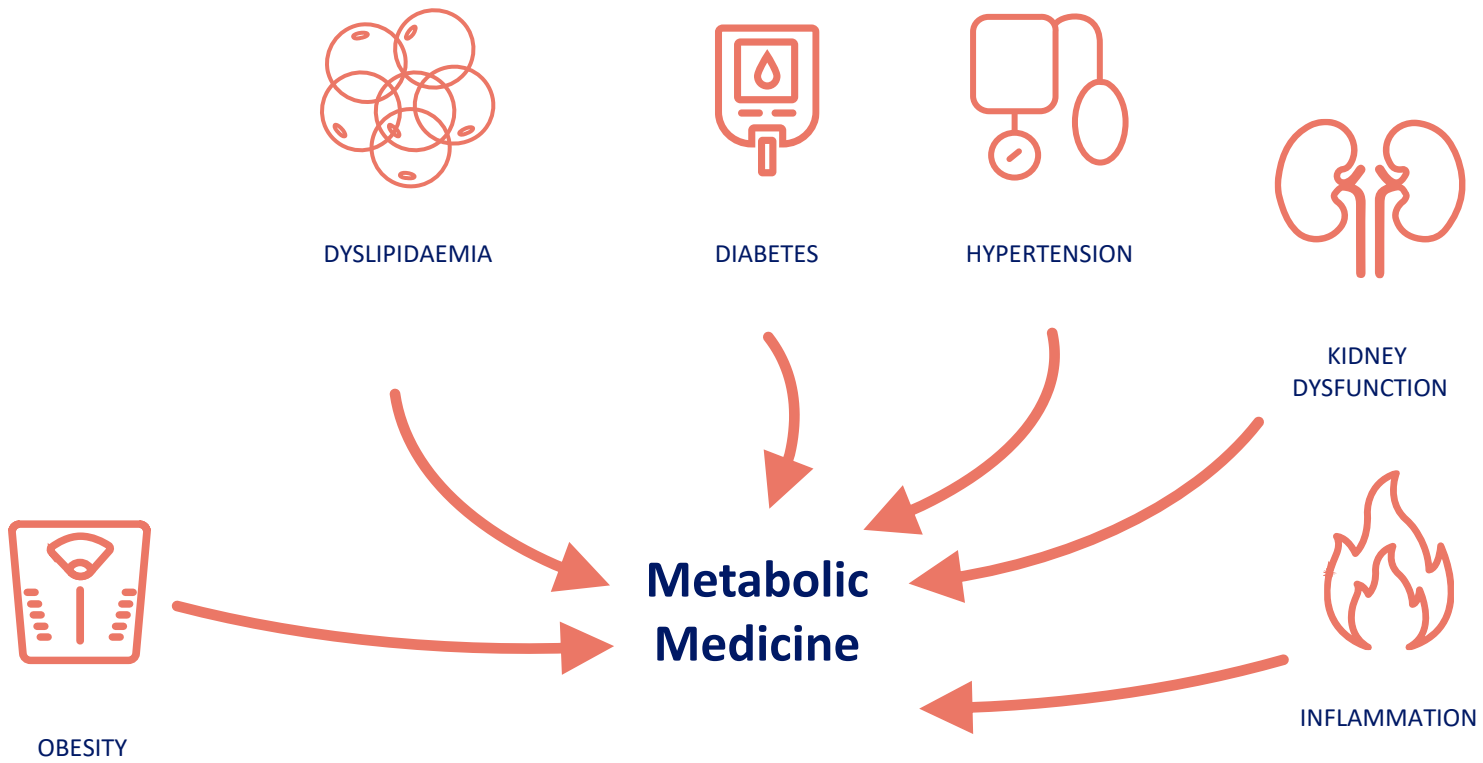
Medical University of Graz | Interdisciplinary Metabolic Medicine Trials Unit

SLGT-2 HEMMER IN DER KARDIO-METABOLISCHEN MEDIZIN

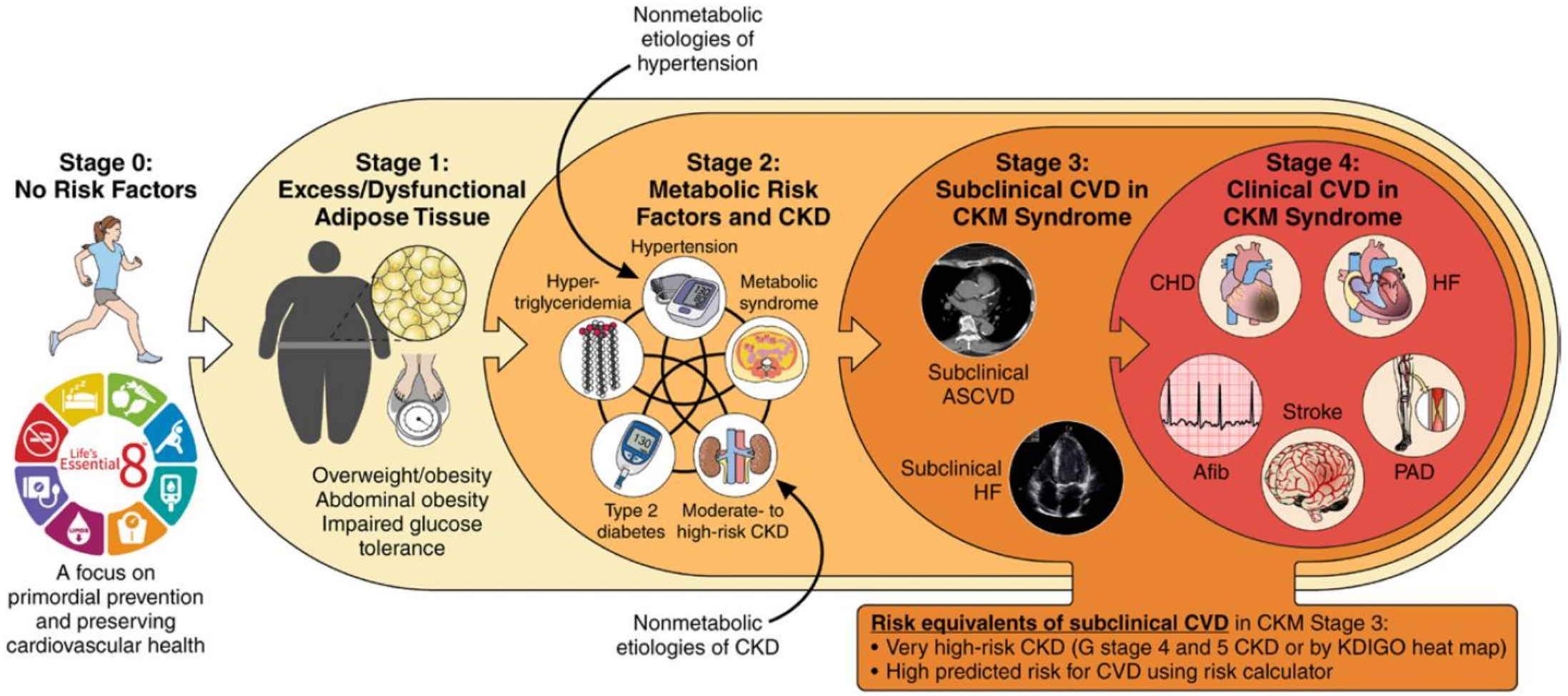
Harald Sourij

Diabetes ≠ Blutzuckerkontrolle



1. Lawler PR, et al. Eur Heart J. 2021;42:113-31. 2. Khafagy R, Dash S. Front Cardiovasc Med. 2021;8:768119. 3. Nishio R, et al. J Cardiol. 2022;79(4):509-514.

Kardiovaskuläre-Renale-Metabolische Gesundheit



Ndumele CE et al. Circulation 2023

Medizinische Vorgeschichte:
Adipositas
Bluthochdruck seit 2 Jahren

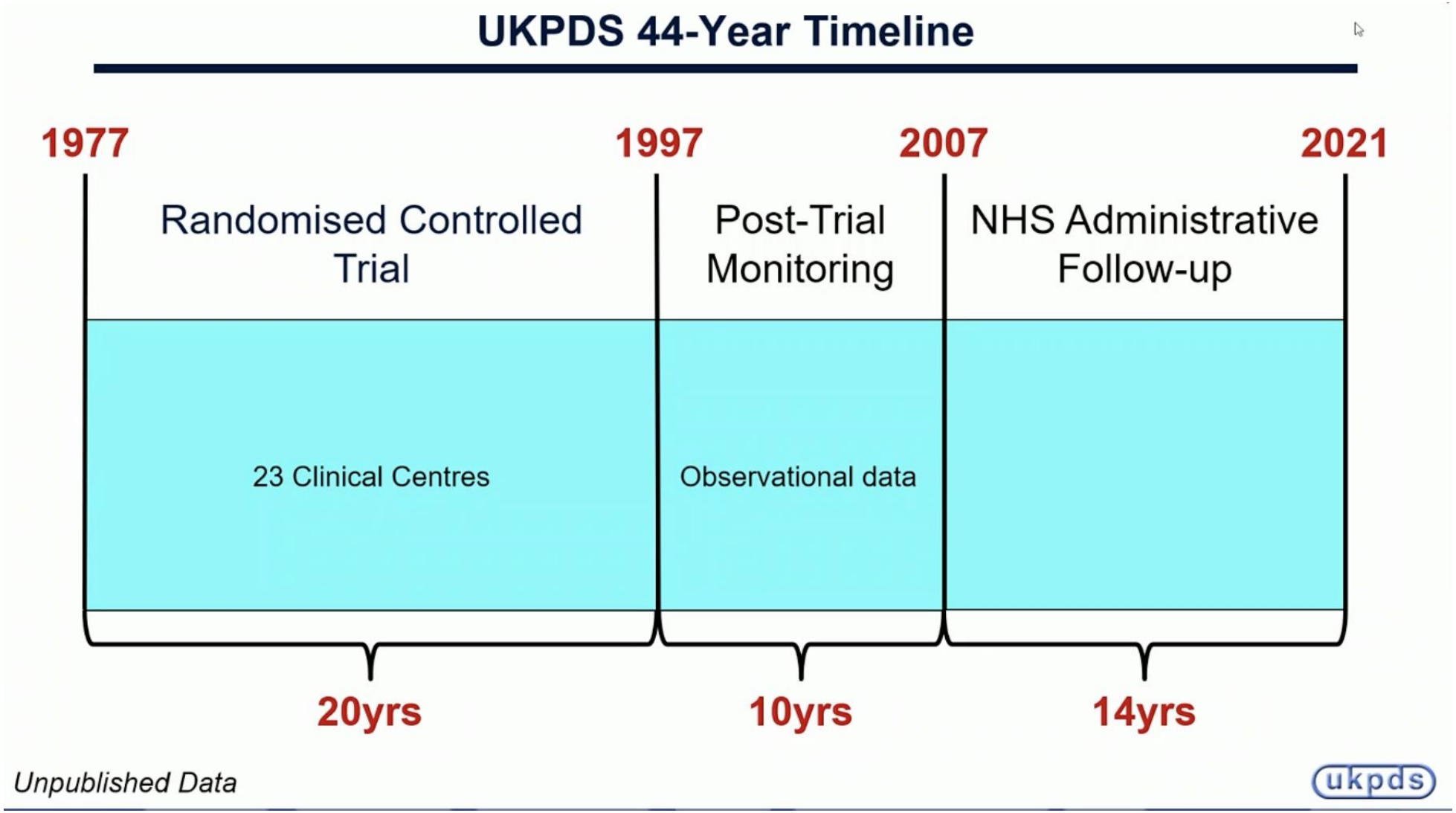
Medikation:
Ramipril 10 mg 1-0-0

87 kg Körpergewicht
1,70 m Körpergröße
BMI: 30.1 kg/m^2

HbA1c 60 mmol/mol (7.7%)
LDL-C 134 mg/dl
eGFR 72 ml/min/1,73 m2
RR 132/84 mmHg

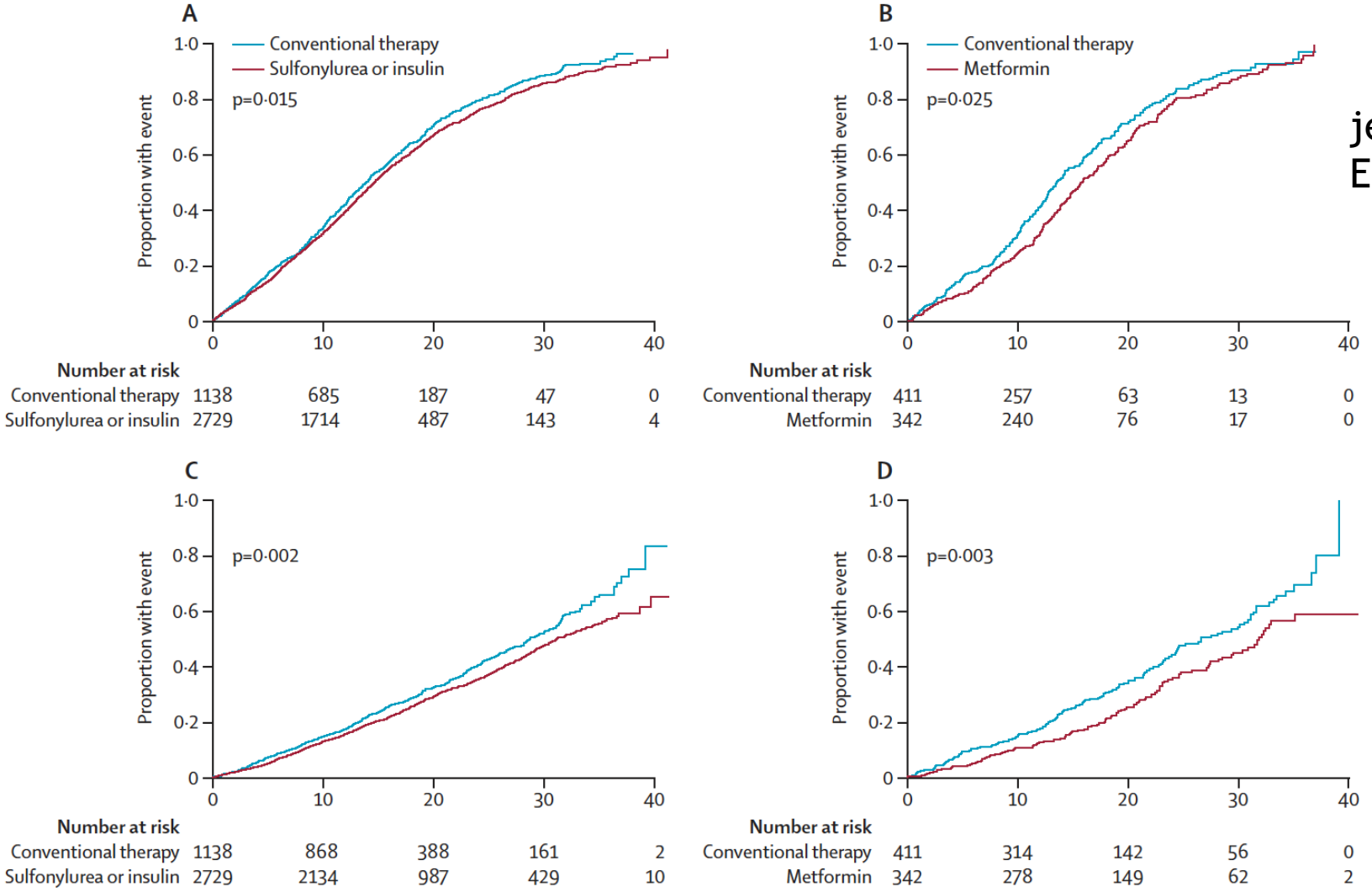
Med Uni Graz

UKPDS – longterm follow-up



Präsentiert EASD 2022

UKPDS Langzeit Follow-up

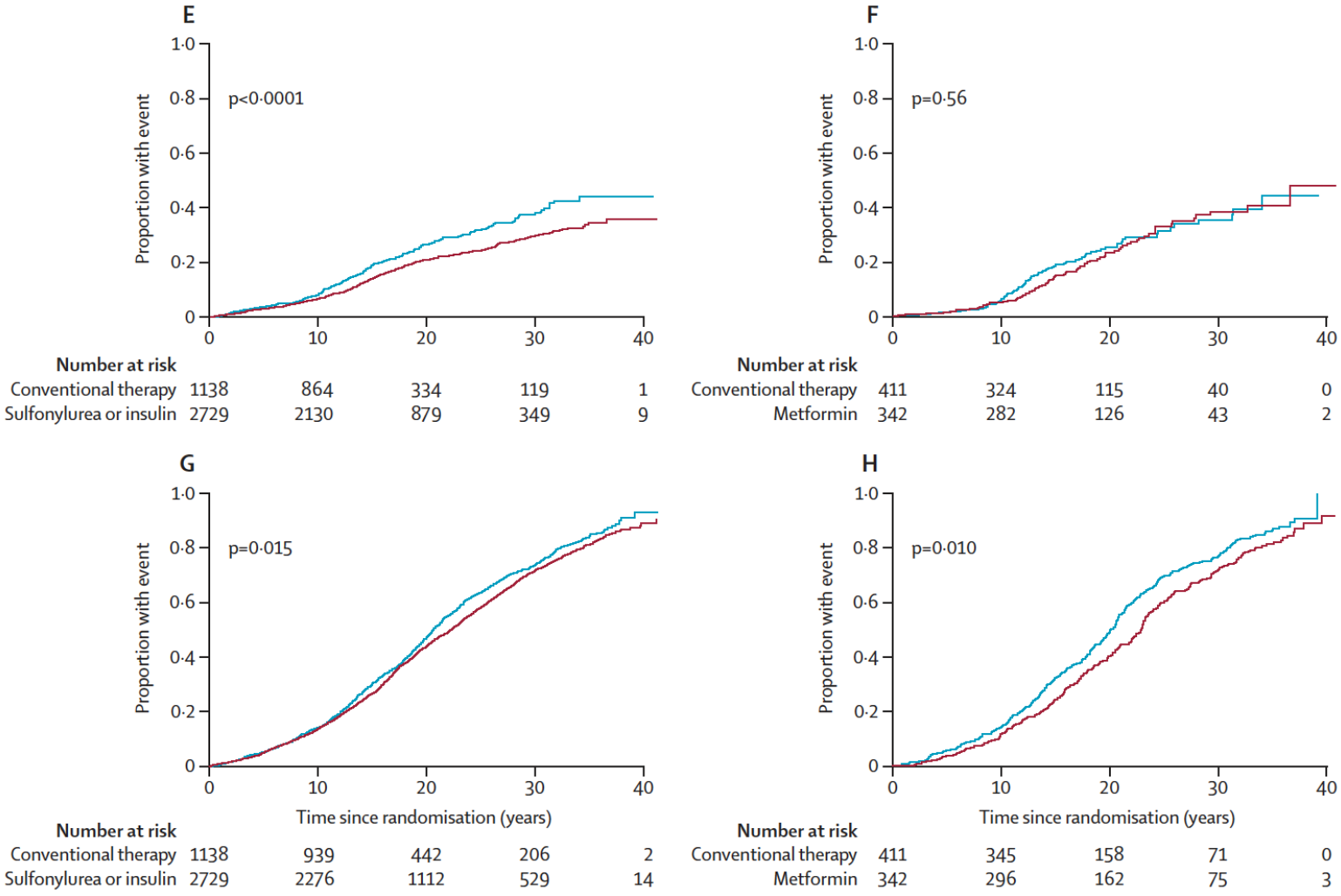


jeglicher Diabetes-bezogener Endpunkt

Myokardinfarkt

Adler A. et al. Lancet 2024

UKPDS Langzeit Follow-up



Mikrovaskuläre Komplikationen

Mortalität

Adler A. et al. Lancet 2024

Therapieziele

HbA1c Ziel	Patientencharakteristika
<6.5% (48 mmol/mol)	• Kurze Diabetesdauer • Lange Lebenserwartung • Keine relevanten kardiovaskulären Erkrankungen
<7.0% (53 mmol/mol)	**Zielwert für die meisten erwachsenen Personen mit Typ 2 Diabetes mellitus**
<8.0% (63 mmol/mol)	• Multiple Spätkomplikationen • Schwere Hypoglykämien • Eingeschränkte Lebenserwartung

Nach Clodi M et al. WieKliWo 2023

Lebensstil modifizierende Therapie

ÖDG Österreichische Diabetes Gesellschaft
helfen, heilen, forschen

Lebensstilmodifizierende Therapie - Gewichtsmanagement, körperliche Aktivität

Anamnestisch bekannte kardiovaskuläre Erkrankung, hohes Risiko für atherosklerotische - kardiovaskuläre Erkrankung, bekannte Herzinsuffizienz (HFpEF, HFmrEF, HFrEF) oder chronische Nierenerkrankung - Kombination unabhängig vom HbA1c

Keine bekannte kardiovaskuläre Erkrankung, Herzinsuffizienz oder chronische Niereninsuffizienz

Metformin als Basistherapie (wenn keine Kontraindikation)

Fokus Gewichtsmanagement / Hypoglykämievermeidung

SGLT2-Hemmer *oder* GLP1-Analogon

HbA1c über dem Zielbereich

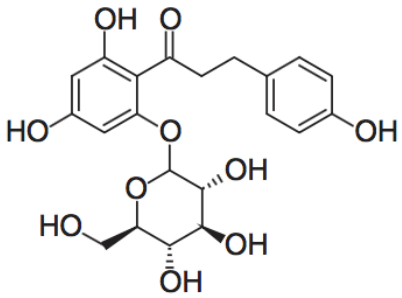
GLP1-Analogon - Tirzepatide [e] *oder* SGLT2-Hemmer

*[a] Entsprechend der Darstellung in Tab. 2, [b] entsprechend der Darstellung in Tab. 3, [c] entsprechend Darstellung in Tab. 4, [d] laut Zulassung der Medikation, [e] Tirzepatide ist von der EMA bereits zugelassen, aber in Österreich vorerst noch nicht verfügbar; HFpEF Heart failure with preserved ejection fraction, HFmrEF Heart failure with mildly reduced ejection fraction, HFrEF Heart failure with reduced ejection fraction. * Metformin ist neben SGLT-2-Hemmern/GLP-1 Analoga erste Wahl und sollte bestmöglich bereits als initiale Kombinationstherapie gegeben werden*

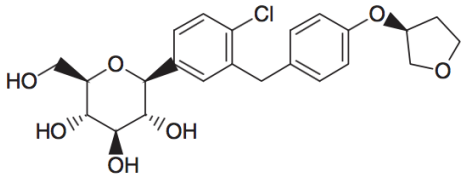
Phlorizin

- Natürlich vorkommend in der Rinde von Birnen-, Apfel-, Kirschen- und anderen Bäumen
- Kompetitiver Hemmer von SGLT-1 und SGLT-2
- Zuckersenkender Effekt bereits 1987 erkannt

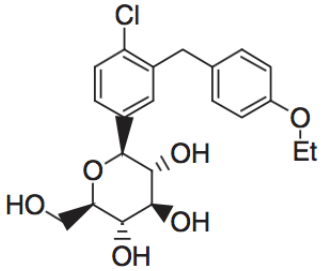
SGLT2-Hemmer im Überblick



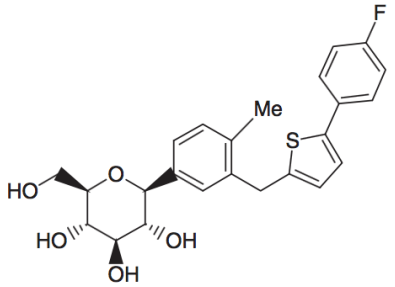
1 Phlorizin



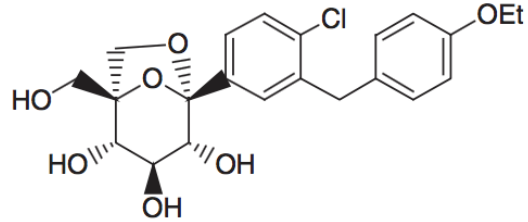
8 Empagliflozin (BI 10773)



5 Dapagliflozin

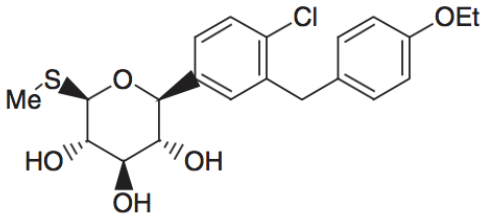


6 Canagliflozin



11 Ertugliflozin (PF-04971729)

	EC_{50} (nM)	Selektivität SGLT2 vs. SGLT1
Sotagliflozin	1,4-1,8	20
Canagliflozin	2,2-2,7	260-414
Dapagliflozin	1,1-1,3	610-1200
Ertugliflozin	0,9-1,4	1300-2300
Empagliflozin	3,1-3,6	1100-2700

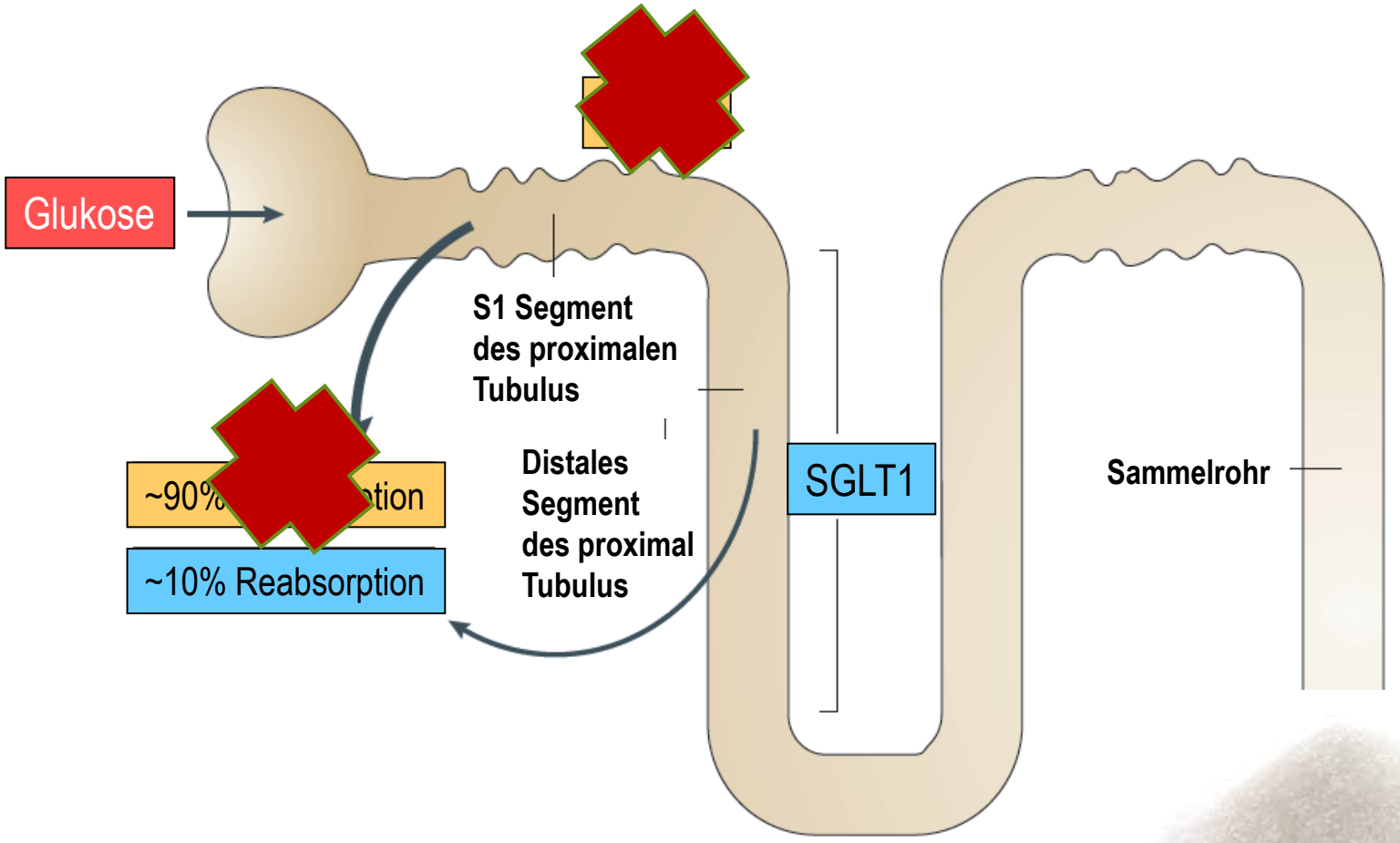


Sotagliflozin

EC_{50} half maximal effective concentration

Washburn & Poucher Expert Opin. Investig. Drugs 2013

SGLT-2 Hemmer



ca. 80 g Glukose pro Tag

Chao EC et al. Nat Rev Drug Discov. 2010;9:551-559. Heise T et al. Diabetes, Obesity and Metabolism 2013;15:613-621

SGLT-2 Hemmer

Wirkstoff	Handelsname
Canagliflozin	Invokana
Dapagliflozin	Forxiga
Empaglifozin	Jardiance
Ertugliflozin	Steglatro

Zusätzliche Effekte:

- Blutdrucksenkung (bis zu 7/3 mmHg)
- Gewichtsreduktion
- Triglyceridsenkung

Nebenwirkungen
Genitale Pilzinfektionen
Euglykämische Ketoazidose

Kontraindikationen
Schwangerschaft

Demographische Daten

632 Personen mit Typ 2 Diabetes mellitus

	Mittelwert / Häufigkeit
Frauen	41,8%
Alter	66,7 ± 10,8 Jahre
Diabetesdauer	12,1 ± 9,2 Jahre
Körpergröße	171 ± 10 cm
Körpergewicht	88,2 ± 20,1 kg
BMI	30,2 ± 6,0 kg/m^2
Raucher*innen	16,8%
Ex-Raucher*innen	29,3%
Pos. Familienanamnese für Typ 2 Diabetes	45,8%

Sourij H., Azhar K, …. Kaser S. Diabetes, Obesity and Metabolism 2024

Begleiterkrankungen

	Häufigkeit
Myokardinfarkt	9,3%
KHK	24,1%
Insult	6,1%
pAVK	8%
Arterielle Hypertonie	64,9%
Diabetische Nierenerkrankung	28,9%
Osteoporose	6,5%
Maligne Erkrankungen	9,3%
COPD	7,2%
Vorhofflimmerarrhythmie	11,5%
Herzinsuffizienz	11,3%
Diabetische Polyneuropathie	13,7%
Diabetische Retinopathie	4,3%
Erektile Dysfunktion	4,2%

Anzahl der Komorbiditäten	n (%)
0–1	218 (34.3)
2–3	265 (41.7)
4+	152 (23.9)

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Antihyperglykämische Therapie

	Häufigkeit
Metformin	75,4%
Sulfonylharnstoffe	8,7%
DPP-4 Hemmer	27,6%
SGLT-2 Hemmer	42,7%
GLP1-RA	15,8%

	Häufigkeit
Basalinsulin	16,4%
Basalinsulin alleine	6,9%
Bolusinsulin	9,9%
Bolusinsulin alleine	0,5%
Basis und Bolusinsulin	9,5%
Mischinsulin	3,2%

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Zielwert-Erreichung

Variables	†LDL-C target	Glycaemic target	Blood pressure target	All targets
	n (%)	n (%)	n (%)	n (%)
All	265 (43.7)	335 (53.3)	311 (56.7)	80 (13.2)
Age–years				
<60	46 (33.8)	68 (49.3)	133 (65.2)	10 (7.6)
60-69	98 (43.4)	120 (51.1)	133 (65.2)	34 (15.0)
70-79	85 (50.6)	105 (59.7)	82 (50.3)	24 (14.1)
80+	35 (47.3)	40 (52.6)	33 (50.8)	12 (16.2)
P-value	*0.029*	*0.236*	*0.018*	*0.172*
Gender				
Men	178 (50.4)	180 (49.7)	178 (55.6)	53 (15.2)
Women	85 (34.4)	153 (59.1)	130 (58.0)	27 (10.8)
P-value	*<0.001*	*0.021*	*0.577*	*0.124*

Sourij H., Azhar K, …. , Kaser S. Diabetes, Obesity and Metabolism 2024

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Nachgewiesene atherosklerotische kardiovaskuläre Erkrankung
Hohes Risiko für eine atherosklerotisch-kardiovaskuläre Erkrankung (Alter ≥ 55 Jahre und eines der folgenden Kriterien)
- linksventrikuläre Hypertrophie
- >50% Stenose der Koronarien, Karotiden oder Beinarterien
- eGFR < 60 ml/min/1,73 m2

GLP-1 Analogon mit kardiovaskulärem Benefit [a]

SGLT2 – Hemmer mit kardiovaskulärem Benefit [a,d]

plus Metformin*

Herzinsuffizienz (HFpEF, HFmrEF, HFrEF)

SGLT2- Hemmer mit nachgewiesenem Benefit in diesem Kollektiv [b,d]

plus Metformin*

Chronische Nierenerkrankung

Bevorzugt:

SGLT2-Hemmer mit nachgewiesenem Benefit in diesem Kollektiv [c,d]

plus Metformin*

Wenn SGLT2-Hemmer nicht möglich:

GLP1-Analogon mit kardiovaskulärem Benefit [a]

*[a] Entsprechend der Darstellung in Tab. 2, [b] entsprechend der Darstellung in Tab. 3, [c] entsprechend Darstellung in Tab. 4, [d] laut Zulassung der Medikation, [e] Tirzepatide ist von der EMA bereits zugelassen, aber in Österreich vorerst noch nicht verfügbar; HFpEF Heart failure with preserved ejection fraction, HFmrEF Heart failure with mildly reduced ejection fraction, HFrEF Heart failure with reduced ejection fraction. * Metformin ist neben SGLT-2-Hemmern/GLP-1 Analoga erste Wahl und sollte bestmöglich bereits als initiale Kombinationstherapie gegeben werden*

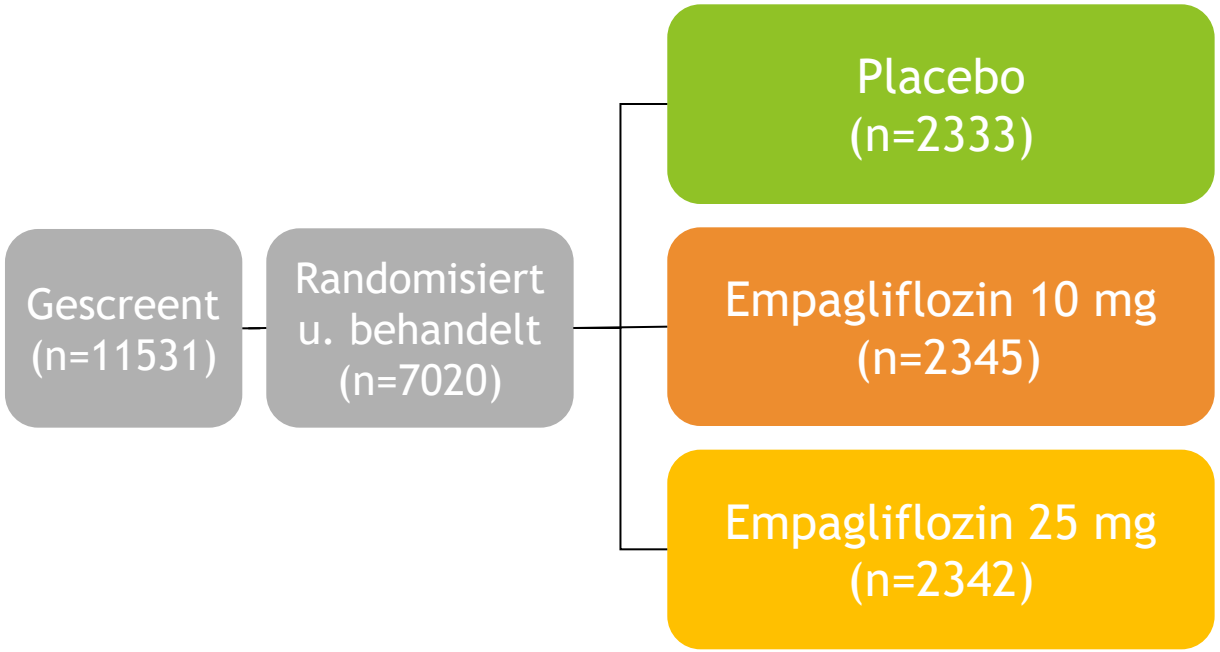
Design

Haupteinschlusskriterien

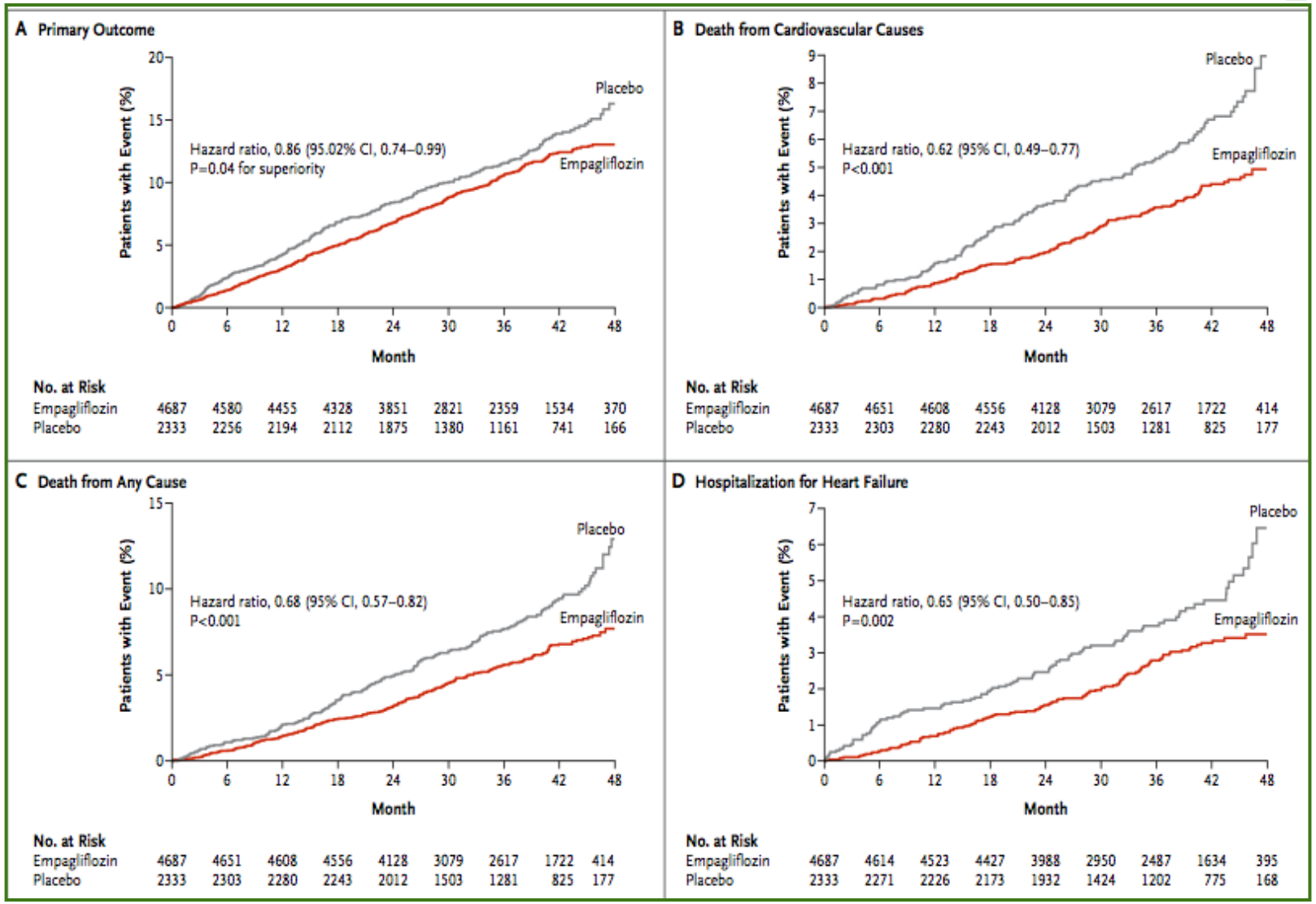
+ Erwachsene mit Typ 2 Diabetes
+ BMI ≤45 kg/m^2
+ HbA1c 7–10%*
+ Vorbestehende kardiovaskuläre Erkrankung
+ Vorangegangener Myokardinfarkt, KHK, Insult, instable AP od. pAVK

Hauptausschlusskriterien

- eGFR <30 mL/min/1.73m^2 (MDRD)



EMPA-REG OUTCOME



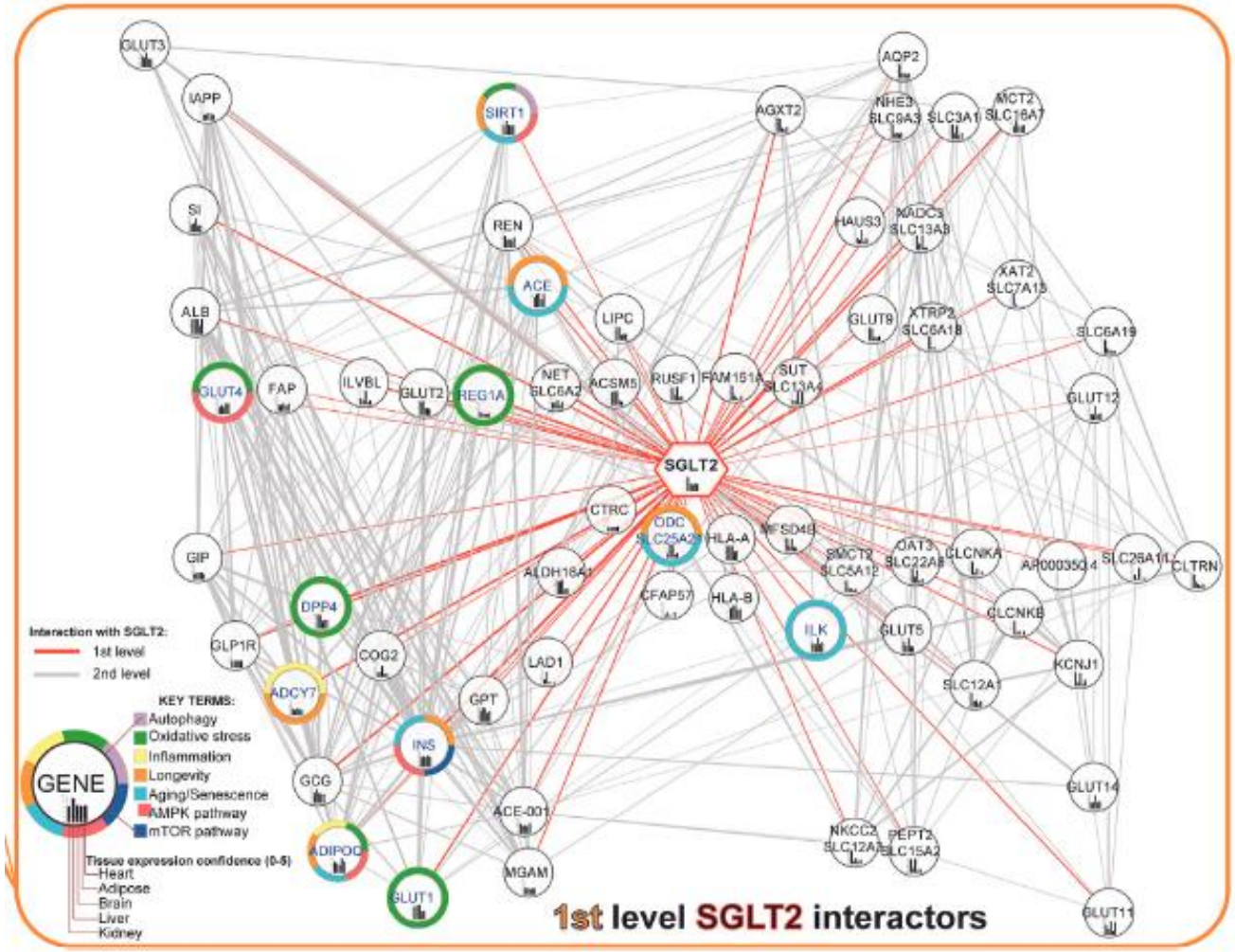
Zinman B. et al. NEJM 2015

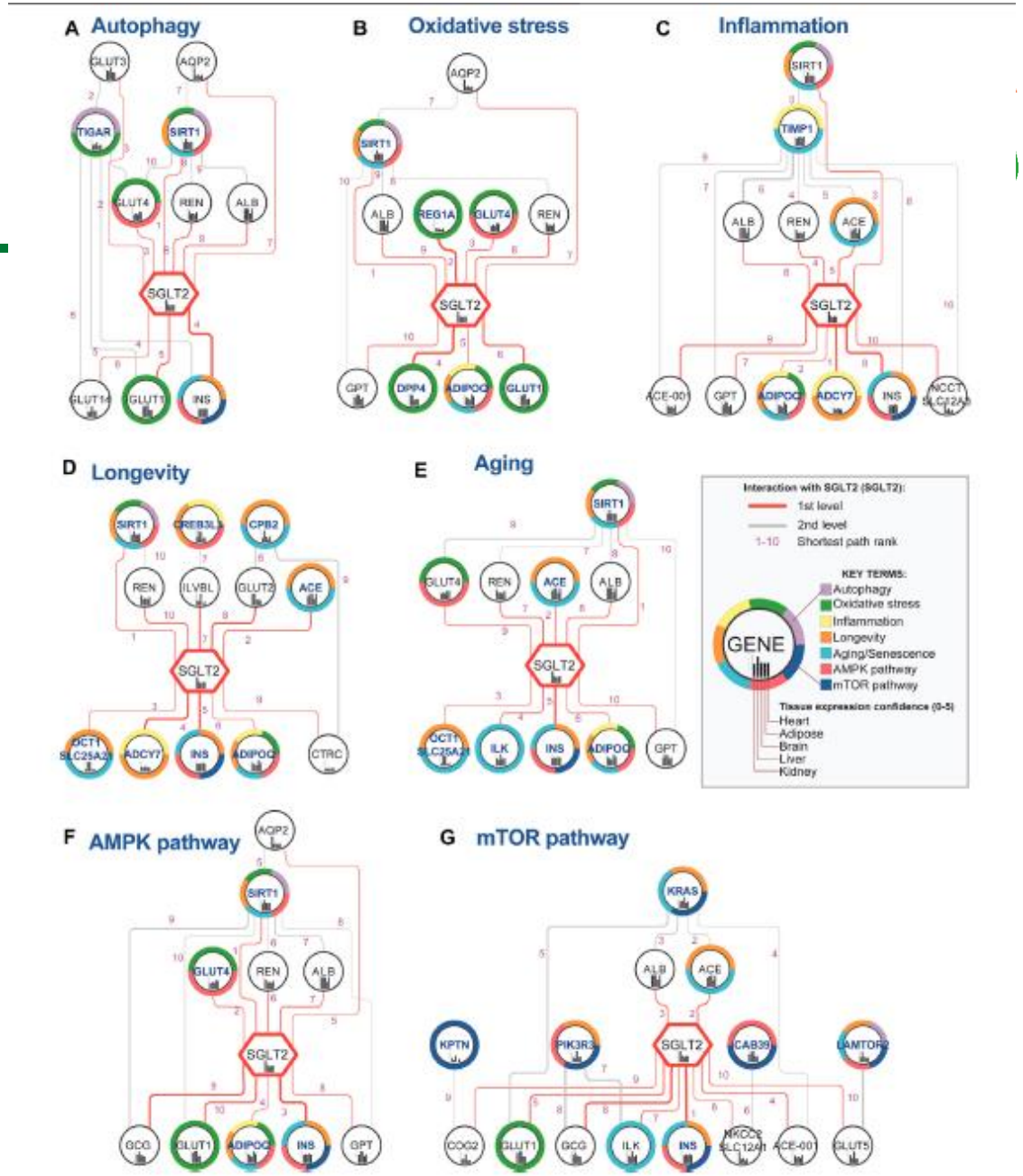
SGLT-2 Hemmer im Vergleich

	EMPA-REG OUTCOME	CANVAS Programm	DECLARE- TIMI 58	VERTIS-CV
Hospitalisierung HI oder kardiovaskulärer Tod			0.83 (0.73 – 0.95)	0.88 (0.75 – 1.03)
Herzinfarkt, Schlaganfall, kardiovask. Tod	0.86 (0.74-0.99)	0.86 (0.75-0.97)	0.93 (0.84-1.03)	0.97 (0.85 - 1.11)
Nicht-tödlicher Herzinfarkt	0.87 (0.70-1.09)	0.85 (0.69-1.05)	0.89 (0.77 – 1.01)	1.00 (0.86 – 1.27)
Nicht-tödlicher Schlaganfall	1.24 (0.92-1.67)	0.90 (0.71-1.15)	1.01 (0.84-1.21)	1.00 (0.76 – 1.32)
Kardiovaskulärer Tod	0.62 (0.49-0.77)	0.87 (0.72-1.06)	0.98 (0.82 -1.17)	0.92 (0.77 – 1.11)
Gesamtsterblichkeit	0.68 (0.57-0.82)	0.87 (0.74-1.01)	0.93 (0.82 – 1.04)	n.r.
Hospitalisierung HI	0.65 (0.50-0.85)	0.67 (0.52-0.87)	0.73 (0.61 – 0.88)	0.70 (0.54 – 0.90)
Komb. Renaler Endpunkt	0.54 (0.40-0.75)*	0.60 (0.47-0.77)**	0.53 (0.43 -0.66)**	0.81 (0.63 – 1.04)

**Verdopplung des Serumkreatinins, Beginn einer Nierenersatztherapie, Tod aufgrund einer Nierenerkrankung*
***40% Reduktion der eGFR, ESRD, Tod aufgrund einer Nierenerkrankung*

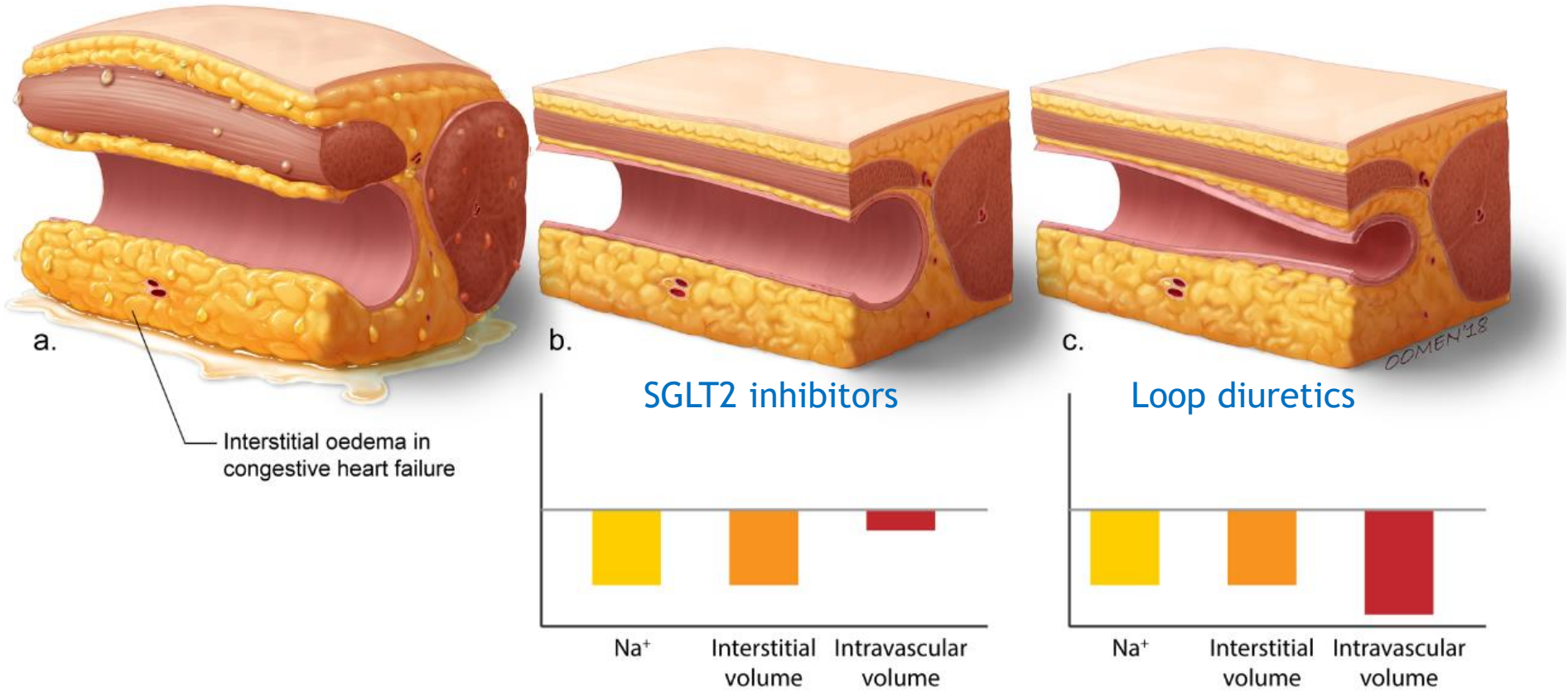
SGLT2-Interaktionen





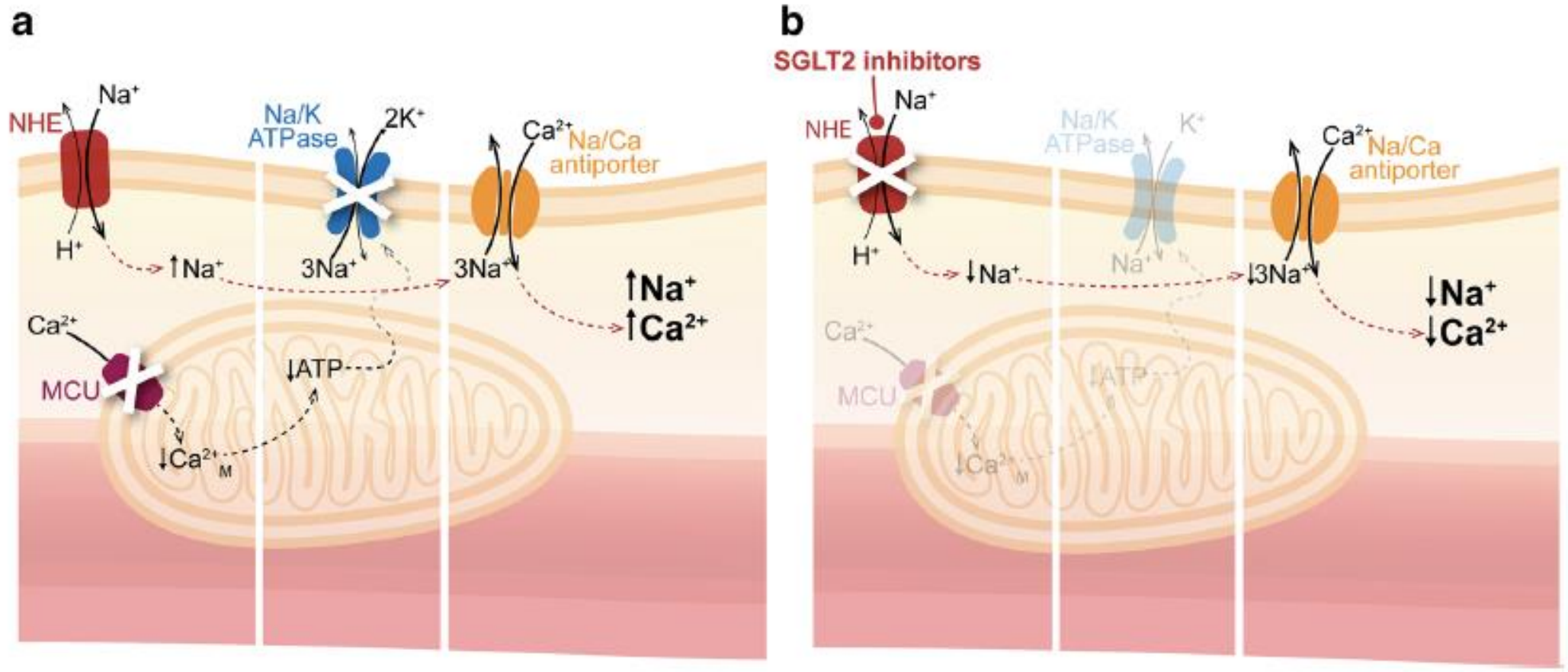
Wicik, Nowak, Jarosz-Popek, Wolska, Eyileten, Siller Matula, von Lewinski, Filipak, Sourij, Postula; Front Pharmacol 2022

Intravasales vs. interstitielles Kompartiment



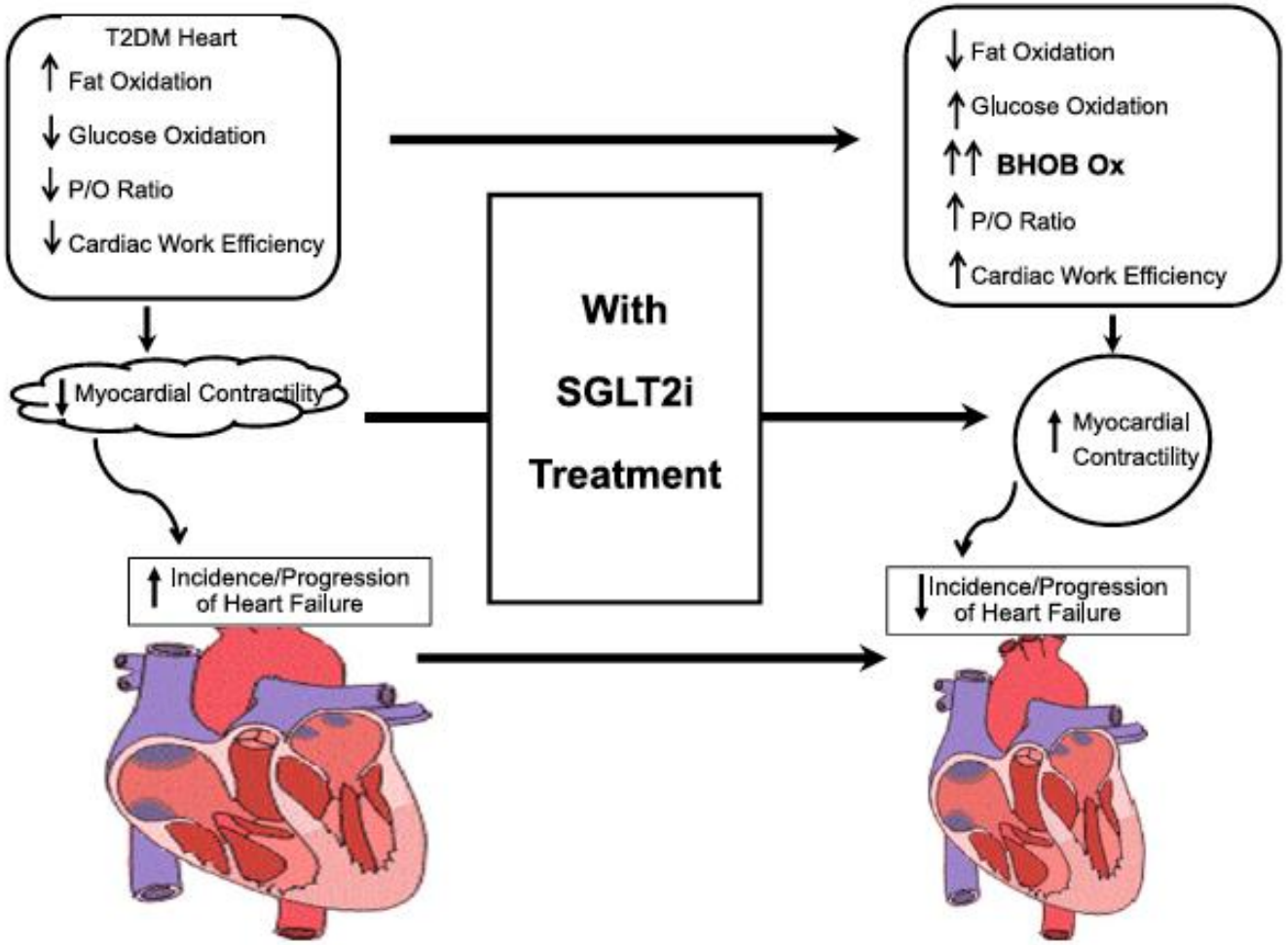
Verma and McMurray (2018) Diabetologia DOI 10.1007/s00125-018-4670-7

Zytoplasmatische Ca2+ / Na+ Überladung



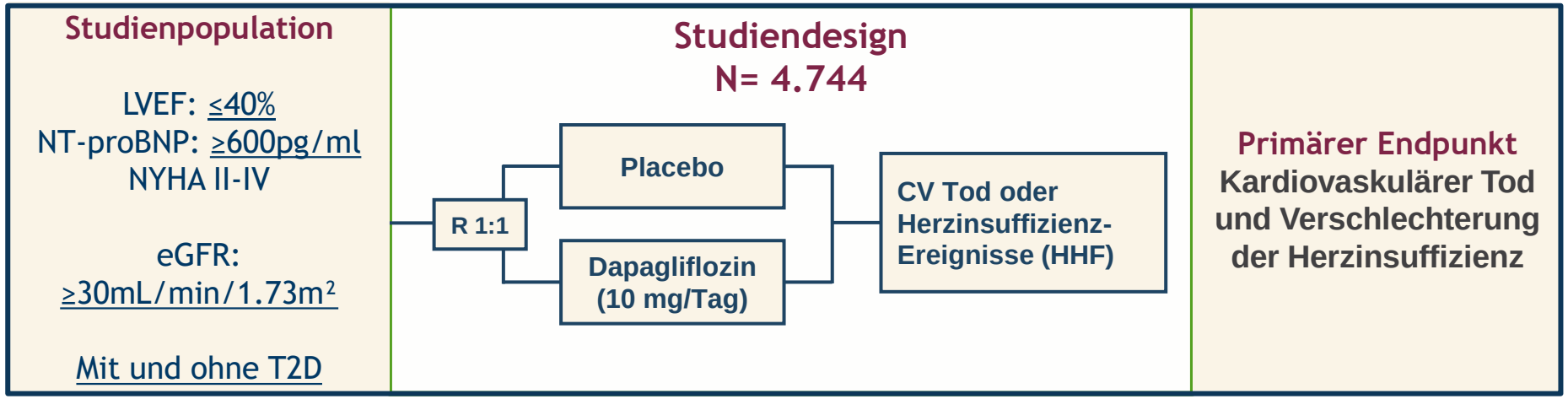
Verma and McMurray (2018) Diabetologia DOI 10.1007/s00125-018-4670-7
© G. Oomen 2018

Fuel Hypothesis



Mudaliar at. al Diabetes Care 2016;

DAPA-HF Design

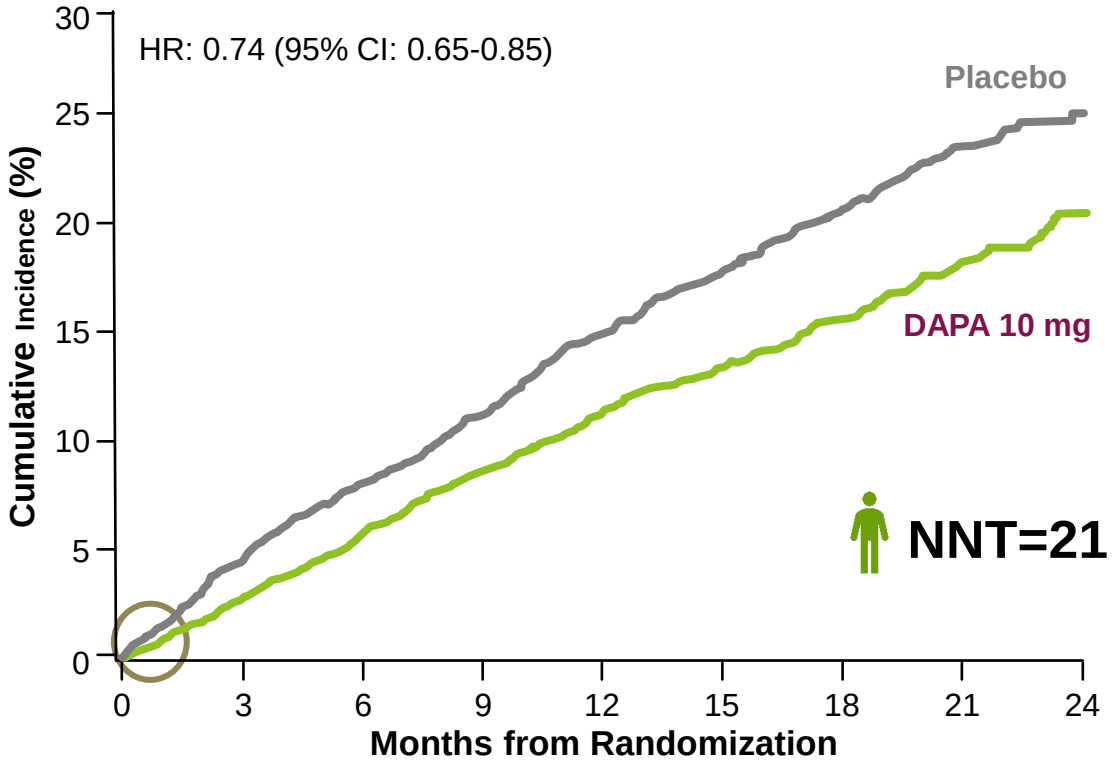


Es werden die relevantesten Charakteristika der Studie dargestellt. (Es besteht kein Anspruch auf Vollständigkeit.) - CV Tod = kardiovaskulärer Tod; LVEF = linksventrikuläre Auswurffraktion; R = Randomisierung, eGFR = geschätzte glomeruläre Filtrationsrate; T2D = Typ 2 Diabetes; RRR = relative Risikoreduktion; HHF = Herzinsuffizienz-Ereignisse: Hospitalisierung oder akuter Arztbesuch wegen Herzinsuffizienz; 1. McMurray JJV et al N Engl J Med. 2019 Nov 21;381(21):1995-2008;

SGLT2i bei HFrEF

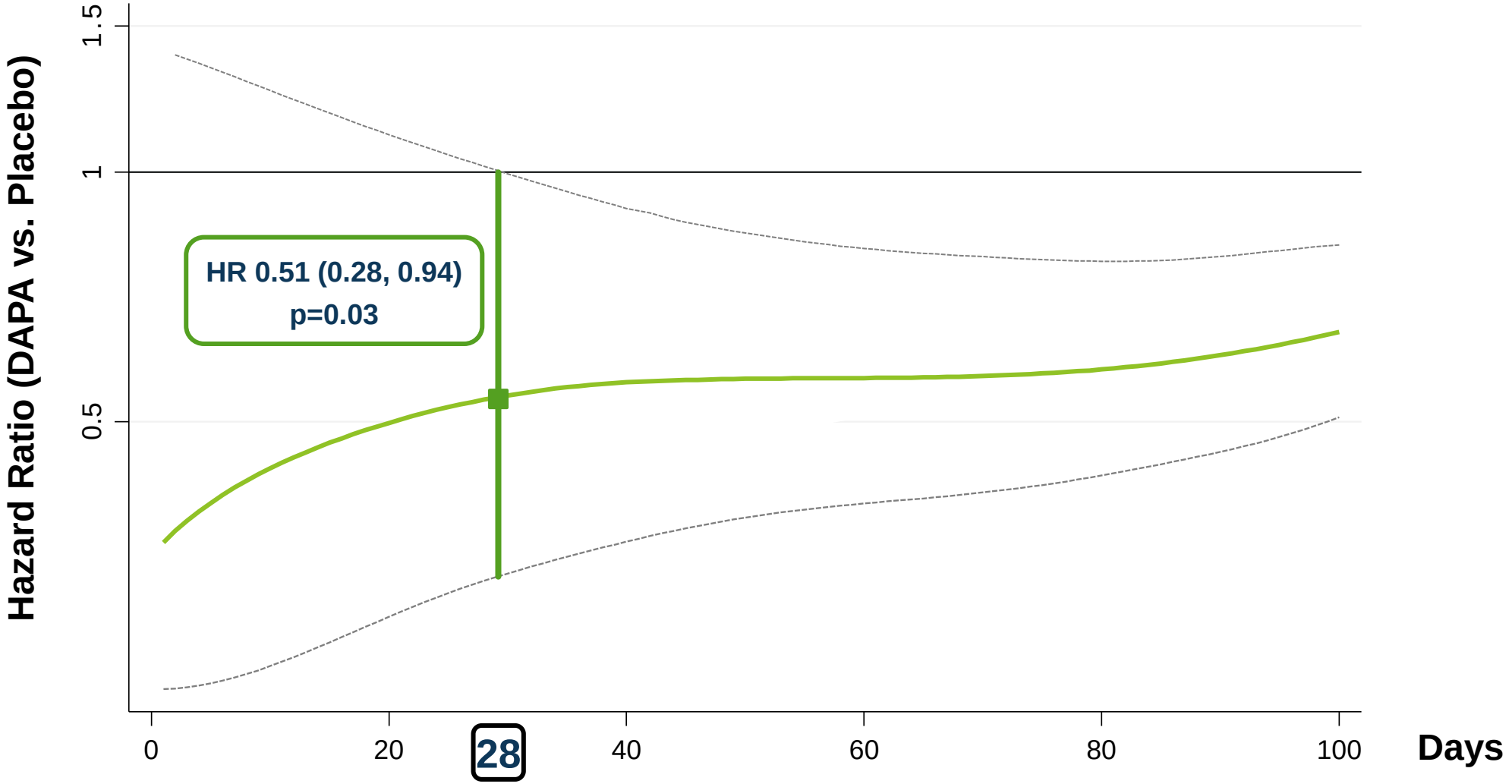
DAPA HF **LVEF ≤40%**
N=4.744

Primärer EP[1]:
CV Tod or HI Verschlechterung



Modifiziert nach: 1. McMurray JJV, et al. N Engl J Med 2019; 381:1995-2008 (inkl. Supplement)

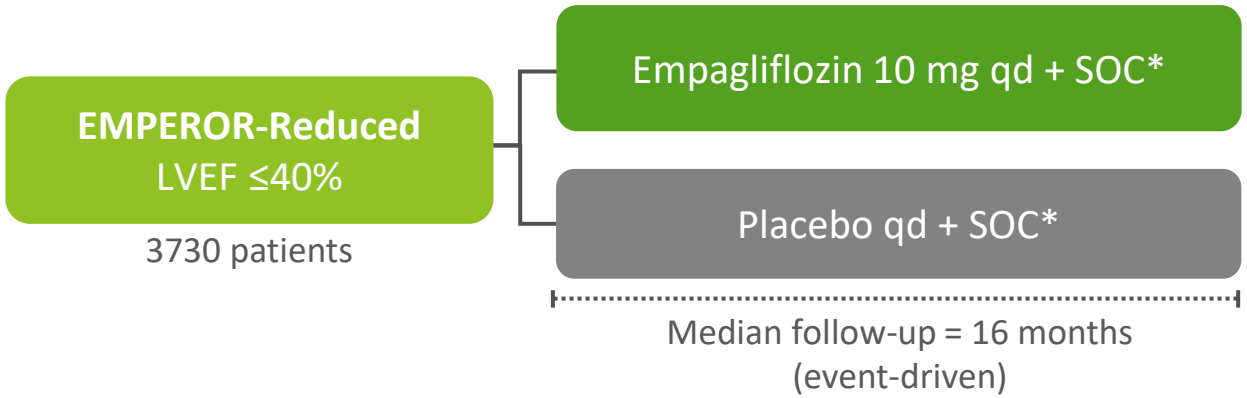
Rascher Wirkungseintritt



Sabatine MS et al. Presented at: AHA Scientific Sessions; November 16-18, 2019; Philadelphia, PA.

EMPEROR-Reduced

Study design[1-3]



NYHA II/III: 75/25%;
EF 27%; NT-proBNP 1900pg/mL
SOC: ~70% RAASi, ~19% ARNI, ~70% MRA, ~95% BB, ~12% CRT, ~31% ICD

Confirmatory endpoints[1,2]

COMPOSITE PRIMARY ENDPOINT

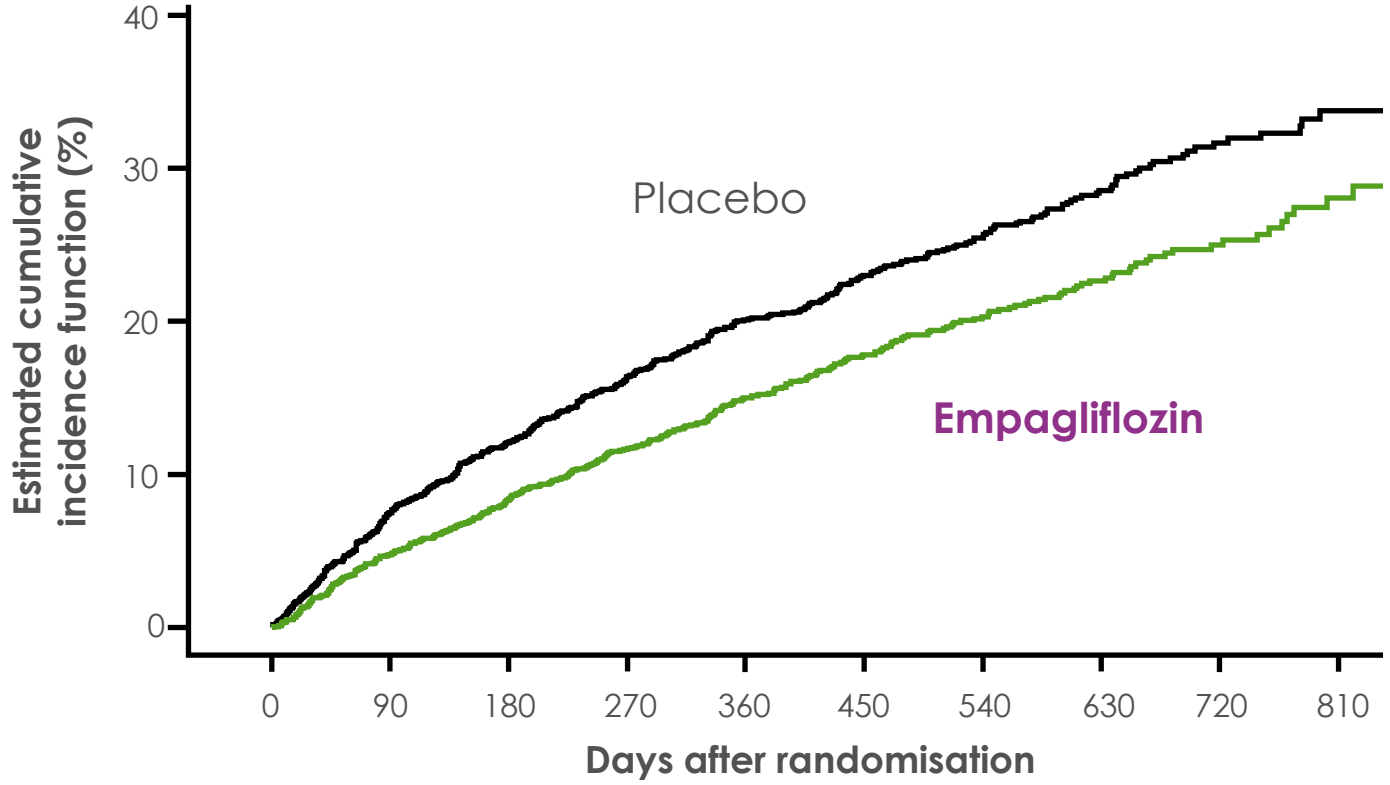
Time to first event of adjudicated CV death or adjudicated HHF

SECONDARY ENDPOINTS

- **First and recurrent adjudicated HHF**
- **Slope of change in eGFR (CKD-EPI) from baseline**

ClinicalTrials.gov. NCT03057977 (accessed Aug 2020); 2. Packer M *et al. Eur J Heart Fail* 2019;21:1270; 3. Packer M et al., NEJM 2020; 29-Aug-2020; DOI: 10.1056/NEJMoa2022190

Primärer Endpunkt



Patients at risk										
Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

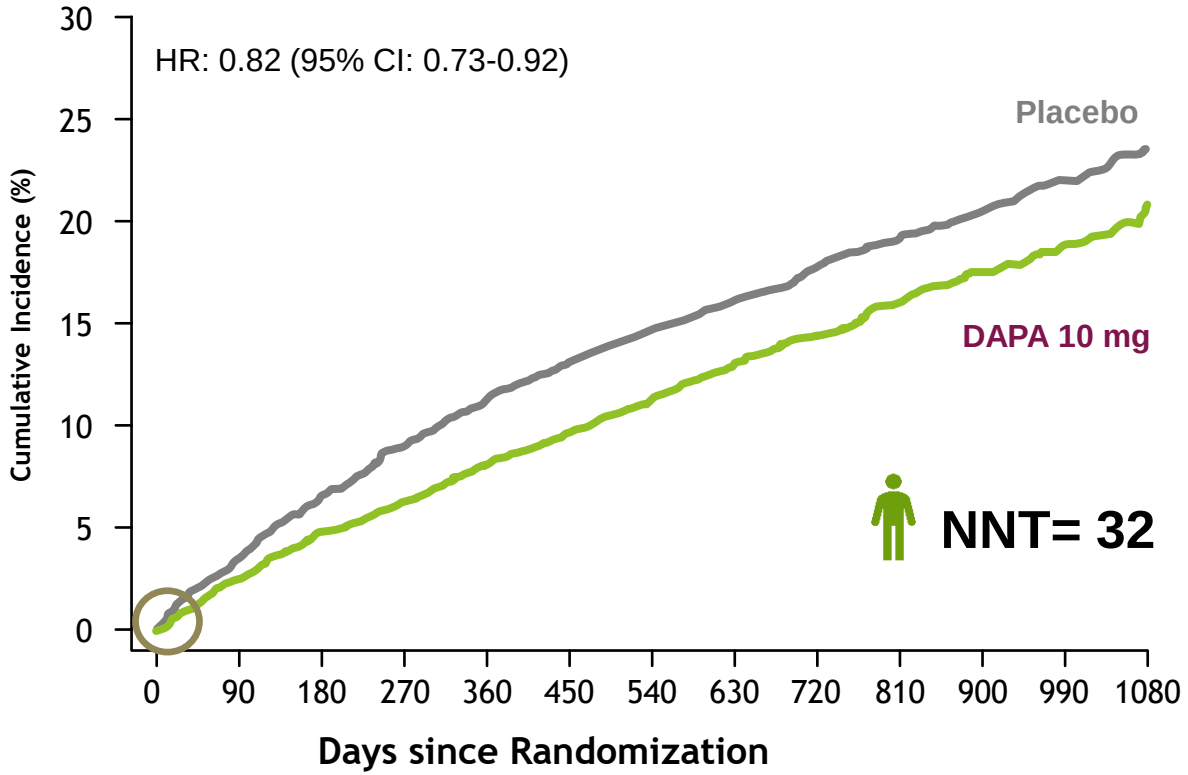
Cox regression model including covariates age, baseline eGFR, geographic region, baseline diabetes status, sex, LVEF and treatment
CV, cardiovascular; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; **ARR, absolute risk reduction; RRR**, relative risk reduction. NNT: Number needed to treat
Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020. DOI: 10.1056/NEJMoa2022190

SGLT2-Hemmer bei HFpEF

DELIVER

Primärer EP

CV Tod or HI Verschlechterung

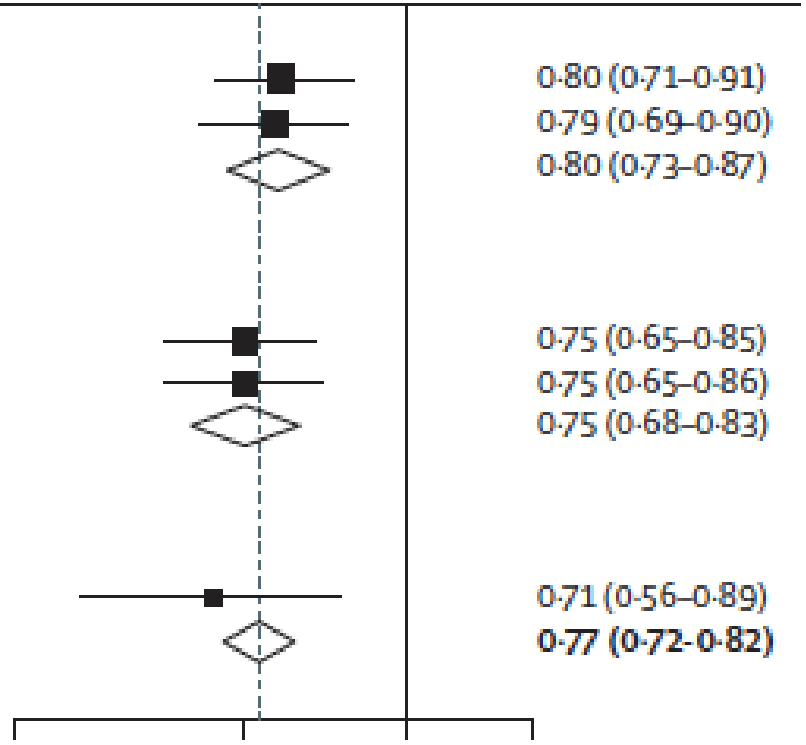


Solomon SD, et al. N Engl J Med 2022

Herzinsuffizienz Metaanalyse

Cardiovascular death or heart failure hospitalisation

	Number with event/ number of patients (%)		Hazard ratio (95% CI)
	SGLT2 inhibitors	Placebo	
HFmrEF/HFpEF			
DELIVER	475/3131 (15·2%)	577/3132 (18·4%)	0·80 (0·71–0·91)
EMPEROR-Preserved	415/2997 (13·8%)	511/2991 (17·1%)	0·79 (0·69–0·90)
Subtotal			0·80 (0·73–0·87)
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·89			
HFrEF			
DAPA-HF	382/2373 (16·1%)	495/2371 (20·9%)	0·75 (0·65–0·85)
EMPEROR-Reduced	361/1863 (19·4%)	462/1867 (24·7%)	0·75 (0·65–0·86)
Subtotal			0·75 (0·68–0·83)
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=1·00			
All LVEF (hospitalised patients)			
SOLOIST-WHF			0·71 (0·56–0·89)
Overall			**0·77 (0·72–0·82)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·87			



Vaduganathan M et al. Lancet 2022

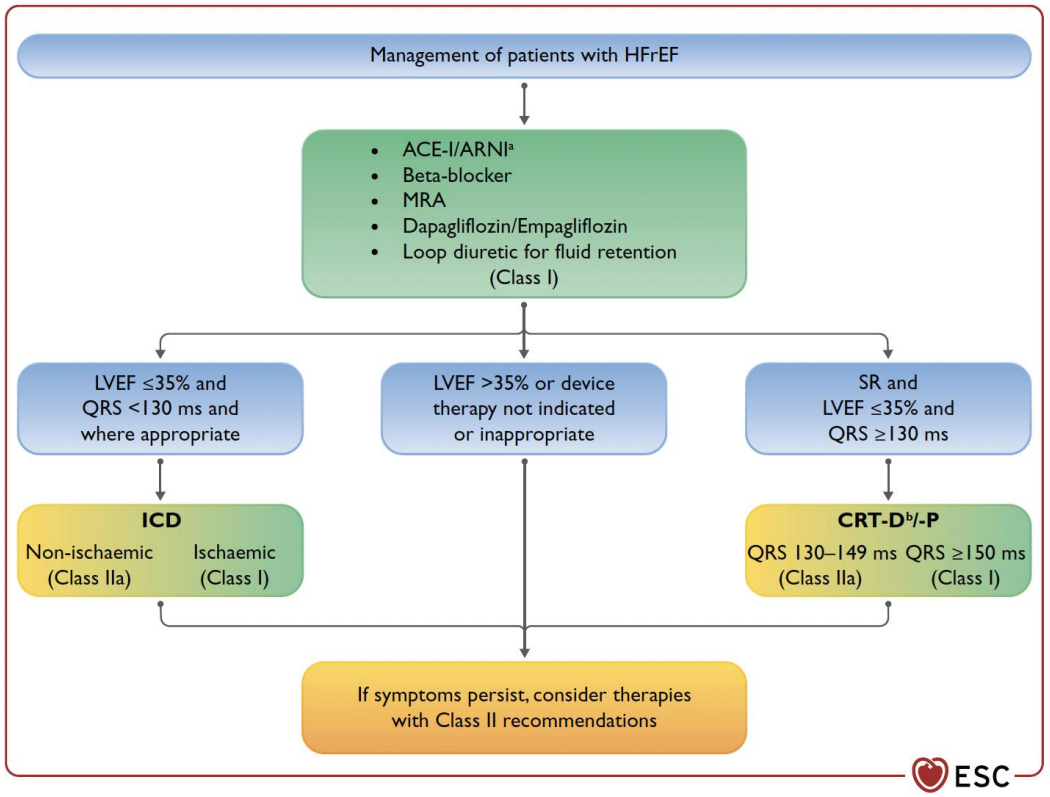
ESC guidelines (2021 und Update 2023)

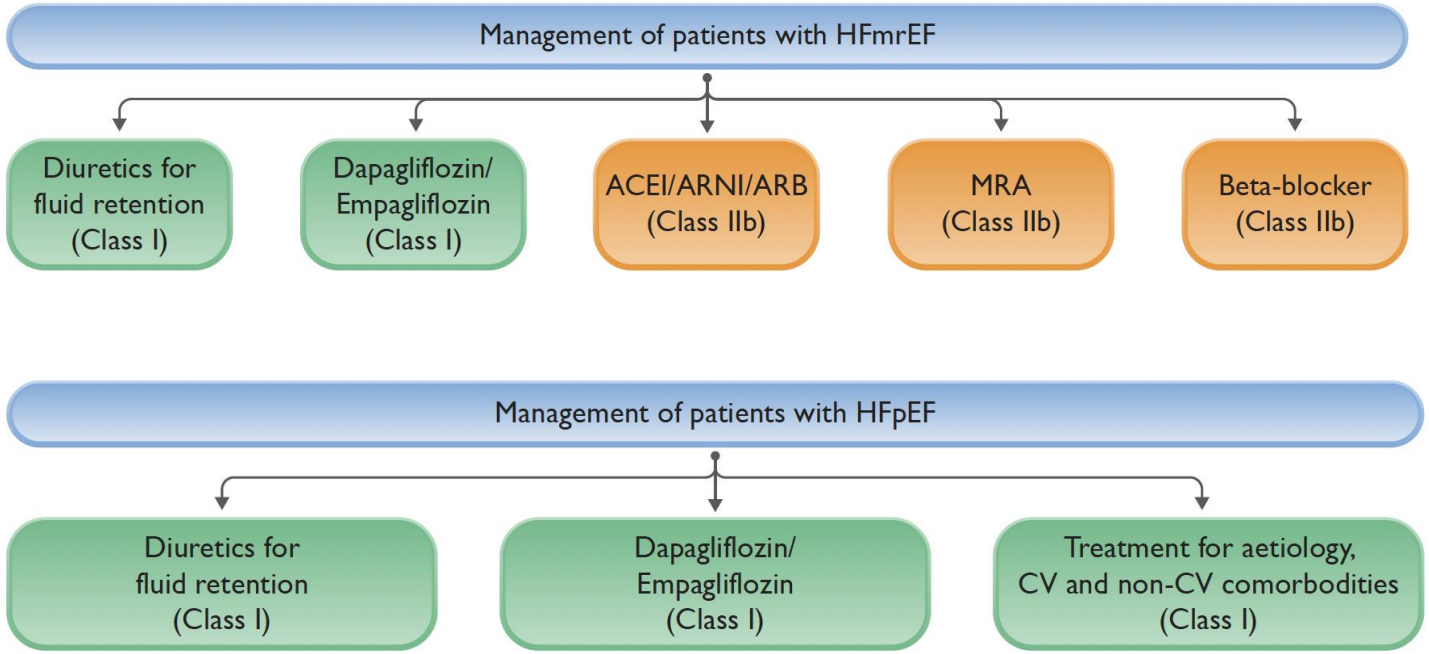
Recommendations for treatment of chronic HF – *HFrEF*	Class
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I

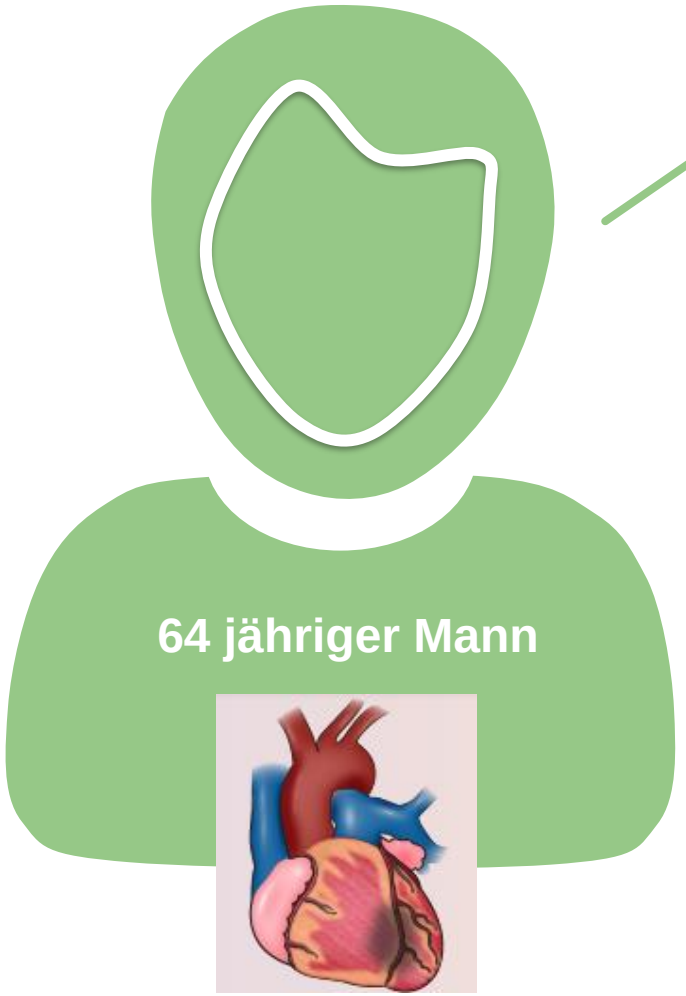
Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

ESC guidelines (2021 und Update 2023)







Medizinische Vorgeschichte:

Adipositas

Bluthochdruck seit 2 Jahren

Diabetes mellitus Typ 2

Hypercholesterinämie

CKD G3a A1

Medikation:

Ramipril 10 mg 1-0-0

Metformin 1000 mg 1-0-1

Rosuvastatin 20 mg 0-0-1

HbA1c 52 mmol/mol (6.9%)

LDL-C 67 mg/dl

Lp(a) 25 mg/dl

eGFR 59 ml/min/1,73 m2

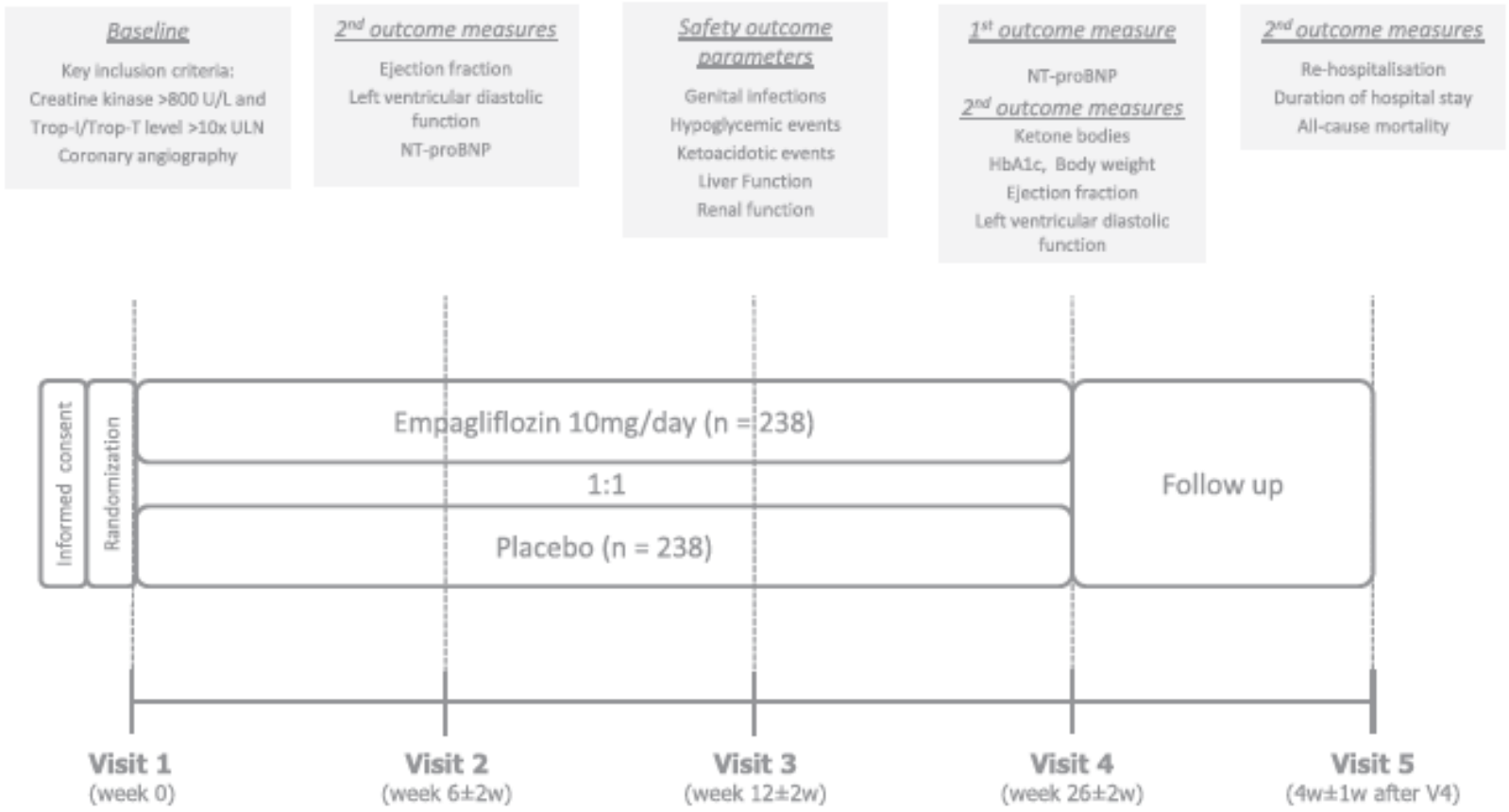
RR 132/84 mmHg

89 kg Körpergewicht

1,70 m Körpergröße

BMI: 30.8 kg/m^2

Study design



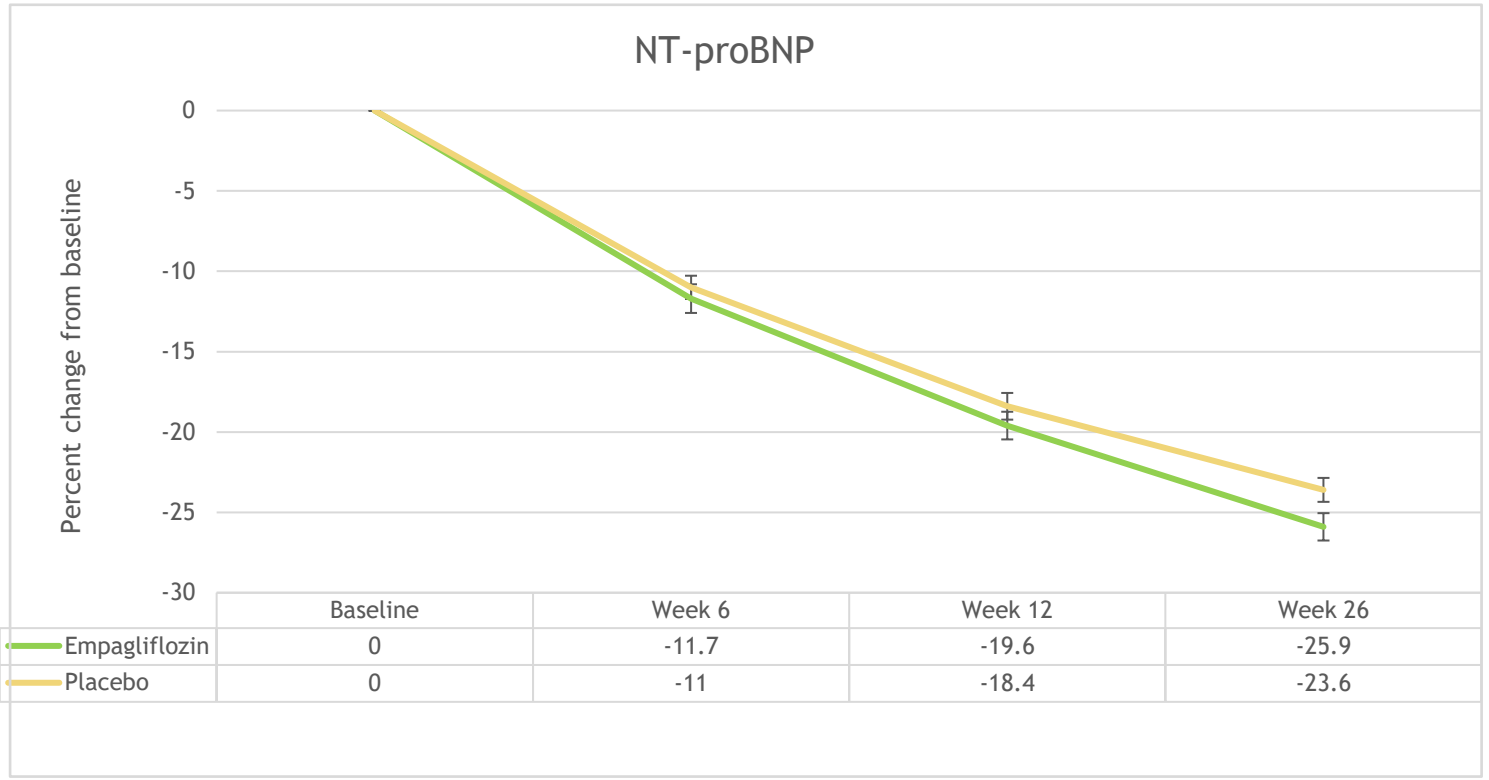
Primary Outcome:

Change in NT-proBNP levels from randomisation to week 26

Tripolt NJ et al. Am Heart J 2020

Primary Outcome

Percent change in log-transformed NT-proBNP from baseline



	Baseline	Week 6	Week 12	Week 26
Empagliflozin	0	-11.7	-19.6	-25.9
Placebo	0	-11	-18.4	-23.6

Relative reduction in NT-proBNP levels at week 26 (comparison empagliflozin vs. placebo)

-15% (95%-CI: -4.4% to -23.6%), p=0.026*

Visit 2:
-10.6% (95%-CI -19.6 to 0.6%), p=0.075*

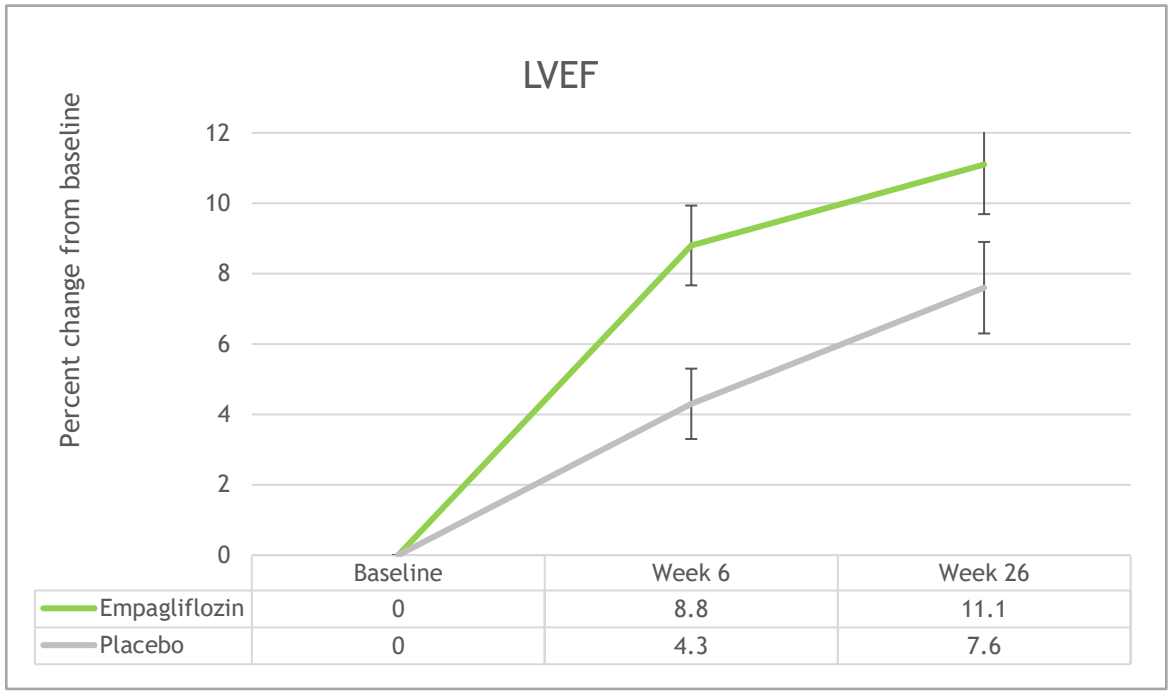
Visit 3:
-13.3% (95%-CI: -22.5% to -3.0%), p=0.021*

*using robust linear mixed effect model adjusted for baseline NT-proBNP, sex and diabetes status

Von Lewinski D,… Sourij H. Eur Heart J 2022

Secondary Outcomes

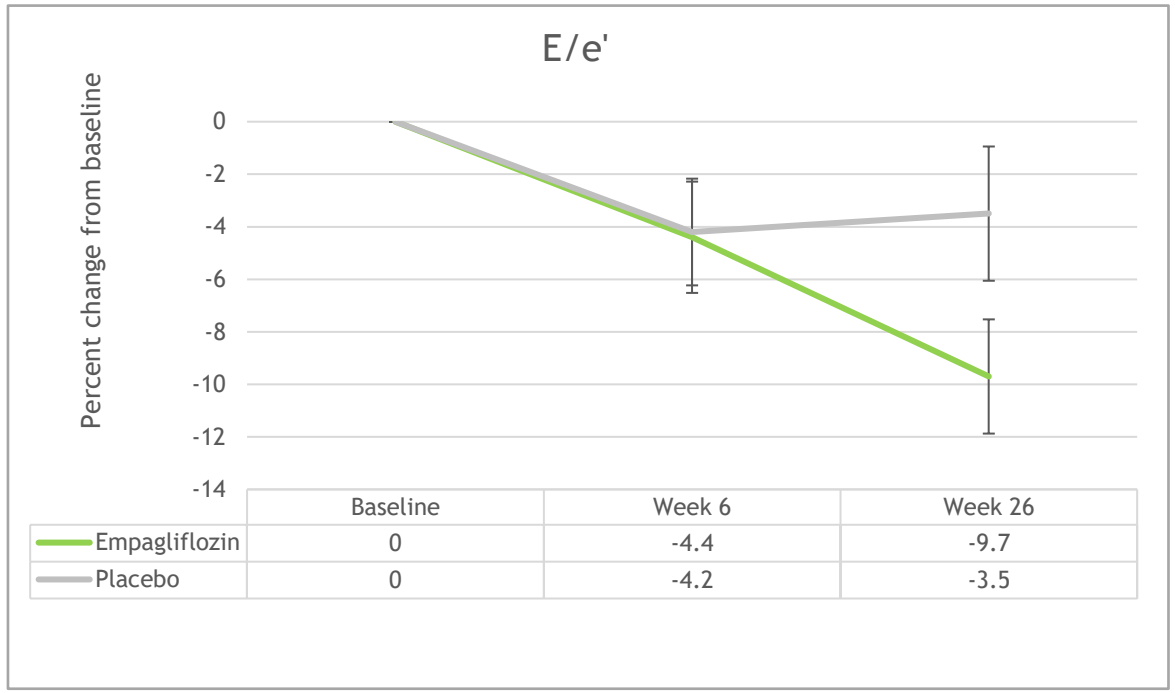
Median baseline EF (%):
Empagliflozin 48 (95%-CI: 43-53)
Placebo 49 (95%-CI: 43-54)



	Baseline	Week 6	Week 26
Empagliflozin	0	8.8	11.1
Placebo	0	4.3	7.6

Difference at weeks 26:
1.5% (95%-CI: 0.2% to 2.9%), p=0.029
(absolute percentage)

Median baseline E/e‘:
Empagliflozin 8 (95%-CI: 7-11)
Placebo 9 (95%-CI: 8-11)



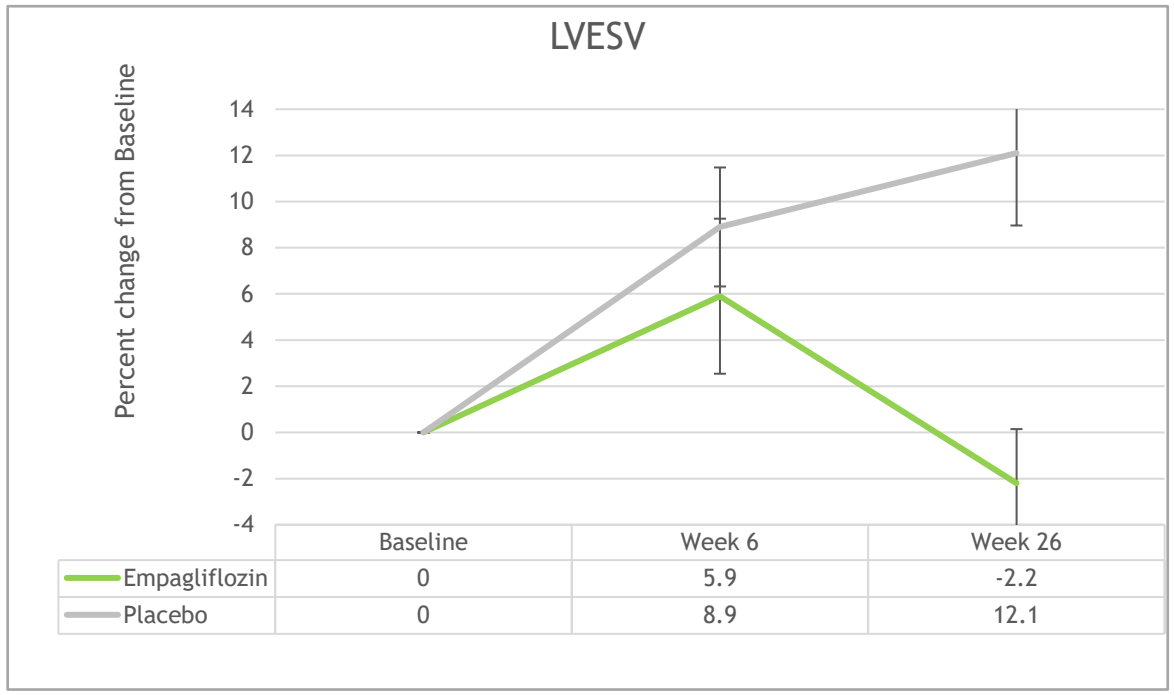
	Baseline	Week 6	Week 26
Empagliflozin	0	-4.4	-9.7
Placebo	0	-4.2	-3.5

Difference at week 26:
-6.8 % (95%-CI: -1.3% to -11.3%), p=0.015

Von Lewinski D,… Sourij H. Eur Heart J 2022

Secondary Outcomes

Median baseline LVESV (ml):
Empagliflozin 61 (95%-CI: 48-76)
Placebo 60 (95%-CI: 46-73)

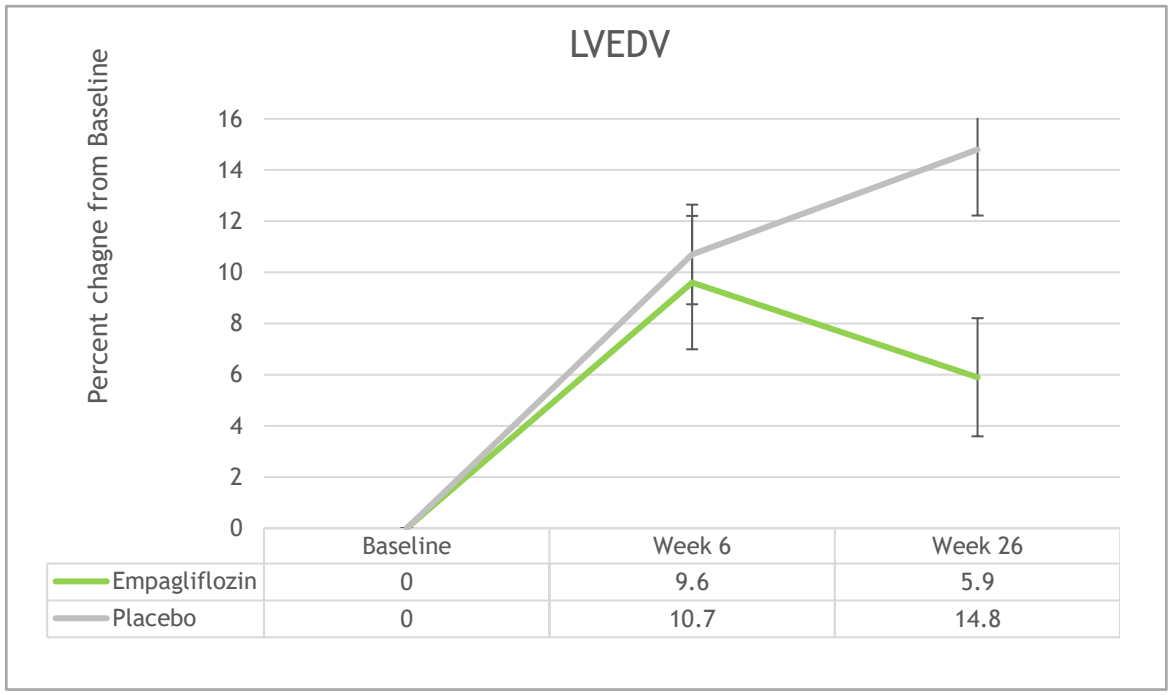


	Baseline	Week 6	Week 26
Empagliflozin	0	5.9	-2.2
Placebo	0	8.9	12.1

Difference at week 26:

-7.5ml (95%-CI:-3.4% to -11.5%), p=0.0003

Median baseline LVEDV (ml):
Empagliflozin 119 (95%-CI: 93-139)
Placebo 114 (95%-CI: 92-134)



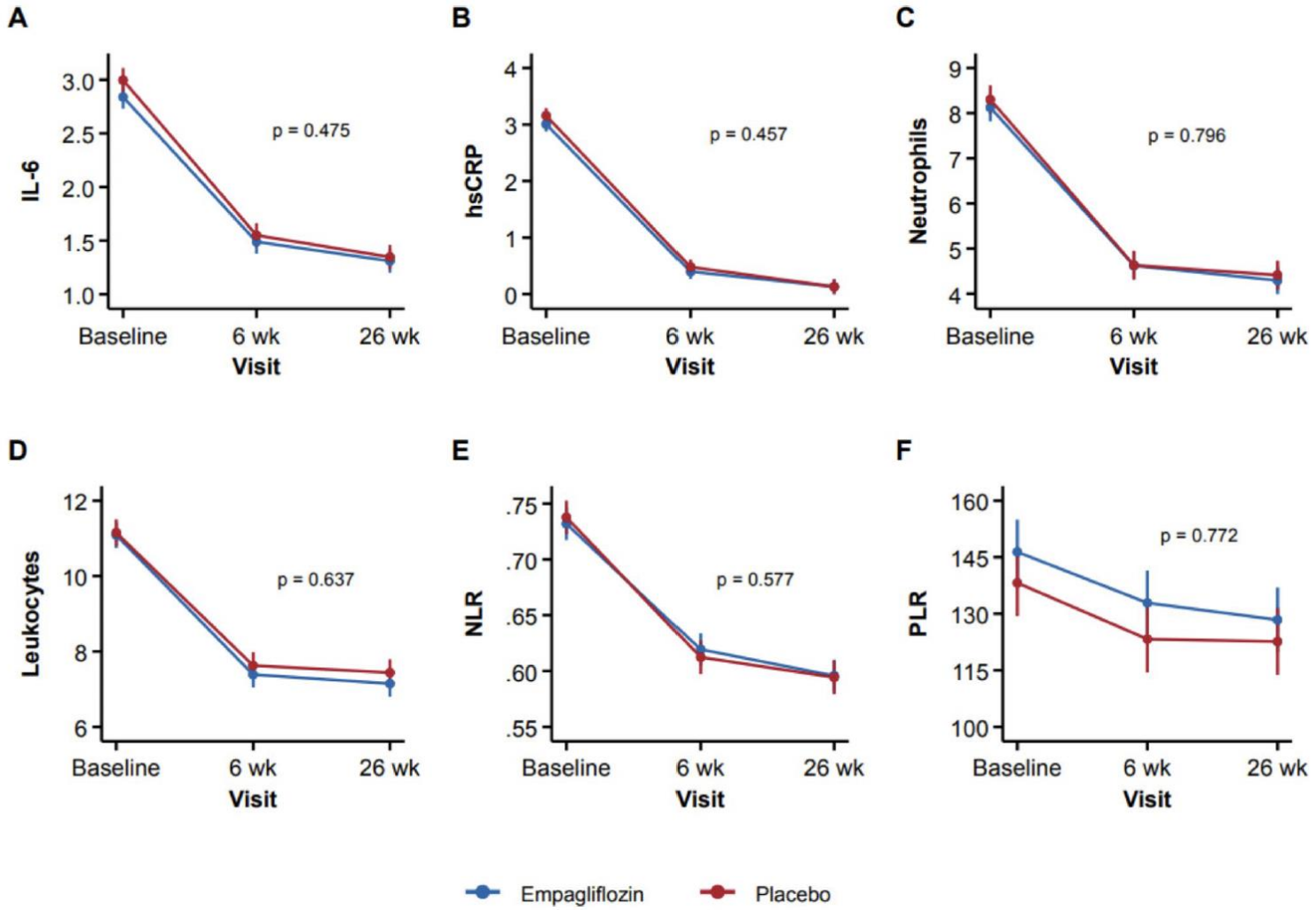
	Baseline	Week 6	Week 26
Empagliflozin	0	9.6	5.9
Placebo	0	10.7	14.8

Difference at week 26:

-9.7ml (95%-CI:-3.7% to -15.7%), p=0.0015

Von Lewinski D,… Sourij H. Eur Heart J 2022

Inflammation und SGLT2-Hemmung



Benedikt M. et al. Cardiovasc Diabetology 2023

SGLT2i nach Myokardinfarkt

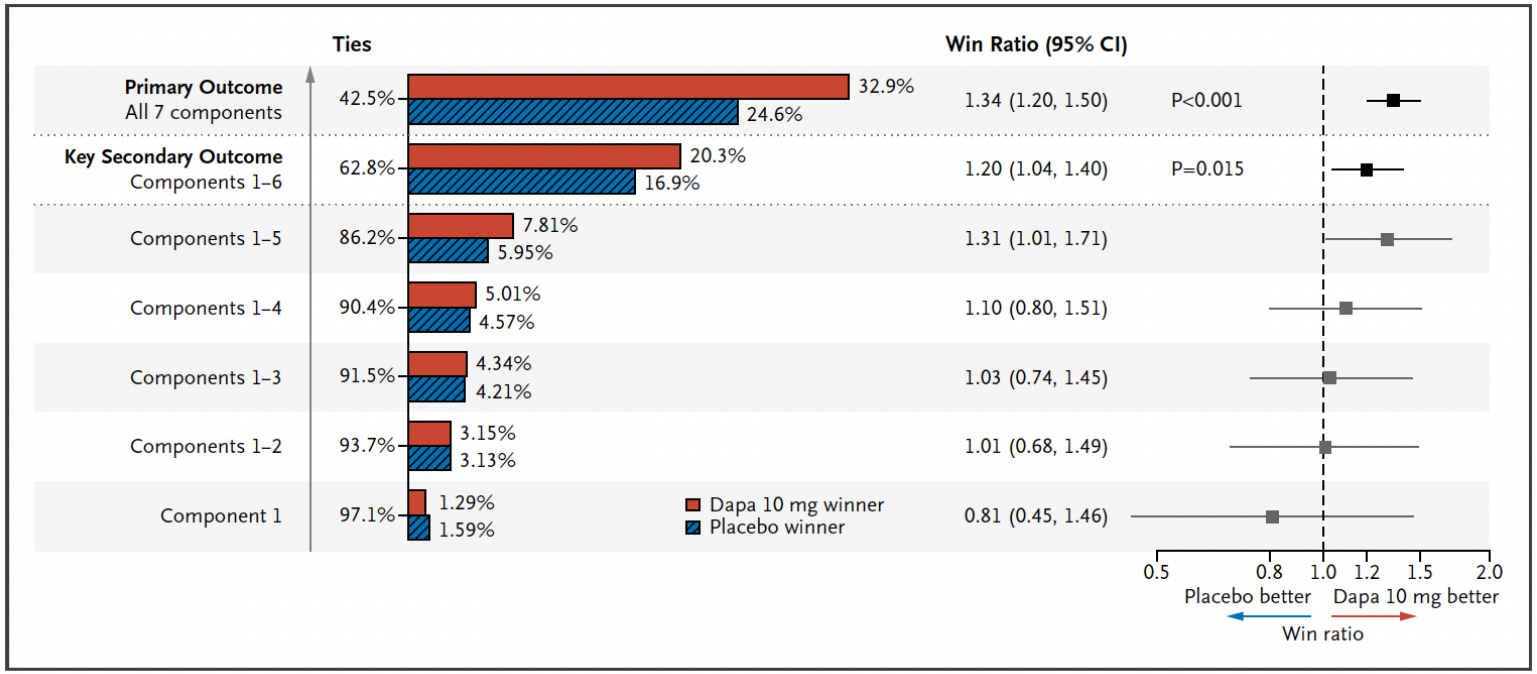


Figure 1. Primary and Key Secondary Hierarchical Composite Outcome, Assessed by the Win Ratio Method.

The results are presented as cumulative estimates where the number of components in the estimate is increased by one component at each step, according to the end point hierarchy, from the bottom and up (for per-component estimates in the hierarchy see Fig. S2). The gray arrow indicates the order of the end point hierarchy. Percentages are percent of 4,033,962 comparisons resulting in a win for Dapa 10 mg, tie, or win for placebo. The components in hierarchical order are as follows: 1. Death, 2. Hospitalization for heart failure, 3. Nonfatal MI, 4. Atrial fibrillation/flutter, 5. New diagnosis of type 2 diabetes, 6. NYHA class, and 7. Weight decrease of 5% or more. CIs for component combinations below the key secondary outcome (gray intervals) have not been adjusted for multiplicity and the inferences drawn may not be reproducible. CI denotes confidence interval; Dapa, dapagliflozin; MI, myocardial infarction; and NYHA, New York Heart Association.

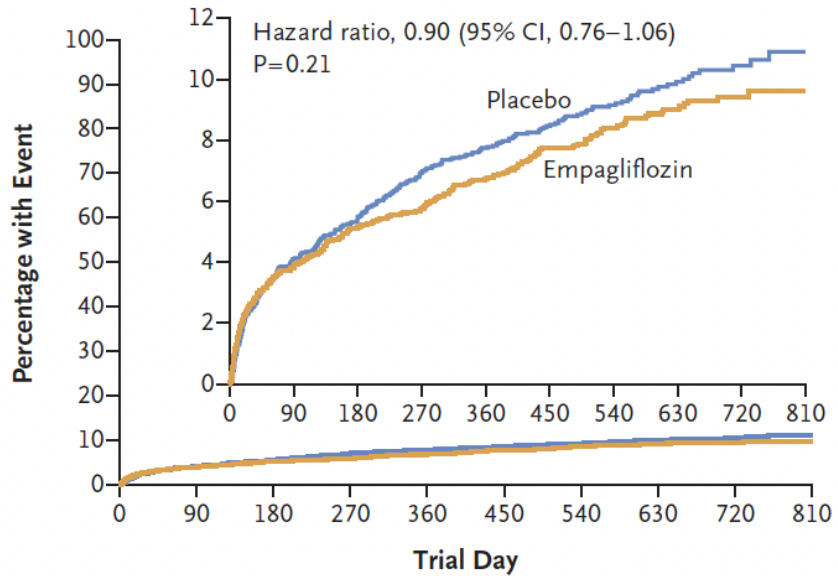
DAPA-MI

James S et al. NEJM Evidence 2023

SGLT2i nach Myokardinfarkt

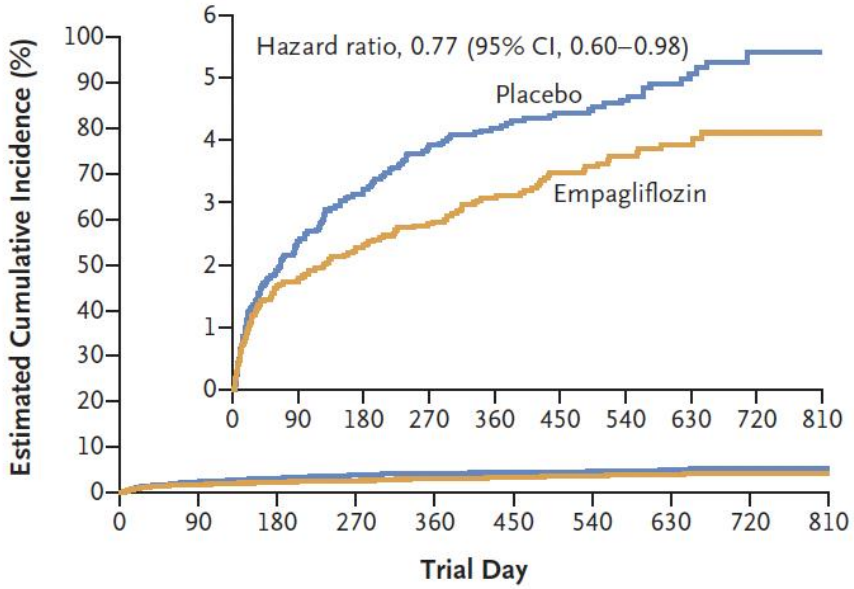
EMPACT-MI

A First Hospitalization for Heart Failure or Death from Any Cause



No. at Risk										
Placebo	3262	3092	3044	2832	2486	2071	1556	1040	551	137
Empagliflozin	3260	3111	3060	2881	2532	2107	1566	1048	531	134

B First Hospitalization for Heart Failure



No. at Risk										
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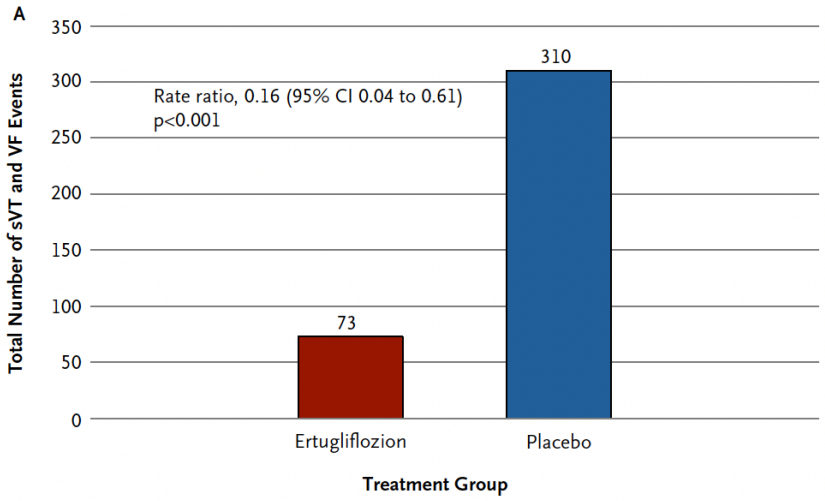
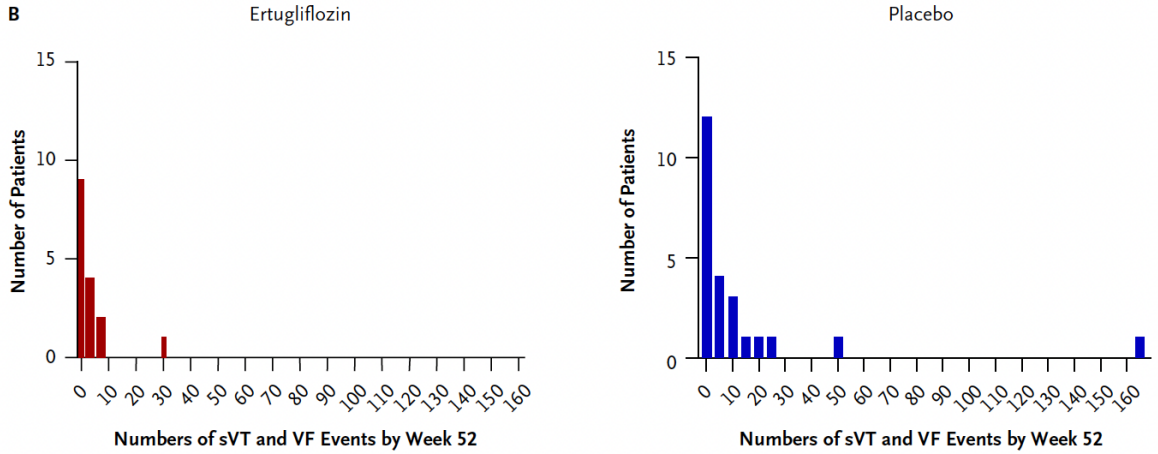
Empagliflozin	3260	3111	3060	2881	2532	2107	1566	1048	531	134

Butler J et al. NEJM 2024

SGLT2i bei ICD/CRT Patient*innen





NEJM Evidence

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Ertugliflozin to Reduce Arrhythmic Burden in Patients with ICDs/CRT-Ds

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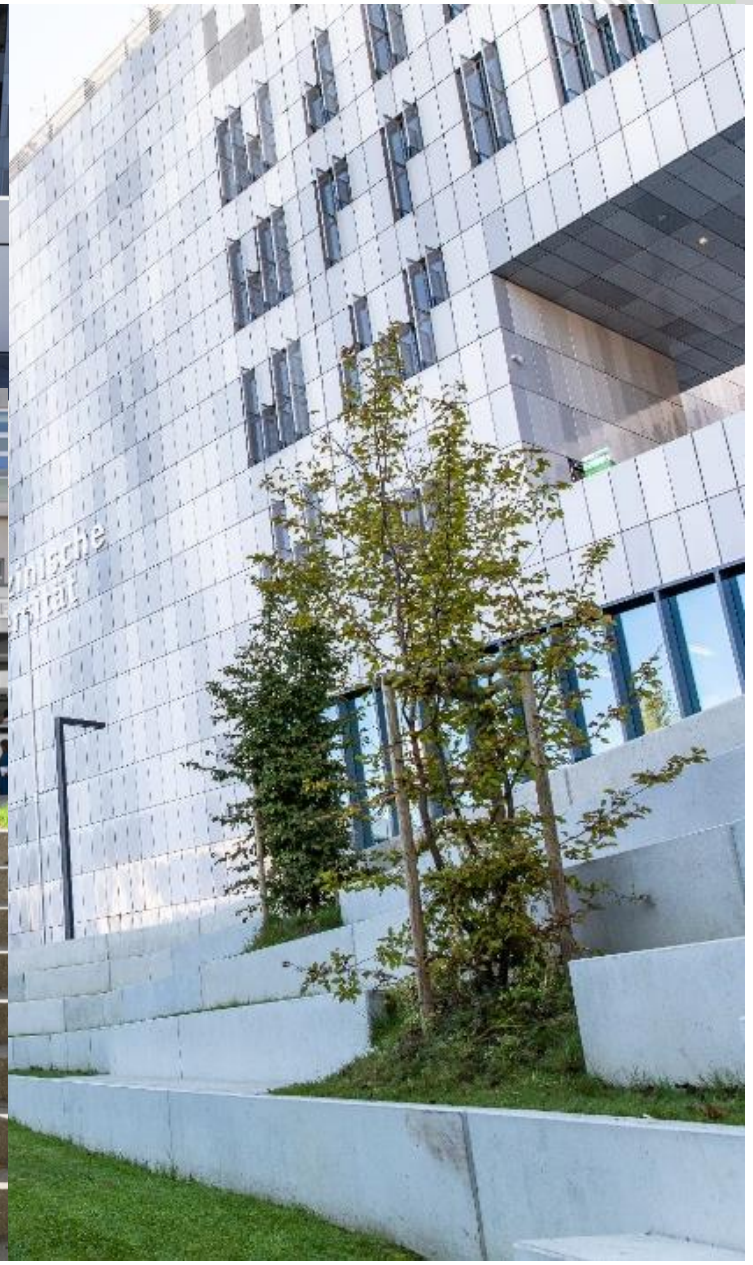
Danke



Fördergeber:

FWF Der Wissenschaftsfonds.

EFSD European Foundation for the Study of Diabetes

FFG Forschung wirkt.

Horizon Europe

Medical University of Graz | Interdisciplinary Metabolic Medicine Trials Unit