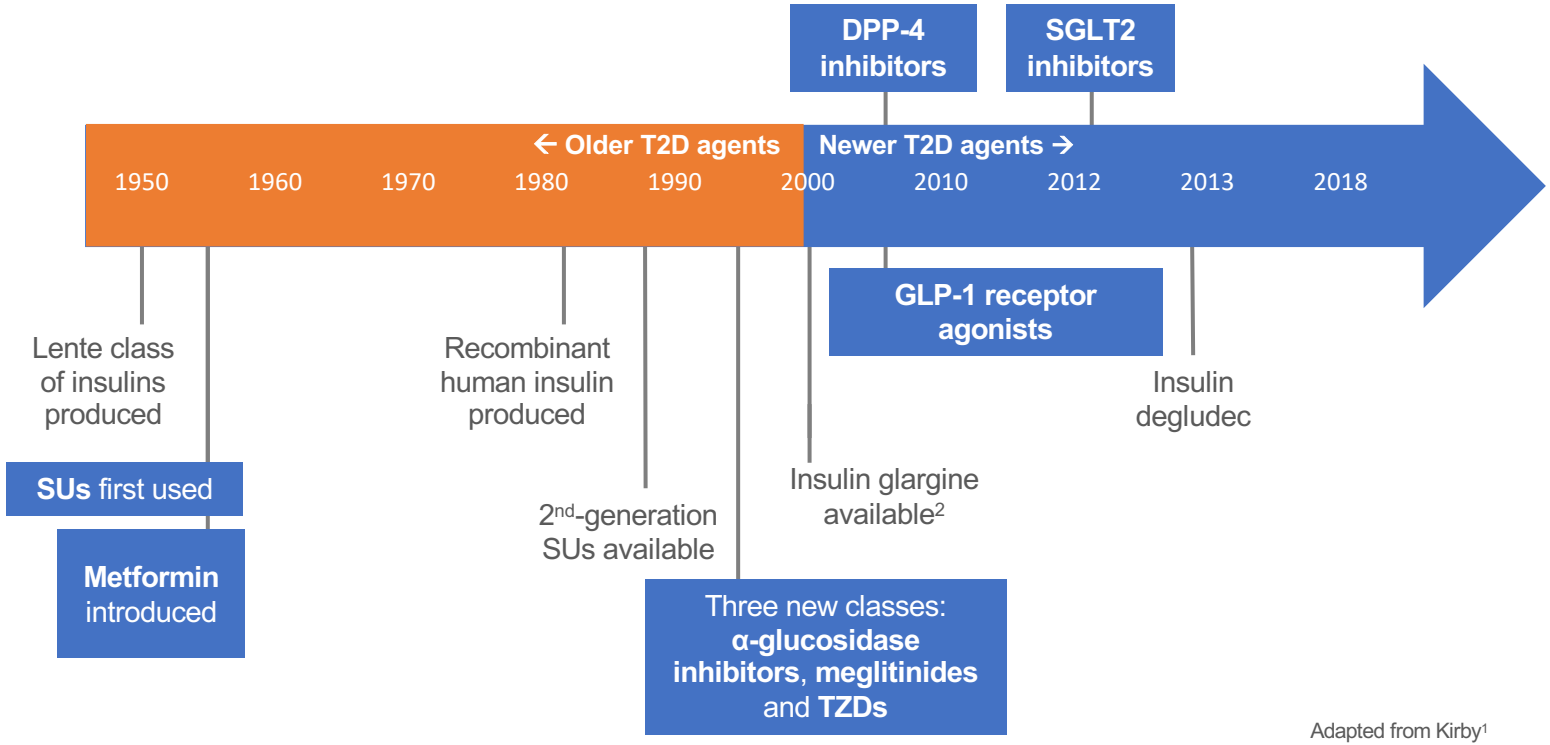
Diabetes mellitus Typ 2: Die Rolle der SGLT-2 Hemmer

Harald Sourij, Graz

Neue Substanzen bei Typ 2 Diabetes mellitus

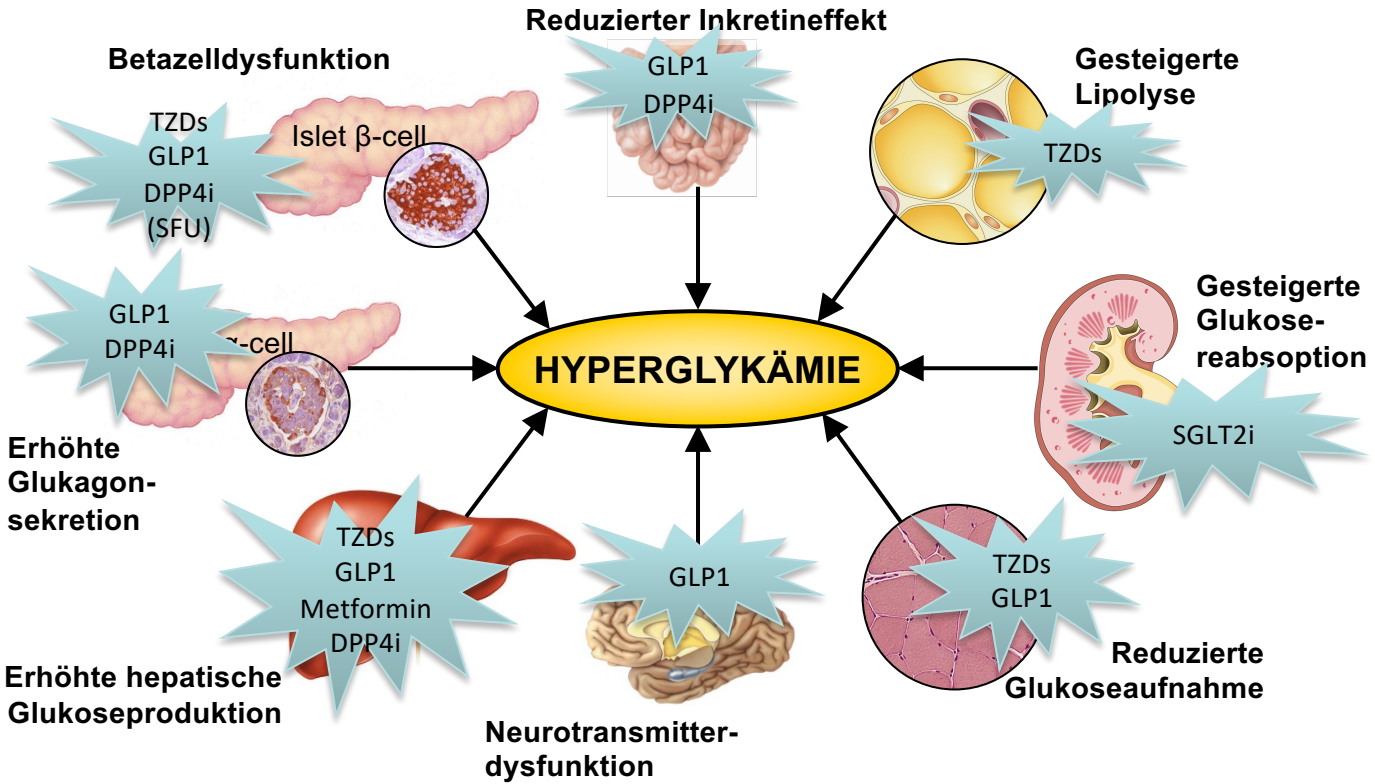


Adapted from Kirby[1]

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium–glucose transporter 2; SU, sulphonylurea; TZD, thiazolidinedione.

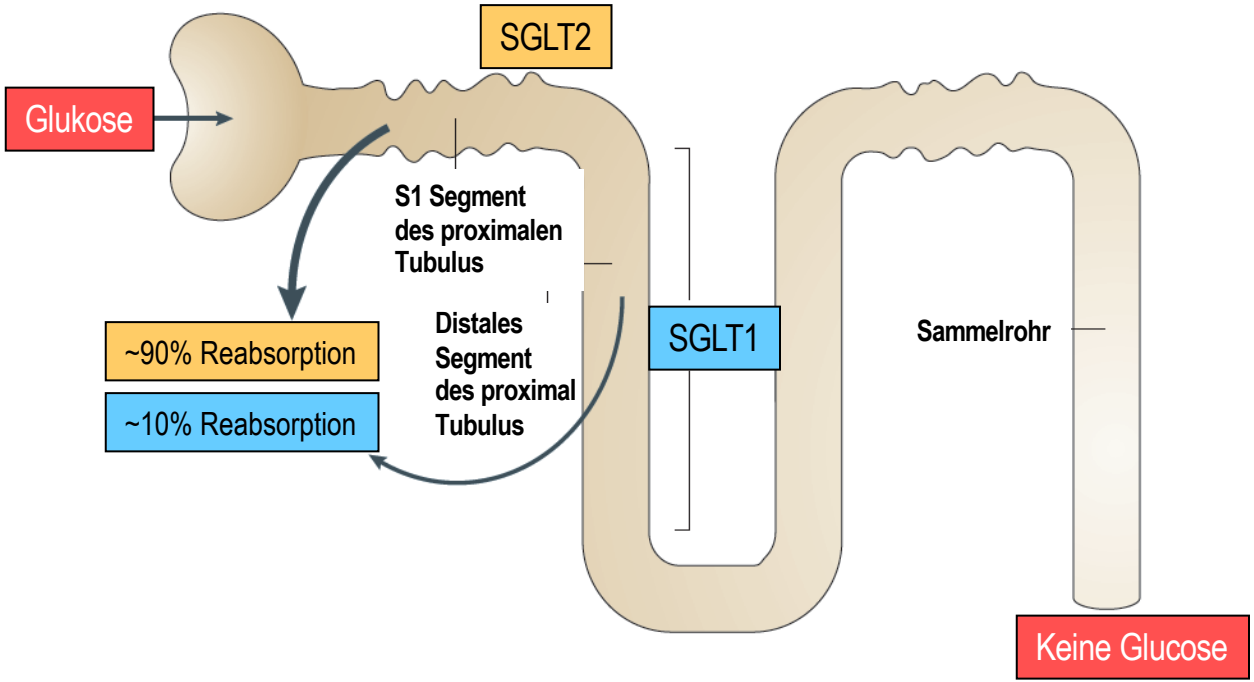
1. Kirby. Br J Diabetes Vasc Dis 2012;12:315–20. 2. Lantus® SPC.

Pathophysiologie des Typ 2 Diabetes mellitus



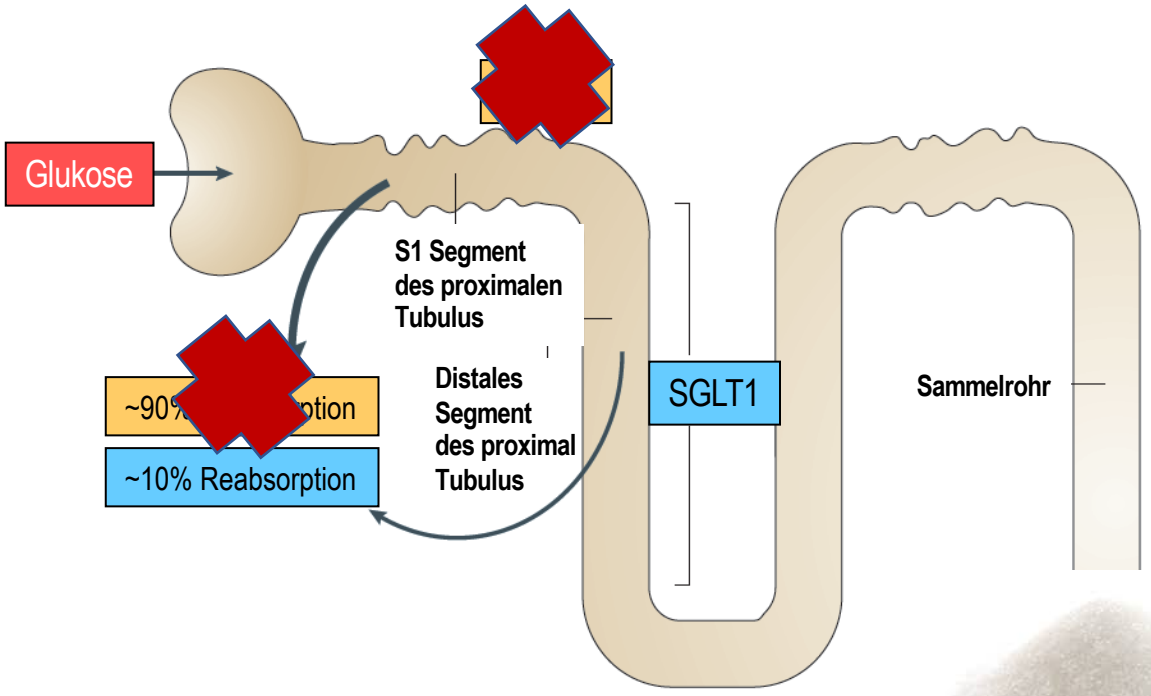
Adapted from DeFronzo RA. Diabetes 2009;58:773–95. ©Wolters Kluwer Health

SGLT2 Hemmer



Chao EC et al. Nat Rev Drug Discov. 2010;9:551–559.

SGLT2 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

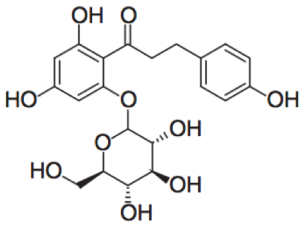
Phlorizin

Natürlich vorkommend in der Rinde von Birnen-, Apfel-, Kirschen- und anderen Bäumen

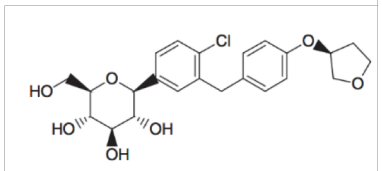
Kompetitiver Hemmer von SGLT-1 und SGLT-2

Zuckersenkender Effekt bereits 1987 erkannt

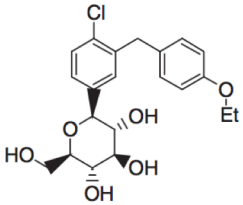
Substanzen im Überblick



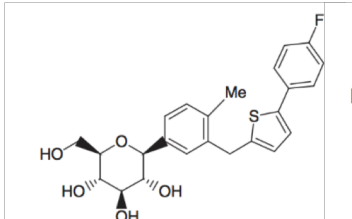
1 Phlorizin



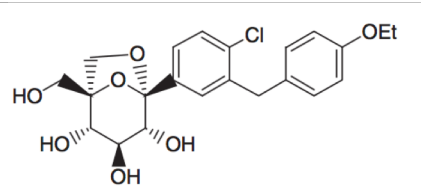
8 Empagliflozin (BI 10773)



5 Dapagliflozin

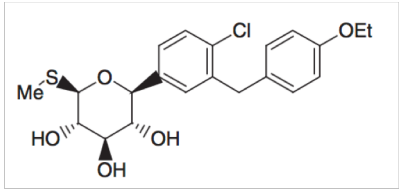


6 Canagliflozin



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



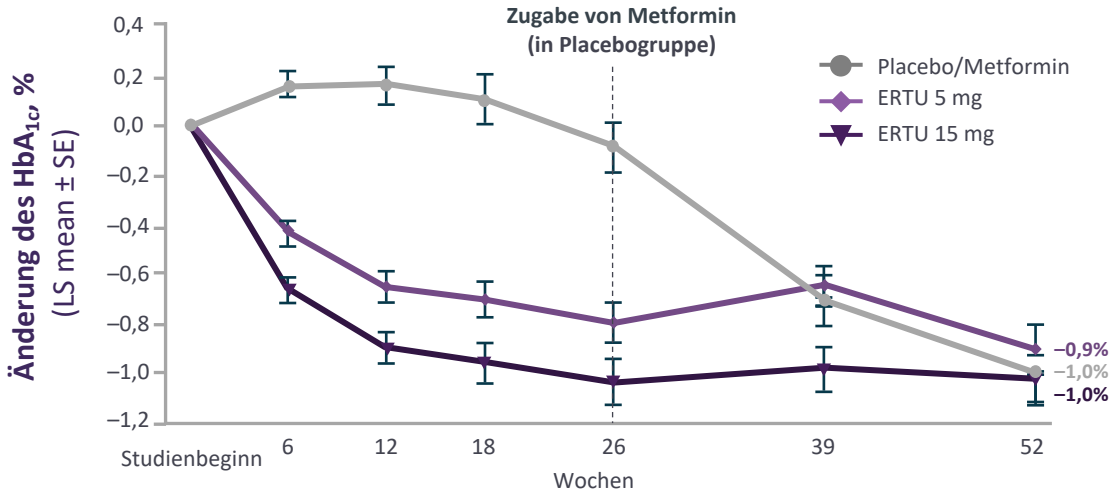
Sotagliflozin

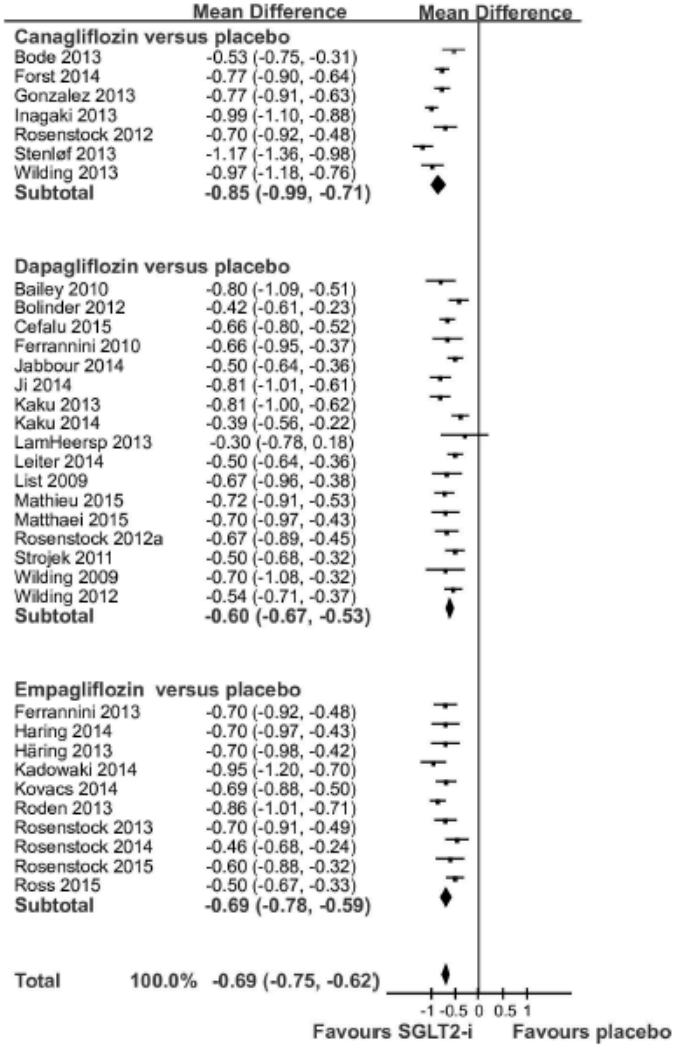
EC_{50} half maximal effective concentration

Washburn & Poucher Expert Opin. Investig. Drugs 2013

HbA1c-Senkung

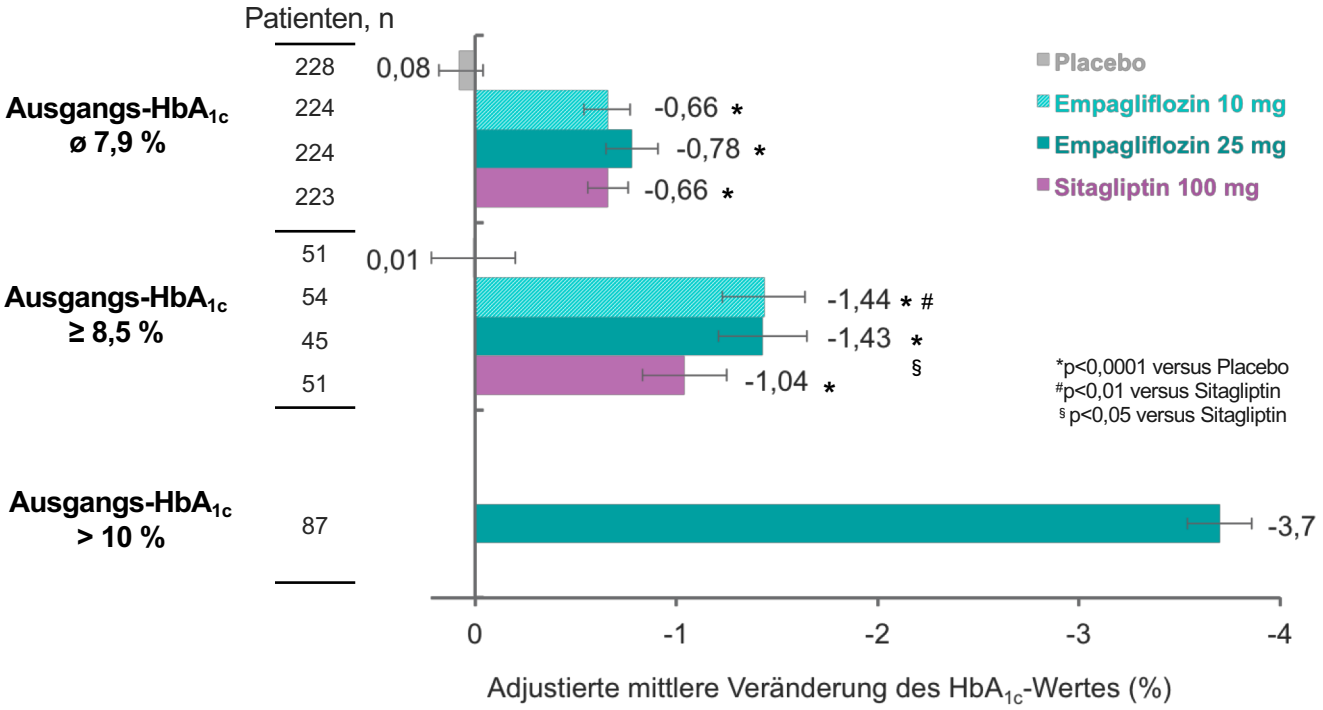
Vertis Mono: HbA1c Senkung nach 52 Wochen





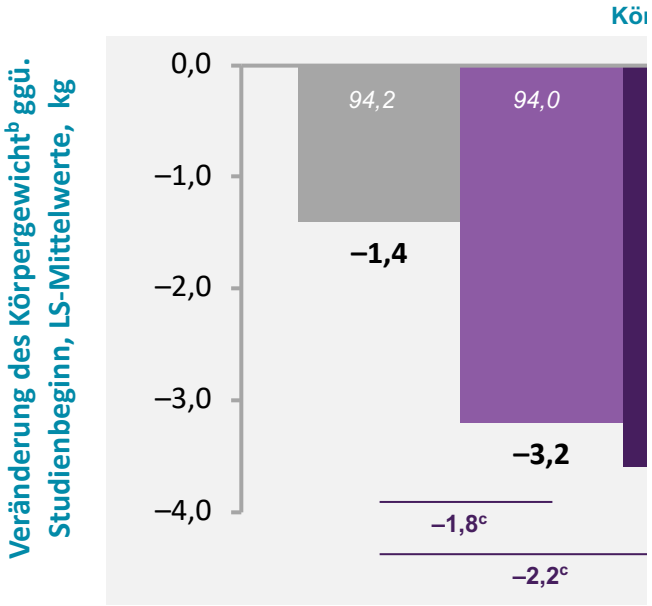
Angepasst von Aronson R et al. Diabetes Obes Metab. 2018;20:1453–1460.; ; Storgard H et al. PlosOne 2016

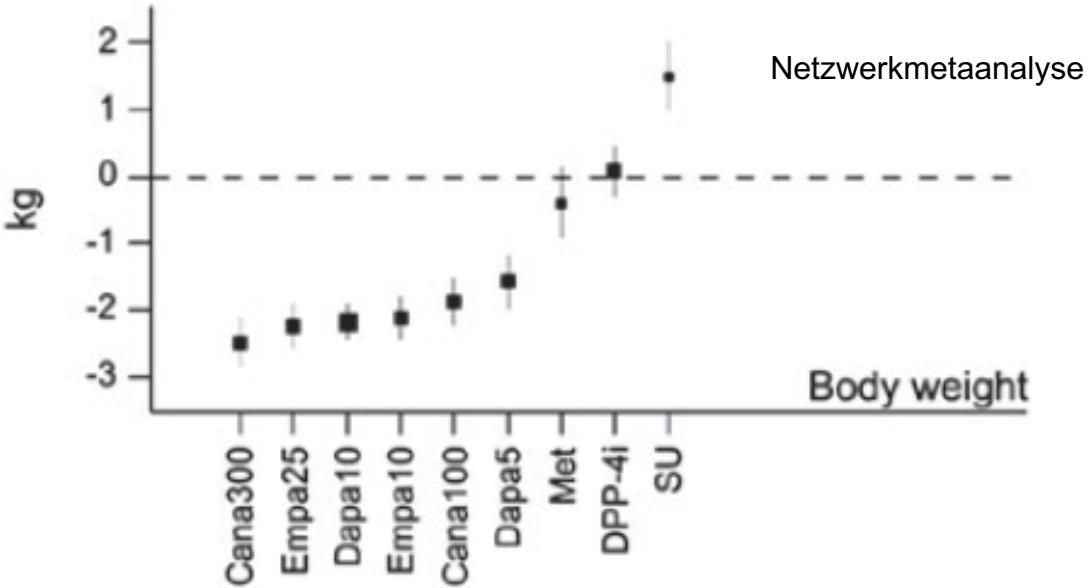
Blutzuckersenkung je nach HbA1c Ausgangswert



ANCOVA, FAS (LOCF).
Roden M, et al. Lancet Diabetes Endocrinol. 2013;1(3):208–219.

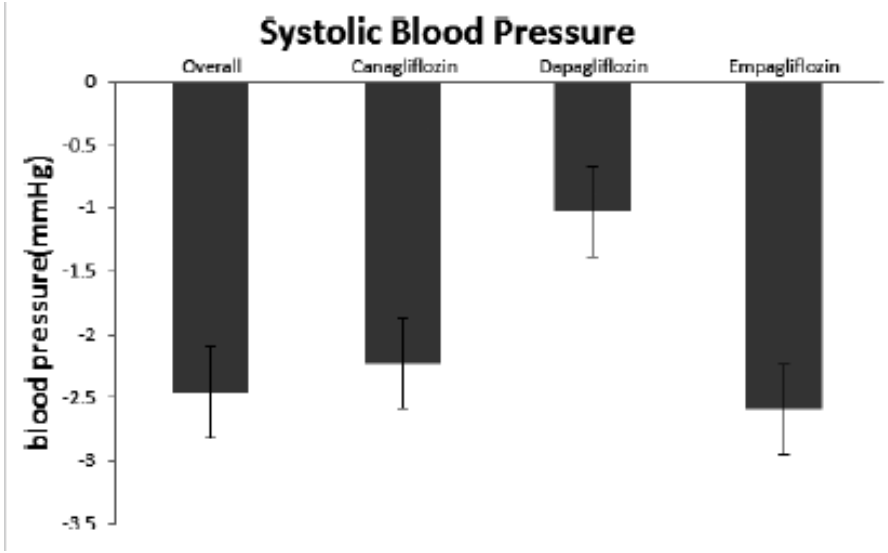
Körpergewichtsreduktion

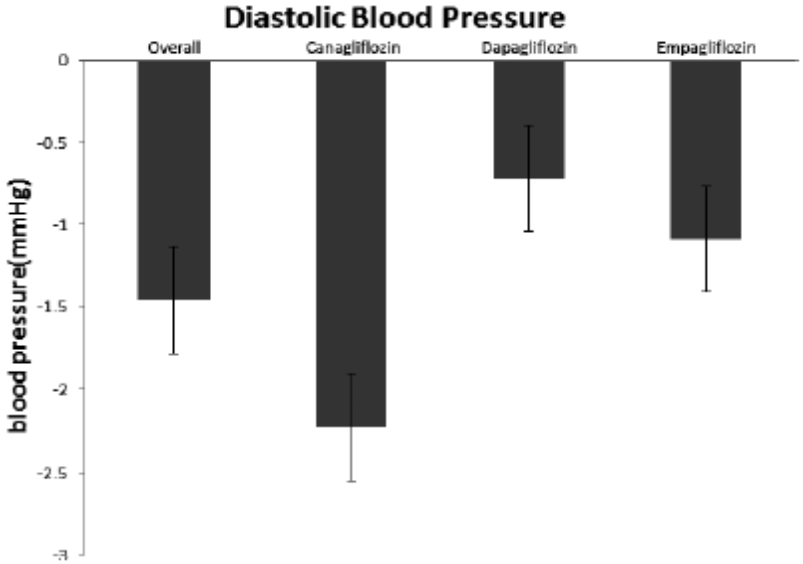




Terra SG et al. Diabetes Obes Metab. 2017;19:721–728. Zaccardi F. et al. Diabetes Obes Metab 2016

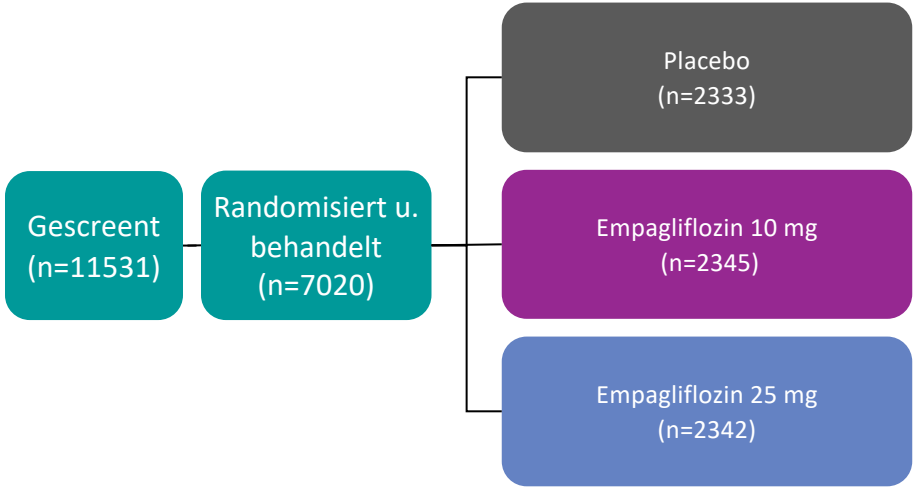
Blutdrucksenkung





Mazidi M. et al. J Am Heart Assoc 2017

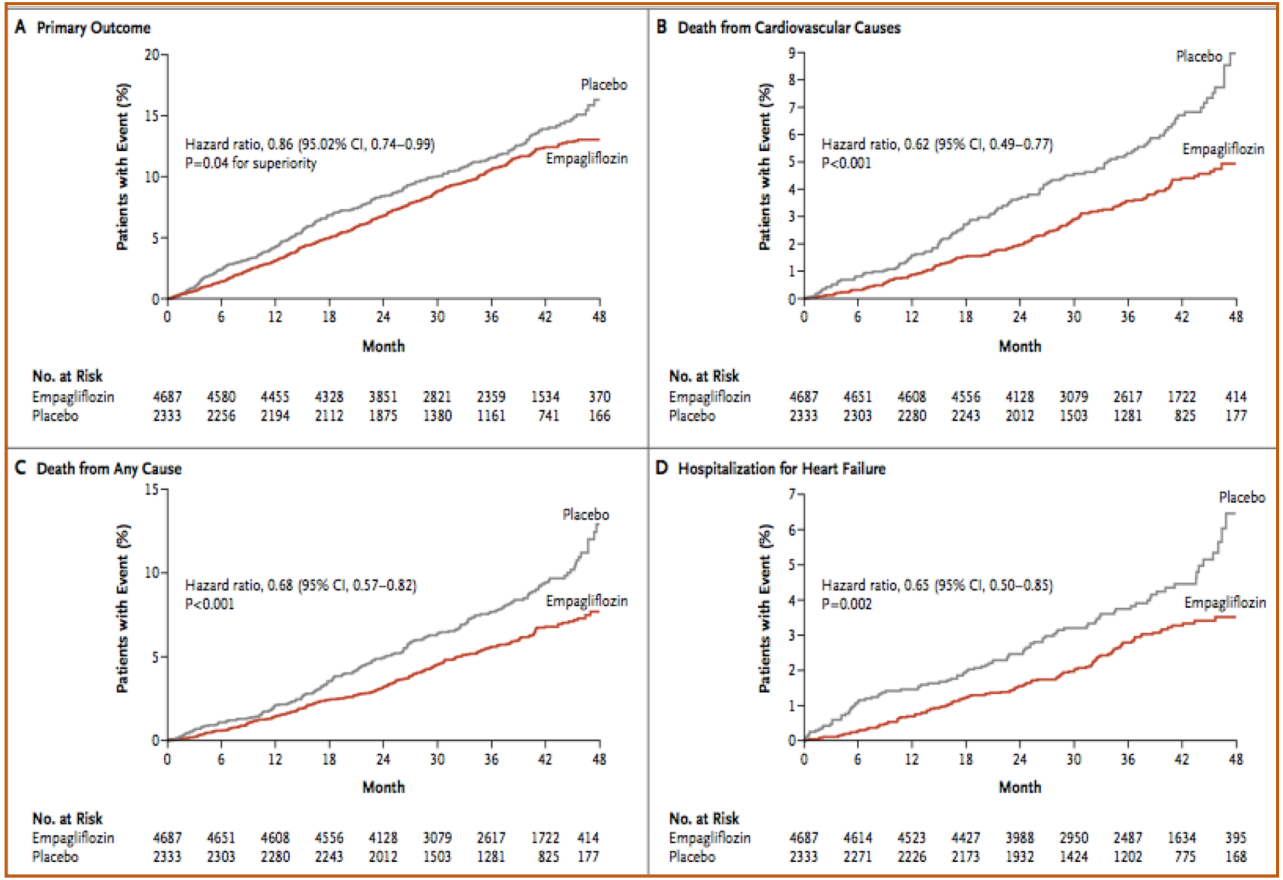
Design – EMPA REG OUTCOME



- Haupteinschlusskriterien
  - Erwachsene mit Typ 2 Diabetes
  - BMI ≤45 kg/m²
  - HbA1c 7–10%*
  - Vorbestehende kardiovaskuläre Erkrankung
    - Vorangegangener Myokardinfarkt, KHK, Insult, instable AP od. pAVK

- Hauptausschlusskriterien
  - eGFR <30 mL/min/1.73m² (MDRD)

EMPA REG OUTCOME



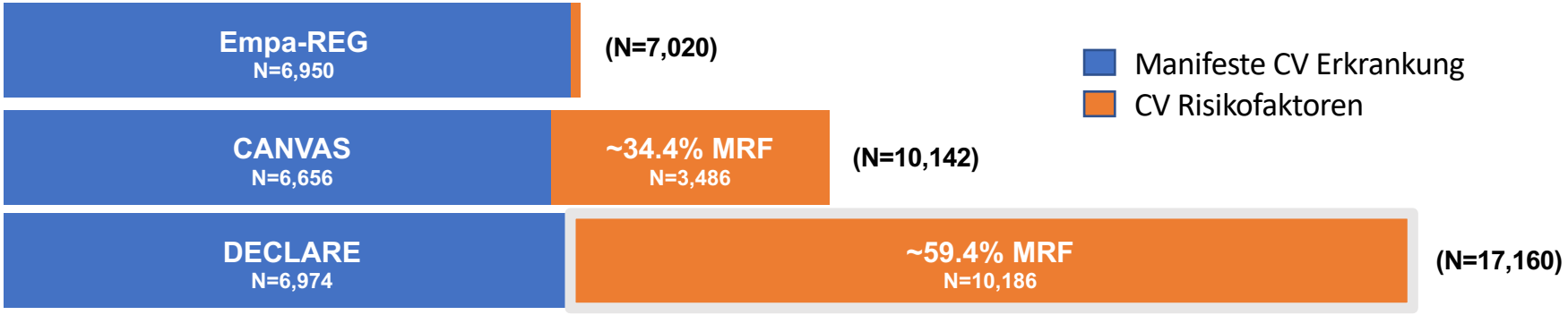
Zinman B. et al. NEJM 2015

SGLT2-Hemmer CVOT im Vergleich

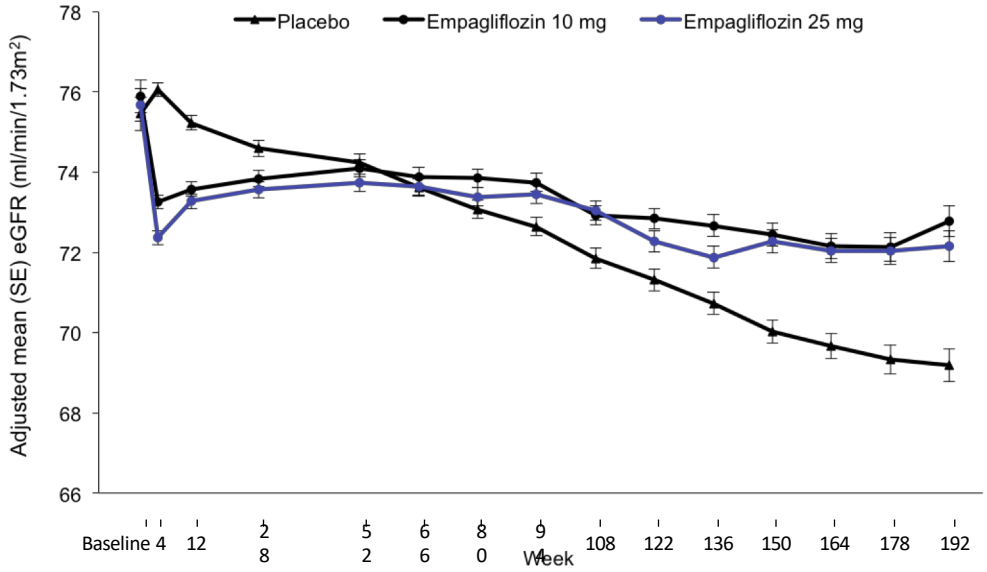
	EMPA-REG OUTCOME	CANVAS Programm	DECLARE- TIMI 58
Hospitalisierung HI oder CV Tod			0.83 (0.73 – 0.95)
3p MACE	0.86 (0.74-0.99)	0.86 (0.75-0.97)	0.93 (0.84-1.03)
Nicht-tödlicher Herzinfarkt	0.87 (0.70-1.09)	0.85 (0.69-1.05)	0.89 (0.77 – 1.01)
Nicht-tödlicher Schlaganfall	1.24 (0.92-1.67)	0.90 (0.71-1.15)	1.01 (0.84-1.21)
CV-Tod	0.62 (0.49-0.77)	0.87 (0.72-1.06)	0.98 (0.82 -1.17)
Gesamtmortalität	0.68 (0.57-0.82)	0.87 (0.74-1.01)	0.93 (0.82 – 1.04)
Hospitalisierung HI	0.65 (0.50-0.85)	0.67 (0.52-0.87)	0.73 (0.61 – 0.88)
Komb. Renaler Endpunkt	0.54 (0.40-0.75)*	0.60 (0.47-0.77)**	0.53 (0.43 -0.66)**

Endpunktstudie mit Ertugliflozin (VERTIS CV) läuft aktuell noch.

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



eGFR (CKD-EPI) über 192 Wochen

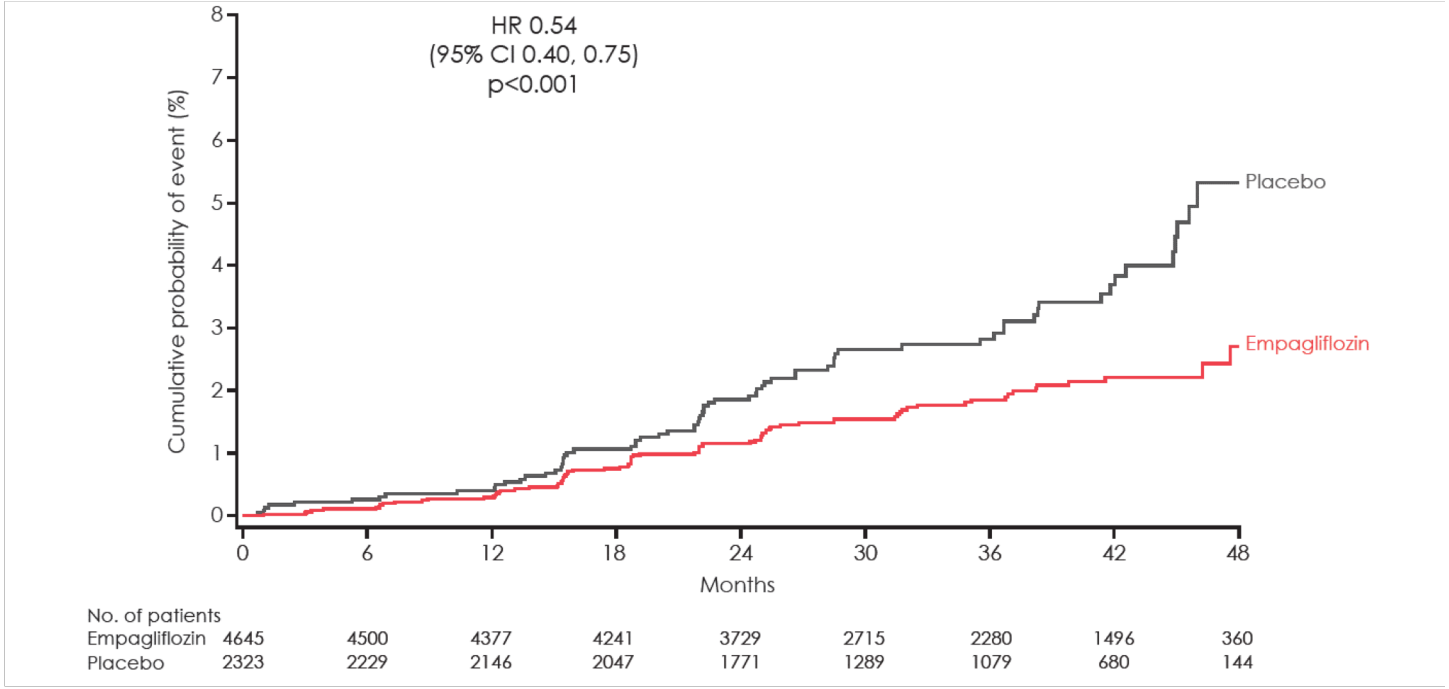


No. analyzed															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in follow-up for adverse/outcome events															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703

eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

Wanner C. et al. NEJM 2016

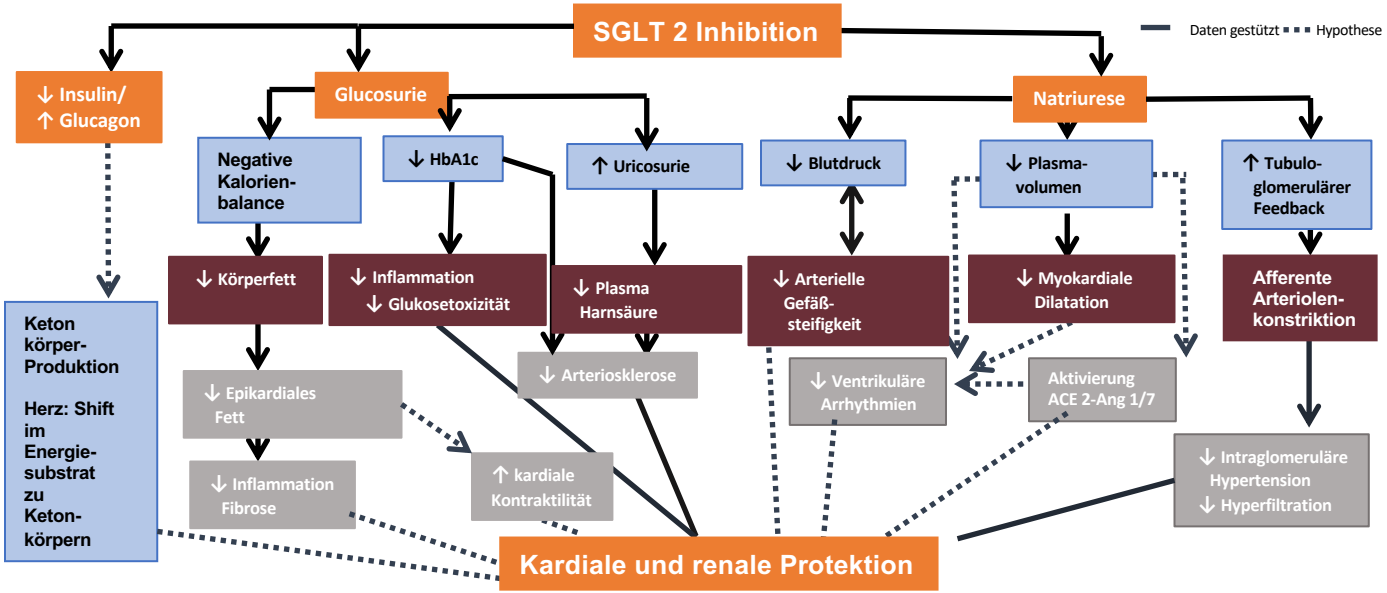
Verdopplung des Serumkreatinins*, Beginn einer Nierenersatztherapie, Tod aufgrund einer Nierenerkrankung



Kaplan-Meier estimate in patients treated with ≥1 dose of study drug.
Hazard ratios are based on Cox regression analyses.
*Accompanied by eGFR [MDRD] ≤45 ml/min/1.73m². HR, hazard ratio; CI, confidence interval. *Post-hoc* analyses.

Wanner C. et al. NEJM 2016

Mechanismen



Modifiziert nach Heerspink H et al. Circulation 2016;34: 752-772

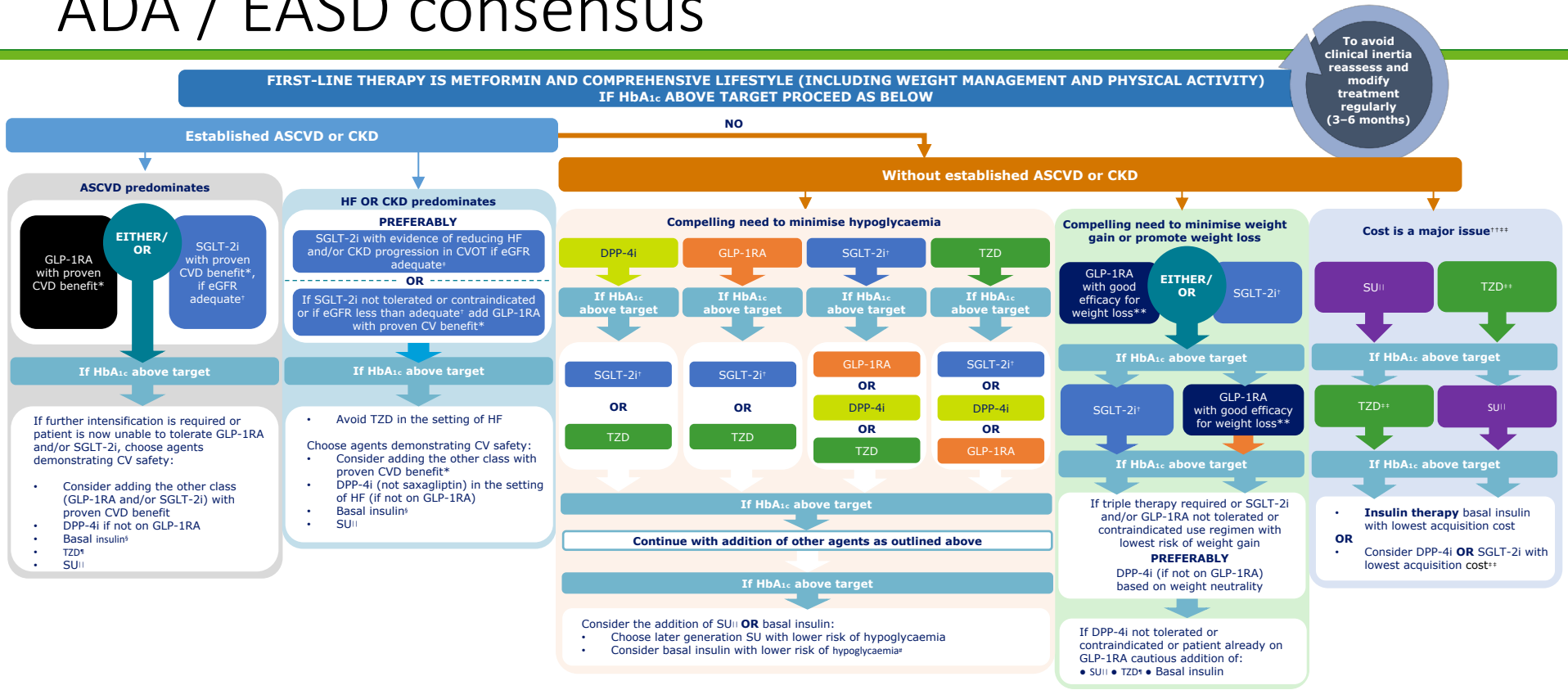
Nebenwirkungen

- Genitale Pilzinfektionen (Risiko verdreifacht)
- Euglykämische Ketoazidosen
  - selten bei PatientInnen mit Typ 2 Diabetes
  - meistens ein auslösender Faktor (Infektionen, reduziere Nahrungs- und Flüssigkeitszufuhr, verstärkter Alkoholgenuss, absoluter Insulinmangel,…)

  → Pausieren im Krankheitsfall

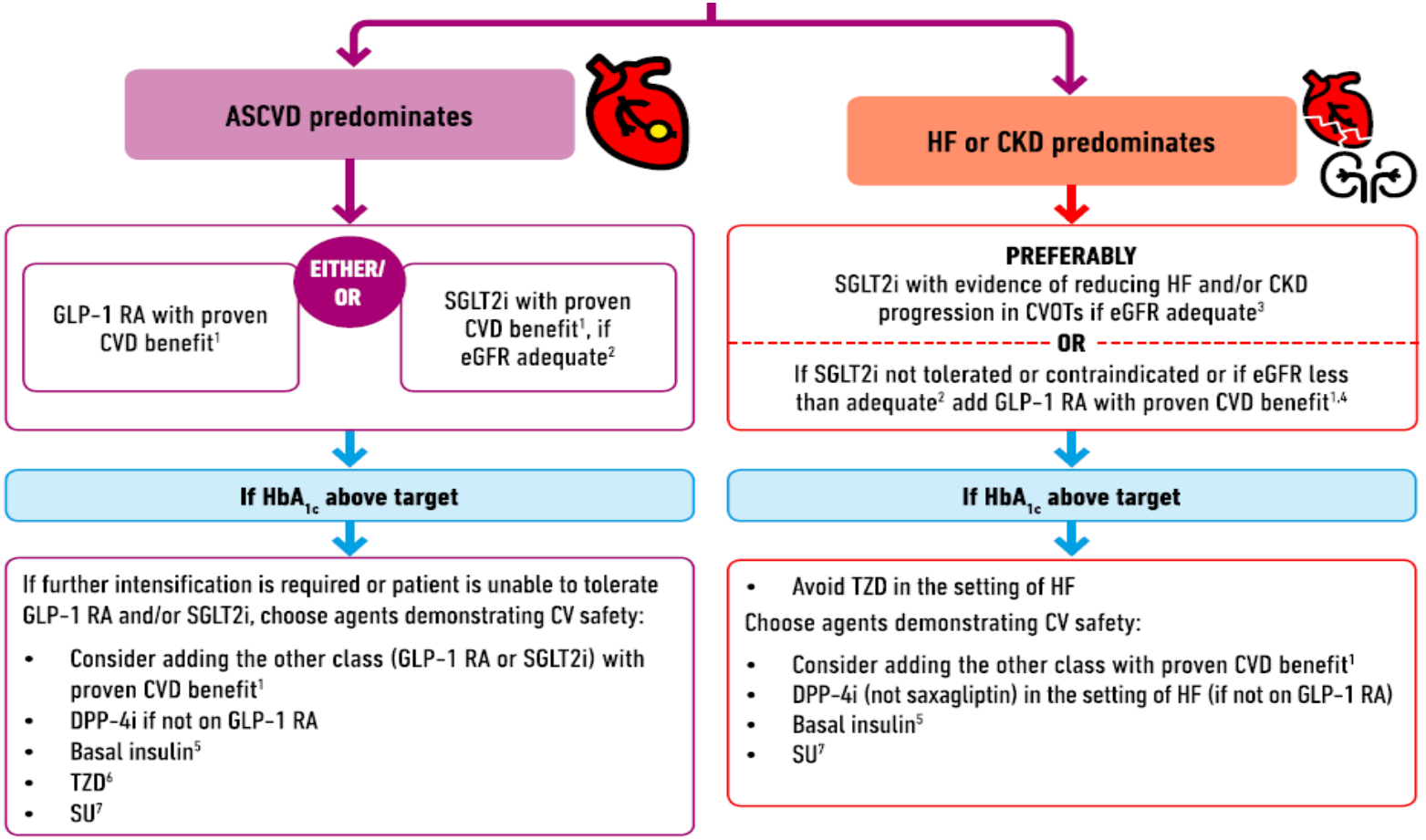
- Erhöhte Raten für periphere Amputationen (nur für Canagliflozin gezeigt)

ADA / EASD consensus



*Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1RA strongest evidence for liraglutide>semaglutide>exenatide extended release. For SGLT-2i evidence modestly stronger for empagliflozin>canagliflozin; †Be aware that SGLT-2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use; ‡Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs; §Degludec or U100 glargine have demonstrated CVD safety; ¶Low dose may be better tolerated though less well studied for CVD effects; ‖Choose later generation SU with lower risk of hypoglycaemia; #Degludec / glargine U300<glargine U100 / detemir<NPH insulin; **Semaglutide>liraglutide>dulaglutide>exenatide>lixisenatide; ††If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities); ‡‡Consider country- and region-specific cost of drugs. In some countries, TZDs relatively more expensive and DPP-4i relatively cheaper*

Davies MJ et al. Diabetologia and Diabetes Care 2018

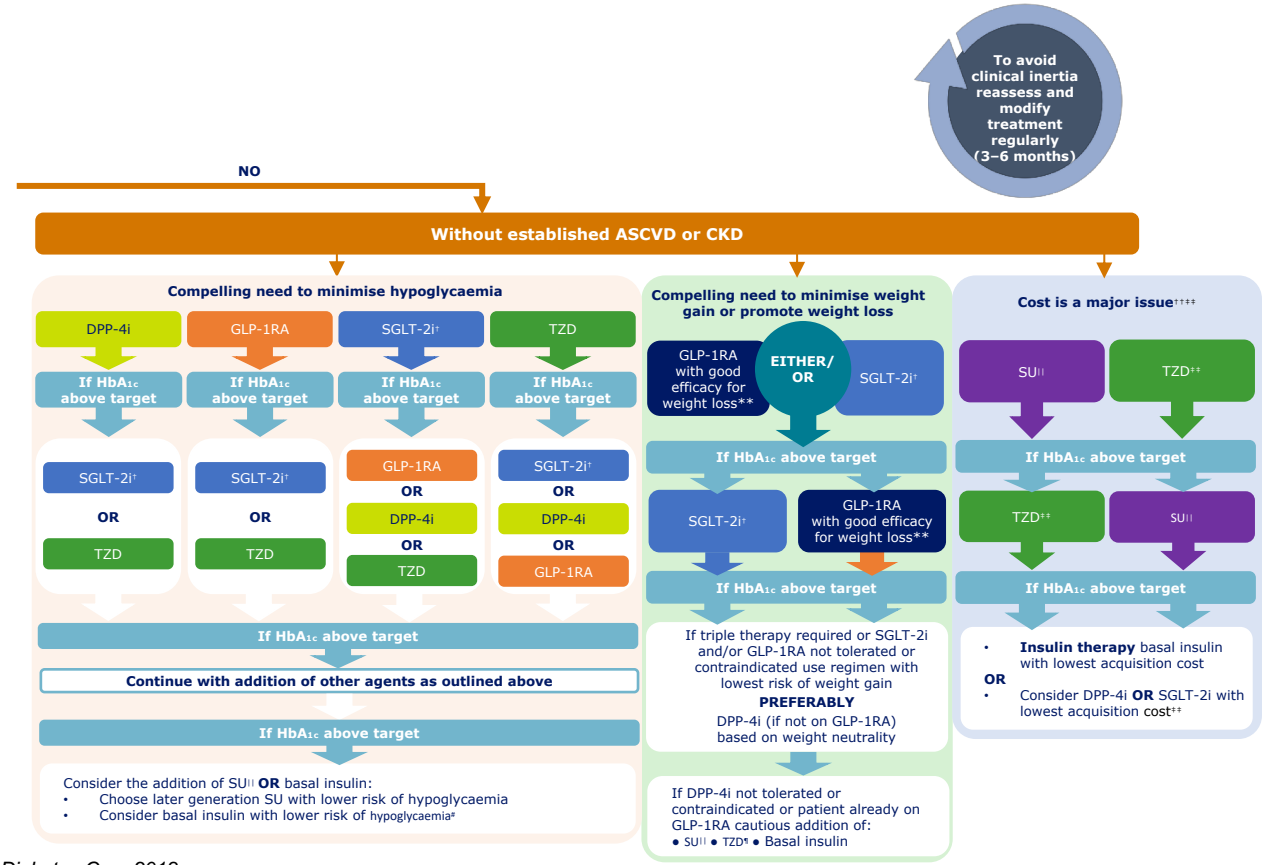


GLP-1 RA with proven CVD benefit:
Liraglutide > Semaglutide > Exenatide LAR

SGLT2-I with proven CVD benefit:
Empagliflozin > Canagliflozin

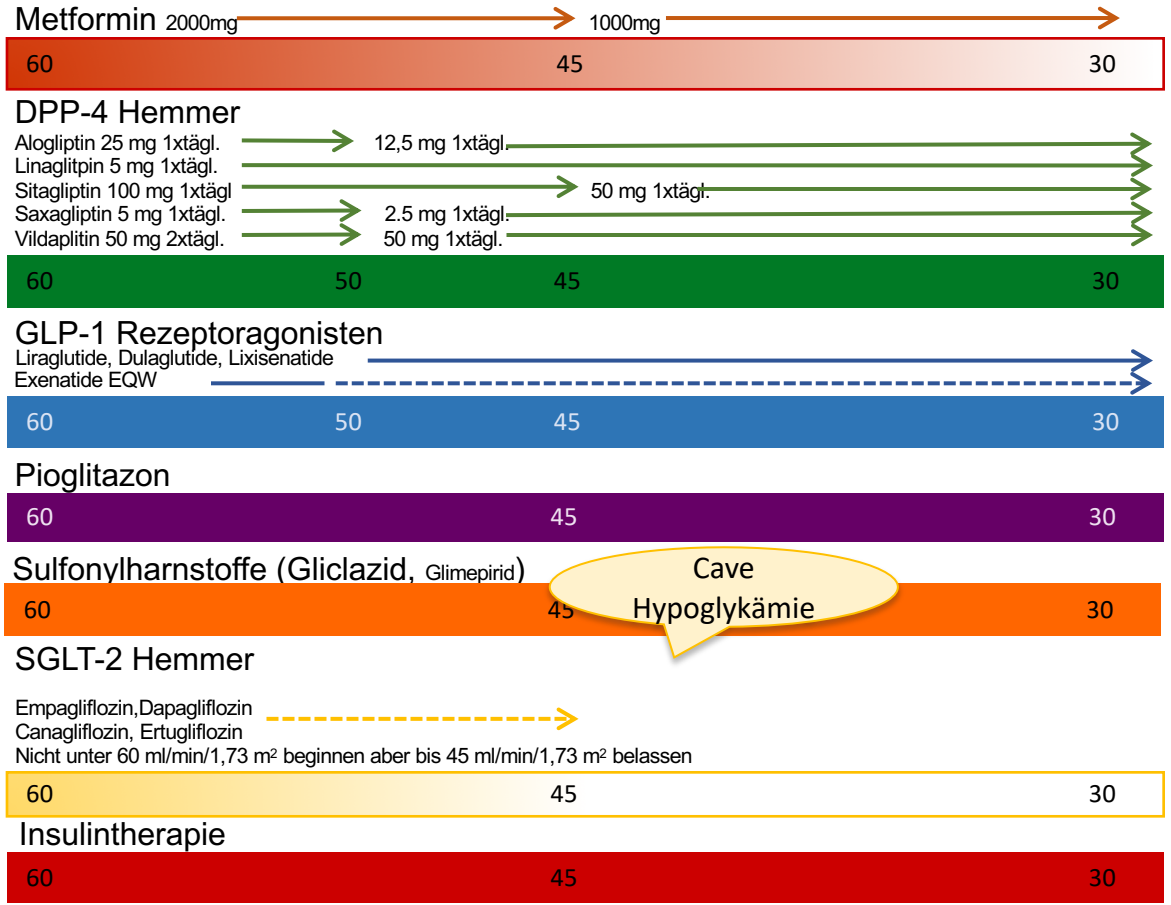
Davies MJ et al. Diabetologia and Diabetes Care 2018

ADA / EASD consensus

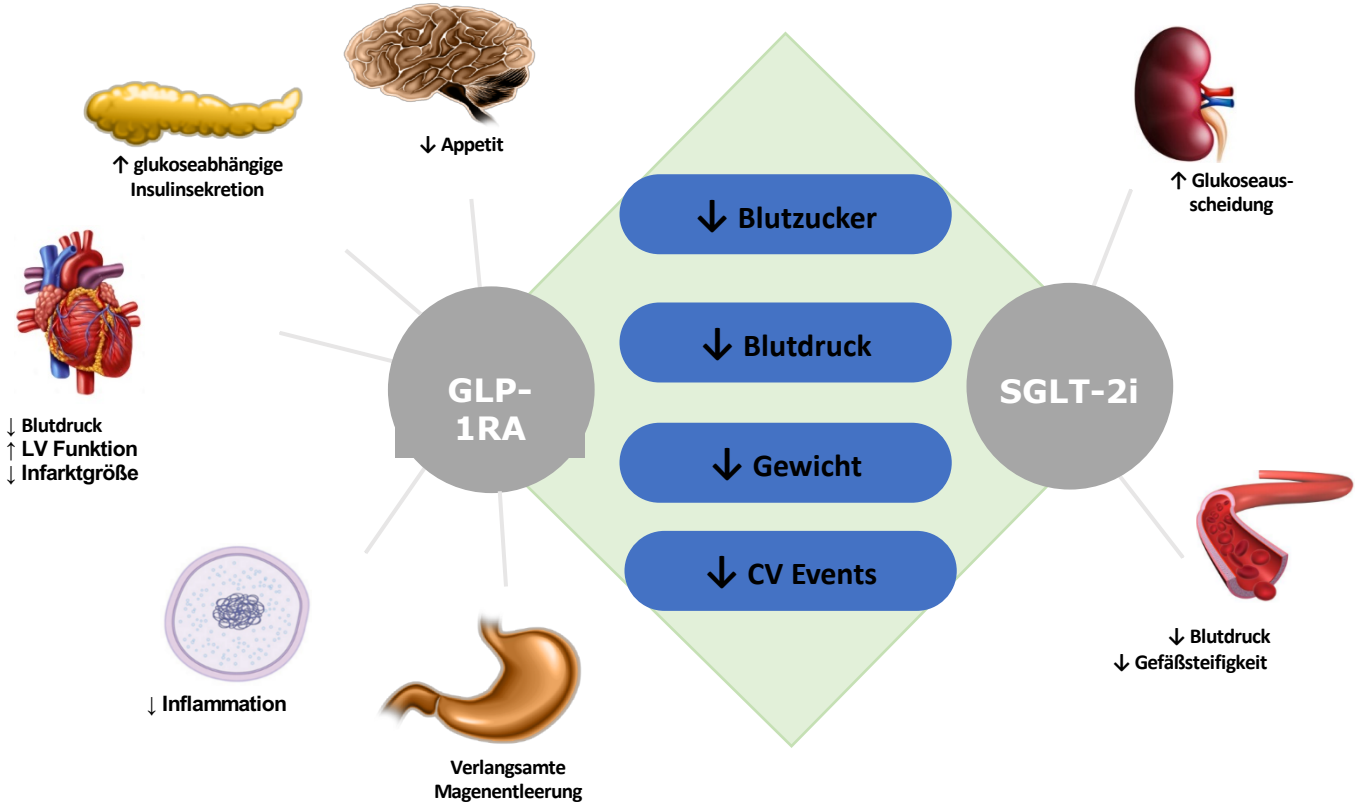


Davies MJ et al. Diabetologia and Diabetes Care 2018

Kreatinin-Clearance 30-60 ml/min

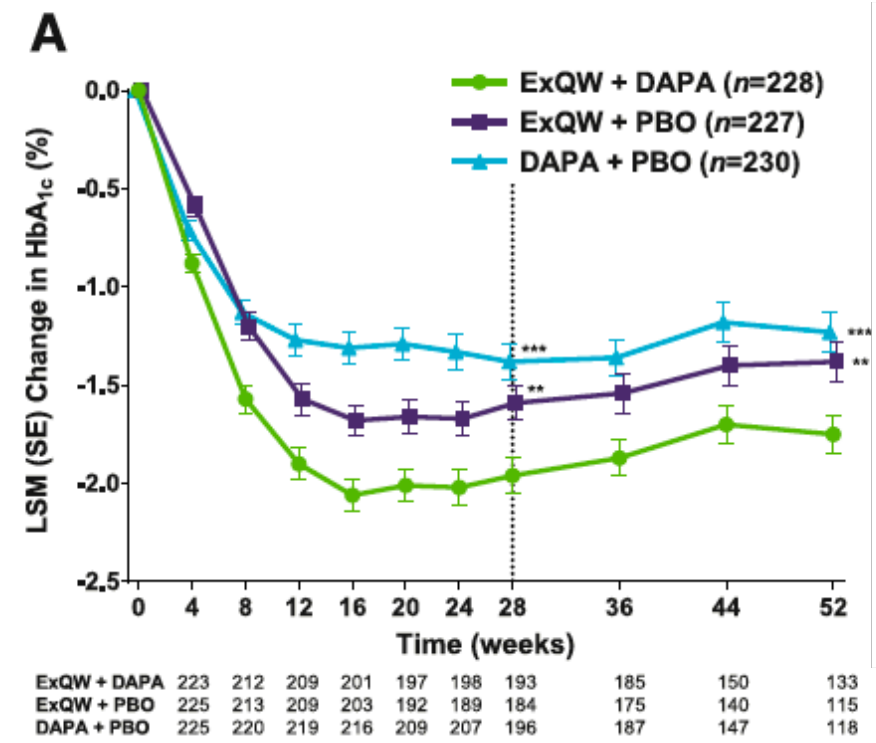


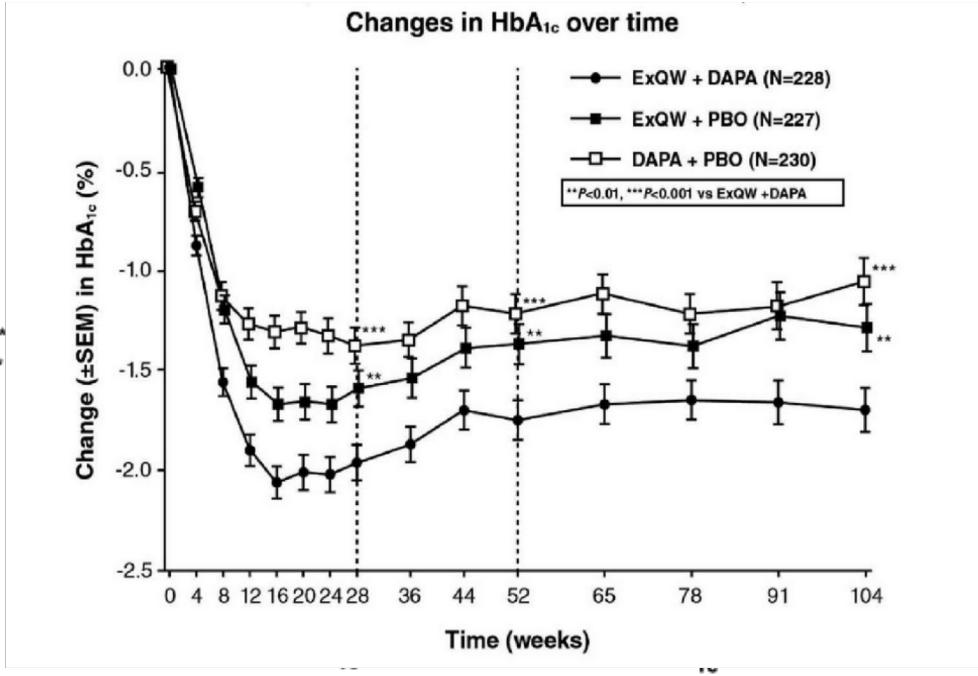
GLP-1RA und SGLT-2 Hemmer in Kombination



Aus der DURATION -8 Präsentation EASD München 2016

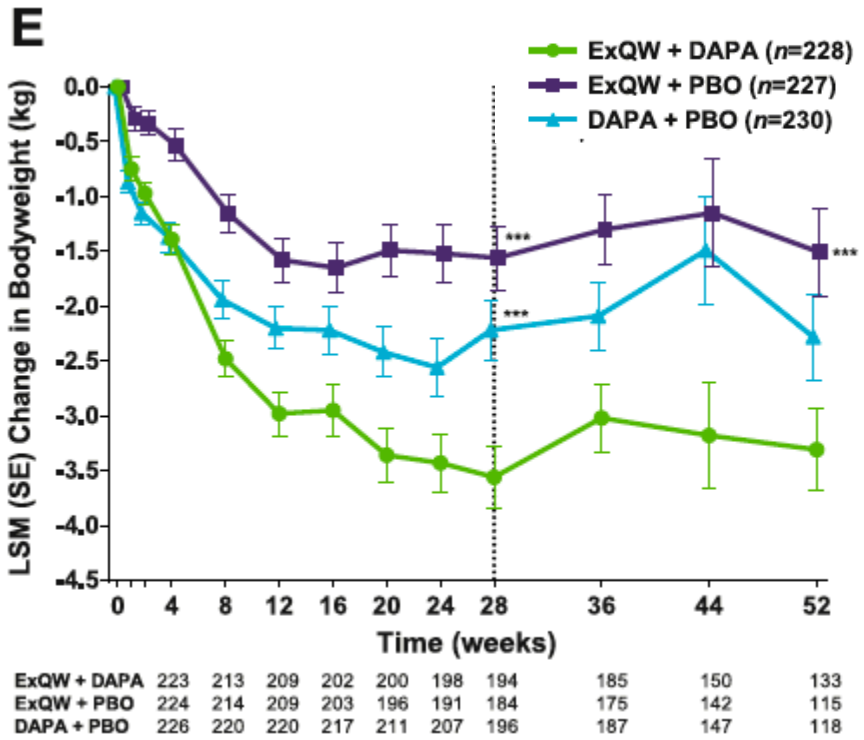
DURATION-8

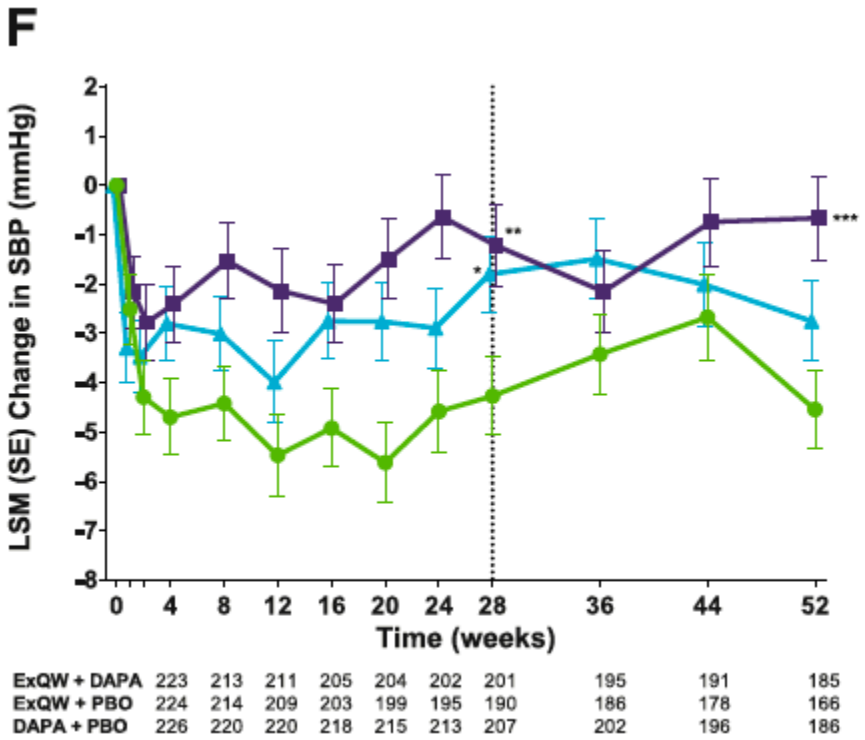




Jabbour SE et al. Diabetes Care 2018; Hardy T. et al Presentation EASD 2018

DURATION-8





Jabbour SE et al. Diabetes Care 2018

Zusammenfassung

- SGLT-2 Hemmer führen zu einer pharmakologisch induzierten Glukosurie.
- SGLT-2 Hemmer reduzieren neben dem Blutzucker auch das Körpergewicht.
- Kardiovaskuläre Endpunkstudie zeigen konstant eine Reduktion der Hospitalisation für Herzinsuffizienz und renaler Endpunkte.
- Es zeigt sich auch eine Reduktion kardiovaskulärer Endpunkte und/oder der Mortalität – je nach Substanz.
- Bei PatientInnen mit kardiovaskulärer Erkrankung sind SGLT-2 Hemmer neben GLP1- Rezeptoragonisten die empfohlenen Zweitlinienpräparate nach Metformin.
- Genitale Pilzinfektionen sind die häufigste Nebenwirkungen der SGLT-2 Hemmer.