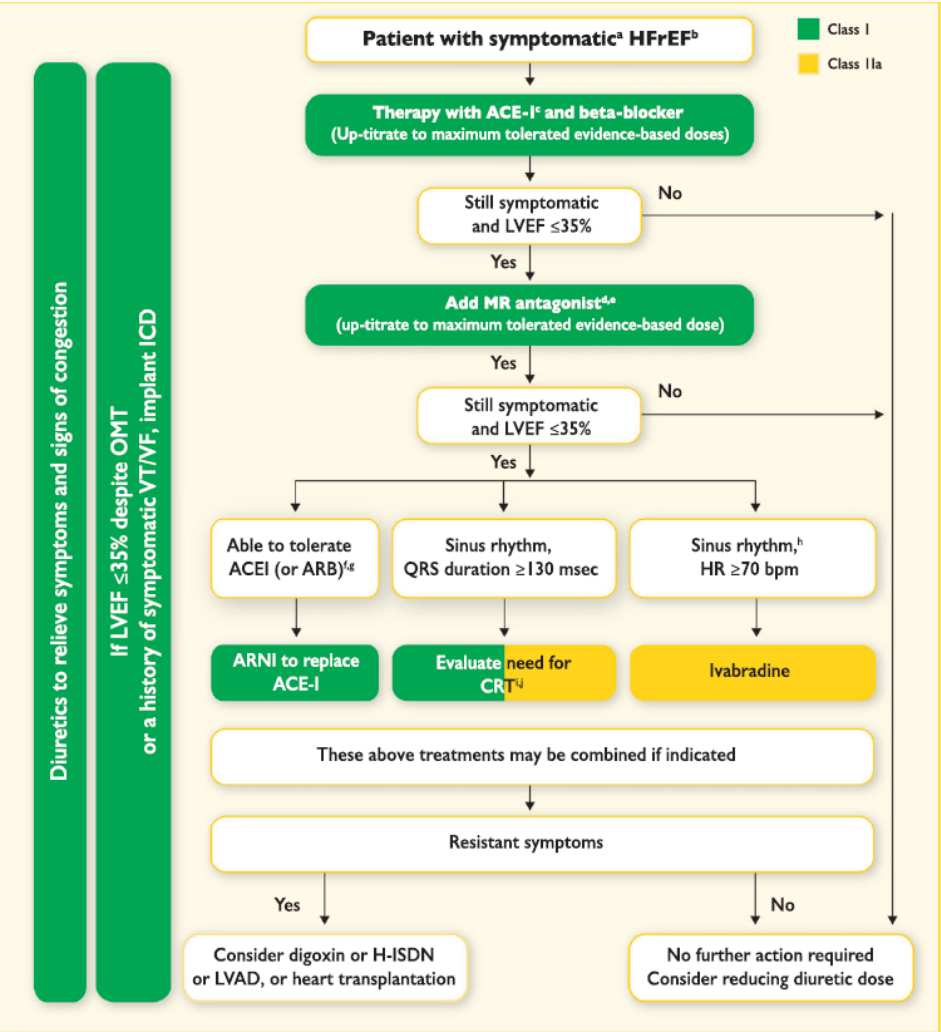
5 years outcome of 39982 patients ≥ 65 years hospitalized for heart failure



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

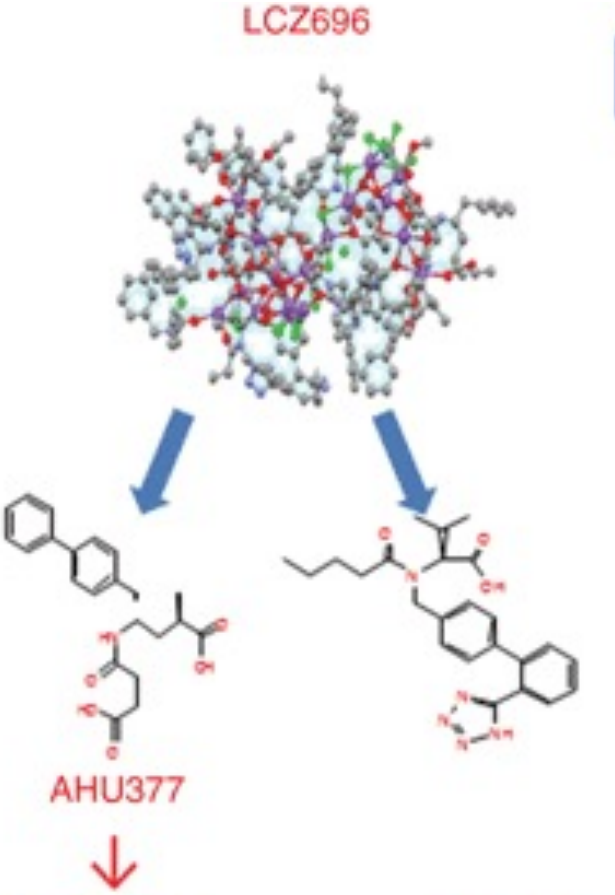
Shah, K.S. et al. J Am Coll Cardiol. 2017;70(20):2476-86.

Patients ≥65 years of age hospitalized for decompensated heart failure (HF) in the GWTG-HF (Get With The Guidelines Heart Failure) registry had a similar percentage of preserved and reduced ejection fraction (EF), with 8% having borderline EF. The 5-year survival outcomes were poor across these subgroups, and rates of HF and cardiovascular (CV) admission were slightly greater in patients with reduced and borderline EF. The event rates for each outcome and HF subgroup are listed in the table. HFbEF = heart failure with borderline ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.



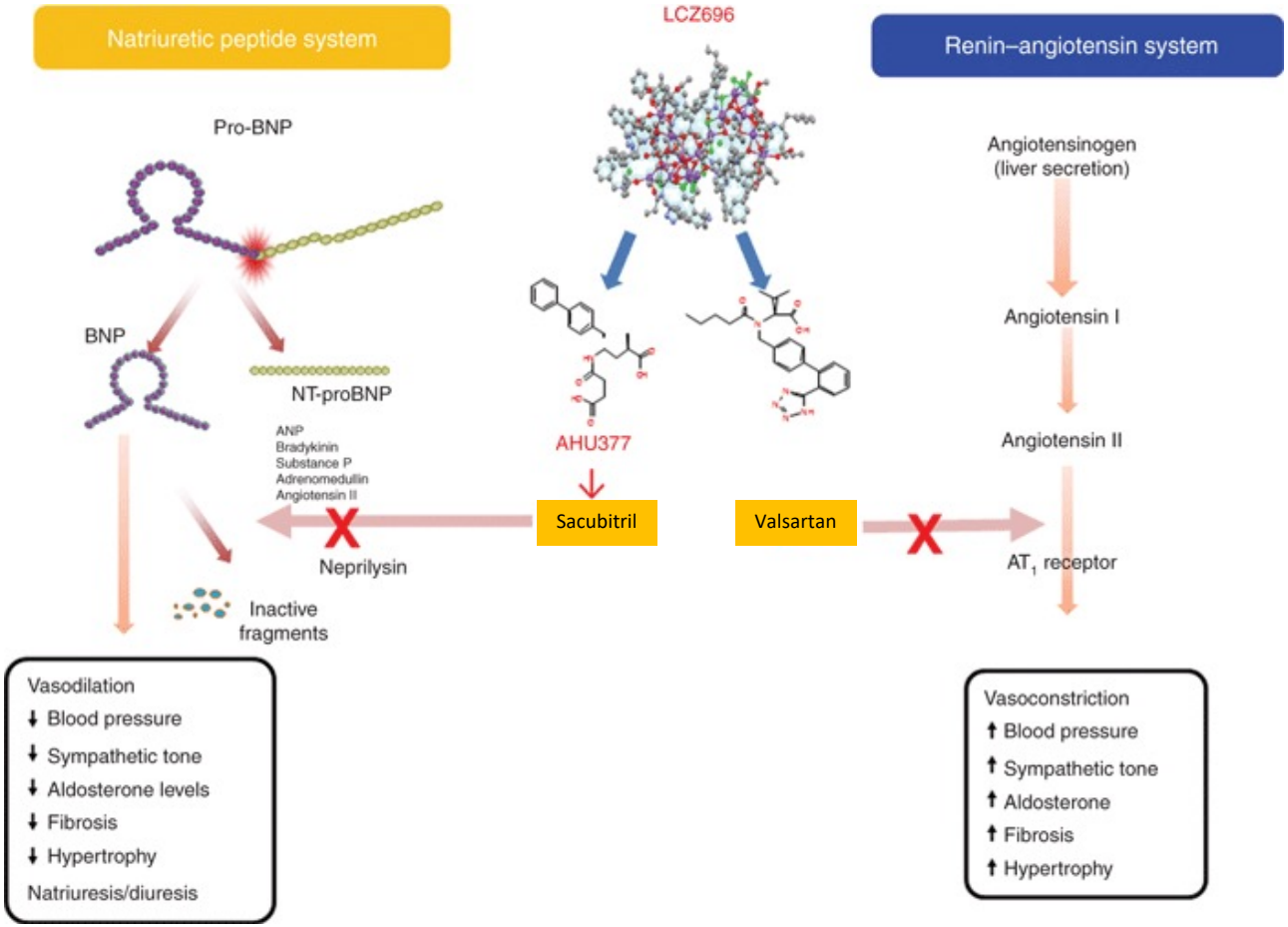
ESC richtlijnen 2016

NEPRILYSIN
INHIBITOR



ANGIOTENSIN
RECEPTOR
BLOKKER

Sacubitril + Valsartan


Natriuretic peptide system
LCZ696
Renin–angiotensin system
Pro-BNP
BNP
NT-proBNP
ANP
Bradykinin
Substance P
Adrenomedullin
Angiotensin II
AHU377
Sacubitril
Neprilysin
Inactive fragments
Angiotensinogen (liver secretion)
Angiotensin I
Angiotensin II
Valsartan
AT1 receptor
Vasodilation
↓ Blood pressure
↓ Sympathetic tone
↓ Aldosterone levels
↓ Fibrosis
↓ Hypertrophy
Natriuresis/diuresis
Vasoconstriction
↑ Blood pressure
↑ Sympathetic tone
↑ Aldosterone
↑ Fibrosis
↑ Hypertrophy

Angiotensine-Neprilysine inhibitie – PARADIGM-HF

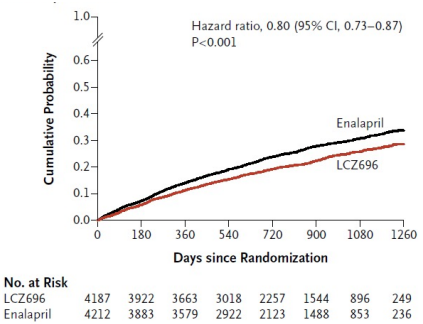
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

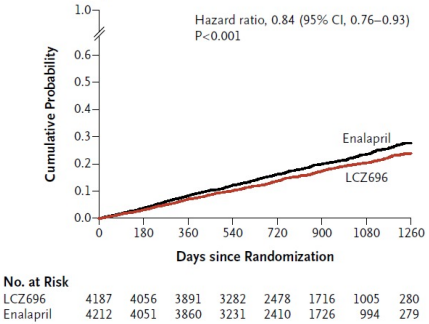
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

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., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

- Angiotensin-Neprilysin versus Enalapril - 8442 patients enrolled between 2009 and 2012
- LVEF ≤ 35-40%; NYHA II-IV heart failure
- At least mild increase in BNP or NT-proBNP
- Any use of ACE-I or ARB, but able to tolerate stable dose equivalent to at least enalapril 10 mg daily for ≥ 4 weeks
- Guideline recommended use of BBL and MRA
- Systolic BP ≥ 95 mmHg, eGFR ≥ 30 ml/min/1,73m² and serum K ≤ 5,4 meq/l



20% reductie cardiovasculaire sterfte en hospitalisatie hartfalen



16% reductie totale sterfte

2013

Angiotensine-Neprilysine inhibitie – PIONEER-HF

The NEW ENGLAND JOURNAL of MEDICINE

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., and Eugene Braunwald, M.D., for the PIONEER-HF Investigators*

- Angiotensin-Neprilysin versus Enalapril - 881 patients
- LVEF ≤ 40%; hospitalized with new diagnose of HFREF
- BNP ≥ 400 pg/ml or NT-proBNP ≥ 1600 pg/ml
- Randomization within 1-10 days during hospitalization
- Systolic BP ≥ 100 mmHg, eGFR ≥ 30 ml/min/1,73m² and serum K ≤ 5,4 meq/l
- No significant differences in deterioration of renal function, hyperkaliemia of hypotension

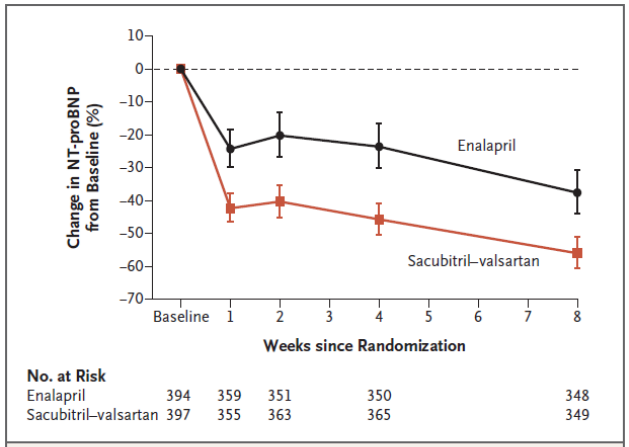


Figure 2. Change in the NT-proBNP Concentration.

The time-averaged reduction in the N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentration was significantly greater in the sacubitril–valsartan group than in the enalapril group; the ratio of the geometric mean of values obtained at weeks 4 and 8 to the baseline value was 0.53 in the sacubitril–valsartan group as compared with 0.75 in the enalapril group (percent change, −46.7% vs. −25.3%; ratio of change with sacubitril–valsartan vs. enalapril, 0.71; 95% CI, 0.63 to 0.81; P<0.001).

2019

Angiotensine-Neprilysine inhibitie
recente studies in hartfalen

- Hartfalen en bewaarde LV functie (HFPEF) (NEJM 2019)
  - PARAGON HF : valsartan vs sacubitril/valsartan
  - Geen significant effect op outcome (p=0,06)

- Tijdens opname voor uitgebreid myocardinfarct (LVEF <40%) maar zonder tekenen van hartfalen (NEJM 2021)
  - PARADISE-MI : ramipril vs sacubitril/valsartan
  - Geen significant effect op outcome (p=0,17)

Entresto® – terugbetaling 2021

- HFREF met LVEF ≤ 35%
- NYHA II-III-IV
- Voorafgaand behandeld met een optimale dosis ACE-remmer of sartane

- Aanvraag kan gedaan worden door cardioloog, internist of geriater
- Verlenging voor 364 dagen

Entresto® – practische aspecten

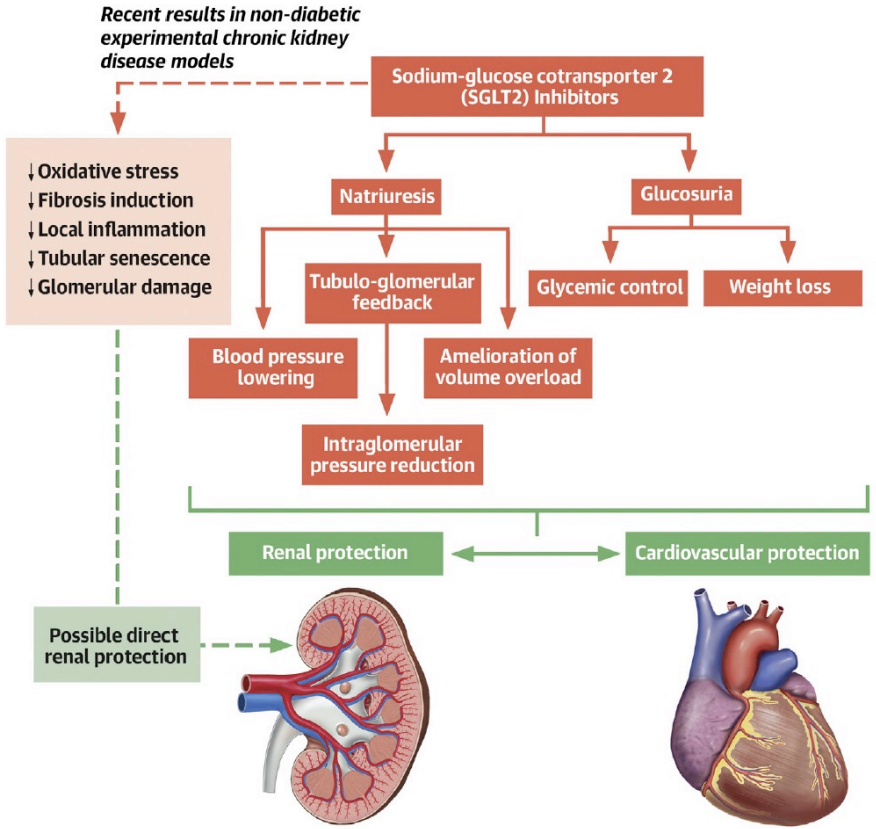
- Opstart
  - LVEF ≤ 35% - NYHA II-III-IV – GFR ≥ 30 ml/min/kg² - Kalium ≤ 5,4 meq/L
  - Systolische bloeddruk ≥ 95 mmHg
  - ACE-remmer 36 uur vooraf te stoppen !
  - Meestal start lage dosis (24mg/26mg sacubitril/valsartan) 2 x dd

- Follow-up
  - Aandachtspunten : hypotensie – angiooedeem – nierfunctie/hyperkaliemie
  - Eerste controle na 2 weken
  - Progressief dosis verhogen tot maximale dosis (97mg/103mg sacubitril/valsartan) 2x dd

Empaglifozine
(JARDIANCE®)

Dapaglifozine
(FORXIGA®)

CENTRAL ILLUSTRATION Sodium-Glucose Cotransporter 2 Inhibitor Cardiorenal Protection Mechanistic Overview



Zelniker, T.A. et al. J Am Coll Cardiol. 2020;75(4):422-34.

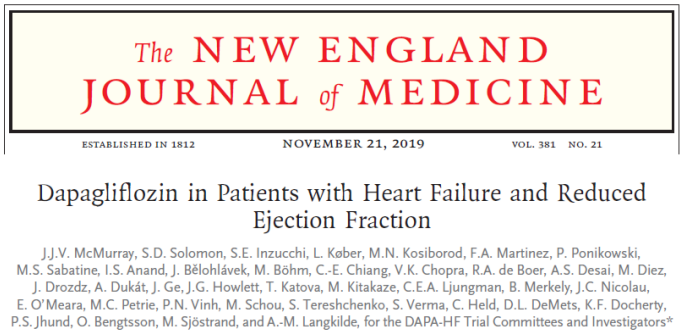
SGLT-2 inhibitoren en cardio-metabole-renale effecten

TABLE 3 Overview of Mechanisms of Favorable Cardio-Metabolic-Renal Effects

	Heart Failure	Atherosclerotic Effect	Diabetic Kidney Disease
Glucose lowering			✓
Reduction in body weight	✓	✓	✓
Lowering of blood pressure	✓	✓	✓
Natriuresis	✓		✓
Anti-inflammation	✓	✓	✓
Antifibrotic	✓		✓
Reduction in extracellular matrix turnover	✓		✓
Amelioration of intrarenal hypoxia			✓
Restoration of the tubuloglomerular feedback			✓
Reduction in natriuretic peptides	✓		✓
Reduction in energy demand	✓		✓
Reduction in liver fat		✓	

Zelniker et al, JACC 2020;75:422-434

SGLT-2 inhibitoren en outcome in HFREF

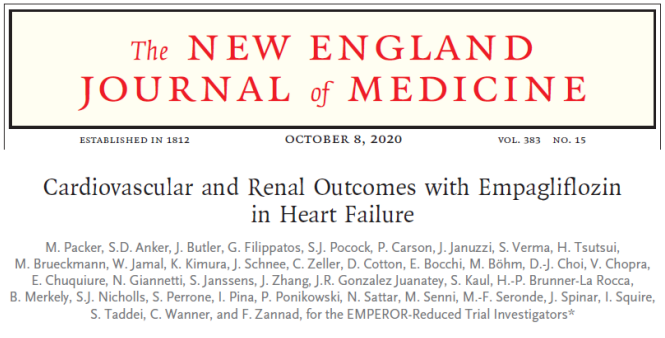


The NEW ENGLAND JOURNAL of MEDICINE

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*



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 8, 2020 VOL. 383 NO. 15

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, H.-P. Brunner-La Rocca, B. Merkely, S.J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M.-F. Seronde, J. Spinar, I. Squire, S. Taddei, C. Wanner, and F. Zannad, for the EMPEROR-Reduced Trial Investigators*

SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials

Faiez Zannad, João Pedro Ferreira, Stuart J Pocock, Stefan D Anker, Javed Butler, Gerasimos Filippatos, Martina Brueckmann, Anne Pernille Ofstad, Egon Pfarr, Waheed Jamal, Milton Packer

Lancet 2020; 396: 819–29

Empaglifozine
(JARDIANCE®)

Dapaglifozine
(FORXIGA®)

	EMPEROR-Reduced		DAPA-HF	
	Empagliflozin	Placebo	Dapagliflozin	Placebo
Number of participants	1863	1867	2373	2371
Age, years	67·2 (10·8)	66·5 (11·2)	66·2 (11·0)	66·5 (10·8)
Sex				
Men	1426 (76·5%)	1411 (75·6%)	1809 (76·2%)	1826 (77·0%)
Women	437 (23·5%)	456 (24·4%)	564 (23·8%)	545 (23·0%)
NYHA functional classification				
II	1399 (75·1%)	1401 (75·0%)	1606 (67·7%)	1597 (67·4%)
III	455 (24·4%)	455 (24·4%)	747 (31·5%)	751 (31·7%)
IV	9 (0·5%)	11 (0·6%)	20 (0·8%)	23 (1·0%)
Mean LVEF, %	27·7 (6·0)	27·2 (6·1)	31·2 (6·7)	30·9 (6·9)
NT-pro BNP, pg/mL	1887 (1077–3429)	1926 (1153–3525)	1428 (857–2655)	1446 (857–2641)
Medical history				
Hospitalisation for heart failure*	577 (31·0%)	574 (30·7%)	1124 (47·4%)	1127 (47·5%)
Diabetes†	927 (49·8%)	929 (49·8%)	1075 (45·3%)	1064 (44·9%)
eGFR, mL/min per 1·73 m²‡	61·8 (21·7)	62·2 (21·5)	66·0 (19·6)	65·5 (19·3)
Heart failure medications				
ACE inhibitor	867 (46·5%)	836 (44·8%)	1332 (56·1%)	1329 (56·1%)
ARB	451 (24·2%)	457 (24·5%)	675 (28·4%)	632 (26·7%)
Mineralocorticoid receptor antagonist	1306 (70·1%)	1355 (72·6%)	1696 (71·5%)	1674 (70·6%)
ARNI	340 (18·3%)	387 (20·7%)	250 (10·5%)	258 (10·9%)
Device therapy				
ICD or CRT-D	578 (31·0%)	593 (31·8%)	622 (26·2%)	620 (26·1%)
CRT-D or CRT-P	220 (11·8%)	222 (11·9%)	190 (8·0%)	164 (6·9%)

Data are n (%), mean (SD), or median (IQR). ACE=angiotensin converting enzyme. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor neprilysin inhibitor. CRT-D=cardiac resynchronisation therapy defibrillator. CRT-P=cardiac resynchronisation therapy pacemaker. eGFR=estimated glomerular filtration rate. ICD=implantable cardiac defibrillator. LVEF=left ventricular ejection fraction. NT-pro BNP=N-terminal pro B-type natriuretic peptide. NYHA=New York Heart Association. *For EMPEROR-Reduced: preceding 12 months. †Determined by a combination of medical history and pre-treatment glycated haemoglobin. ‡Chronic Kidney Disease Epidemiology Collaboration formula.

Table 1: **Overview of main characteristics of the two trial populations at baseline**

Lancet 2020; 396: 819–29

SGLT-2 inhibitoren en outcome in HFREF

Eindpunt	% risico reductie (HR en 95% CI)
Totale sterfte	13 % (HR 0,87, 95%CI 0,77-0,98), p=0,018
CV sterfte	14% (HR 0,86, 95% CI 0,76-0,98), p=0,027
CV sterfte of eerste hospitalisatie hartfalen	26% (HR 0,74, 95%CI 0,68-0,82), p<0,0001
CV sterfte of eerste of herhaalde hospitalisaties hartfalen	25% (HR 0,75, 95% CI 0,68-0,84), p<0,0001
Eerste hospitalisatie hartfalen	31% (HR 0,69, 95% CI 0,62-0,78), p<0,0001
Renaal eindpunt (≥50% daling eGFR, ESRD (eGFR<15), dialyse of niertransplantie) of renale sterfte	38% (HR 0,62, 95% CI 0,43-0,90), p<0,0001

Geen verschillen in effect van behandeling voor diabetes, geslacht, ARNI behandeling, leeftijd, geschiedenis van hospitalisatie voor hartfalen, eGFR en BMI subgroepen
Wel significante interactie voor NYHA klasse II versus NYHA klasse III-IV

Lancet 2020; 396: 819-29

SGLT-2 inhibitoren en bijwerkingen bij HFREF

	EMPEROR-Reduced		DAPA-HF	
	Empagliflozin (n=1863)	Placebo (n=1867)	Dapagliflozin (n=2373)	Placebo (n=2371)
Serious adverse events	772 (41·4%)	896 (48·1%)	846 (35·7%)	951(40·2%)
Any renal adverse event	175 (9·4%)	192 (10·3%)	141 (6·0%)	158 (6·7%)
Volume depletion	197 (10·6%)	184 (9·9%)	170 (7·2%)	153 (6·5%)
Ketoacidosis	0	0	3 (0·1%)	0
Severe hypoglycaemic events	6 (0·3%)	7 (0·4%)	4 (0·2%)	4 (0·2%)
Bone fractures	45 (2·4%)	42 (2·3%)	48 (2·0%)	47 (2·0%)
Lower limb amputation	13 (0·7%)	10 (0·5%)	13 (0·5%)	12 (0·5%)
Fournier's Gangrene	1 (0·1%)	0	0	1 (0·1%)

Data are n(%). Definitions of medical concepts describing adverse events of interest were not exactly similar between the two trials. The absolute numbers of events cannot be compared across the two trials because of different definitions and observation periods. For EMPEROR-Reduced, we show here adverse events up to 7 days after discontinuation of study medication, and for lower limb amputations up to the end of the trial. For DAPA-HF, we show here on-treatment analysis set for all adverse events, except for lower limb amputation shown on and off treatment. See appendix (p 4) for additional details on adverse event definitions.

Table 2: **Relevant adverse events reported in the two trials**

Lancet 2020; 396: 819–29

SGLT-2 inhibitoren voor HFREF

- Bewezen effecten op mortaliteit en rehospitalisatie
  - on top of andere evidence based medicatie voor HFREF
  - grootste effect indien (recente) voorgeschiedenis van hospitalisatie voor hartfalen
  - multifactoriele werking, niet louter het gevolg van het diuretisch effect
- Bewezen remmend effect op achteruitgang van de nierfunctie
- Bewezen positief effect op de levenskwaliteit

- Eenvoudige toediening 1 x dd
- Geen majeure bijwerkingen
- Dosis reductie of stop bij mogelijke hypovolemie (chirurgische ingrepen, infecties,…)

SGLT-2 inhibitoren – terugbetaling 5/2021

- Diabetes type 2 behandeld gedurende 3 maanden met minstens 1 ander antidiabeticum waaronder metformine
- GFR ≥ 60 ml/min/1,73 m²
- HbA1c 7%-9%

- Geen incretinemimeticum, geen ander glifozine, geen gliptine

- Verlenging mits HbA1c ≤ 7,5% of daling met ≥ 0,5% (eerste verlenging) of voldoende glycemische controle (latere verlenging)

SGLT-2 inhibitoren – terugbetaling 5/2021

- Diabetes type 2 behandeld gedurende 3 maanden met minstens 1 ander antidiabeticum waaronder metformine
- GFR ≥ 60 ml/min/1,73 m²
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<u>Najaar 2021 ?</u>
Dapaglifozine
Empaglifozine

HFREF (LVEF ≤ 40%)
Met of zonder diabetes
NYHA II-III-IV
Optimale hartfalen therapie
GFR ≥ 30 ml/min/1,73m²

Hoekstenen van de medicamenteuse behandeling van HFREF in 2021

Triple therapie

- ACE remmer of ARB
- Betablokker
- Aldosterone antagonist

Quadruple therapie

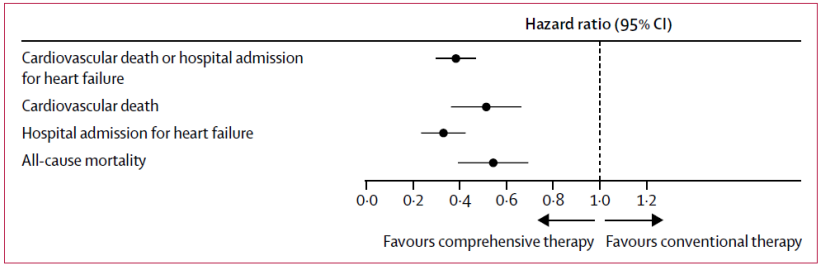
- ARNI (of ACE remmer of ARB)
- Betablokker
- Aldosterone antagonist
- SGLT-2 inhibitor

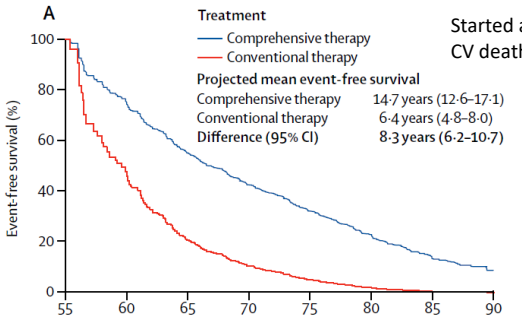
Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials

Muthiah Vaduganathan, Brian L Claggett, Pardeep S Jhund, Jonathan W Cunningham, João Pedro Ferreira, Faiez Zannad, Milton Packer, Gregg C Fonarow, John J V McMurray, Scott D Solomon

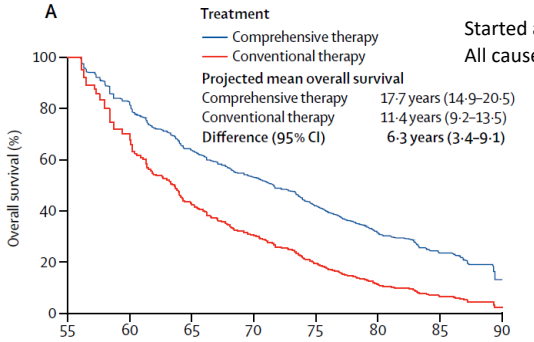
Lancet 2020; 396: 121–28

- Comparison of conventional therapy (ACE or ARB and BBL) versus comprehensive therapy (ARNI/BBL/MRA/SGLT-2i)
- Cross-trial analyss of EMPASIS-HF, PARADIGM-HF and DAPA-HF
- Primary endpoint : CV death or first hospitalisation for heart failure
- Secundary enpoints : CV death, first hospitalisation for heart failure, all- cause mortality





Started at age 55 years
CV death or hospitalization for HF



Started at age 55 years
All cause mortality

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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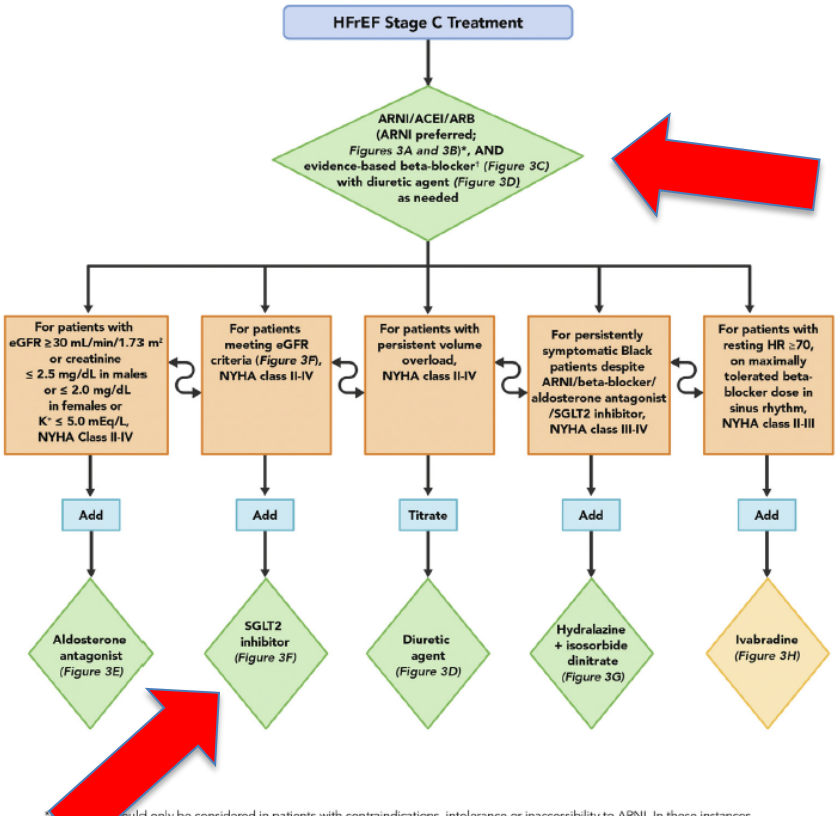
VOL. ■, NO. ■, 2021

EXPERT CONSENSUS DECISION PATHWAY

2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction

A Report of the American College of Cardiology Solution Set Oversight Committee

FIGURE 2 Treatment Algorithm for Guideline-Directed Medical Therapy Including Novel Therapies



*…ould only be considered in patients with contraindications, intolerance or inaccessibility to ARNI. In those instances, plea…sult Figure 3 and text for guidance on initiation.

†Carvedilol, metoprolol succinate, or bisoprolol.

ACEI = angiotensin-converting enzyme inhibitors; ARNI = angiotensin receptor-neprilysin inhibitors; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; K⁺ = potassium; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter-2.

Green color identifies a Class I therapy from clinical practice guidelines, whereas yellow color indicates a Class II therapy.

Hoekstenen van de medicamenteuse behandeling van HFREF in 2021

Triple therapie

- ACE remmer of ARB
- Betablokker
- Aldosterone antagonist

Quadruple therapie

- ARNI (of ACE remmer of ARB)
- Betablokker
- Aldosterone antagonist
- SGLT-2 inhibitor

Therapeutisch inertie ?
Patient compliance ?
Kostprijs – terugbetaling ?

HARTCENTRUM GENT

E17 ziekenhuis netwerk

MARIA MIDDELARES

Hartfalen in het tijdperk van SGLT2-remmers en ARNI's

Johan De Sutter