Uniklinikum Würzburg

Diabetes mellitus und Herzinsuffizienz - Therapieempfehlungen

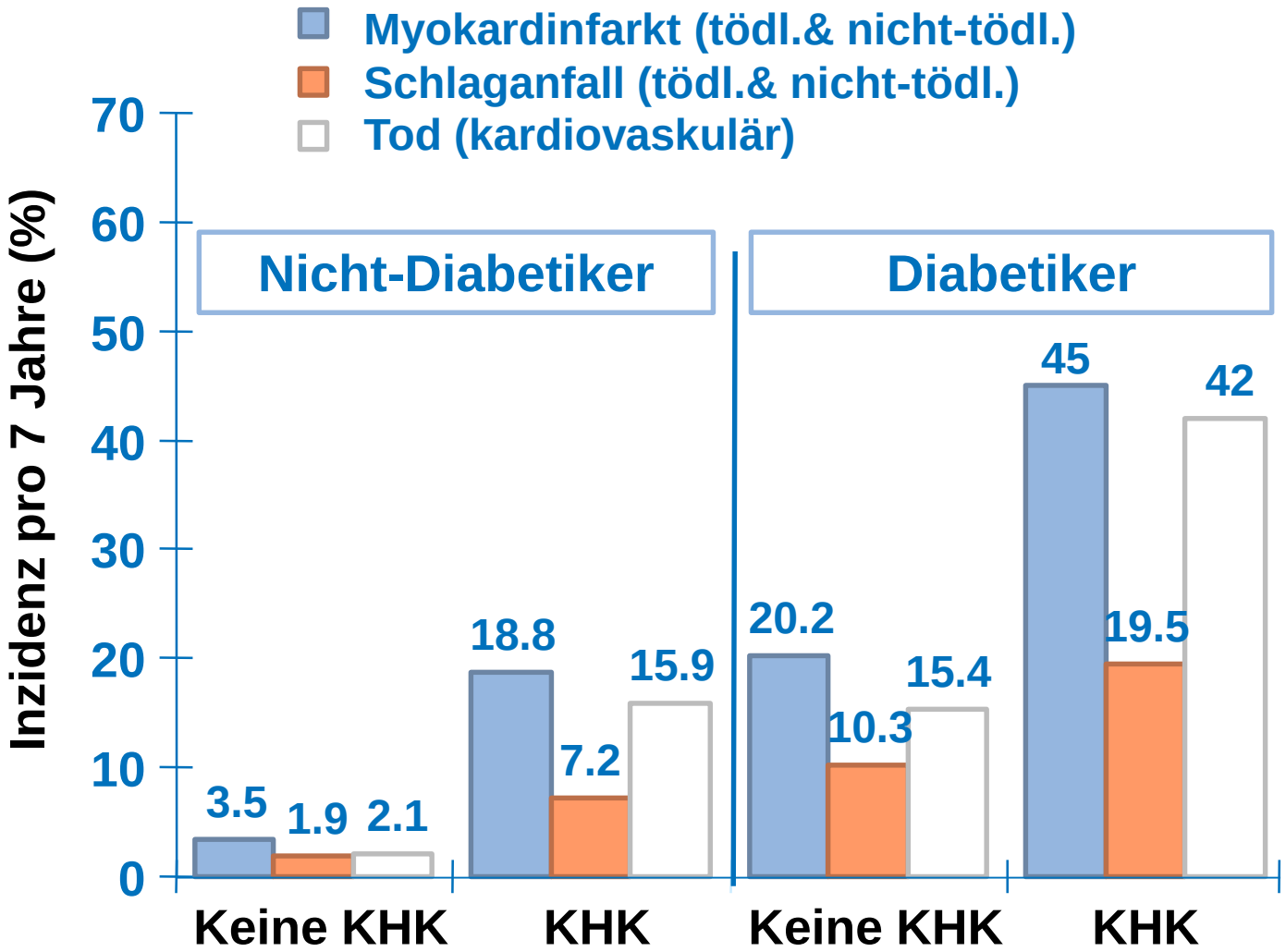
Medizinische Klinik und Poliklinik I
Direktor: Prof. Dr. S. Frantz

medeins
MEDIZINISCHE KLINIK & POLIKLINIK I

Disclosures

- Honoraria: Amgen, Astra, Bayer, Boehringer, Daiichi, Novartis, Pfizer, Roche, Sanofi, Servier, Vifor
- Advisory Board: Boehringer, Novartis, Pfizer, Sanofi, Vifor

Diabetiker sind kardiovaskuläre Hochrisikopatienten

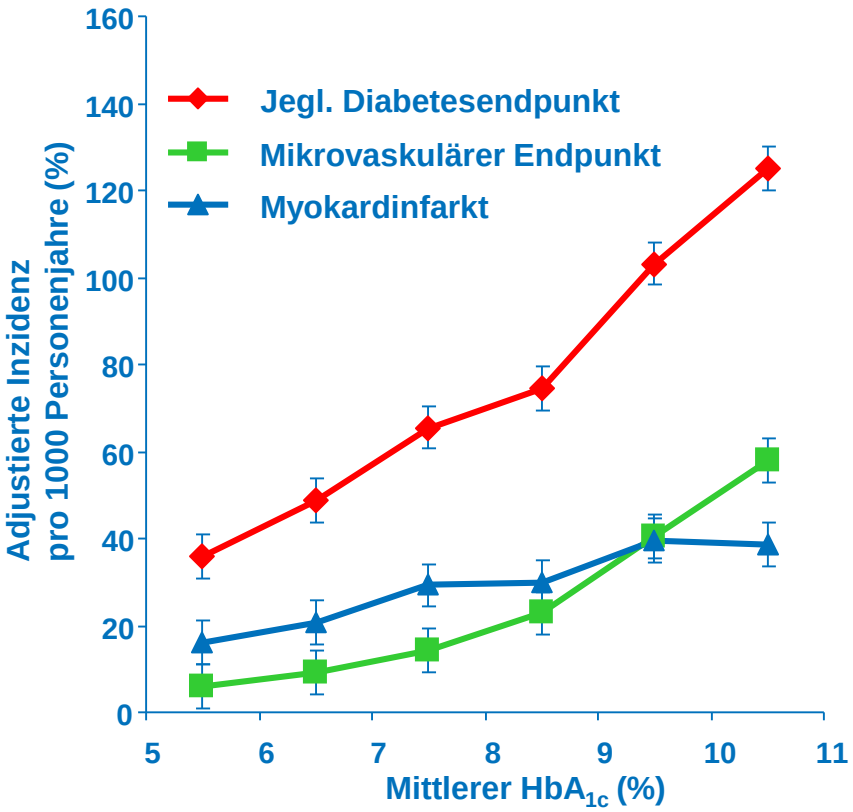


Haffner, N Engl J Med 1998

Komplikationen bei DM Typ 2

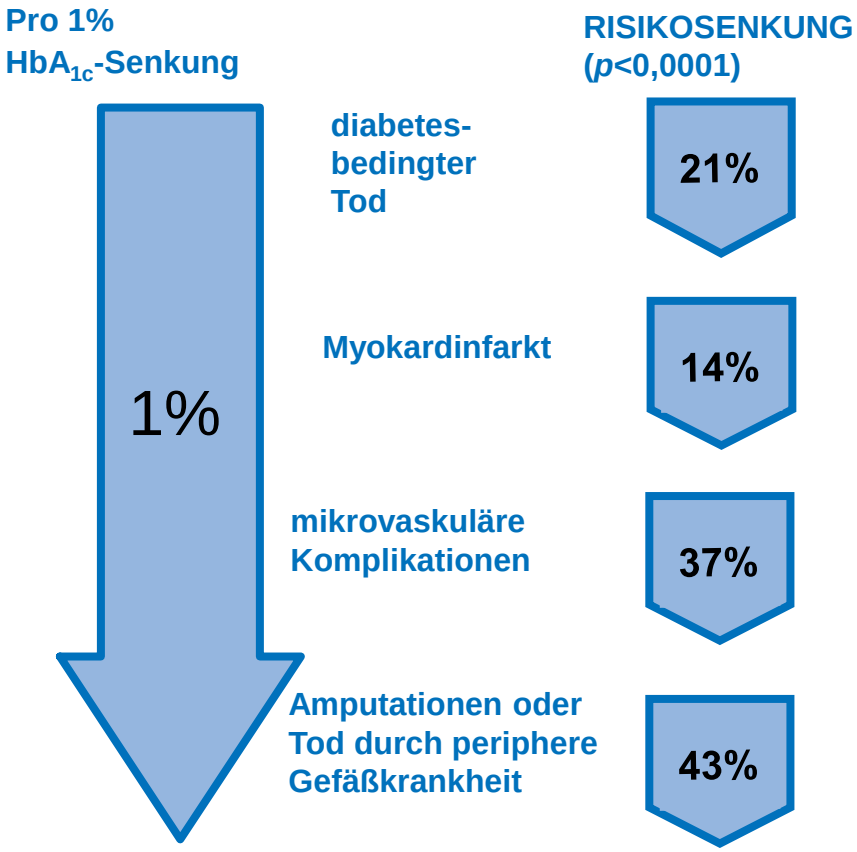
Inzidenz der Komplikationen

n=4585



Relatives Risiko

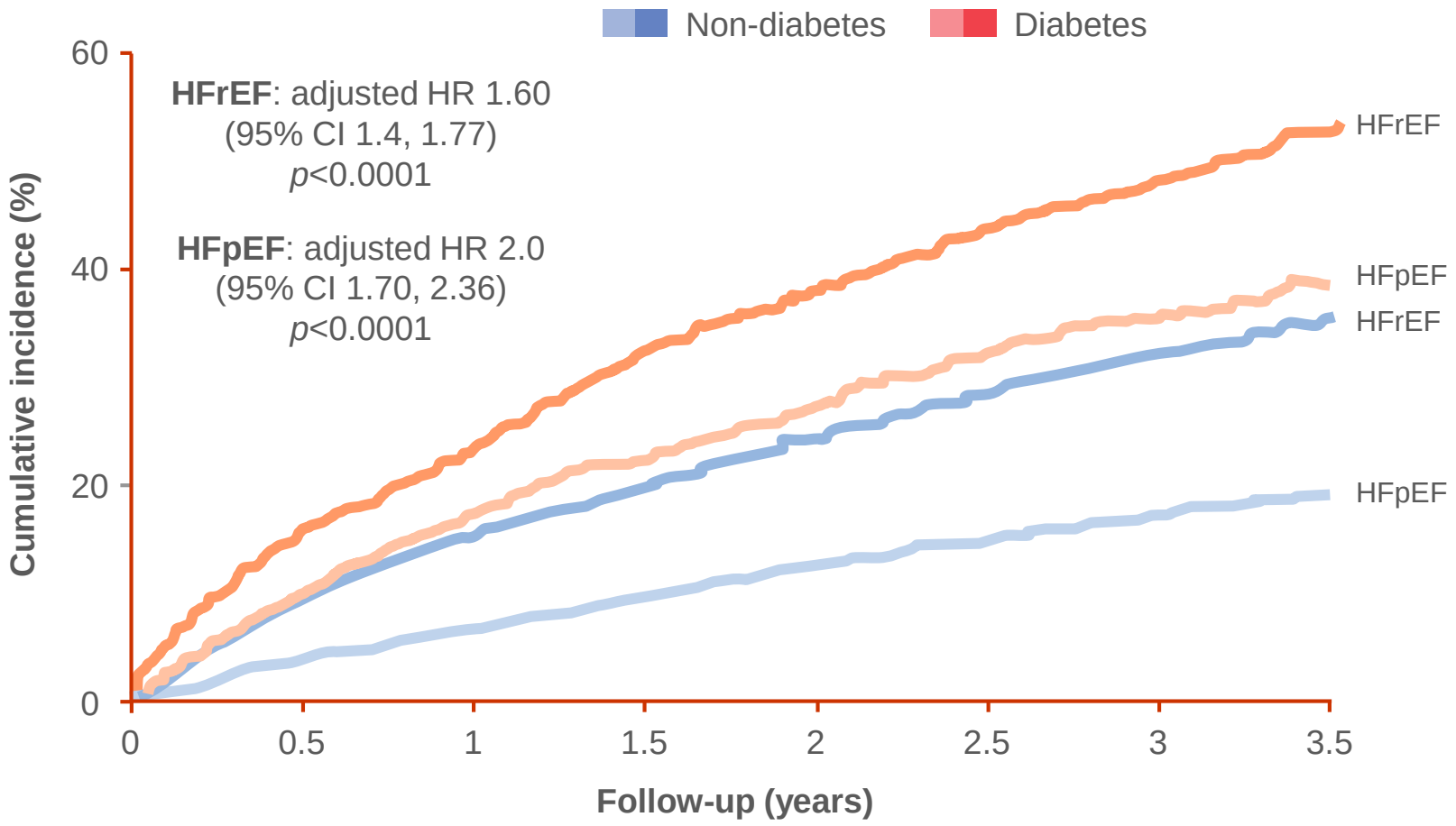
n=3642



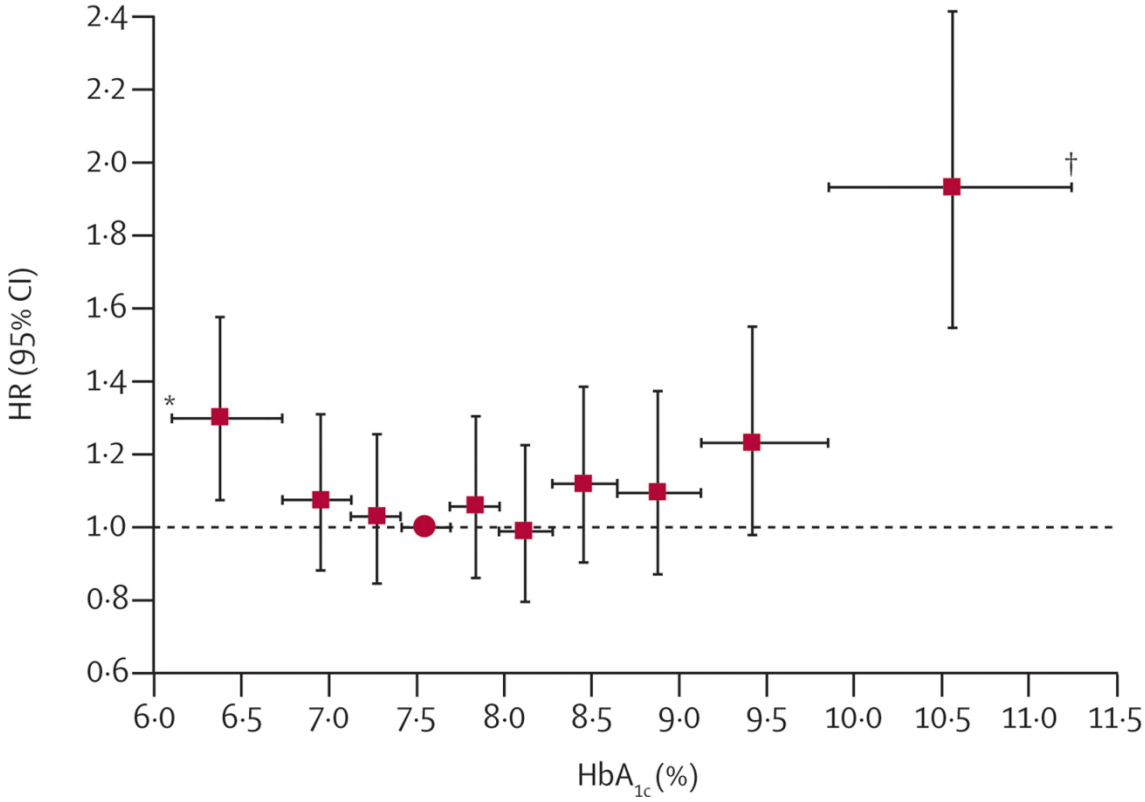
Stratton IM et al. UKPDS 35. *BMJ* 2000;321:405–412

Diabetes und Herzinsuffizienz

- Kardiovaskulärer Tod & HI Hospitalisierung

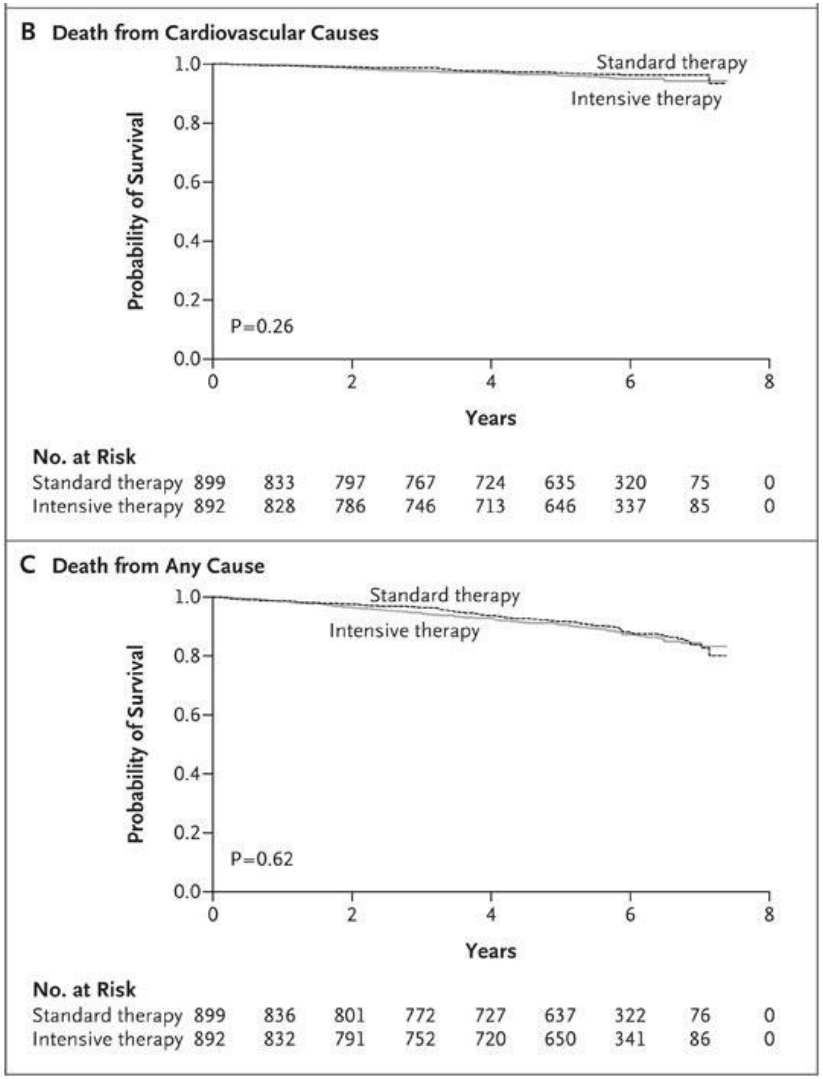


Überleben in Abhängigkeit vom HbA1c



Currie, Lancet, 2010

Intensive (HbA1c <6) vs. Standard- (HbA1c <9) Blutzuckereinstellung ohne Überlebensvorteil DM2

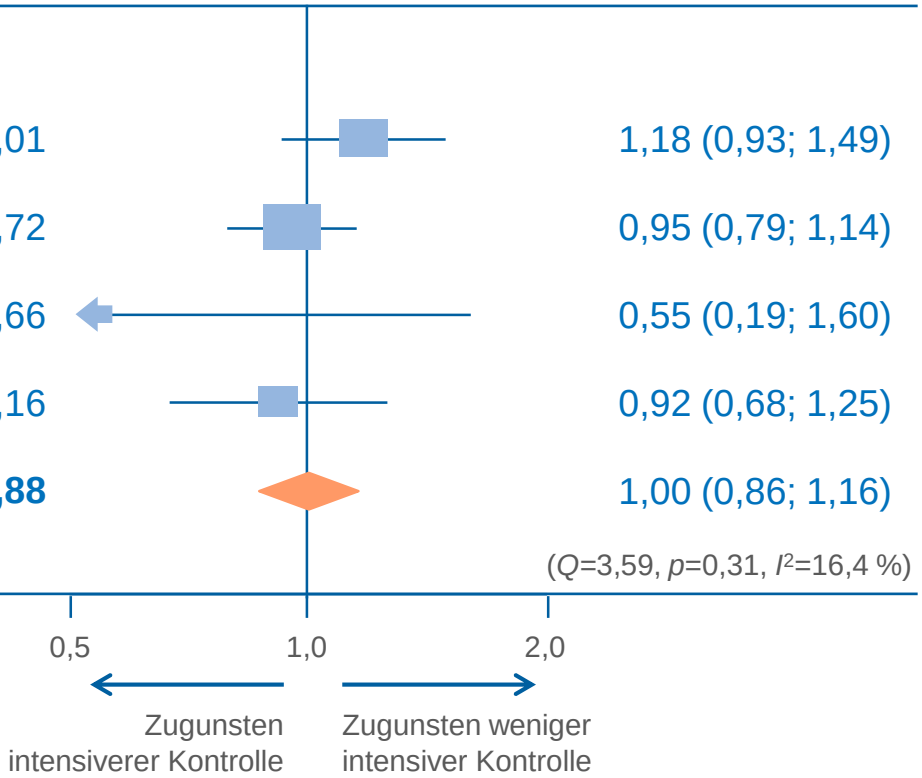


Duckworth W et al. N Engl J Med 2009;360:129-139.

Blutzuckerkontrolle ist nicht entscheiden für Mortalität bei Herzinsuffizienz

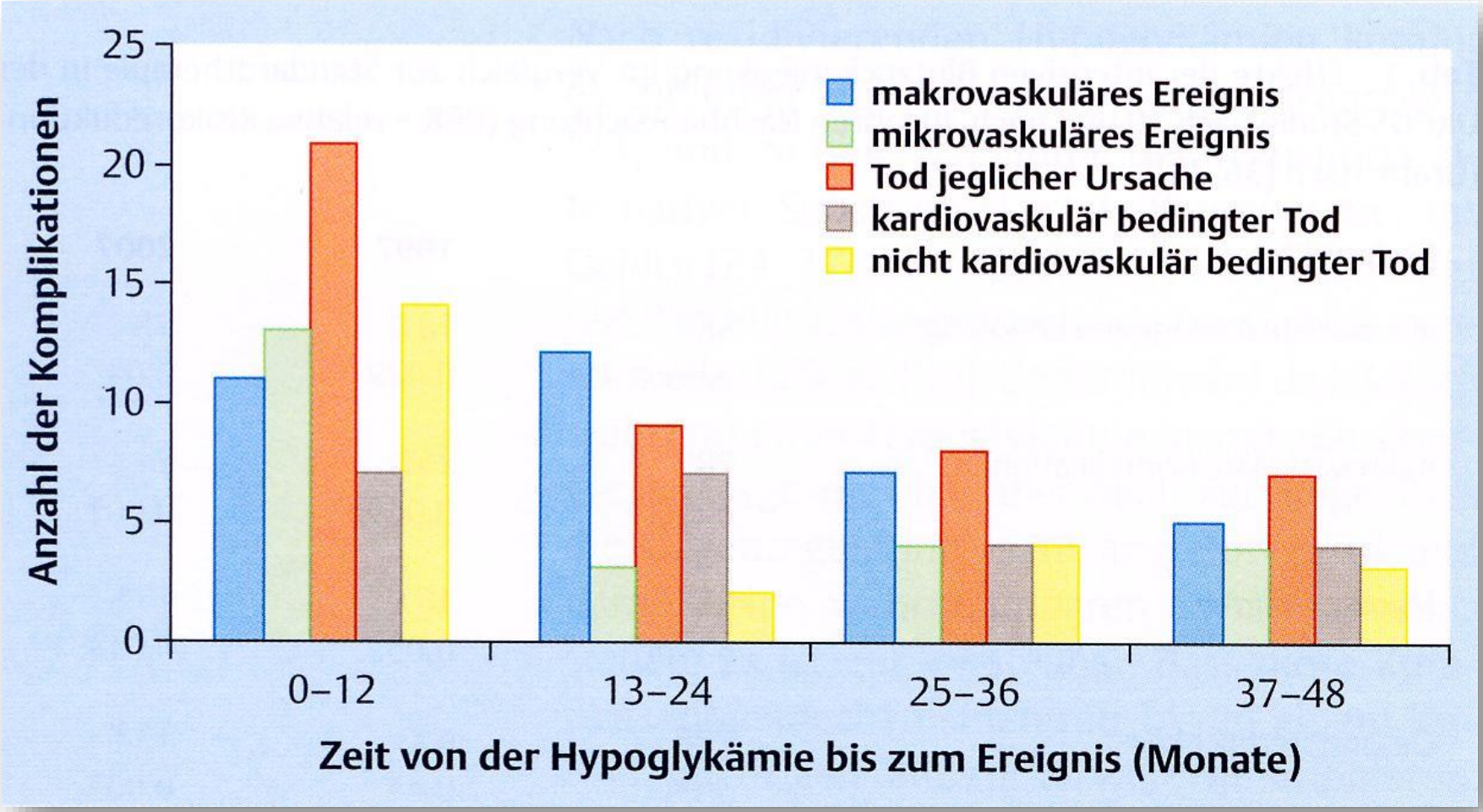
	Anzahl der Ereignisse (Jahresrate, %)		Δ HbA1c (%)	HR (95 %-KI)
	Intensiver	Weniger intensiv		
Hospitalisierung/tödliche HI				
ACCORD	152 (0,90)	124 (0,75)	-1,01	1,18 (0,93; 1,49)
ADVANCE	220 (0,83)	231 (0,88)	-0,72	0,95 (0,79; 1,14)
UKPDS	8 (0,06)	6 (0,11)	-0,66	0,55 (0,19; 1,60)
VADT	79 (1,80)	85 (1,94)	-1,16	0,92 (0,68; 1,25)
Gesamt	**459**	**446**	**-0,88**	1,00 (0,86; 1,16)

(Q=3,59, p=0,31, I^2=16,4 %)



***Gegenüber einer weniger intensiven glykämischen Kontrolle**
HbA1c, glykiertes Hämoglobin; HI, Herzinsuffizienz; HR, Hazard Ratio
Turnbull FM *et al. Diabetologia* 2009;52:2288

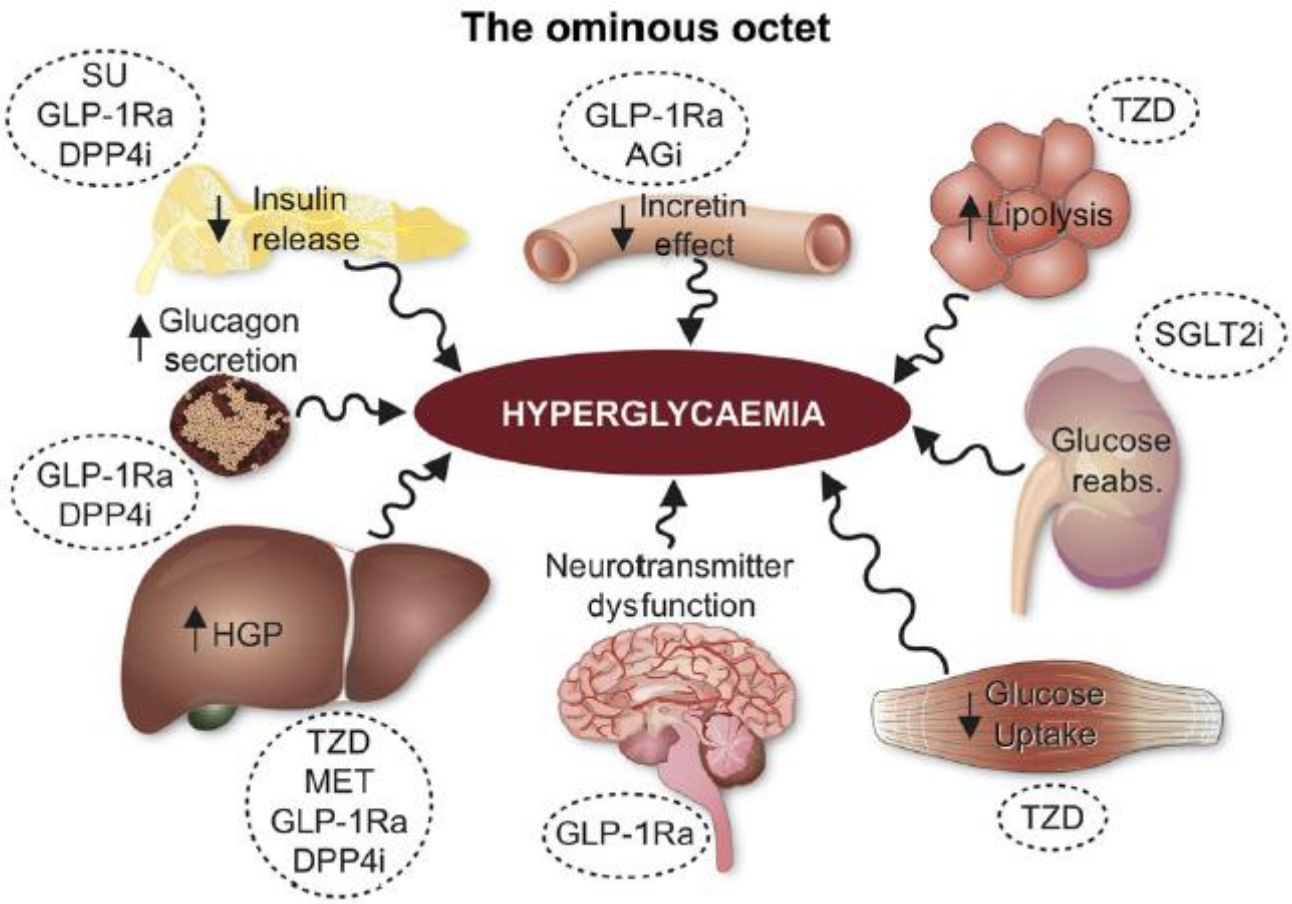
Hypoglykämien haben kardiovaskuläre und zerebrale Auswirkungen



Zoungas S, NEJM 2010 (Advance)

Welche Antidiabetika machen beim kardiovaskulären Patienten Sinn?

Mechanismen Hyperglykämie



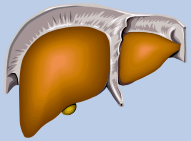
Ferraninni et al, EHJ, 2015

Diabetesbehandlung und kardiale Endpunkte

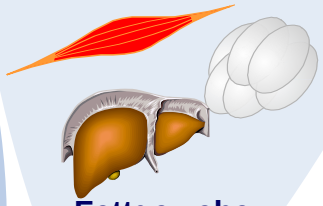
Orale Antidiabetika

Biguanide
Metformin *Glucophage®*

Leber

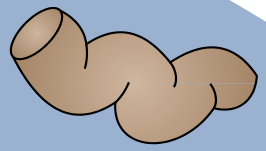


Glitazone
•Pioglitazon *Actos®*
•Rosiglitazon *Avandia®*



Fettgewebe, Muskel, Leber

Darm



α-Glucosidasehemmer
•Acarbose *Glucobay®*

Pankreas

Sulfonylharnstoffe
•Glibenclamid *Euglucon® N*
•Glimepirid *Amaryl®*

Pankreas

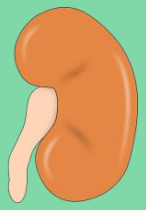
Glinide
•Repaglinid *Novonorm®*
•Nateglinid *Starlix®*

Pankreas

DPP-4 Inhibitoren
• Sitagliptin *Januvia®*
• Vildagliptin *Eucreas®*

GLP-1RA
• Exenatide *Bayetta®*

Niere

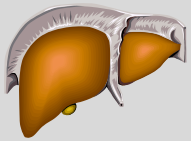


SGLT2i
• Empagliflozin

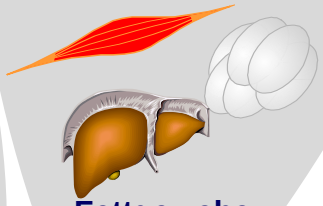
Orale Antidiabetika

Biguanide
Metformin *Glucophage®*

Leber

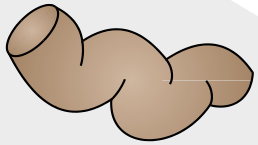


Glitazone
•Pioglitazon *Actos®*
•Rosiglitazon *Avandia®*



Fettgewebe, Muskel, Leber

Darm

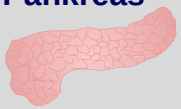


α-Glucosidasehemmer
•Acarbose *Glucobay®*

Pankreas

Sulfonylharnstoffe
•Glibenclamid *Euglucon® N*
•Glimepirid *Amaryl®*

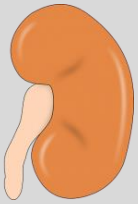
Pankreas



DPP-4 Inhibitoren
• Sitagliptin *Januvia®*
• Vildagliptin *Eucreas®*

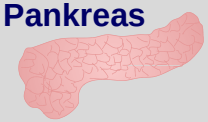
GLP-1RA
• Exenatide *Bayetta®*

Niere



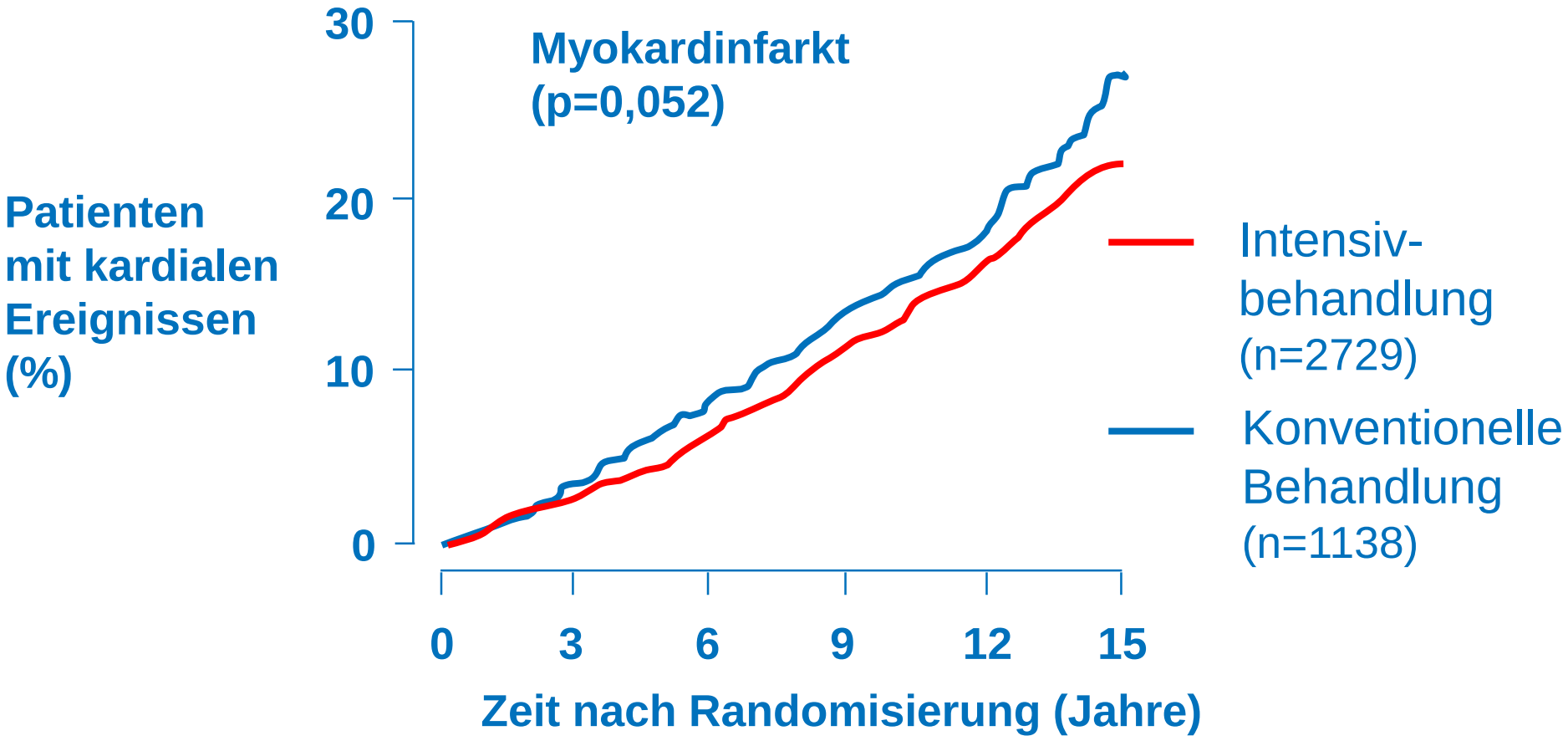
SGLT2i
• Empagliflozin

Pankreas



Glinide
•Repaglinid *Novonorm®*
•Nateglinid *Starlix®*

Intensive Blutzuckerkontrolle durch Sulfonylharnstoffe oder Insulin hat keinen signifikanten Einfluss auf die Inzidenz akuter Myokardinfarkte bei Typ-2-Diabetikern

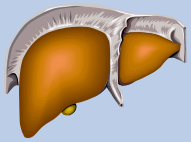


UKPDS-Group, Lancet 1998

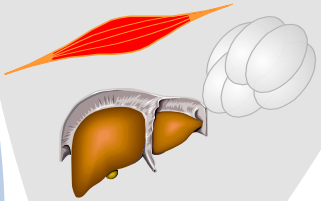
Orale Antidiabetika

Biguanide
Metformin *Glucophage®*

Leber

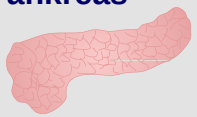


Glitazone
•Pioglitazon *Actos®*
•Rosiglitazon *Avandia®*

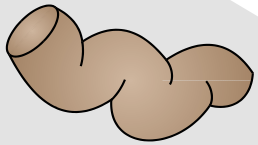


Fettgewebe, Muskel, Leber

Pankreas



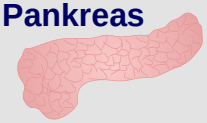
Sulfonylharnstoffe
•Glibenclamid *Euglucon® N*
•Glimepirid *Amaryl®*



Darm

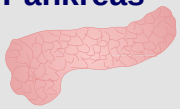
α-Glucosidasehemmer
•Acarbose *Glucobay®*

Pankreas



Glinide
•Repaglinid *Novonorm®*
•Nateglinid *Starlix®*

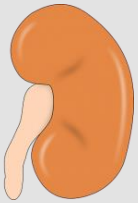
Pankreas



DPP-4 Inhibitoren
• Sitagliptin *Januvia®*
• Vildagliptin *Eucreas®*

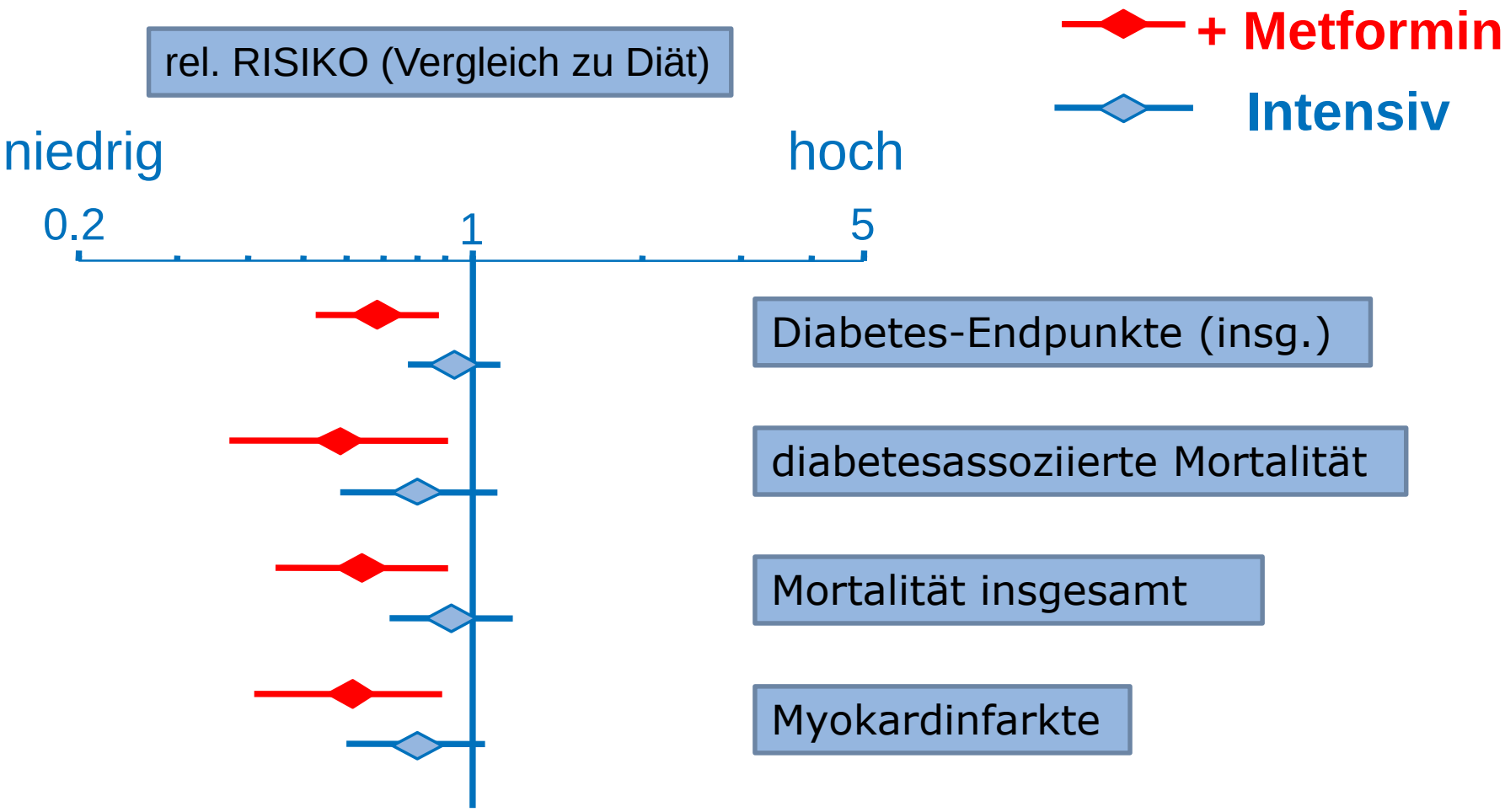
GLP-1RA
• Exenatide *Bayetta®*
•Liraglutide Victoza ®

Niere



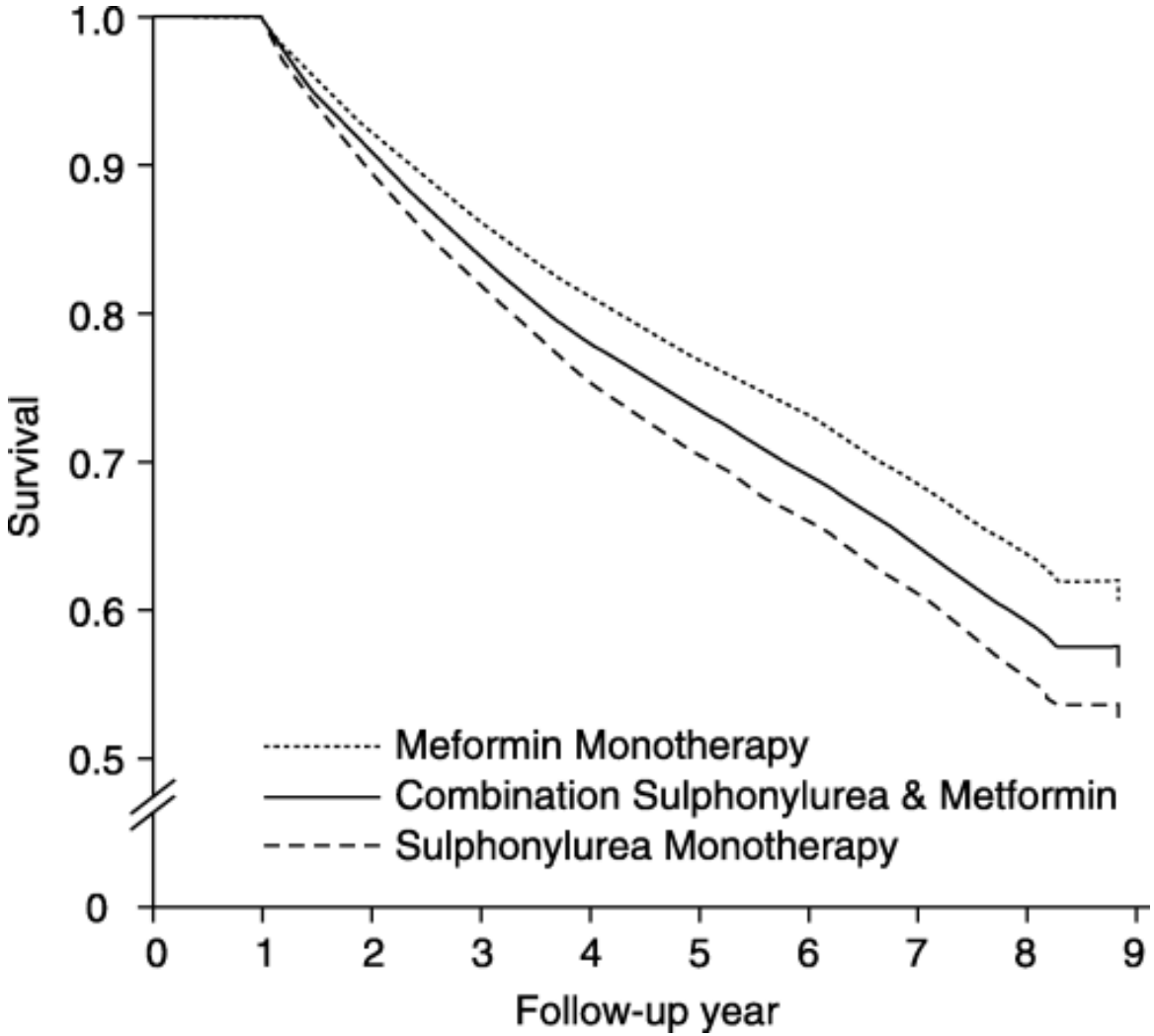
SGLT2i
• Empagliflozin

Metformin reduziert signifikant kardiovaskuläre Ereignisse beim Typ 2 Diabetiker



UKPDS Study Group, Lancet (1998); 352: 854-865

Metformin und Überleben

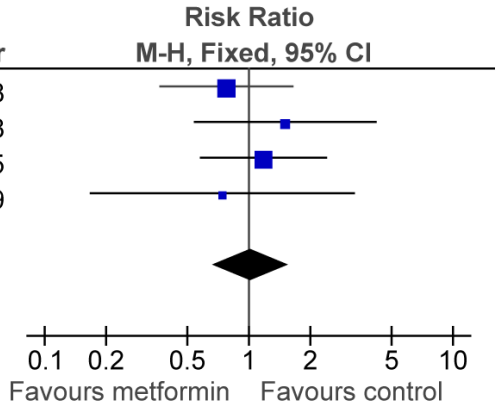


Metaanalyse Metformin bei Herzinsuffizienz

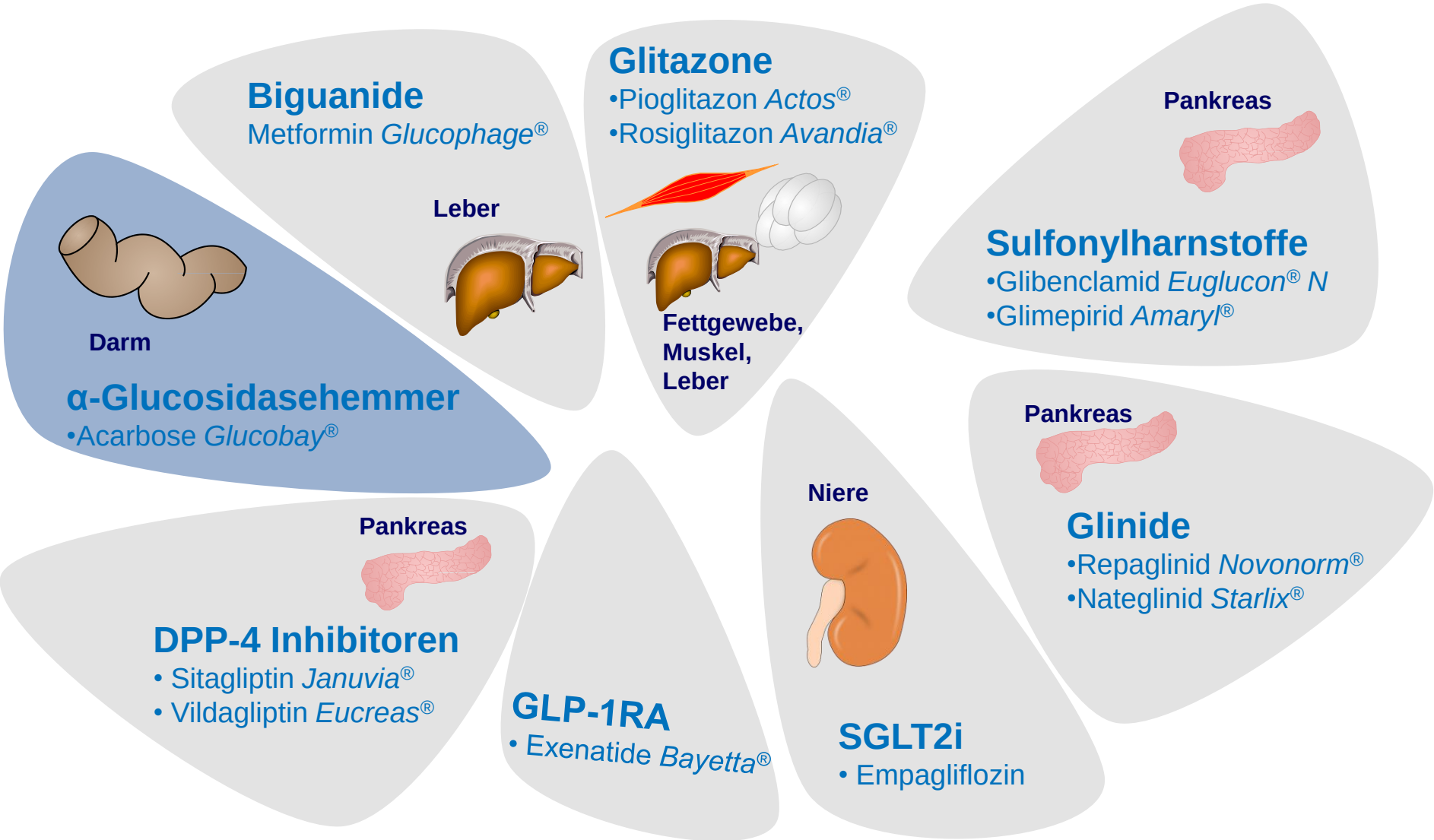
Study or Subgroup	Metformin Events	Metformin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
UKPDS 34a	11	342	17	411	38.3%	0.78 [0.37, 1.64]	1998
UKPDS 34b	9	268	6	269	14.8%	1.51 [0.54, 4.17]	1998
COSMIC	51	7227	9	1505	36.9%	1.18 [0.58, 2.39]	2005
HOME	3	196	4	194	10.0%	0.74 [0.17, 3.27]	2009
Total (95% CI)		**8033**		**2379**	**100.0%**	**1.03 [0.67, 1.59]**	
Total events	74		36				

Heterogeneity: Chi² = 1.41, df = 3 (P = 0.70); I² = 0%

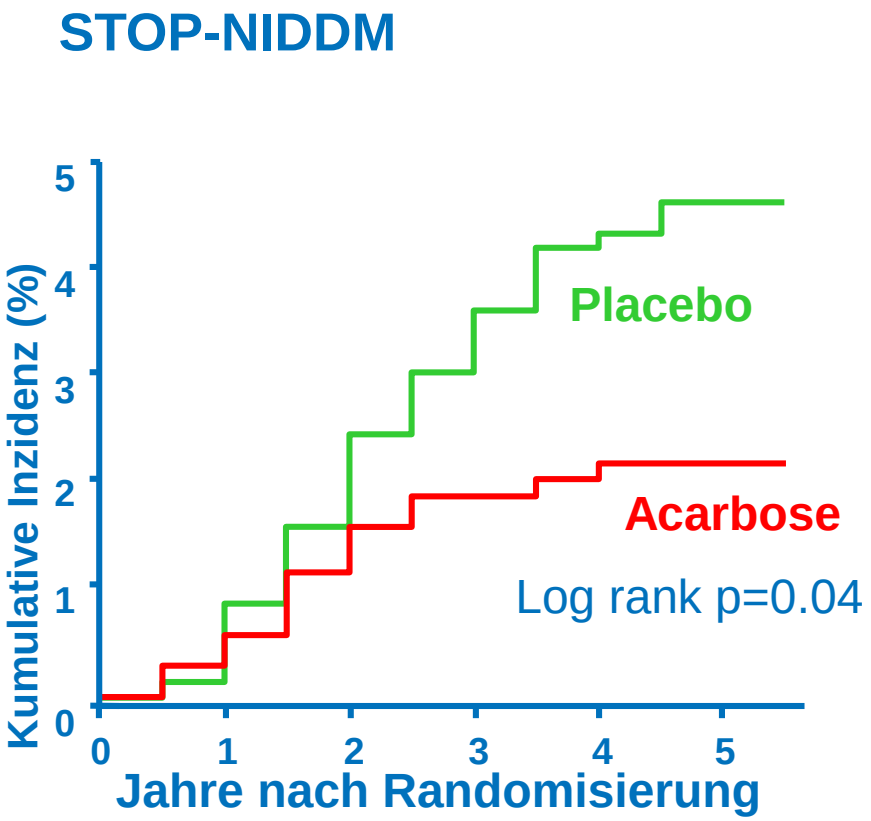
Test for overall effect: Z = 0.14 (P = 0.89)



Orale Antidiabetika



Reduktion kardiovaskulärer Ereignisse bei gestörter Glucosetoleranz durch Acarbose

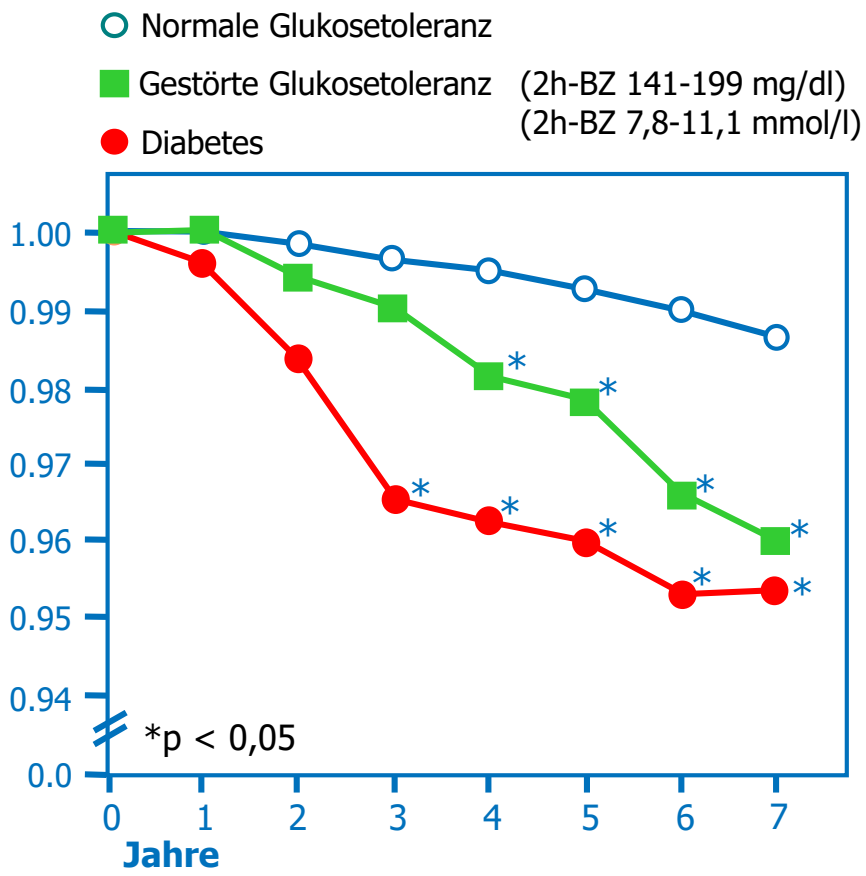


JAMA, 2003

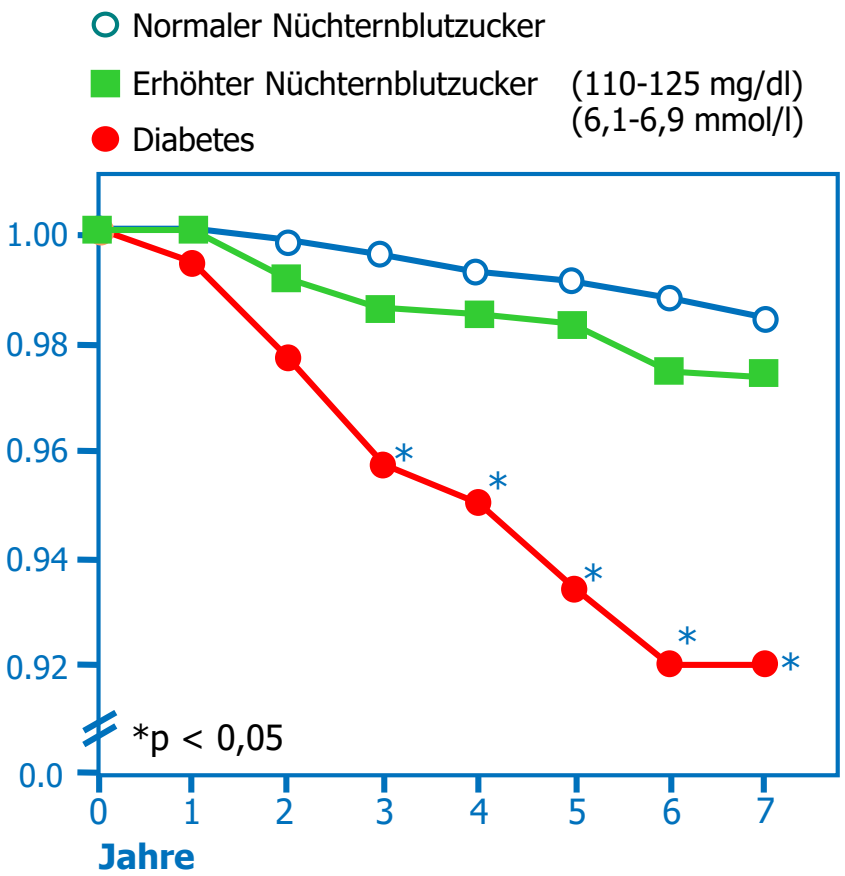
Ein erhöhter Nüchternblutzucker ist kein Risikofaktor für KHK

Mortalität infolge KHK oder Schlaganfall

bei erhöhtem pp-Blutzucker



bei erhöhtem Nüchternblutzucker



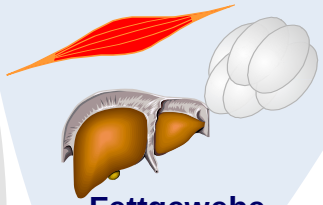
Funagata Diabetes Study (7 Jahre Follow up, n = 2.651)

Orale Antidiabetika

Biguanide
Metformin *Glucophage®*

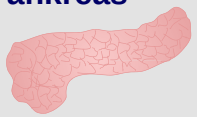
Leber

Glitazone
•Pioglitazon *Actos®*
•Rosiglitazon *Avandia®*

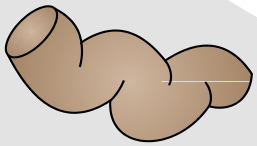


Fettgewebe, Muskel, Leber

Pankreas



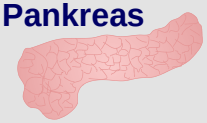
Sulfonylharnstoffe
•Glibenclamid *Euglucon® N*
•Glimepirid *Amaryl®*



Darm

α-Glucosidasehemmer
•Acarbose *Glucobay®*

Pankreas



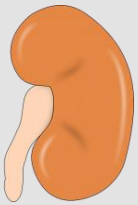
Glinide
•Repaglinid *Novonorm®*
•Nateglinid *Starlix®*

Pankreas

DPP-4 Inhibitoren
• Sitagliptin *Januvia®*
• Vildagliptin *Eucreas®*

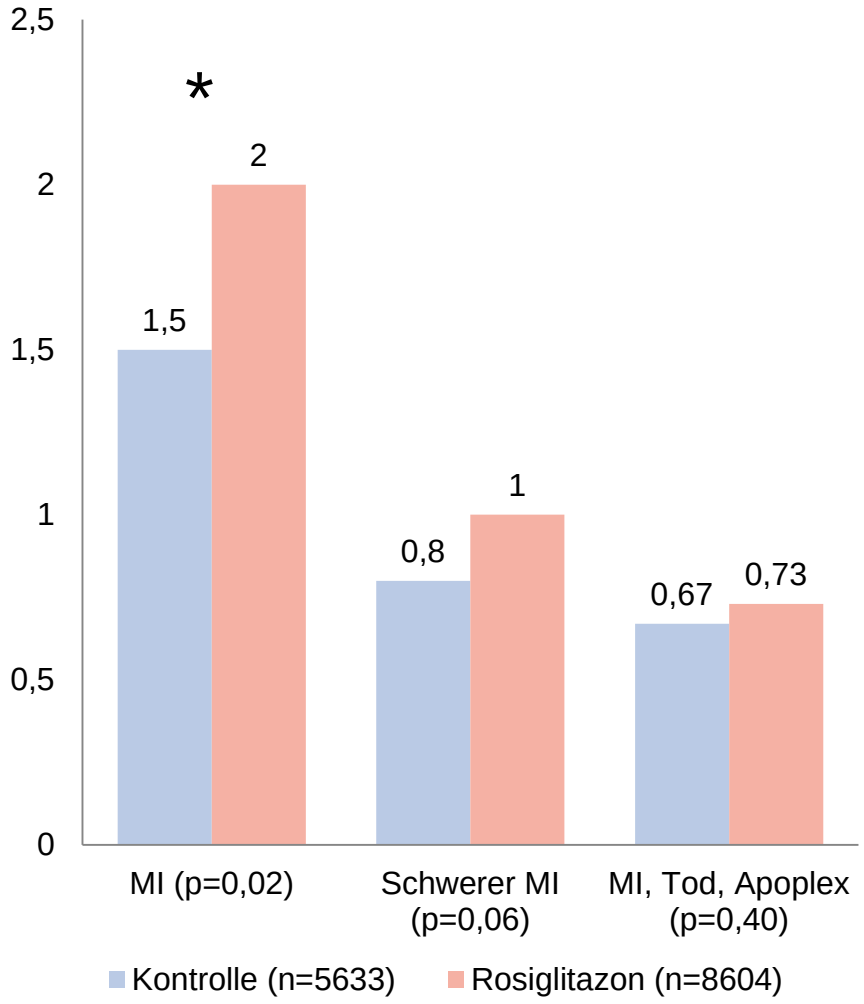
GLP-1RA
• Exenatide *Bayetta®*

Niere



SGLT2i
• Empagliflozin

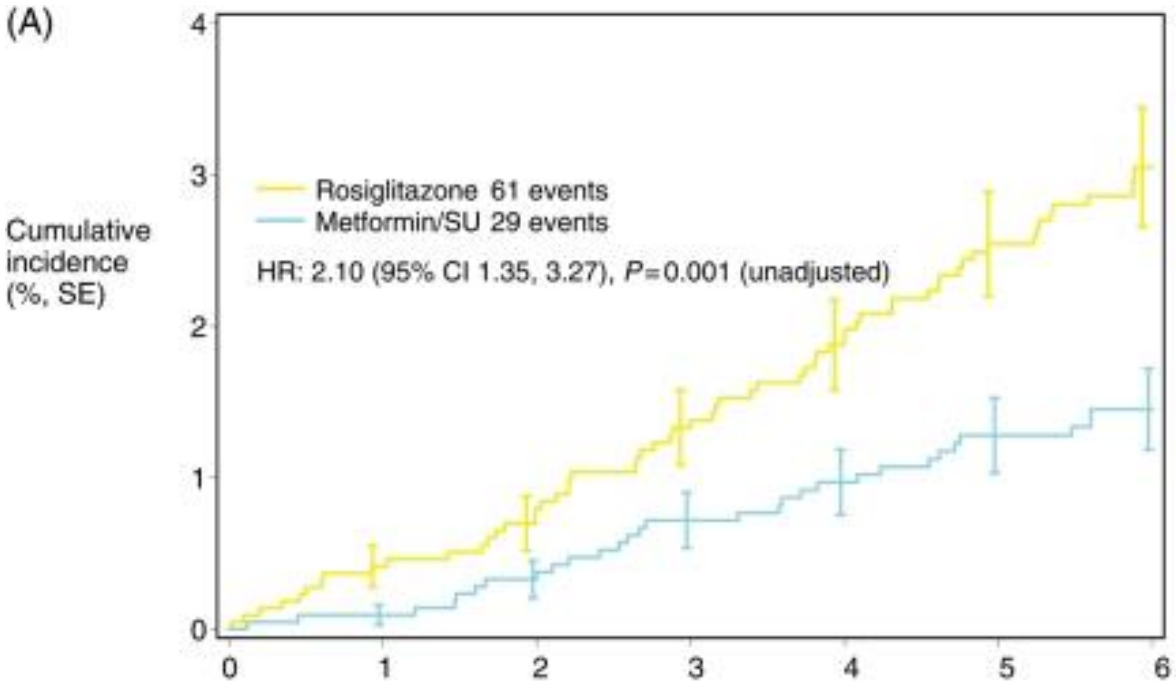
Glitazone und CV-Ereignisse
Rosiglitazon: Metaanalyse



- Rosiglitazon bei Typ 2 Diabetikern ist assoziiert mit gesteigertem Risiko für Myokardinfarkt (MI)
- Seit 2010 ist auf BfArM-Empfehlung der Vertrieb in Deutschland eingestellt.

Rosen, NEJM, 2007

Rosiglitazon und Herzinsuffizienz

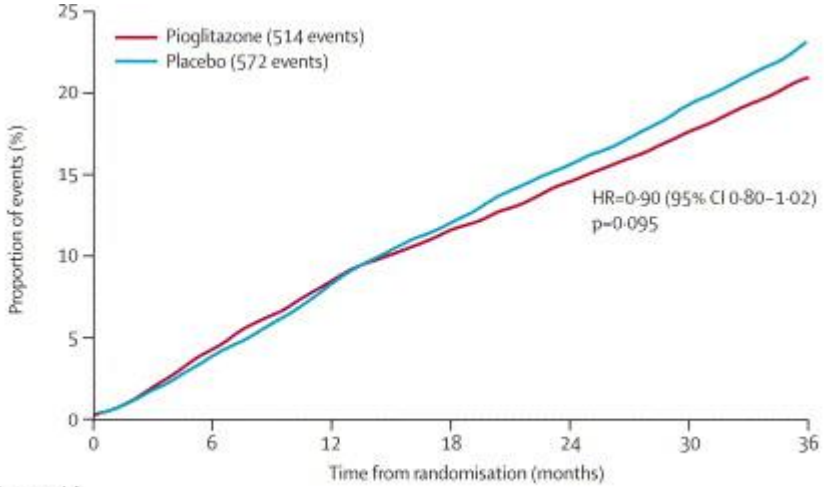


Number at risk							
Rosiglitazone	2220	2130	2069	2008	1944	1884	1017
Metformin/SU	2227	2146	2078	2014	1949	1877	1012

Komajda et al, EHJ, 2010

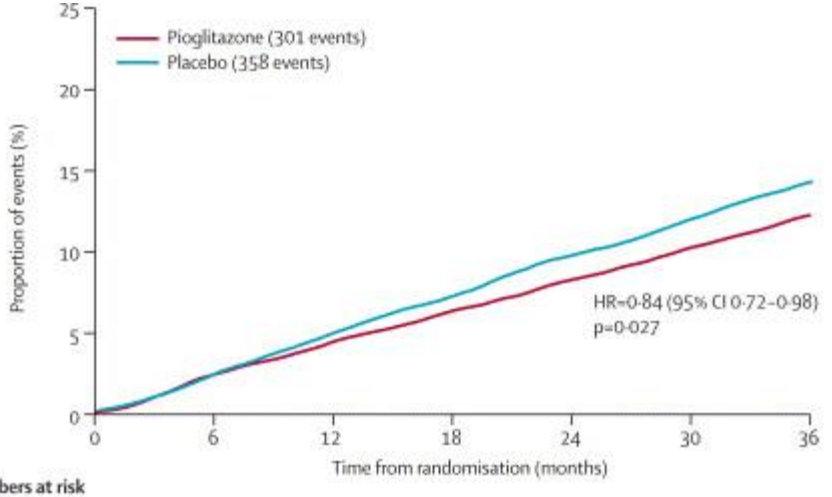
Glitazone und CV-Ereignisse
Pioglitazon: Proactive Studie

Primärer Endpunkt



Numbers at risk						
Pioglitazone	2488	2373	2302	2218	2146	348
Placebo	2530	2413	2317	2215	2122	345

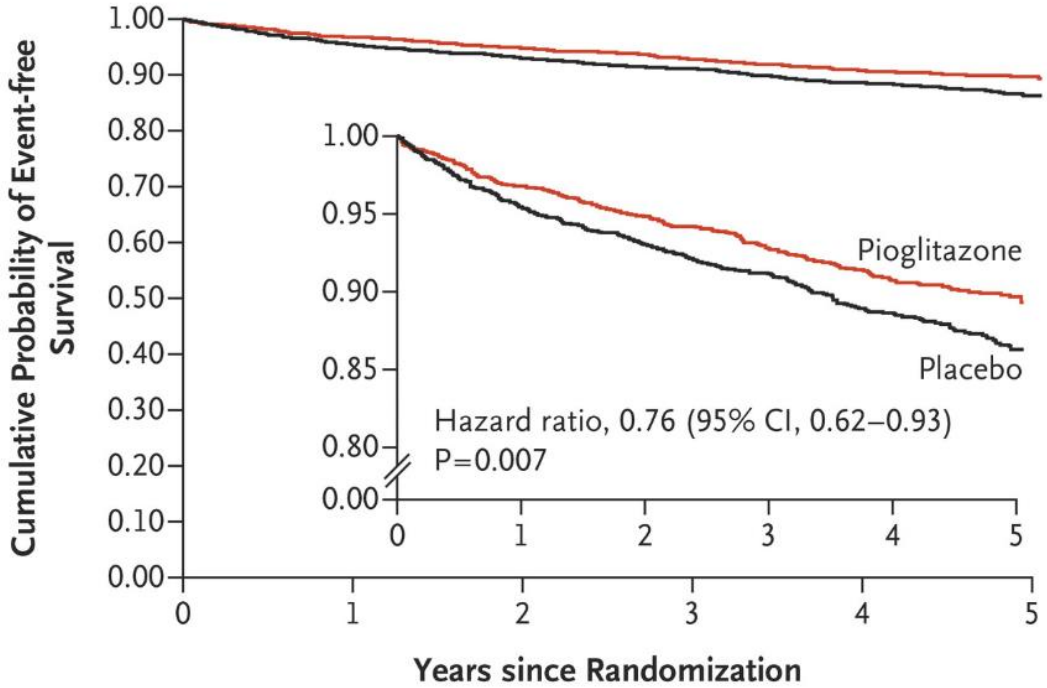
Tod und MI



Numbers at risk						
Pioglitazone	2536	2487	2435	2381	2336	396
Placebo	2566	2504	2442	2371	2315	390

Dormandy et al., Lancet, 2005

Schlaganfall und Pioglitazon bei Patienten mit gestörter Glucosetoleranz, IRIS



No. at Risk						
Pioglitazone	1939	1793	1701	1491	1196	481
Placebo	1937	1778	1690	1476	1182	459

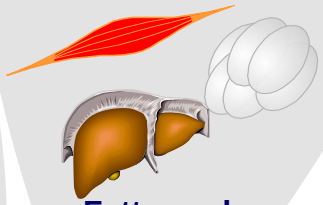
Kernan et al, NEJM, 2016

Orale Antidiabetika

Biguanide
Metformin *Glucophage®*

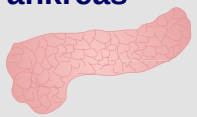
Leber

Glitazone
•Pioglitazon *Actos®*
•Rosiglitazon *Avandia®*

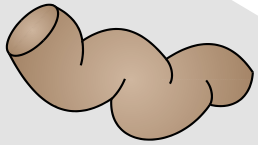


Fettgewebe, Muskel, Leber

Pankreas



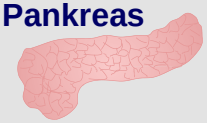
Sulfonylharnstoffe
•Glibenclamid *Euglucon® N*
•Glimepirid *Amaryl®*



Darm

α-Glucosidasehemmer
•Acarbose *Glucobay®*

Pankreas



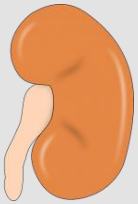
Glinide
•Repaglinid *Novonorm®*
•Nateglinid *Starlix®*

Pankreas

DPP-4 Inhibitoren
• Sitagliptin *Januvia®*
• Vildagliptin *Eucreas®*

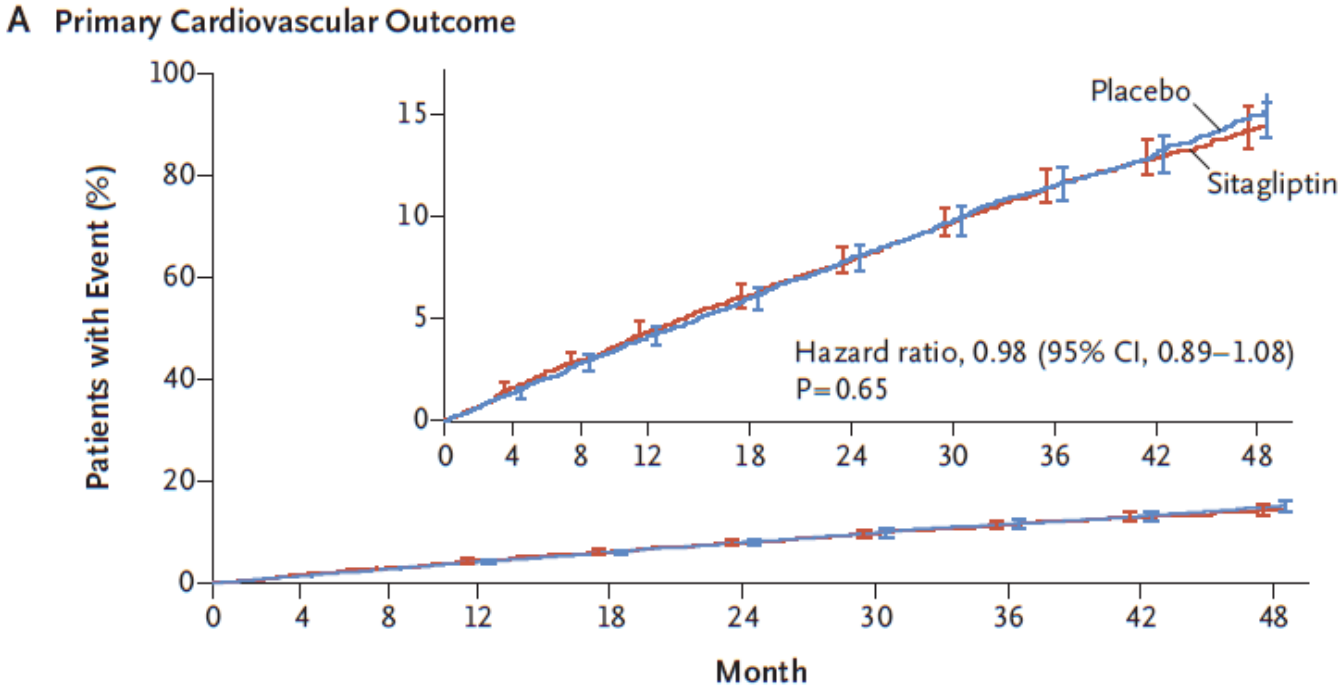
GLP-1RA
• Exenatide *Bayetta®*

Niere



SGLT2i
• Empagliflozin

TECOS-Studie



No. at Risk

Sitagliptin	7332	7131	6937	6777	6579	6386	4525	3346	2058	1248
Placebo	7339	7146	6902	6751	6512	6292	4411	3272	2034	1234

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

Herzinsuffizienz und Gliptin

Study	Antidiabetic drug	Comparator	Results
DPP4 inhibitors			
SAVOR-TIMI 53[16,17]	Saxagliptin	Placebo	Increase in HF hospitalization
EXAMINE[19,184]	Alogliptin	Placebo	No statistically significant increase in HF hospitalization
TECOS[18,185]	Sitagliptin	Placebo	No effect on HF hospitalization

Herzinsuffizienz ↔ bei DPP-4-Inhibitoren

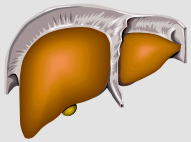
Table 3. Association between Treatment with Incretin-based Drugs versus Oral Antidiabetic-Drug Combinations and Hospitalization for Heart Failure among Patients with a History of Heart Failure.*

Treatment†	Hospitalization for Heart Failure		Adjusted Hazard Ratio (95% CI)‡	I^2§
	Case Patients (N=6536)	Controls (N=100,480)		
	no. (%)			%
Two or more oral antidiabetic drugs	684 (10.5)	10,608 (10.6)	1.00 (reference)	
Incretin-based drugs	940 (14.4)	12,394 (12.3)	0.86 (0.62–1.19)	66.0
DPP-4 inhibitors	905 (13.8)	11,651 (11.6)	0.87 (0.63–1.21)	66.3
GLP-1 analogues	35 (0.5)	743 (0.7)	0.75 (0.22–2.51)	44.5
Duration of treatment with incretin-based drugs				
<365 days	664 (10.2)	9,061 (9.0)	0.68 (0.43–1.06)	81.1
365–729 days	172 (2.6)	2,012 (2.0)	1.09 (0.86–1.37)	6.5
≥730 days	103 (1.6)	1,312 (1.3)	0.95 (0.73–1.22)	0.0

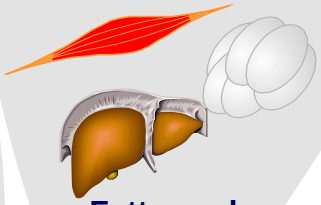
Orale Antidiabetika

Biguanide
Metformin *Glucophage®*

Leber

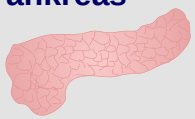


Glitazone
•Pioglitazon *Actos®*
•Rosiglitazon *Avandia®*

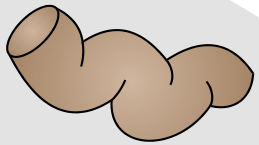


Fettgewebe, Muskel, Leber

Pankreas



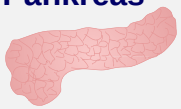
Sulfonylharnstoffe
•Glibenclamid *Euglucon® N*
•Glimepirid *Amaryl®*



Darm

α-Glucosidasehemmer
•Acarbose *Glucobay®*

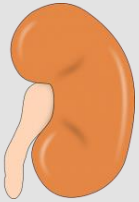
Pankreas



DPP-4 Inhibitoren
• Sitagliptin *Januvia®*
• Vildagliptin *Eucreas®*

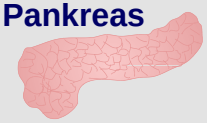
GLP-1RA
• Exenatide *Bayetta®*
•Liraglutide Victoza ®

Niere



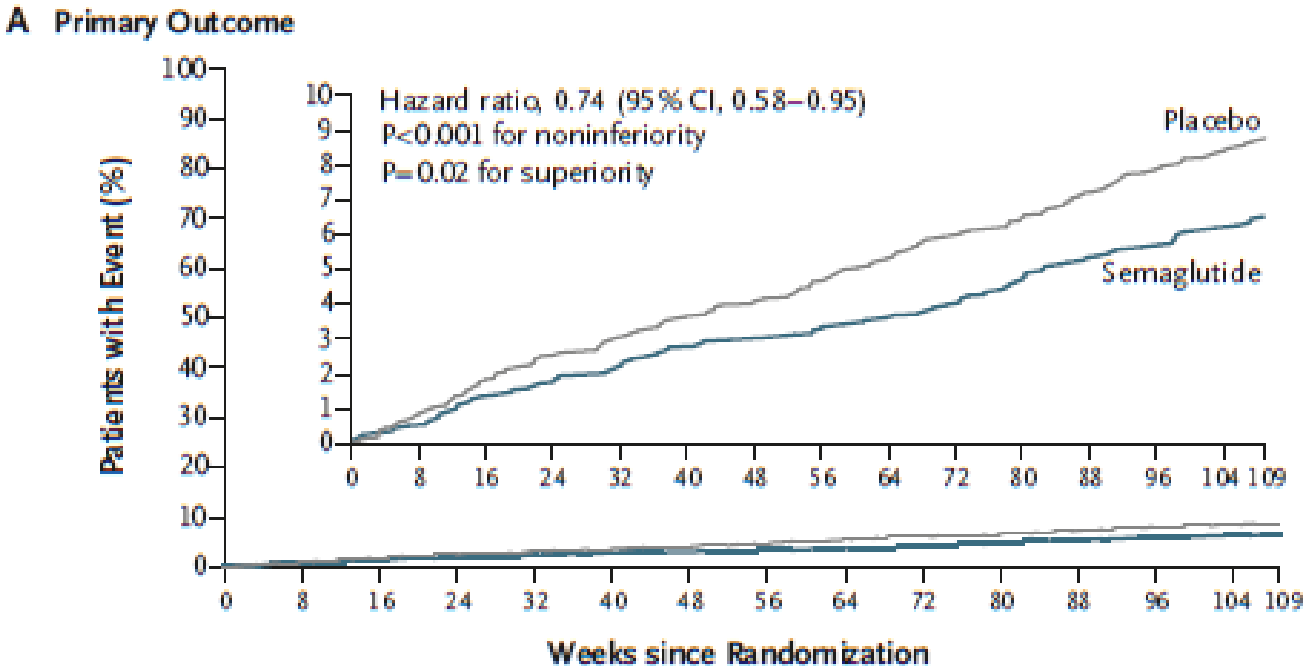
SGLT2i
• Empagliflozin

Pankreas



Glinide
•Repaglinid *Novonorm®*
•Nateglinid *Starlix®*

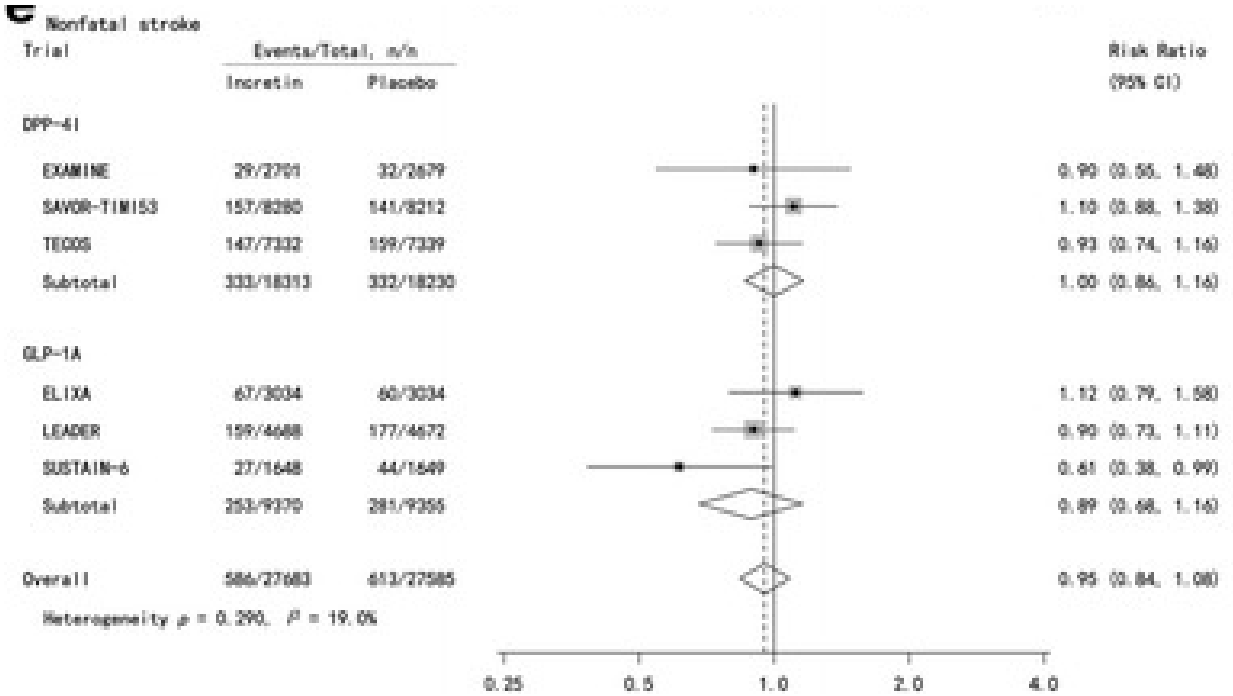
SUSTAIN-6: Semaglutide & MI/ Schlaganfall/ Tod



No. at Risk							
Placebo	1649	1616	1586	1567	1534	1508	1479
Semaglutide	1648	1619	1601	1584	1568	1543	1524

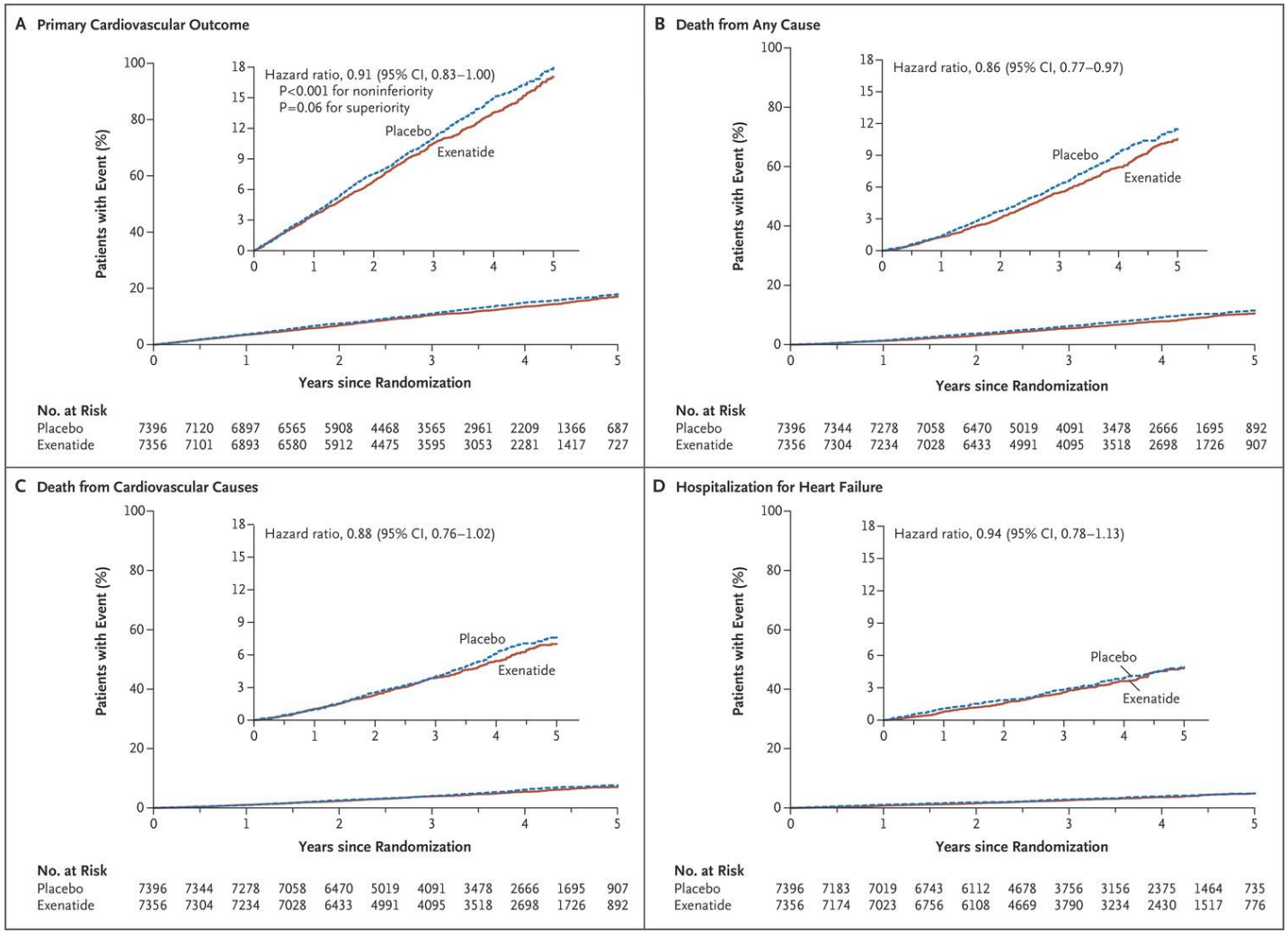
Marso et al, NEJM, 2016

Herzinsuffizienzrisiko



Zhang et al, CV Diabetol, 2017

Keine Unterschiede bei Exenatide

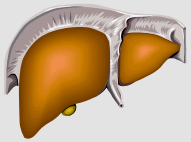


Holmann et al, NEJM, 2017

Orale Antidiabetika

Biguanide
Metformin *Glucophage®*

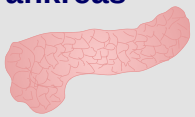
Leber



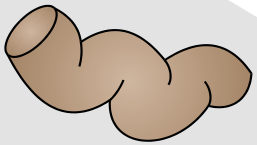
Glitazone
•Pioglitazon *Actos®*
•Rosiglitazon *Avandia®*

Fettgewebe, Muskel, Leber

Pankreas



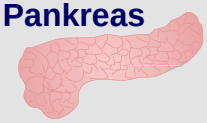
Sulfonylharnstoffe
•Glibenclamid *Euglucon® N*
•Glimepirid *Amaryl®*



Darm

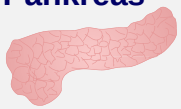
α-Glucosidasehemmer
•Acarbose *Glucobay®*

Pankreas



Glinide
•Repaglinid *Novonorm®*
•Nateglinid *Starlix®*

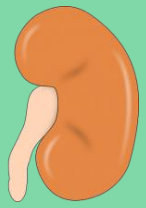
Pankreas



DPP-4 Inhibitoren
• Sitagliptin *Januvia®*
• Vildagliptin *Eucreas®*

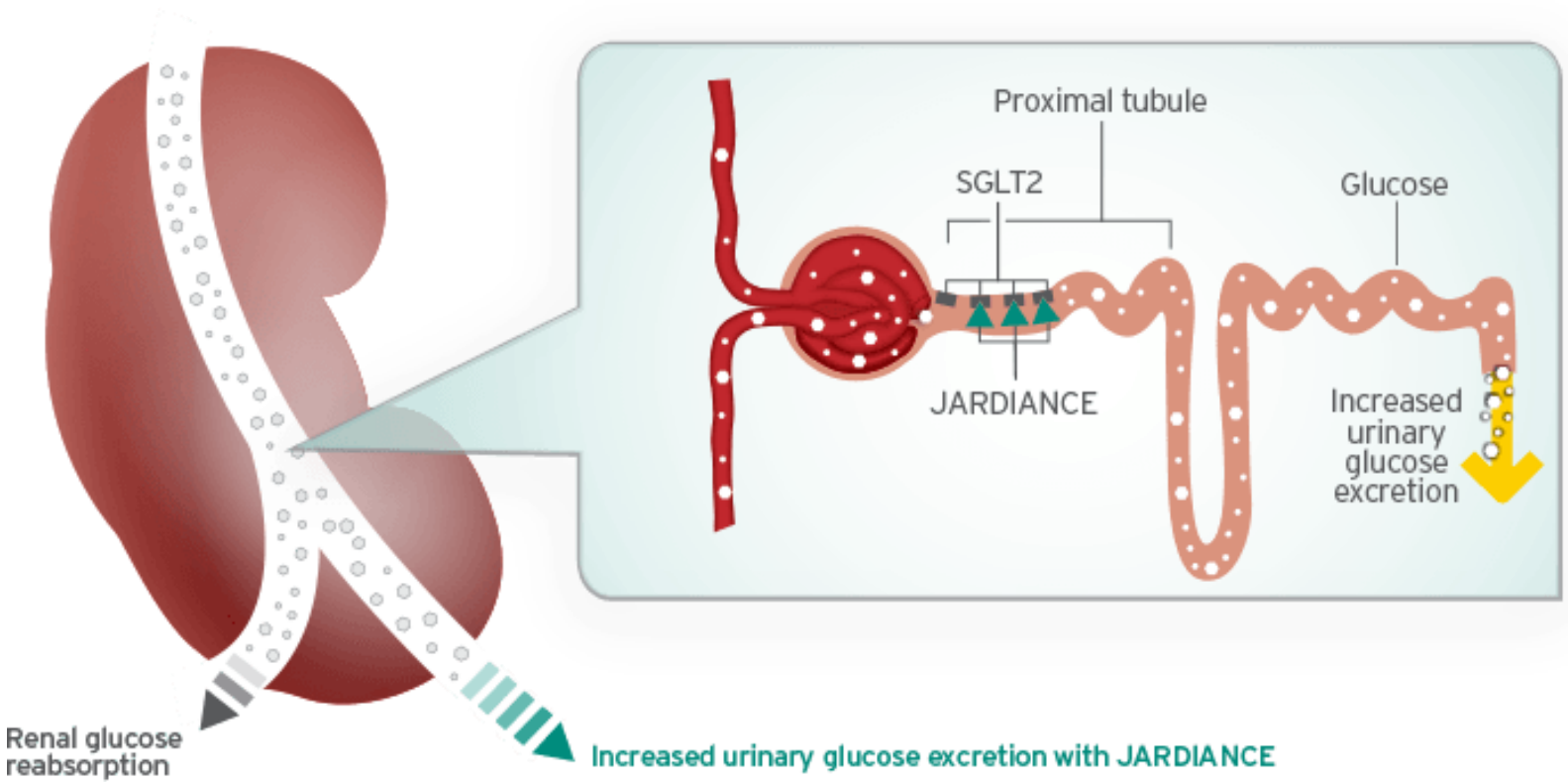
GLP-1RA
• Exenatide *Bayetta®*
•Liraglutide Victoza ®

Niere

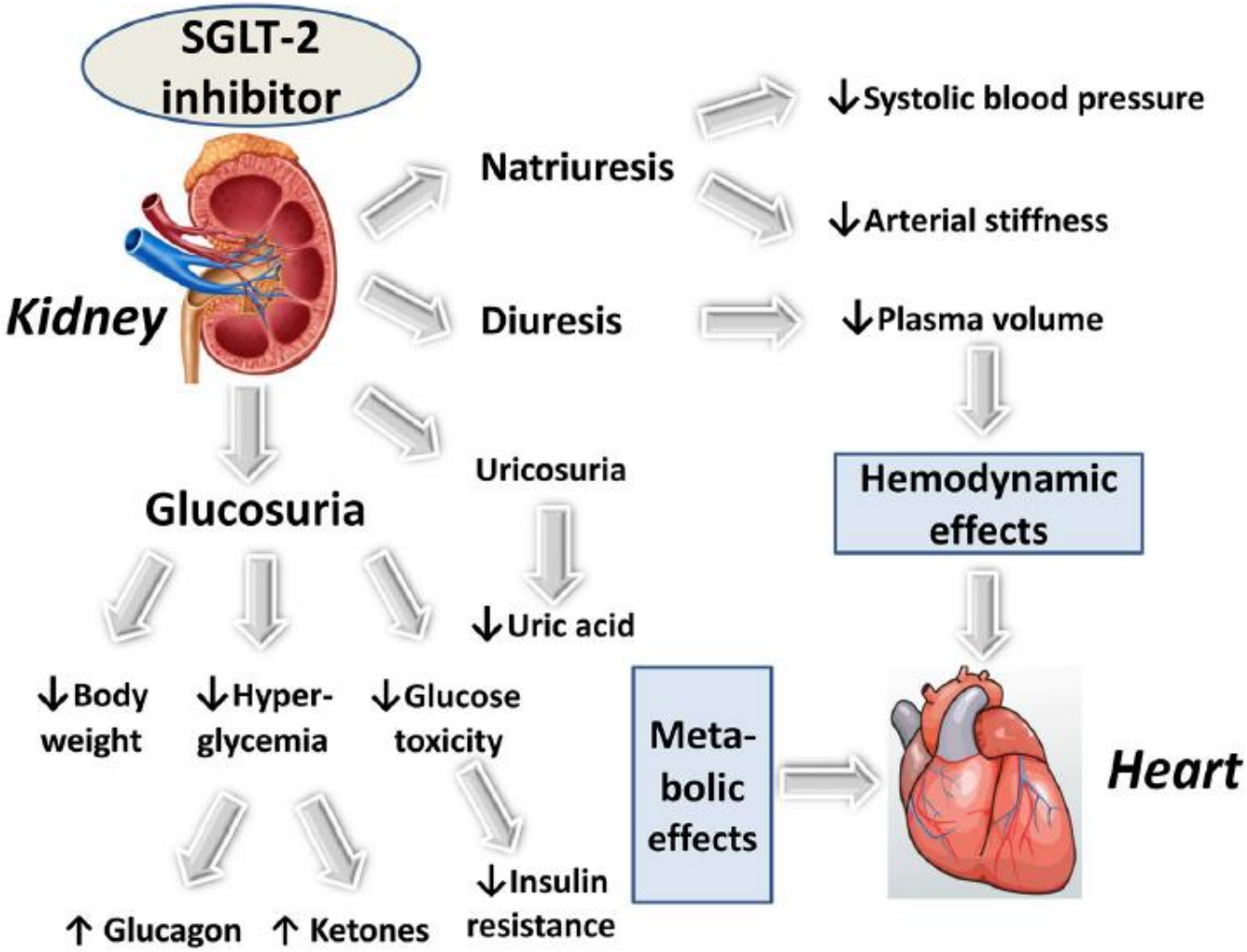


SGLT2i
• Empagliflozin

Empagliflozin; Handelsname Jardiance

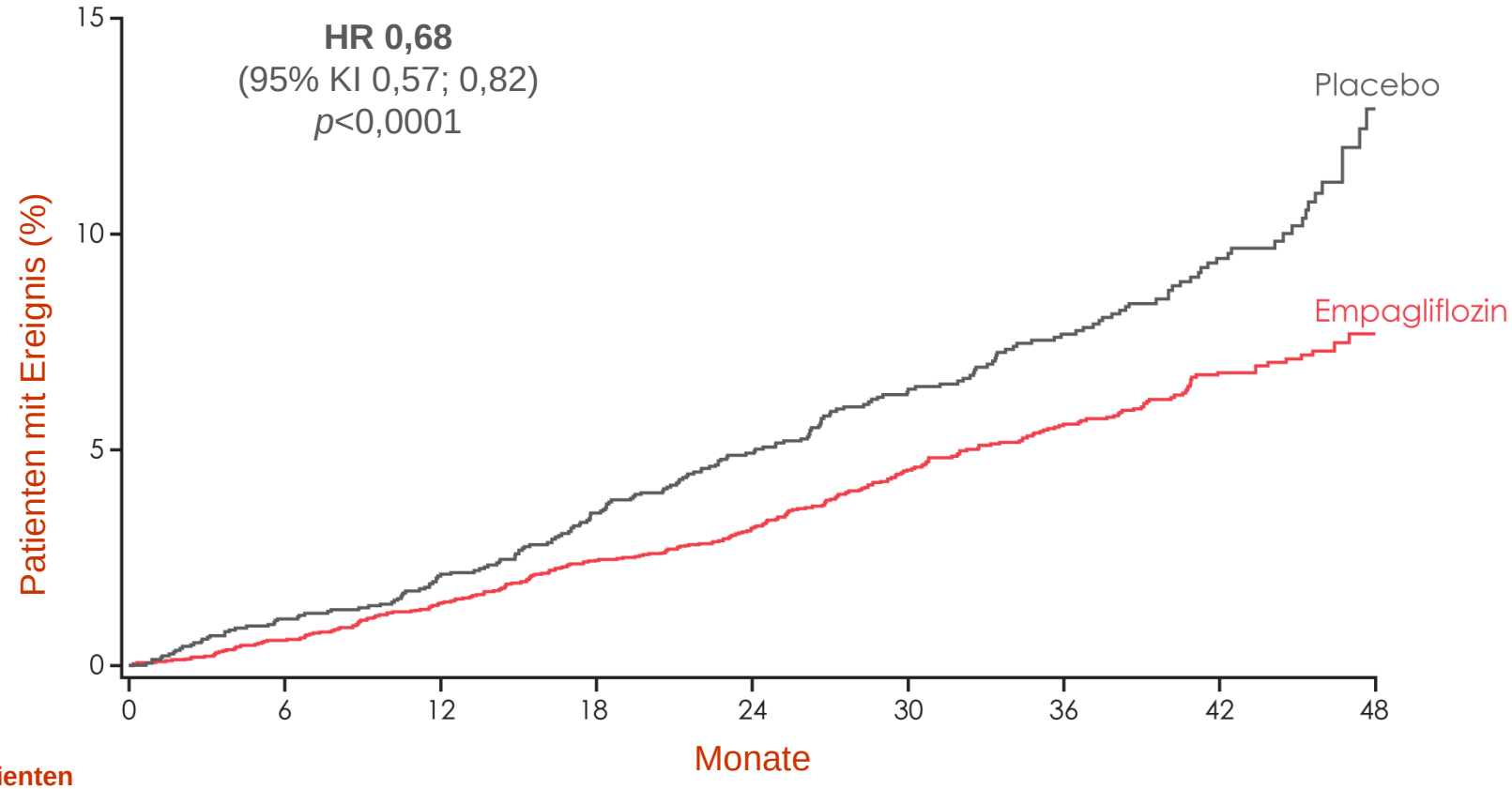


SGLT-2 Inhibition und Herz



Scheen, Circ Res, 2018

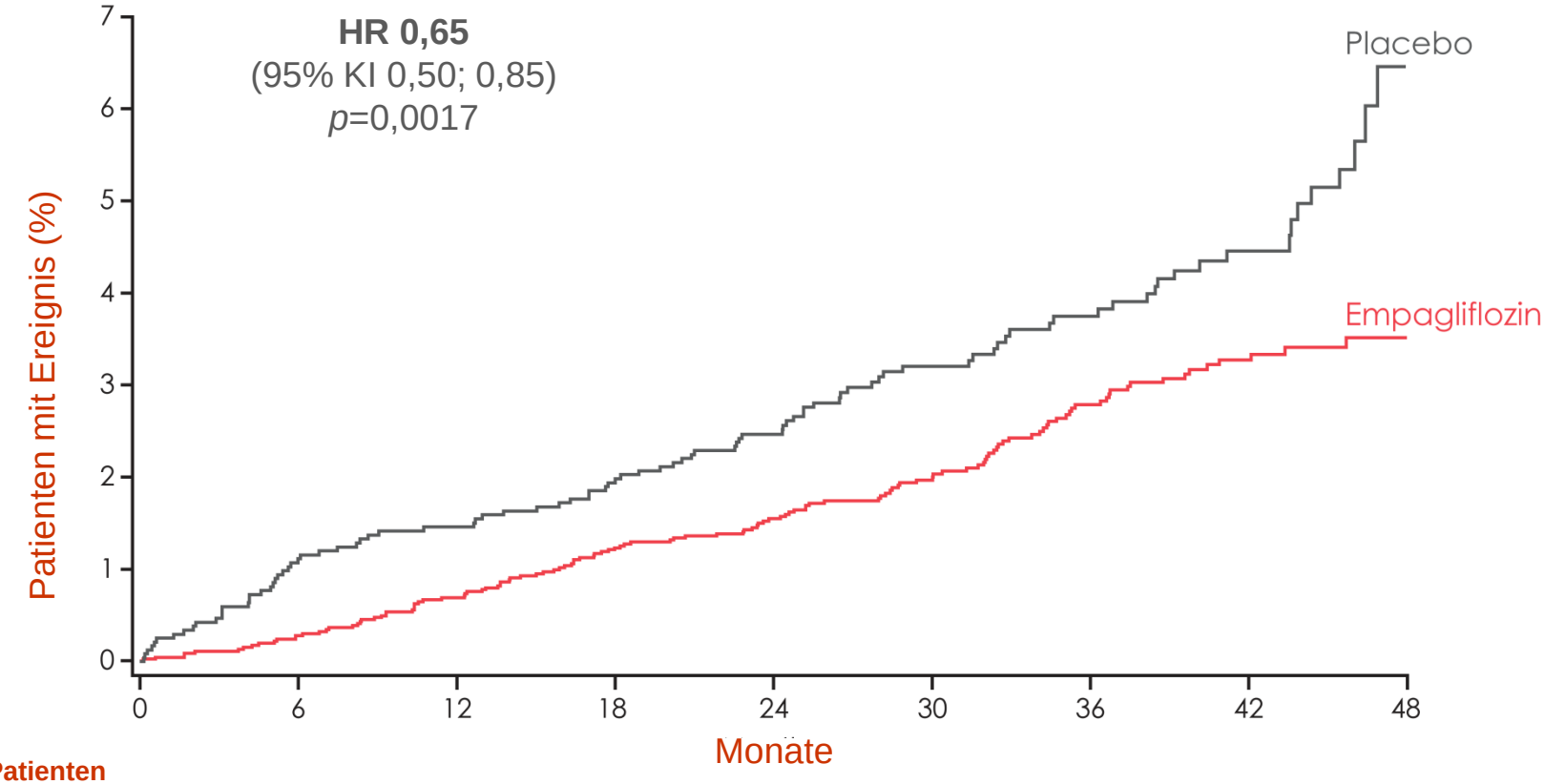
Gesamtmortalität



Anzahl Patienten

Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

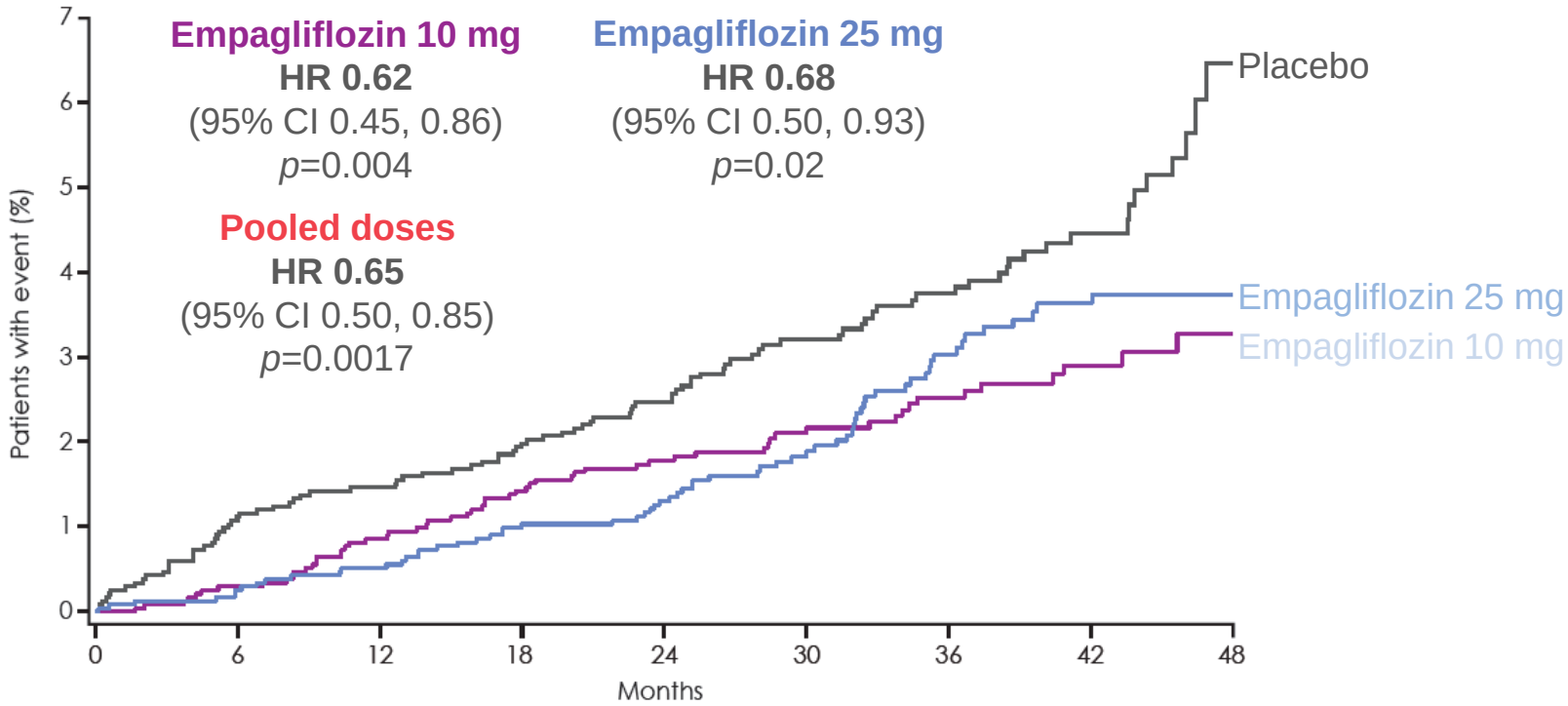
Hospitalisierung aufgrund von Herzinsuffizienz



Anzahl Patienten

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

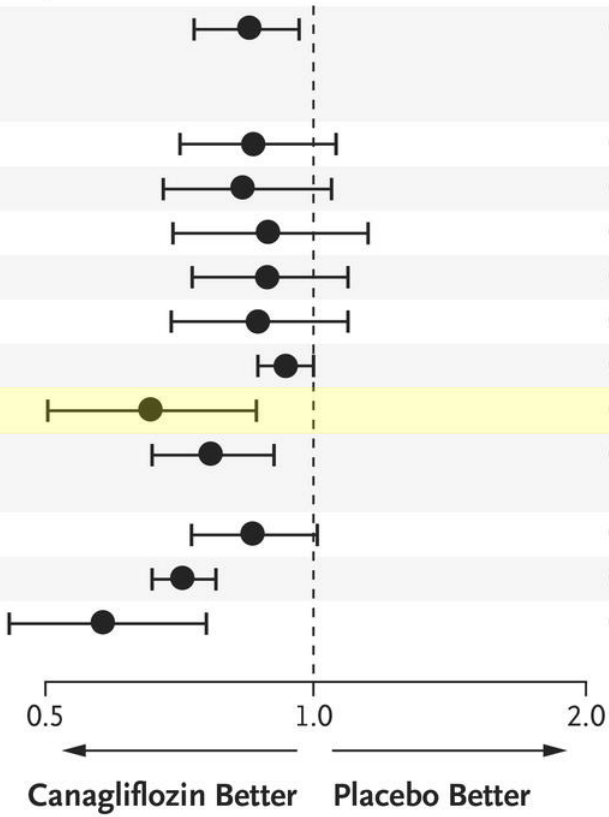
Hospitalisierung nicht Dosis-abhängig



No. of patients									
Empagliflozin 10 mg	2345	2306	2256	2204	1981	1473	1240	804	188
Empagliflozin 25 mg	2342	2308	2267	2223	2007	1477	1247	830	207
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

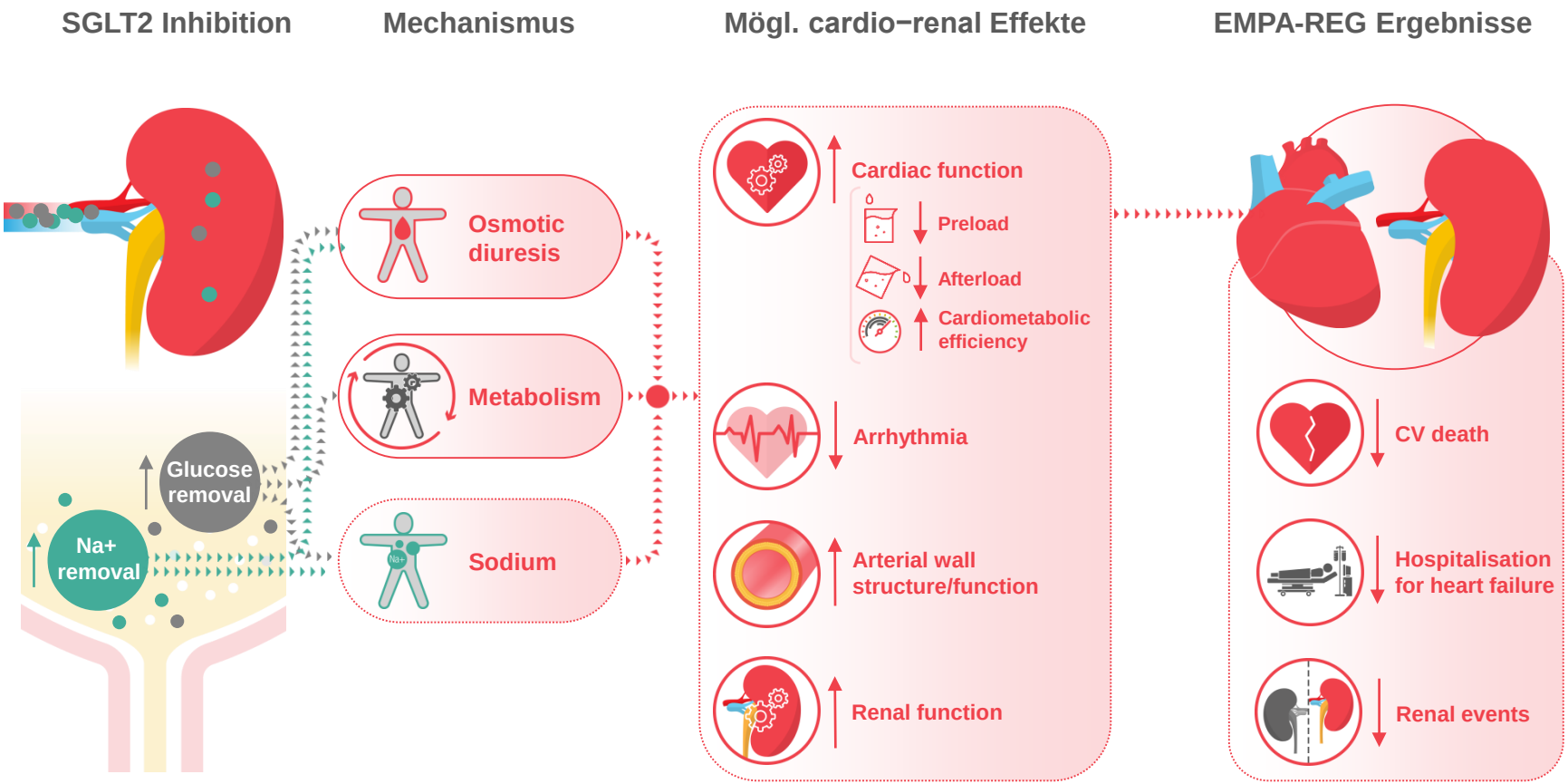
Canvas

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)

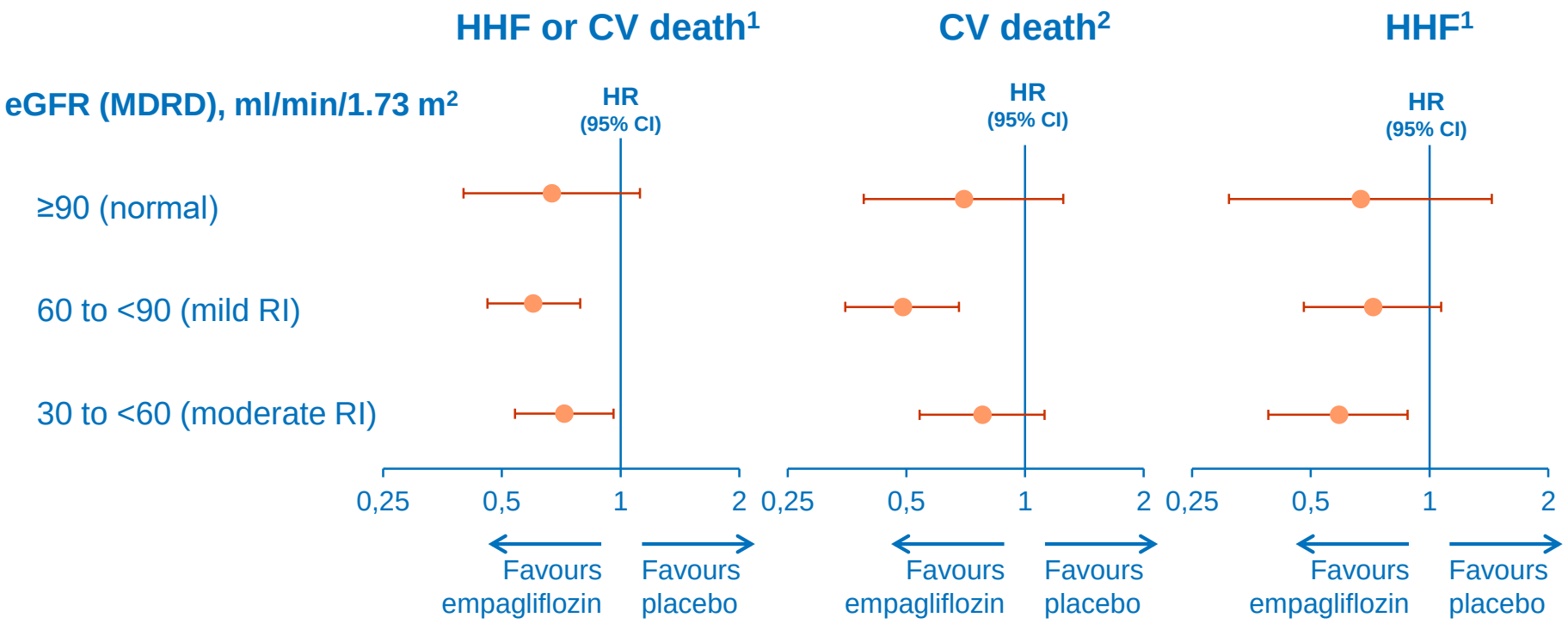


Neal et al, NEJM, 2017

Potentielle Mechanismen der Protektion



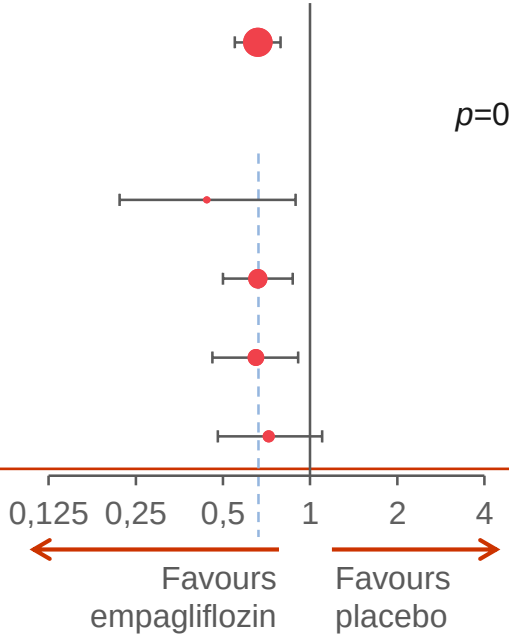
Renale Funktion hatte keine Einfluss auf Endpunkte bei EMPA-REG OUTCOME



1. Fitchett D *et al. Eur Heart J* 2016;37:1526; 2. Zinman B *et al. N Engl J Med* 2015;373:2117; 3: Data on file

HbA1c hatte keine Einfluss auf Risikoreduktion

	n with event/analysed (%)				Treatment by subgroup interaction
	Empagliflozin	Placebo	HR (95% CI)	HR (95% CI)	
All patients	265/4687 (5.7)	198/2333 (8.5)	0.66 (0.55, 0.79)		
HbA1c at baseline					*p*=0.6881
<7.0%	16/297 (5.4)	15/127 (11.8)	0.44 (0.22, 0.89)		
7.0% to <8.0%	114/2042 (5.6)	86/1029 (8.4)	0.66 (0.50, 0.87)		
8.0% to <9.0%	77/1534 (5.0)	60/795 (7.5)	0.65 (0.46, 0.91)		
≥9.0%	57/812 (7.0)	37/382 (9.7)	0.72 (0.48, 1.10)		



EMPEROR-Reduced und EMPEROR-Preserved Herzinsuffizienz Endpunktstudien

Endpunkte

	EMPEROR-Reduced[1]	EMPEROR-Preserved[2]
Primärer Endpunkt	Zeit bis zum ersten Auftreten eines **adjudizierten KV Tod** oder **adjudizierten Hospitalisierung aufgrund einer Herzinsuffizienz (HHI)**	
Sekundäre Endpunkte	Auftreten einer adjudizierten HHI (erstmalig und wiederholt) Zeit bis zum ersten Auftreten einer adjudizierten HHI Zeit bis zum adjudizierten KV Tod Zeit bis zum Tod jeglicher Ursache Zeit bis zum Auftreten einer Diabeteserkrankung Auftreten einer Hospitalisierung jeglicher Ursache (erstmalig und wiederholt) Änderung zur baseline in KCCQ in Woche 52 eGFR (CKD-EPI Gleichung) Steigungsveränderung gegenüber baseline	

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, errechnete glomeruläre Filtrationsrate; HHI, Hospitalisierung aufgrund einer Herzinsuffizienz; KCCQ, Kansas City Cardiomyopathy Questionnaire
1. ClinicalTrials.gov NCT03057977; 2. ClinicalTrials.gov NCT03057951

EMPEROR HEART FAILURE STUDIES

Zusammenfassung

Study	Antidiabetic drug	Comparator	Results
DPP4 inhibitors			
SAVOR-TIMI 53[16,17]	Saxagliptin	Placebo	Increase in HF hospitalization
EXAMINE[19,184]	Alogliptin	Placebo	No statistically significant increase in HF hospitalization
TECOS[18,185]	Sitagliptin	Placebo	No effect on HF hospitalization
GLP-1 receptor agonists			
ELIXA[23]	Lixisenatide	Placebo	No effect on HF hospitalization
LEADER[22]	Liraglutide	Placebo	No effect on HF hospitalization
SUSTAIN-6[186]	Semaglutide	Placebo	No effect on HF hospitalization
EXSCEL[24]	Exenatide	Placebo	No effect on HF hospitalization
SGLT2 inhibitors			
EMPA-REG OUTCOME[20]	Empagliflozin	Placebo	Reduced HF hospitalization
CANVAS[21]	Canagliflozin	Placebo	Reduced HF hospitalization

Zusammenfassung

Improves Overall Cardiovascular and HF Outcomes	Improves Overall Cardiovascular Outcomes but Not HF outcomes	No Effect on Overall Cardiovascular or HF Outcomes	No Effect on Overall Cardiovascular Outcomes But Potential HF Harm
Empagliflozin (EMPA-REG OUTCOME[92])	Liraglutide (LEADER[70])	Insulin glargine (ORIGIN[30])	Pioglitazone (PROactive[56])
Canagliflozin (CANVAS/ CANVAS-R[95])	Semaglutide (SUSTAIN-6[73])	Acarbose (ACE[29])	Rosiglitazone (RECORD[58])
		Lixisenatide (ELIXA[69])	Saxagliptin (SAVOR-TIMI 53[83])
		Exenatide (EXSCEL[79])	
		Alogliptin (EXAMINE[82])	
		Sitagliptin (TECOS[85])	

Vijayakumar et al, Circ, 2018

Antidiabetika bei Herzinsuffizienz

Medikament	Gewicht	Hypoglykämie-risiko	HF-Hospital.	HbA_{1c} Senkung
Biguanide	↓	↔	↔	1,5
Acarbose	↔	↔	↔	0,8
Sulfonyl-Harnstoffe	↑	↑↑	↔	1,5
Insulin	↑	↑↑	↔	>2,5
Rosiglitazon	↑	↑	↑	1
Glinide	↑	↑	↔	1,5
DPP-4-Inhibitor	↓	↔	↔	0,5
Inkretin-Mimetika	↔	↔	↓	1,5
SGLT2-Inhibitoren	↓	↔	↓	0,6