Therapie des Typ 2 Diabetes: Was wird sich ändern?

Zertifiziertes
Hypertonie-Zentrum DHL®
Deutsche Hochdruckliga e.V.
Deutsche Gesellschaft für Hypertonie und Prävention

DDG
Deutsche Diabetes Gesellschaft
Zertifizierte Einrichtung gemäß der Richtlinien der Deutschen Diabetes Gesellschaft
Basisanerkennung DDG

P. Baumgart, Clemenshospital Münster

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

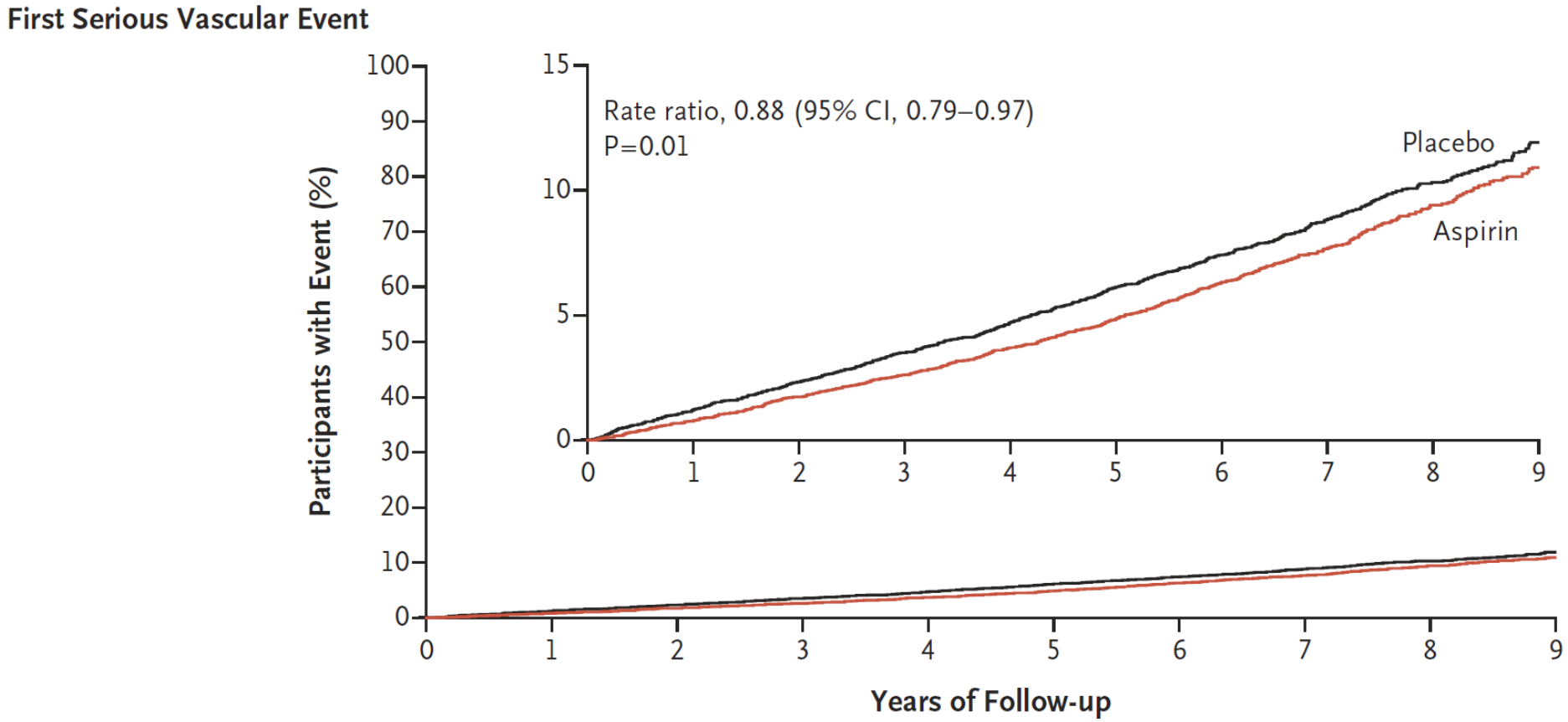
The ASCEND Study Collaborative Group*

CONCLUSIONS

Aspirin use prevented serious vascular events in persons who had diabetes and no evident cardiovascular disease at trial entry, but it also caused major bleeding events. The absolute benefits were largely counterbalanced by the bleeding hazard.

N Engl J Med 2018; 379:1529-1539

MI + Stroke + TIA + KV-Tod : ASS vs Placebo (ASCEND)

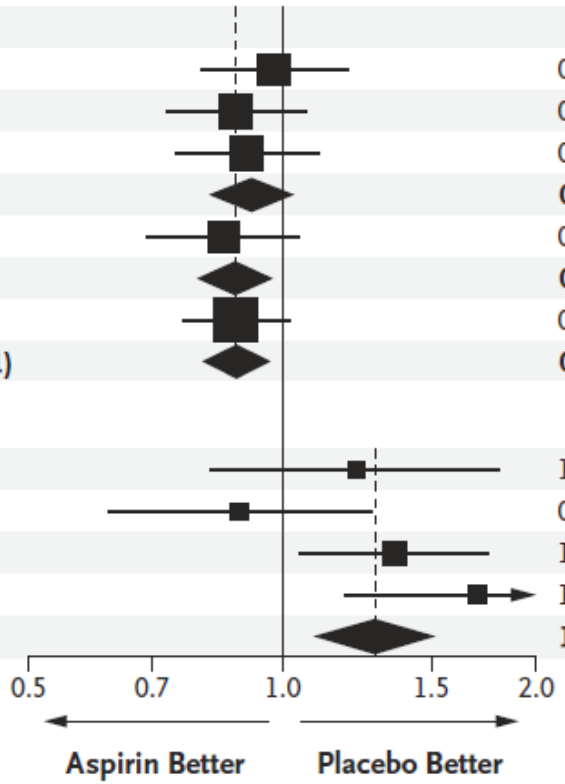


No. at Risk										
Placebo	7740	7618	7486	7342	7188	7001	5771	3890	2200	1430
Aspirin	7740	7655	7536	7404	7252	7096	5825	3966	2222	1428
Cumulative benefit per 1000 participants in aspirin group		4±2	6±2	9±3	10±3	13±4	11±4	12±5	9±6	10±7

N Engl J Med 2018; 379:1529-1539

ASCEND: Nutzen vs. Risiken von ASS in der Primärprävention bei Diabetikern

Type of Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of participants with event (%)			
Vascular Outcomes				
Nonfatal myocardial infarction	191 (2.5)	195 (2.5)	0.98 (0.80–1.19)	
Nonfatal presumed ischemic stroke	202 (2.6)	229 (3.0)	0.88 (0.73–1.06)	
Vascular death excluding intracranial hemorrhage	197 (2.5)	217 (2.8)	0.91 (0.75–1.10)	
Any serious vascular event excluding TIA	**542 (7.0)**	**587 (7.6)**	**0.92 (0.82–1.03)**	
TIA	168 (2.2)	197 (2.5)	0.85 (0.69–1.04)	
Any serious vascular event including TIA	**658 (8.5)**	**743 (9.6)**	**0.88 (0.79–0.97)**	**0.01**
Any arterial revascularization	340 (4.4)	384 (5.0)	0.88 (0.76–1.02)	
Any serious vascular event or revascularization	**833 (10.8)**	**936 (12.1)**	**0.88 (0.80–0.97)**	
Major Bleeding				
Intracranial hemorrhage	55 (0.7)	45 (0.6)	1.22 (0.82–1.81)	
Sight-threatening bleeding in eye	57 (0.7)	64 (0.8)	0.89 (0.62–1.27)	
Serious gastrointestinal bleeding	137 (1.8)	101 (1.3)	1.36 (1.05–1.75)	
Other major bleeding	74 (1.0)	43 (0.6)	1.70 (1.18–2.44)	
Any major bleeding	**314 (4.1)**	**245 (3.2)**	**1.29 (1.09–1.52)**	**0.003**



N Engl J Med 2018; 379:1529-1539

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of n–3 Fatty Acid Supplements in Diabetes Mellitus

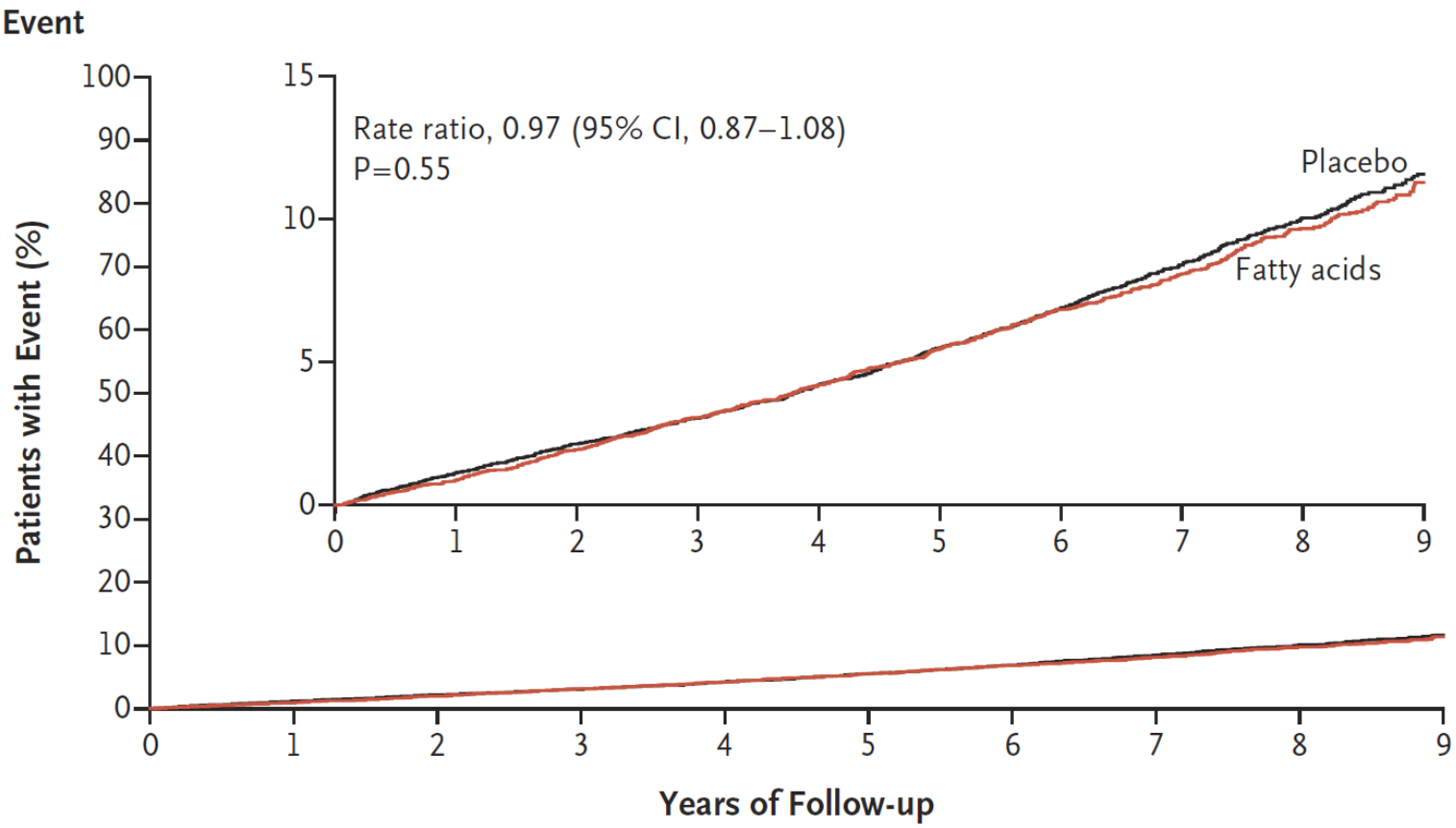
The ASCEND Study Collaborative Group*

CONCLUSIONS

Among patients with diabetes without evidence of cardiovascular disease, there was no significant difference in the risk of serious vascular events between those who were assigned to receive n–3 fatty acid supplementation and those who were assigned to receive placebo. (Funded by the British Heart Foundation and others;

N Engl J Med 2018; 379:1540-1550

MI+Stroke+TIA+KV-Tod : Omega-3 FS (1 g/Tag) vs Placebo (ASCEND)



No. at Risk

Placebo	7740	7627	7503	7377	7222	7047	5792	3934	2224	1428
Fatty acids	7740	7646	7519	7369	7218	7050	5804	3922	2198	1430
Cumulative benefit per 1000 patients in fatty acid group		3±2	2±2	0±3	0±3	0±4	1±4	3±5	4±6	3±7

N Engl J Med 2018; 379:1540-1550

The NEW ENGLAND JOURNAL of MEDICINE

NEJM 2019, 380:11-22

ORIGINAL ARTICLE

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

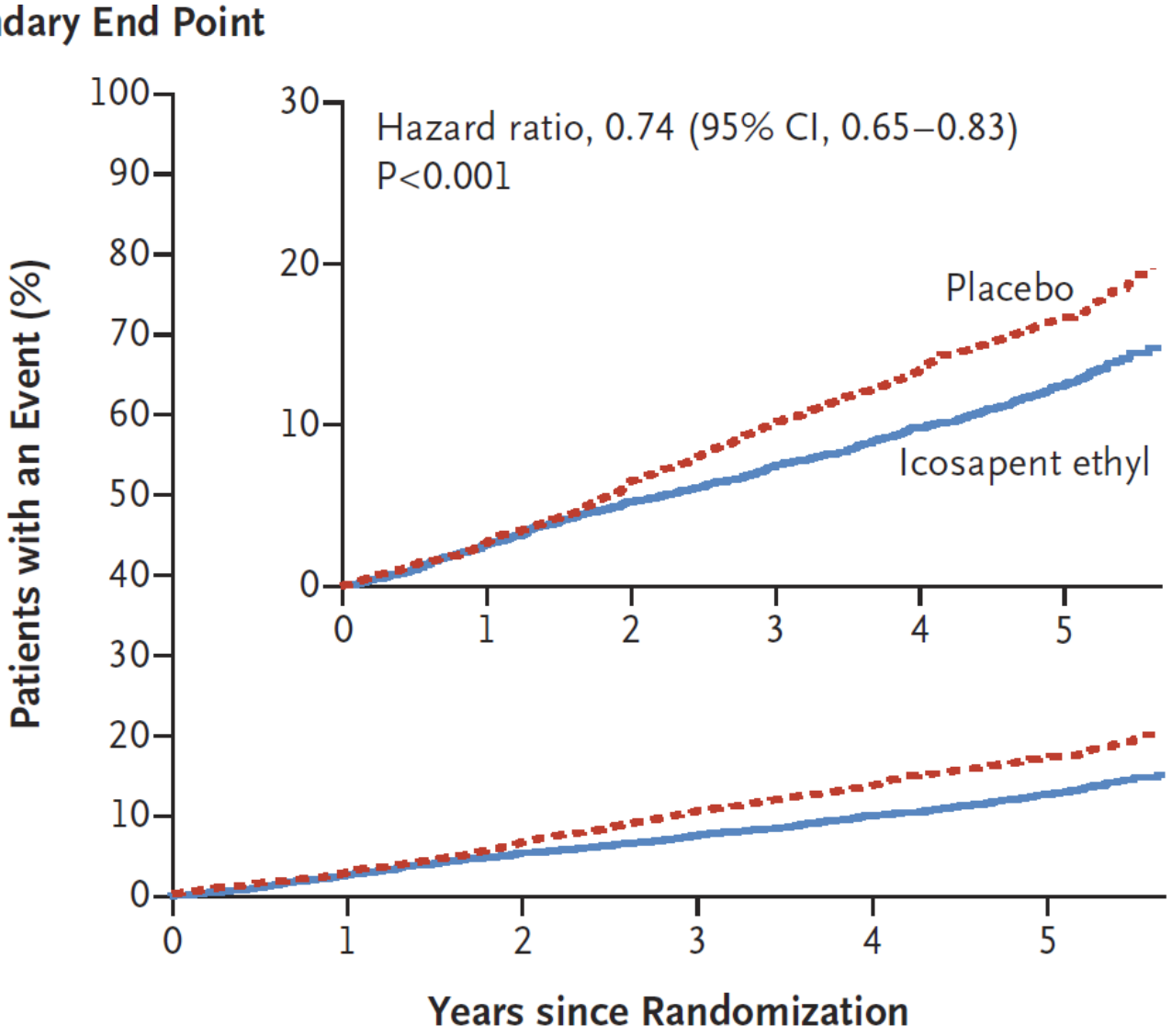
Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

8.179 Patienten
> 45 J. + kardiovask Erkrankung (~ 70% der Pat.)
> 50 J. + Diabetes + Risikofaktor
LDL-C 41-100mg/dl (Ø 75 mg/dl, Statine)
TG 200-500mg/dl mg/dl, Ø 216 mg/dl

REDUCE-IT: EPA 2x2g/Tag vs Placebo bei Hypertriglyzeridämie

Kardiovask. Tod
Myokardinfarkt
Schlaganfall

NEJM 2019, 380:11-22

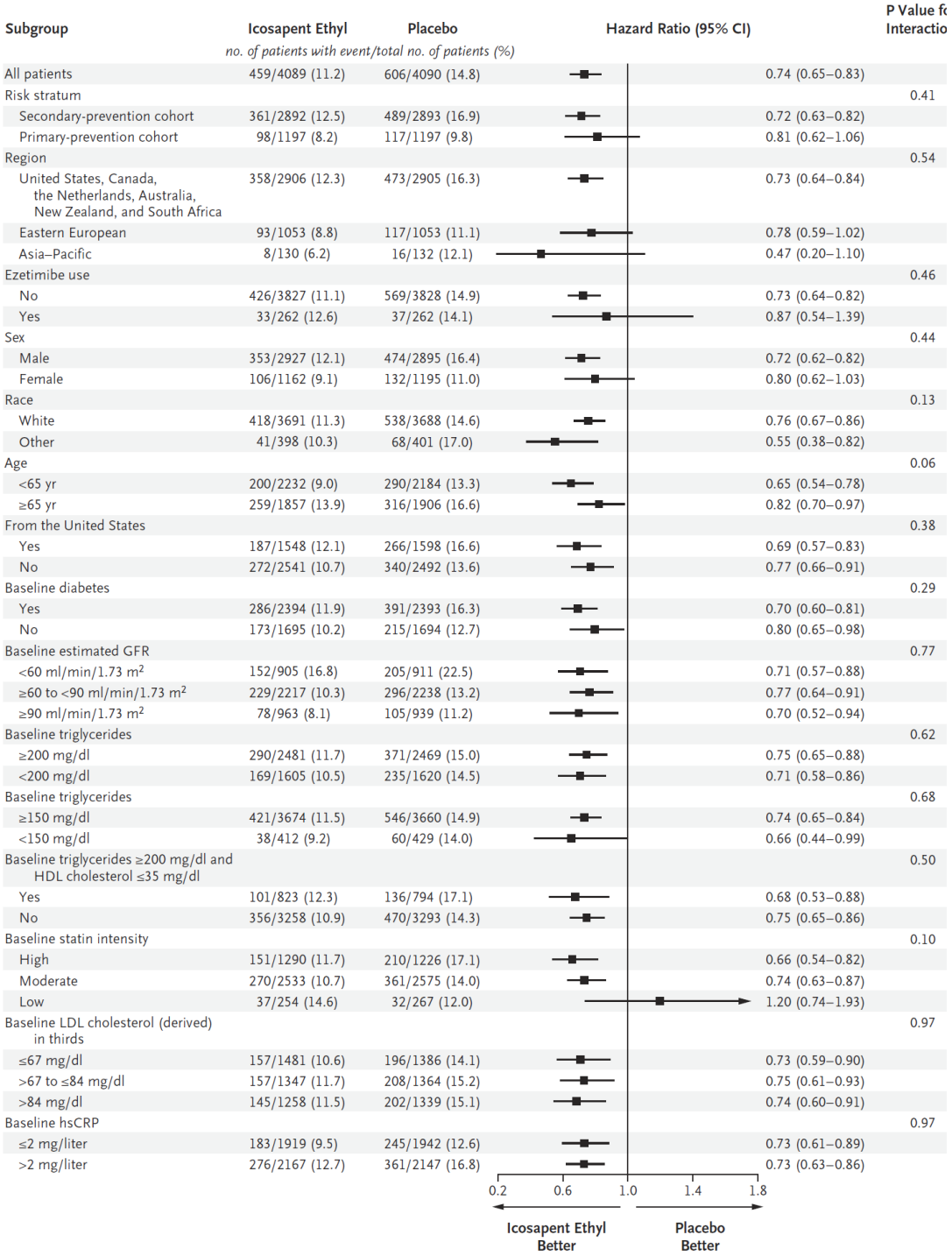


REDUCE-IT

Kardiovask. Tod
Myokardinfarkt
Schlaganfall

In Subgruppen

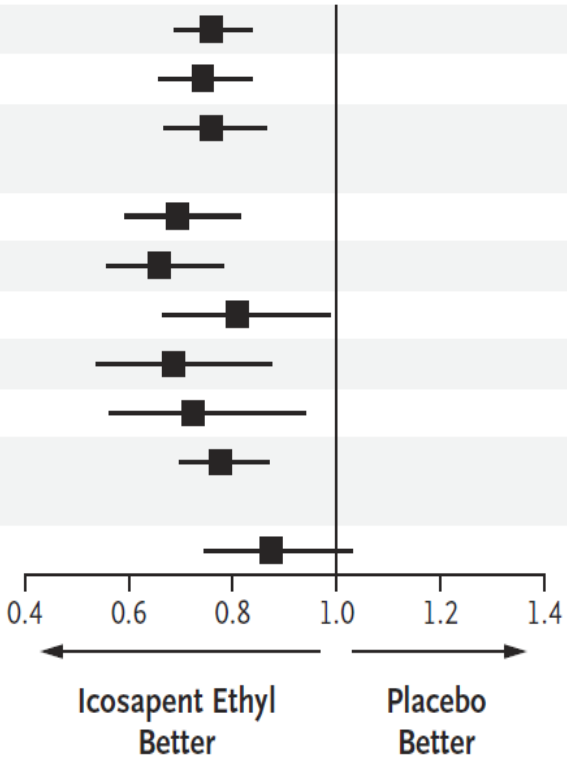
NEJM 2019, 380:11-22



Subgroup	Icosapent Ethyl	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients with event/total no. of patients (%)			
All patients	459/4089 (11.2)	606/4090 (14.8)	0.74 (0.65–0.83)	
Risk stratum				0.41
Secondary-prevention cohort	361/2892 (12.5)	489/2893 (16.9)	0.72 (0.63–0.82)	
Primary-prevention cohort	98/1197 (8.2)	117/1197 (9.8)	0.81 (0.62–1.06)	
Region				0.54
United States, Canada, the Netherlands, Australia, New Zealand, and South Africa	358/2906 (12.3)	473/2905 (16.3)	0.73 (0.64–0.84)	
Eastern European	93/1053 (8.8)	117/1053 (11.1)	0.78 (0.59–1.02)	
Asia–Pacific	8/130 (6.2)	16/132 (12.1)	0.47 (0.20–1.10)	
Ezetimibe use				0.46
No	426/3827 (11.1)	569/3828 (14.9)	0.73 (0.64–0.82)	
Yes	33/262 (12.6)	37/262 (14.1)	0.87 (0.54–1.39)	
Sex				0.44
Male	353/2927 (12.1)	474/2895 (16.4)	0.72 (0.62–0.82)	
Female	106/1162 (9.1)	132/1195 (11.0)	0.80 (0.62–1.03)	
Race				0.13
White	418/3691 (11.3)	538/3688 (14.6)	0.76 (0.67–0.86)	
Other	41/398 (10.3)	68/401 (17.0)	0.55 (0.38–0.82)	
Age				0.06
<65 yr	200/2232 (9.0)	290/2184 (13.3)	0.65 (0.54–0.78)	
≥65 yr	259/1857 (13.9)	316/1906 (16.6)	0.82 (0.70–0.97)	
From the United States				0.38
Yes	187/1548 (12.1)	266/1598 (16.6)	0.69 (0.57–0.83)	
No	272/2541 (10.7)	340/2492 (13.6)	0.77 (0.66–0.91)	
Baseline diabetes				0.29
Yes	286/2394 (11.9)	391/2393 (16.3)	0.70 (0.60–0.81)	
No	173/1695 (10.2)	215/1694 (12.7)	0.80 (0.65–0.98)	
Baseline estimated GFR				0.77
<60 ml/min/1.73 m^2	152/905 (16.8)	205/911 (22.5)	0.71 (0.57–0.88)	
≥60 to <90 ml/min/1.73 m^2	229/2217 (10.3)	296/2238 (13.2)	0.77 (0.64–0.91)	
≥90 ml/min/1.73 m^2	78/963 (8.1)	105/939 (11.2)	0.70 (0.52–0.94)	
Baseline triglycerides				0.62
≥200 mg/dl	290/2481 (11.7)	371/2469 (15.0)	0.75 (0.65–0.88)	
<200 mg/dl	169/1605 (10.5)	235/1620 (14.5)	0.71 (0.58–0.86)	
Baseline triglycerides				0.68
≥150 mg/dl	421/3674 (11.5)	546/3660 (14.9)	0.74 (0.65–0.84)	
<150 mg/dl	38/412 (9.2)	60/429 (14.0)	0.66 (0.44–0.99)	
Baseline triglycerides ≥200 mg/dl and HDL cholesterol ≤35 mg/dl				0.50
Yes	101/823 (12.3)	136/794 (17.1)	0.68 (0.53–0.88)	
No	356/3258 (10.9)	470/3293 (14.3)	0.75 (0.65–0.86)	
Baseline statin intensity				0.10
High	151/1290 (11.7)	210/1226 (17.1)	0.66 (0.54–0.82)	
Moderate	270/2533 (10.7)	361/2575 (14.0)	0.74 (0.63–0.87)	
Low	37/254 (14.6)	32/267 (12.0)	1.20 (0.74–1.93)	
Baseline LDL cholesterol (derived) in thirds				0.97
≤67 mg/dl	157/1481 (10.6)	196/1386 (14.1)	0.73 (0.59–0.90)	
>67 to ≤84 mg/dl	157/1347 (11.7)	208/1364 (15.2)	0.75 (0.61–0.93)	
>84 mg/dl	145/1258 (11.5)	202/1339 (15.1)	0.74 (0.60–0.91)	
Baseline hsCRP				0.97
≤2 mg/liter	183/1919 (9.5)	245/1942 (12.6)	0.73 (0.61–0.89)	
>2 mg/liter	276/2167 (12.7)	361/2147 (16.8)	0.73 (0.63–0.86)	

REDUCE-IT: Endpunkte

End Point	Icosapent Ethyl (N=4089)	Placebo (N=4090)	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients with event (%)			
Primary composite	705 (17.2)	901 (22.0)	0.75 (0.68–0.83)	<0.001
Key secondary composite	459 (11.2)	606 (14.8)	0.74 (0.65–0.83)	<0.001
Cardiovascular death or nonfatal myocardial infarction	392 (9.6)	507 (12.4)	0.75 (0.66–0.86)	<0.001
Fatal or nonfatal myocardial infarction	250 (6.1)	355 (8.7)	0.69 (0.58–0.81)	<0.001
Urgent or emergency revascularization	216 (5.3)	321 (7.8)	0.65 (0.55–0.78)	<0.001
Cardiovascular death	174 (4.3)	213 (5.2)	0.80 (0.66–0.98)	0.03
Hospitalization for unstable angina	108 (2.6)	157 (3.8)	0.68 (0.53–0.87)	0.002
Fatal or nonfatal stroke	98 (2.4)	134 (3.3)	0.72 (0.55–0.93)	0.01
Death from any cause, nonfatal myocardial infarction, or nonfatal stroke	549 (13.4)	690 (16.9)	0.77 (0.69–0.86)	<0.001
Death from any cause	274 (6.7)	310 (7.6)	0.87 (0.74–1.02)	—



DOI: 10.1056/NEJMoa1812792

This article was published on November 10, 2018, at NEJM.org.

The NEW ENGLAND JOURNAL of MEDICINE

NEJM 2019, 380:11-22

ORIGINAL ARTICLE

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

CONCLUSIONS

Among patients with elevated triglyceride levels despite the use of statins, the risk of ischemic events, including cardiovascular death, was significantly lower among those who received 2 g of icosapent ethyl twice daily than among those who received placebo. (Funded by Amarin Pharma; REDUCE-IT ClinicalTrials.gov number, NCT01492361.)

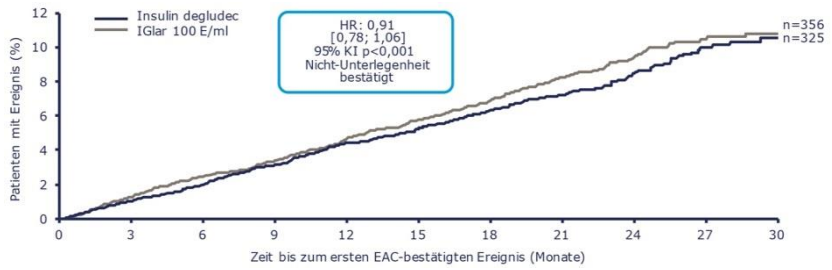
DEVOTE: Insulin Degludec vs Insulin Glargin bei TDM2

7.637 Pat. mit hohem kardiovaskuläres Risiko
≥1 orales oder injizierbares Antidiabetikum
HbA_{1c} ≥7,0% oder HbA_{1c} <7,0%, Basalinsulin-Therapie ≥20 E/Tag
randomisiert, doppel-blind, reat-to-arget,
Nicht-Unterlegenheitsstudie

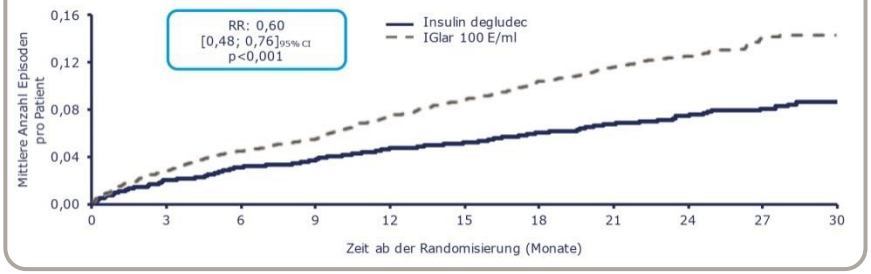
Insulin Degludec:

- **kardiovaskuläre Sicherheit: Nicht unterlegen**
- DEVOTE: 752 schwere Hypoglykämien
- **- 40% schwere Hypoglykämien**
- **- 53% nächtliche schwere Hypoglykämien**
- vergleichbare HbA_{1c}-Werte
- niedrigerere Nüchtern-Plasmaglucose

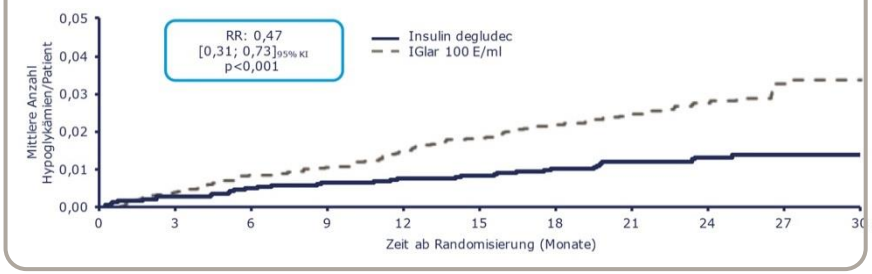
Primärer Endpunkt (3-MACE)



Schwere Hypoglykämien (Fremdhilfe erforderlich)



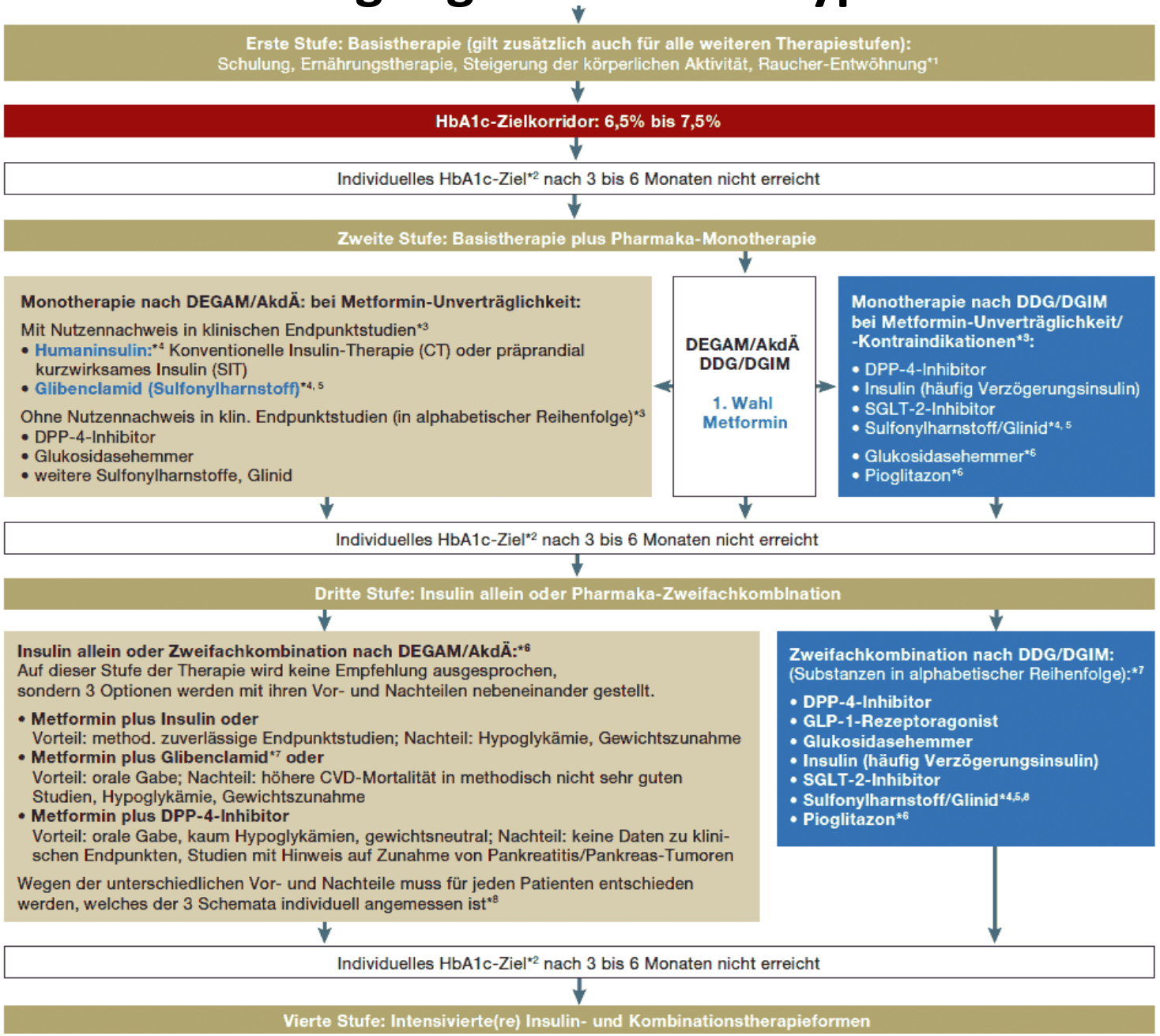
Nächtliche schwere Hypoglykämien



Seit Nov.18 wieder in Deutdschland verfügbar!

HR, Hazard-Ratio; IGlar 100 E/ml, Insulin glargin 100 E/ml; CI, Confidence interval, Konfidenzintervall; RR, Rate Ratio, Raten-Verhältnis.
Marso et al. N Engl J Med 2017;377:723–732

Nationale Versorgungsleitlinie für Typ 2 Diabetes 2014



Dtsch Arztebl 2013; 110(40): A-1875 / B-1655 / C-1623

Bisherige Behandlungsrealität in Deutschland:

1. Häufigste Zweitmedikamente nach Metformin:
   DPP4-Hemmer
   auch bei:
   - KHK, pAVK, CVD
   - Herzinsuffizienz
   - Niereninsuffizienz

2. Wir sind Insulin-Weltmeister

ADA/EASD Consensus Report 2018

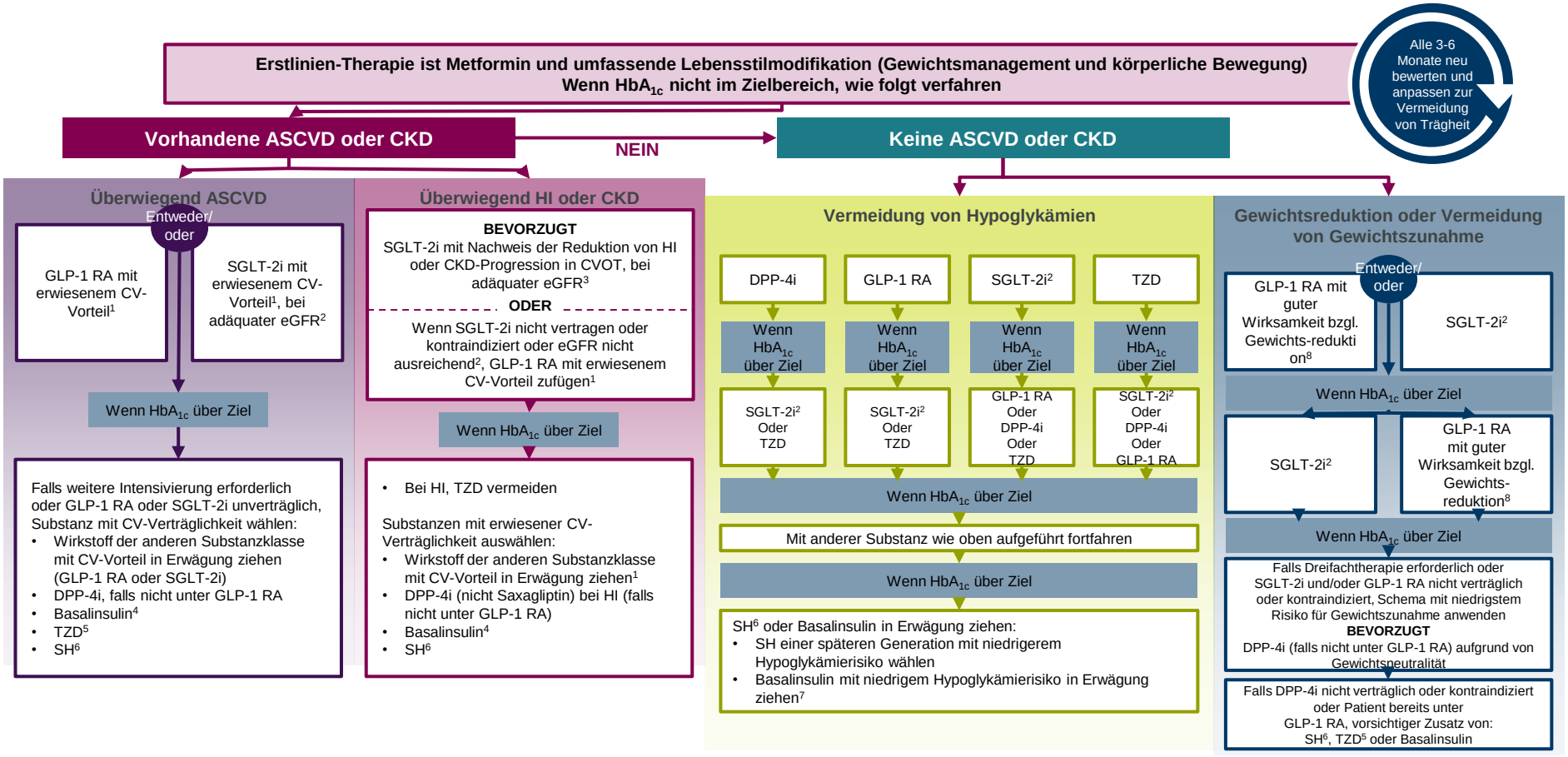
Diabetologia
https://doi.org/10.1007/s00125-018-4729-5

CONSENSUS REPORT

Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Melanie J. Davies [1,2] · David A. D'Alessio [3] · Judith Fradkin [4] · Walter N. Kernan [5] · Chantal Mathieu [6] · Geltrude Mingrone [7,8] · Peter Rossing [9,10] · Apostolos Tsapas [11] · Deborah J. Wexler [12,13] · John B. Buse [14]

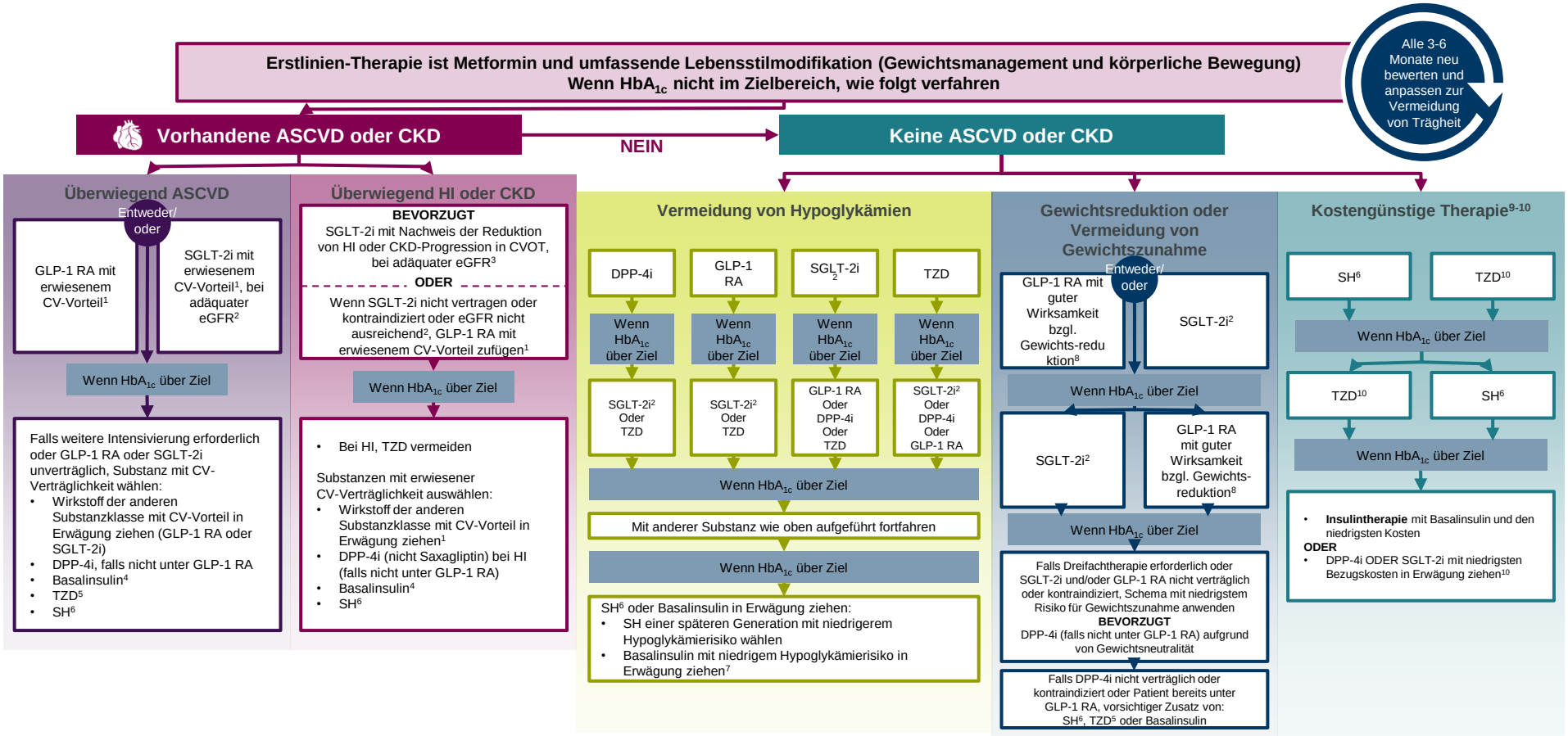
ADA/EASD 2018: Empfehlungen zur Therapie des TYP 2 Diabetes



ASCVD, atheroskeloritsche kardiovaskuläre Erkrankung; CKD, chronische Nierenerkrankung; CV, kardiovaskulär; CVOT, kardiovaskuläre Endpunkt-Studien; DPP-4i, Dipeptidylpeptidase-4-Inhibitor; eGFR, geschätzte glomeruläre Filtrationsrate; GLP-1 RA, Glukagon-like-Peptide-1-Rezeptoragonist; HI, Herzinsuffizienz; SGLT-2i, Natrium-Glukose-Contransporter-2-Inhibitor; SH, Sulfonylharnstoff; TZD, Thiazolidindion.

Modifiziert nach: Davies MJ, et al. Diabetes Care 2018; doi 10.2337/dci18-0033; [Epub ahead of print].

ADA/EASD 2018: Empfehlungen zur Therapie des TYP 2 Diabetes



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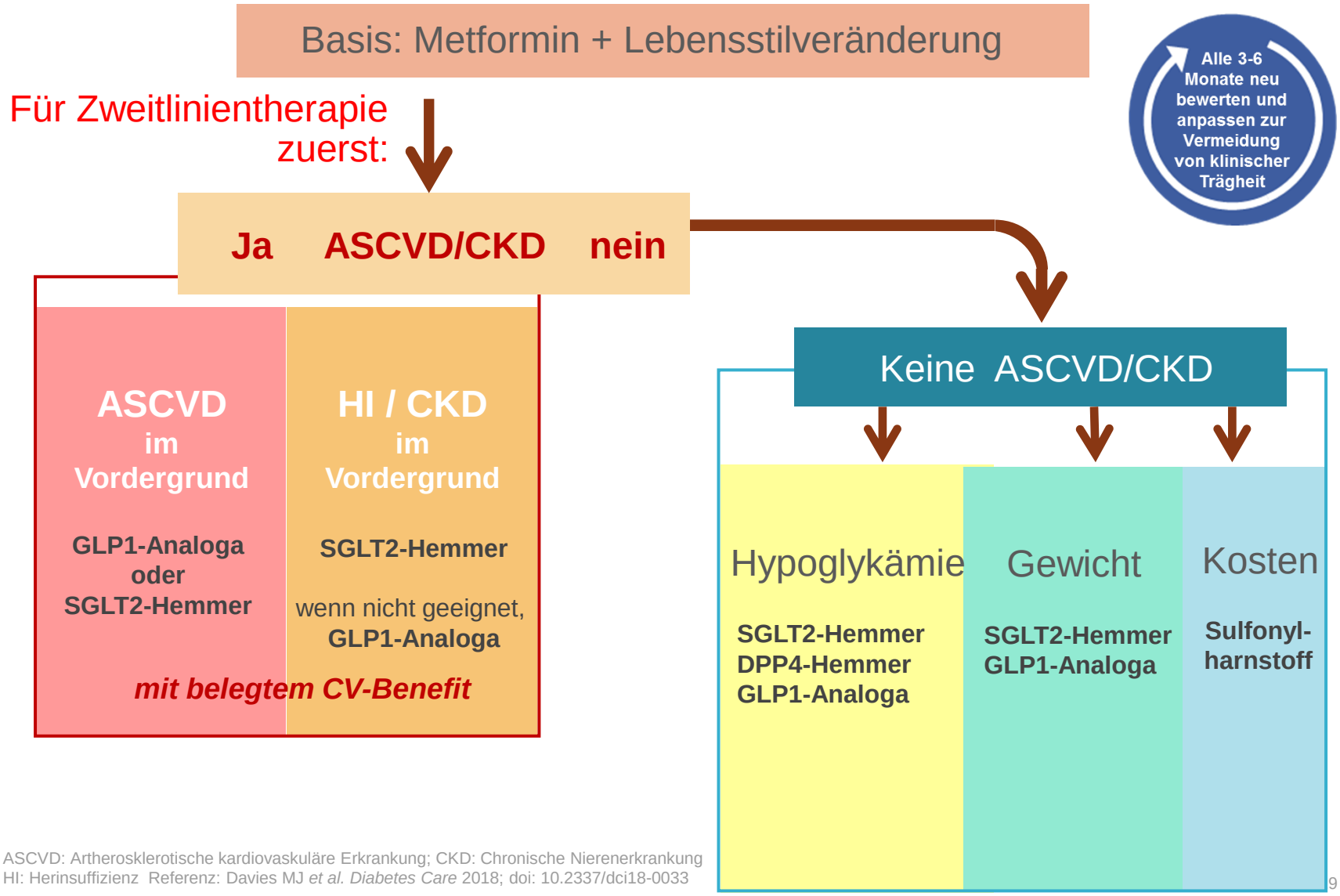
Modifiziert nach: Davies MJ, et al. Diabetes Care 2018; doi 10.2337/dci18-0033; [Epub ahead of print].

ADA/EASD Consensus Report 2018: Allgemeine Vorgehensweise bei der Wahl von Antidiabetika bei Typ-2-Diabetes



ASCVD: Artherosklerotische kardiovaskuläre Erkrankung; CKD: Chronische Nierenerkrankung
HI: Herinsuffizienz Referenz: Davies MJ *et al. Diabetes Care* 2018; doi: 10.2337/dci18-0033

DE/EMP/01688

ADA/EASD Consensus Report 2018 - Auswahl von Antidiabetika für T2D-Patienten mit artherosklerotischer kardiovaskulärer Erkrankung (ASCVD) oder chronischer Niereninsuffizienz (CKD)

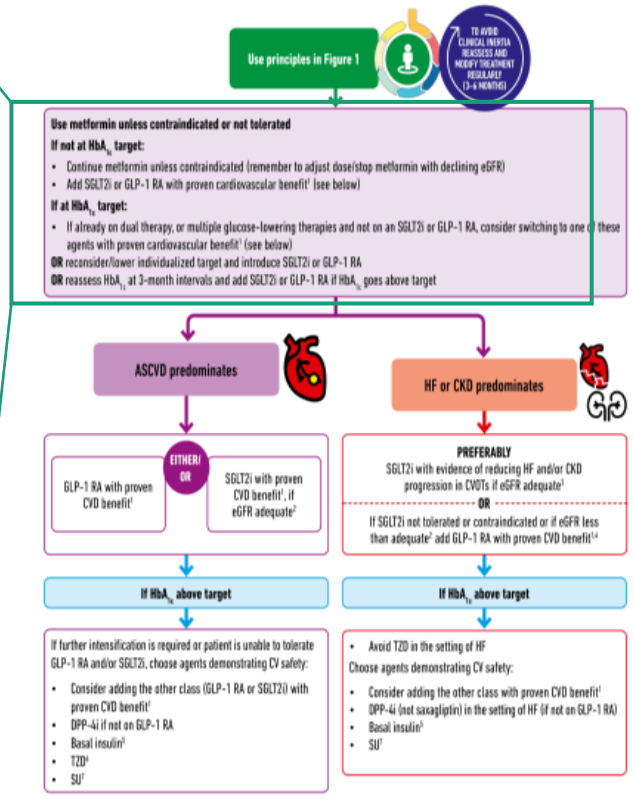
Metformin, ausser wenn kontraindiziert oder nicht vertragen

Bei HbA1c über dem im Zielbereich:

- Metformin beibehalten, wenn nicht kontraindiziert (Dosis anpassen oder absetzen bei geringer eGFR)
- **SGLT2-Hemmer** oder GLP-1-RAn **mit belegter kardiovaskulärer Wirksamkeit dazugeben**

Bei HbA1c im Zielbereich:

- Wenn bereits Zweifach- oder Mehrfachtherapie und bisher ohne **SGLT2-Hemmer** oder GLP-1-RA, ***Switch*** zu einem dieser Wirkstoffe **mit belegter kardiovaskulärer Wirksamkeit** in Betracht ziehen
- **ODER** ein niedrigeres individuelles HbA1c-Ziel erwägen und die ***zusätzliche Therapie*** mit einem **SGLT2-Hemmer** oder GLP-1-RA beginnen
- **ODER** den HbA1c in 3-monatigen Intervallen ***erneut prüfen*** und die zusätzliche Therapie mit einem **SGLT2-Hemmer** oder GLP-1-RA beginnen, sobald der HbA1c über den Zielwert steigt



T2D::Typ-2-Diabetes; RA: Rezeptoragonist; eGFR: estimated glomerular filtration rate; HF: heart failure;
Referenz: Davies MJ et al. Diabetologia 2018; 61(12): 2461–98.

Praxisempfehlungen der Deutschen Diabetes Gesellschaft

Therapie des Typ-2-Diabetes

Nov 2018

DE/EMP/01682

Thearpiealgorhithmus für Menschen mit Typ-2-Diabetes (1)

In die Therapie einzubeziehen:
Hyperglykämie – Fettstoffwechselstörung – arterielle Hypertonie – Rauchen – Adipositas

1. Stufe: Basistherapie (gilt zusätzlich auch für alle weiteren Therapiestufen):
Schulung, Ernährungstherapie, Steigerung der körperlichen Aktivitäten, Raucherentwöhnung, Stressbewältigung

individuelles HbA1c-Ziel nach 3–6 Monaten nicht erreicht:
2. Stufe: Basistherapie + Pharmaka-Monotherapie

1. Wahl:
Metformin

Monotherapie bei Metformin-Unverträglichkeit/Kontraindikationen
(alphabetische Reihenfolge)

- DPP-4-Inhibitor
- GLP-1-Rezeptoragonist
- Glukosidasehemmer
- Insulin (meist langerwirkend)
- Repaglinid (bei eGFR <25ml/min)
- SGLT2-Inhibitor
- Sulfonylharnstoff

Bei Menschen mit Typ-2-Diabetes und kardiovaskulären und renalen Komplikationen sollten aufgrund der Evidenzen bevorzugt SGLT2-Hemmer und GLP-1-RA eingesetzt werden.

Landgraf R et al. Diabetologie 2018; 13 (Suppl 2): S144–S165

Therapiealgorhythmus für Menschen mit Typ-2-Diabetes (2)

individuelles HbA1c-Ziel nach 3–6 Monaten nicht erreicht:

3. Stufe: Kombination mit einem 2. und evtl. 3. Antidiabetikum

Monotherapie bei Metformin-Unverträglichkeit/Kontraindikationen (alphabetische Reihenfolge)

- DPP-4-Inhibitor
- GLP-1-Rezeptoragonist
- Glukosidasehemmer
- Insulin (meist langerwirkend)
- Pioglitazon
- Repaglinid (bei eGFR <25ml/min)
- SGLT2-Inhibitor
- Sulfonylharnstoff

Bei Menschen mit Typ-2-Diabetes und kardiovaskulären und renalen Komplikationen sollten aufgrund der Evidenzen bevorzugt SGLT2-Hemmer und GLP-1-RA eingesetzt werden.

individuelles HbA1c-Ziel nach 3–6 Monaten nicht erreicht:

4. Stufe: Insulintherapie

Zusätzlich zu oralen Antidiabetika oder als Insulin-Monotherapie:

- GLP-1-RA-unterstützte orale Therapie (GUT) oder
- Verzögerungsinsulin tagsüber oder zur Nacht (BOT) oder
- Basalinsulin + GLP-1-RA (Zulassungsstatus beachten) oder
- präprandiales kurzwirkendes Insulin (SIT) oder
- konventionelle Insulintherapie (Mischinsuline; CT) oder
- intensivierte Insulintherapie (ICT, CSII)

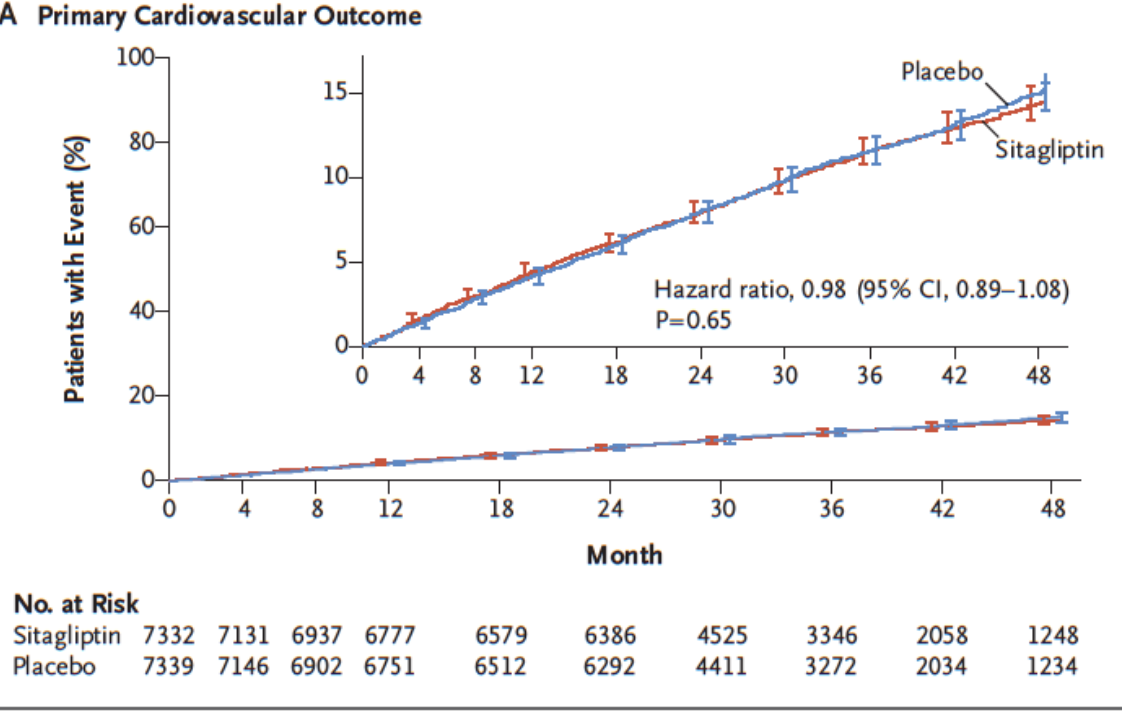
Landgraf R et al. Diabetologie 2018; 13 (Suppl 2): S144–S165

Frühzeitige Zweifachtherapie empfohlen

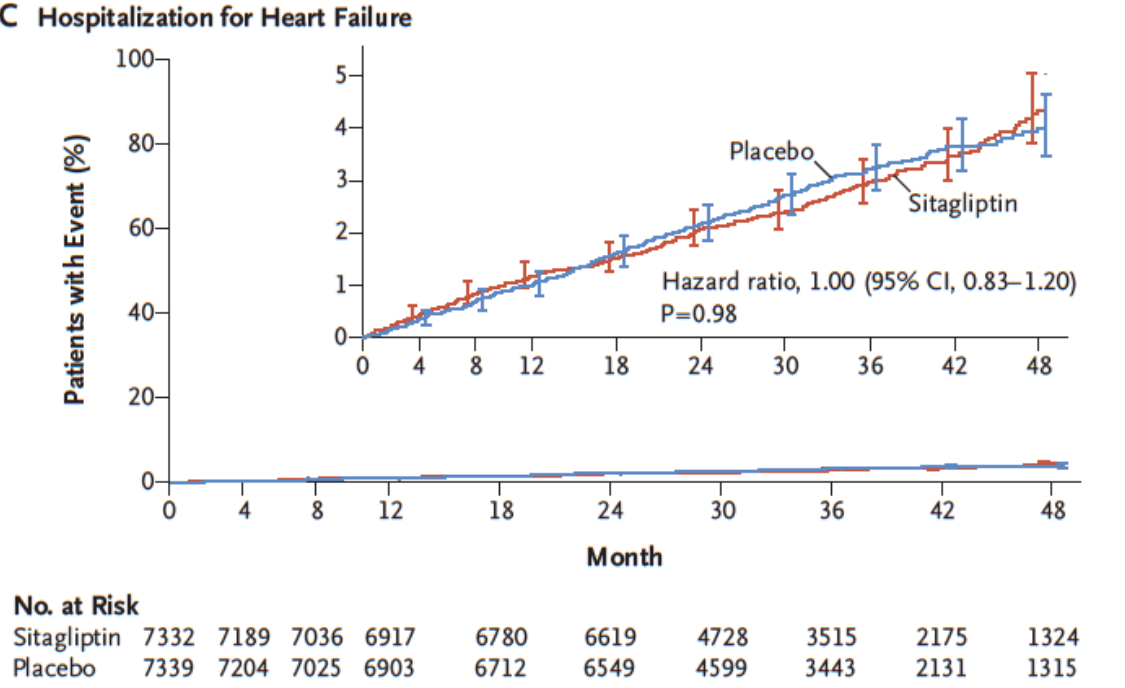
- Bei **Patienten mit vorbestehenden kardiovaskulären Erkrankungen** sollen primär Substanzen eingesetzt werden, die nachweislich kardiovaskuläre Erkrankungen und Mortalität reduzieren
- **Frühzeitige** Kombinationstherapie, um vereinbarten Zielbereich nicht weit zu überschreiten
- Überprüfung der Zielwerte alle 3 bis 6 Monate
- Auswahl der Kombinationen nach
  - Evidenz
  - Patientenpräferenzen
  - individuellen Therapiezielen
  - Einfachheit der Behandlung
  - vorhandenen kardiovaskuläre Erkrankungen
  - eventuellen Kontraindikationen

Landgraf R et al. Diabetologie 2018; 13 (Suppl 2): S144–S165

TECOS:
DPP4-Hemmer ohne Einfluß auf kv. Risiko



Kardiovask. Mortalität + Herzinfarkt + Schlaganfall + Hospitalisation wegen instab. Angina



Herzinsuffizienz-Hospitalisation

N Engl J Med 2015;373:232-42.

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2016; 375:380-382

ORIGINAL ARTICLE

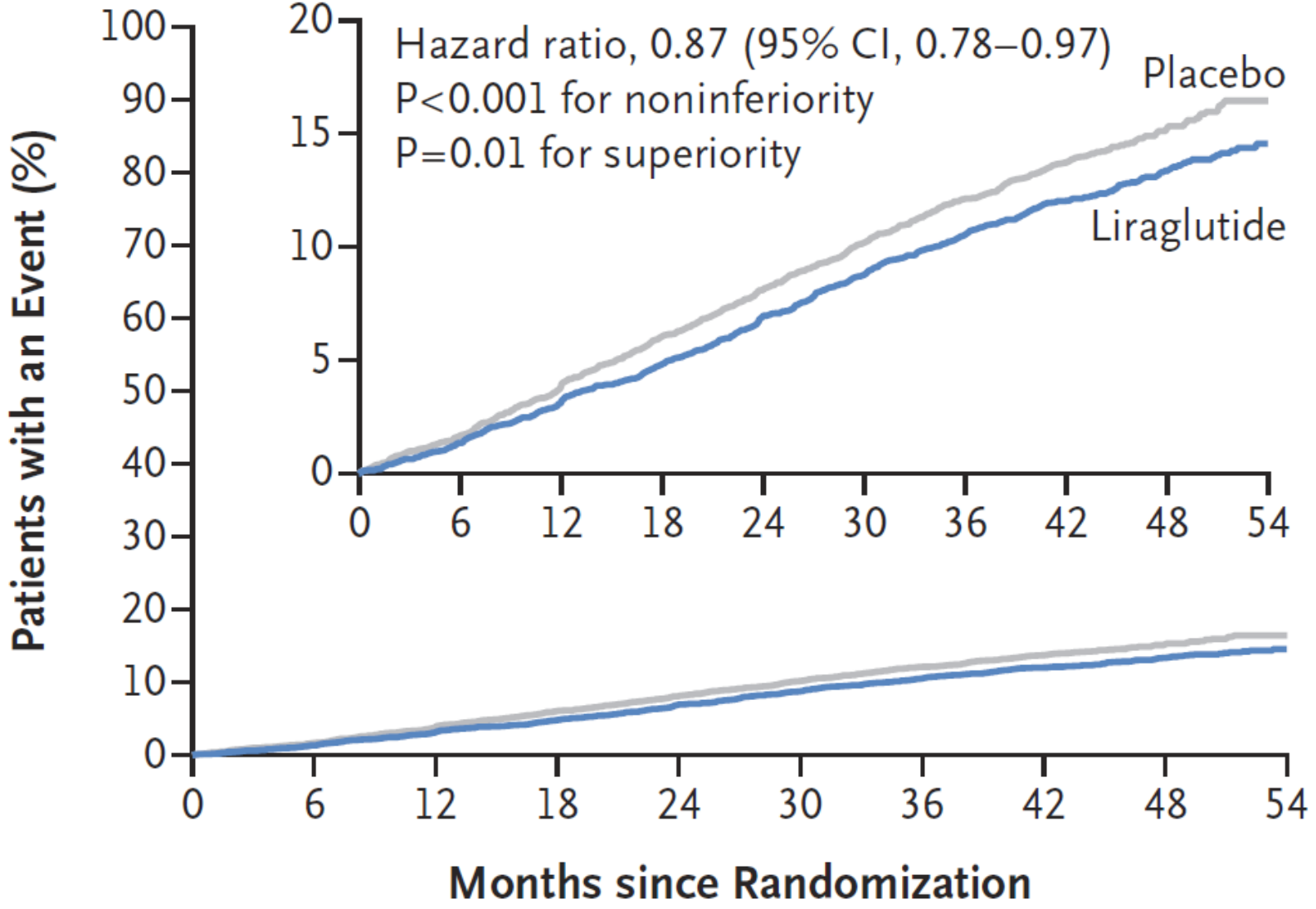
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D.,

CONCLUSIONS

In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo. (Funded by Novo Nordisk and the National Institutes of Health; LEADER ClinicalTrials.gov number, NCT01179048.)

A Primary Outcome **Kardiovaskulärer Tod + MI + Schlaganfall**

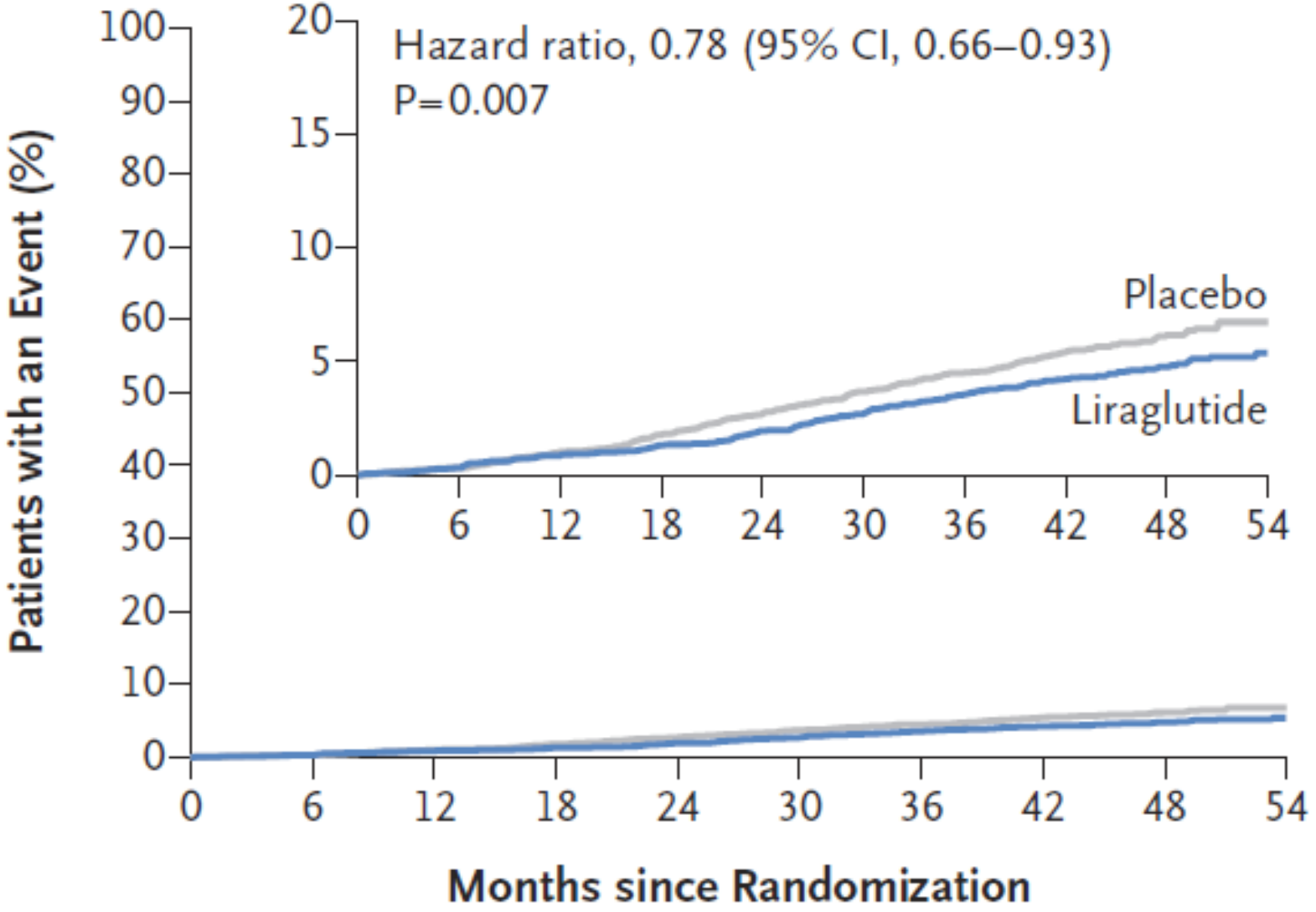


N Engl J Med 2016; 375:380-382

No. at Risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

B **Death from Cardiovascular Causes**

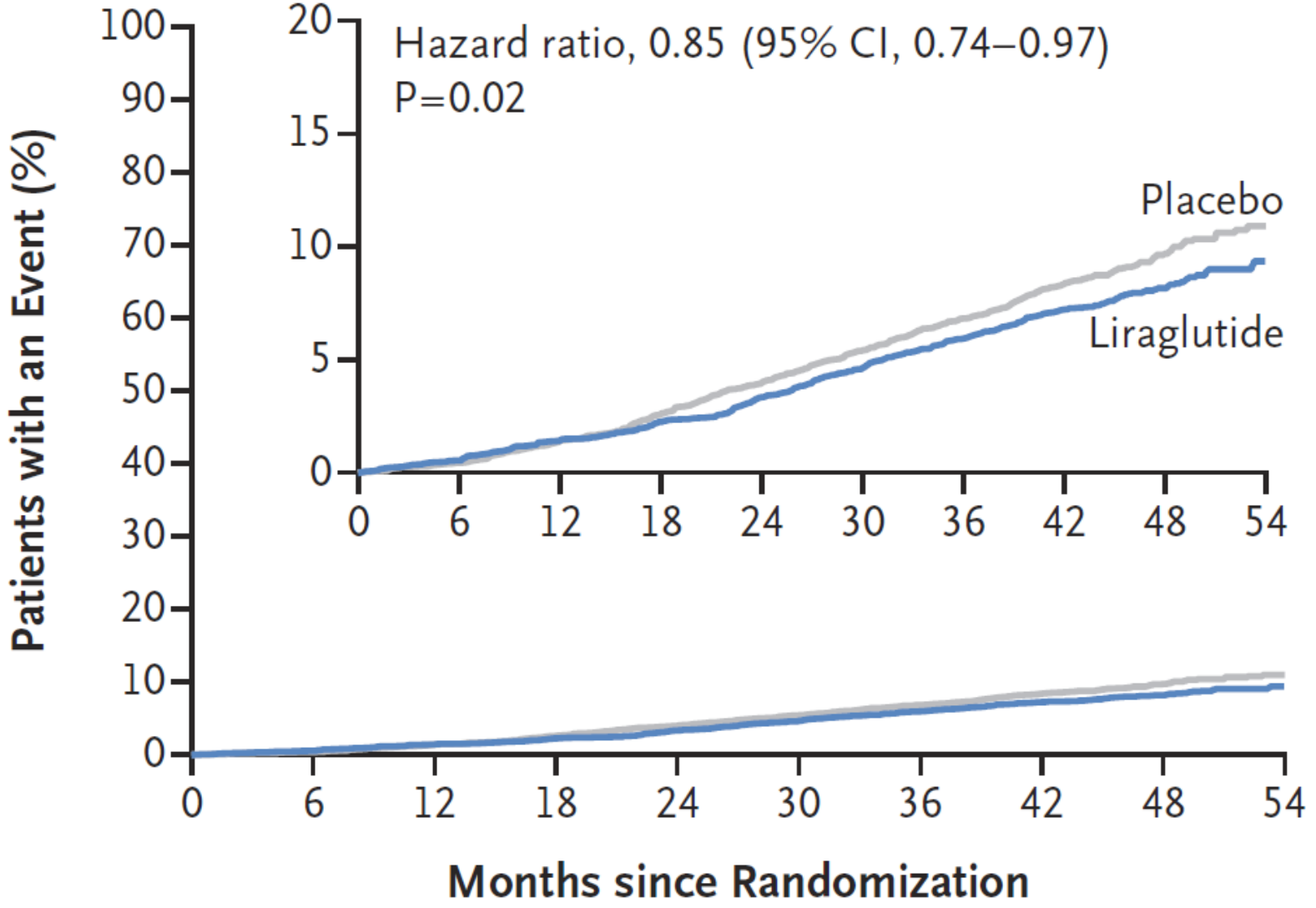


No. at Risk

Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

N Engl J Med 2016; 375:380-382

E **Death from Any Cause**

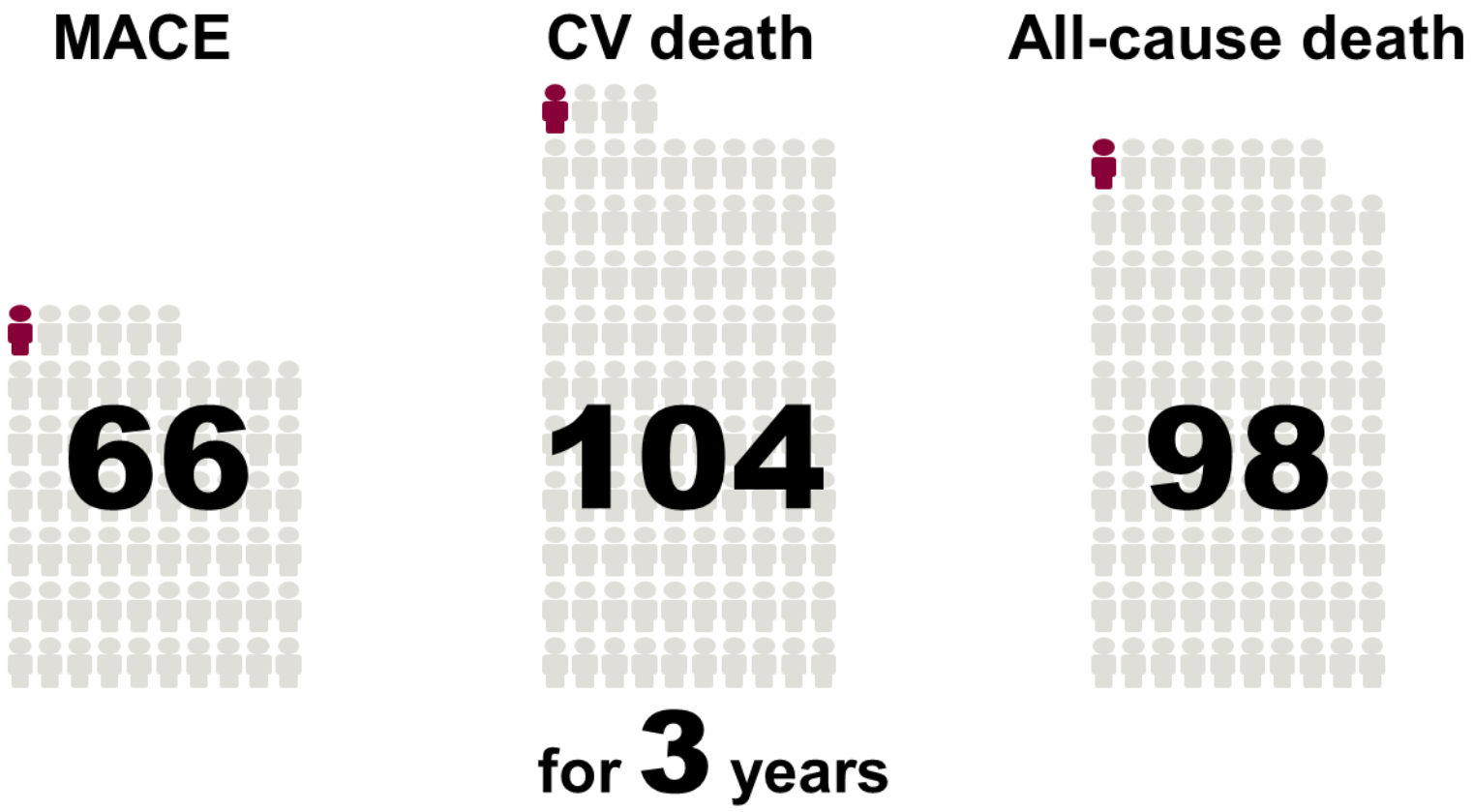


No. at Risk

Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	1709	465

N Engl J Med 2016; 375:380-382

Number needed to treat to prevent one…



CV: cardiovascular; MACE: major adverse cardiovascular event.
Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

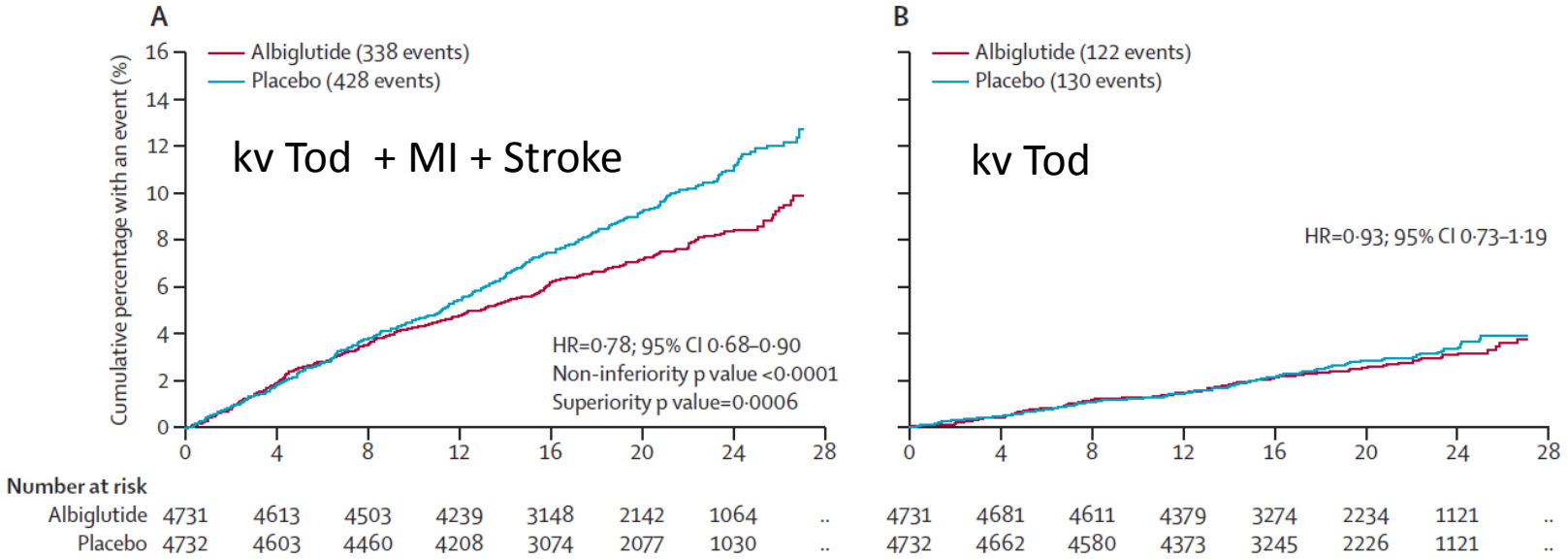
Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial

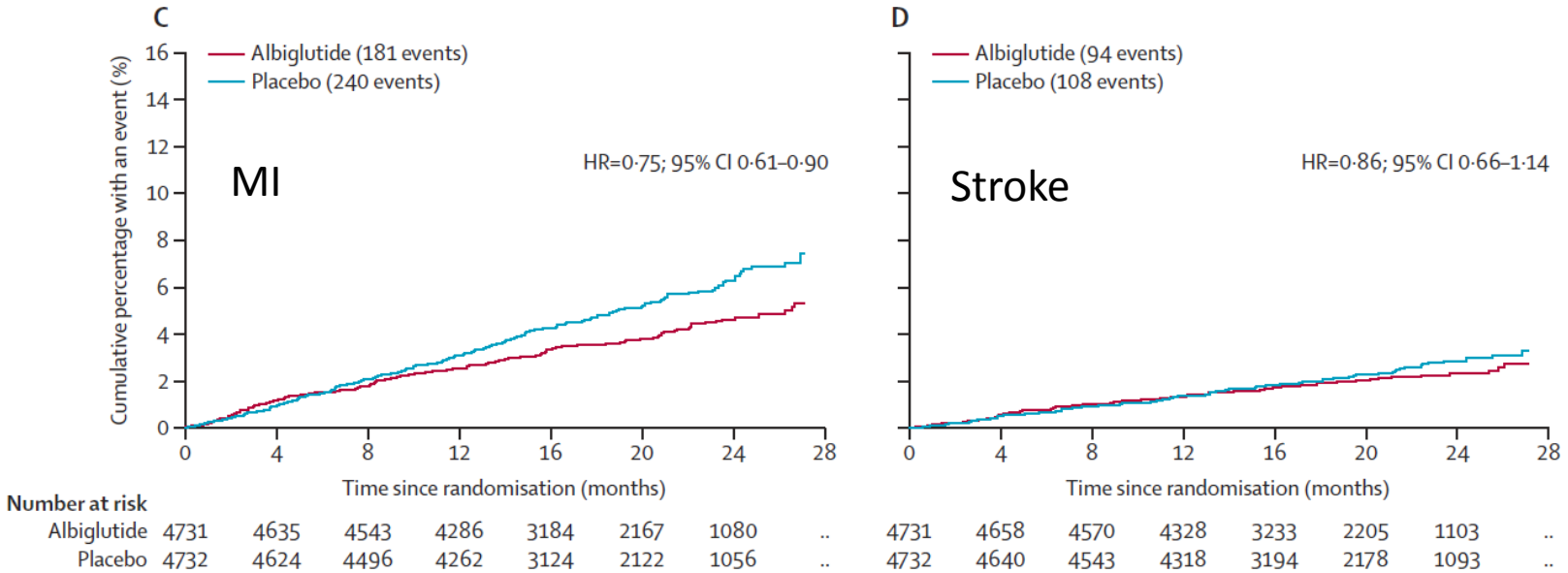
*Adrian F Hernandez, Jennifer B Green, Salim Janmohamed, Ralph B D'Agostino Sr, Christopher B Granger, Nigel P Jones, Lawrence A Leiter, Anne E Rosenberg, Kristina N Sigmon, Matthew C Somerville, Karl M Thorpe, John J V McMurray, Stefano Del Prato, for the Harmony Outcomes committees and investigators**

Interpretation In patients with type 2 diabetes and cardiovascular disease, albiglutide was superior to placebo with respect to major adverse cardiovascular events. Evidence-based glucagon-like peptide 1 receptor agonists should therefore be considered as part of a comprehensive strategy to reduce the risk of cardiovascular events in patients with type 2 diabetes.

http://dx.doi.org/10.1016/
S0140-6736(18)32261-X

Albiglutide 1x/W sc. vs Placebo bei Typ2 Diabetes: Endpunkte (HARMONY)

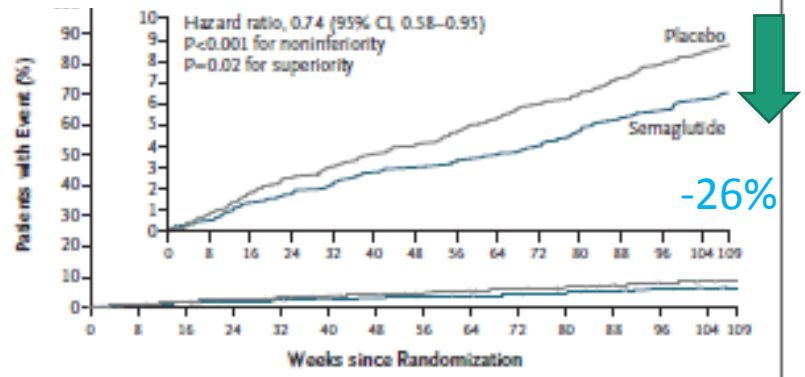




http://dx.doi.org/10.1016/S0140-6736(18)32261-X

Semaglutide:
Kardiovaskuläre Daten SUSTAIN-6 Studie

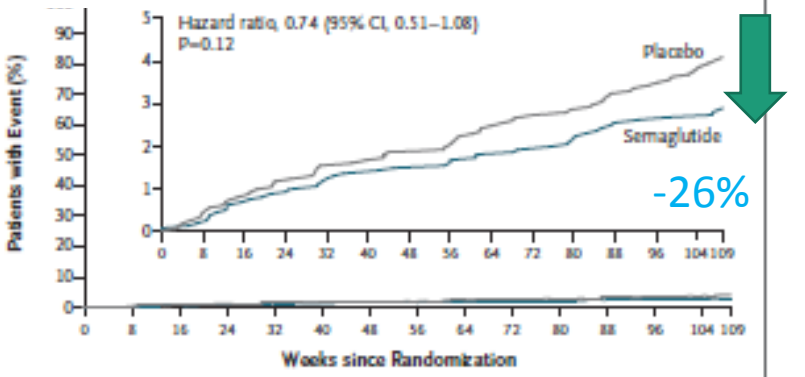
Primärer Endpunkt (MACE-3)



No. at Risk

Placebo	1649	1616	1586	1567	1534	1508	1479
Semaglutide	1648	1619	1601	1584	1568	1543	1524

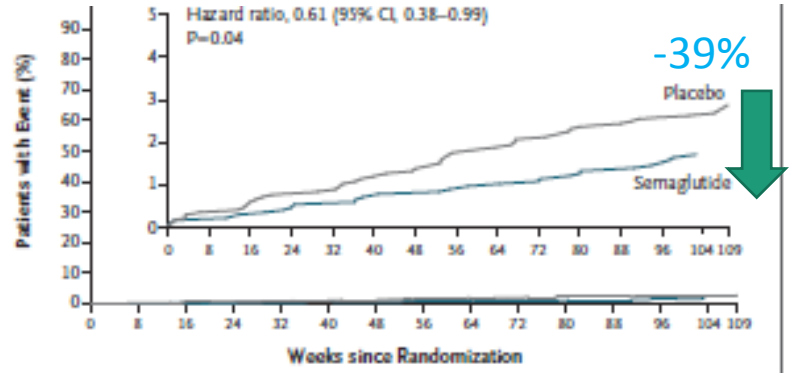
Nicht-tödl. Myokardinfarkt



No. at Risk

Placebo	1649	1624	1598	1587	1562	1542	1516
Semaglutide	1648	1623	1609	1595	1582	1560	1543

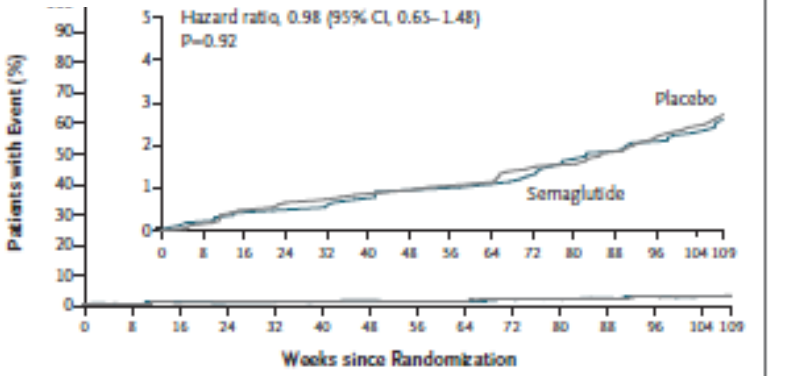
Nicht-tödl. Schlaganfall



No. at Risk

Placebo	1649	1629	1611	1597	1571	1548	1528
Semaglutide	1648	1630	1619	1606	1593	1572	1558

Tod durch CV Ursachen



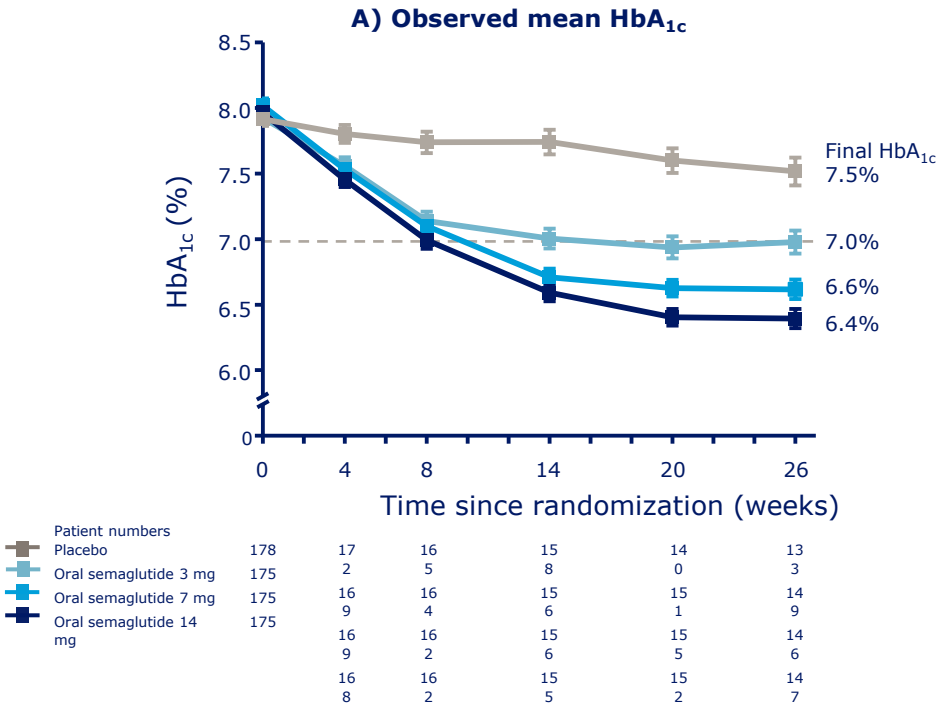
No. at Risk

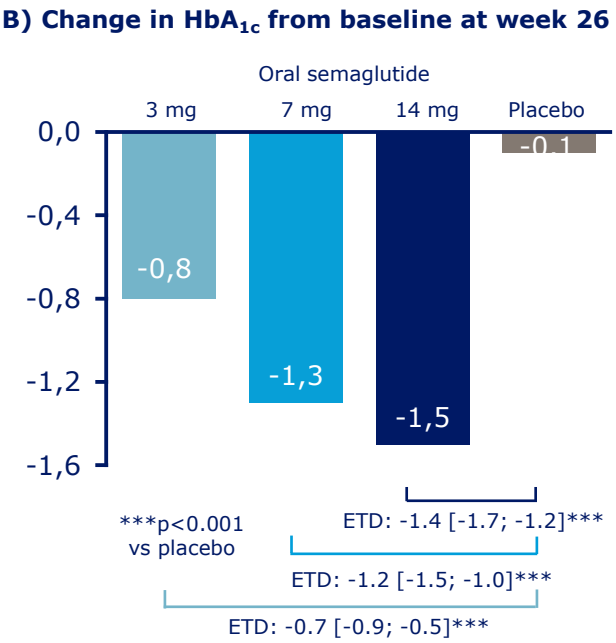
Placebo	1649	1637	1623	1617	1600	1584	1566
Semaglutide	1648	1634	1627	1617	1607	1589	1579

N Engl J Med 2016; 375:1834-1844

SEMAGLUTID oral

ON-TREATMENT PRINCIPLE





Primary estimand (ITT principle): Estimated mean changes from baseline in HbA_{1c} [%] (± SE) at week 26 were -0.9 ± 0.1, -1.2 ± 0.1, and -1.4 ± 0.1 for oral semaglutide 3, 7 and 14 mg, respectively and -0.3 ± 0.1 for placebo. Estimated treatment differences in HbA_{1c} (%-points) [95%CI] for oral semaglutide vs placebo at week 26 were: 3 mg, -0.6 [-0.8; -0.4]; 7 mg, -0.9 [-1.1; -0.6]; 14 mg, -1.1 [-1.3; -0.9]; p<0.001 for all

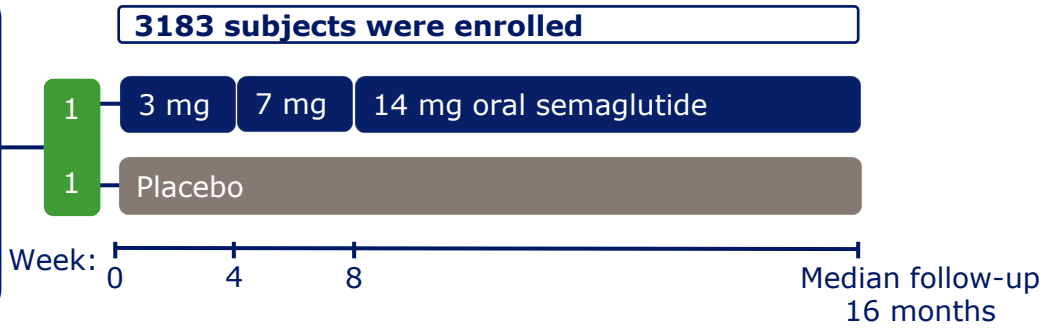
A) Values are mean ± standard error; B) changes and treatment differences are least squares means; ETD, estimated treatment difference .

PIONEER 6

Gesamtmortalität: - 49%
kardiovaskuläre Mortalität: - 51%

Key inclusion criteria

- Age ≥50 years and clinical evidence of CV disease OR age ≥60 years and subclinical evidence of CV disease
- Diagnosed with T2D



Trial information

- Randomised, double-blind, placebo-controlled trial designed to rule out an excess cardiovascular risk of 80% for oral semaglutide vs. placebo when added to standard of care in subjects with T2D at high risk of CV events (pre-approval CVOT)
- Event-driven trial and will be continued until at least 122 first MACEs confirmed by adjudication

Primary endpoint

- Time to first MACE (CV death, non-fatal stroke, or non-fatal MI)

Key secondary endpoints

- Time to first occurrence of individual components of MACE
- Time to all-cause mortality
- Time to expanded MACE endpoint

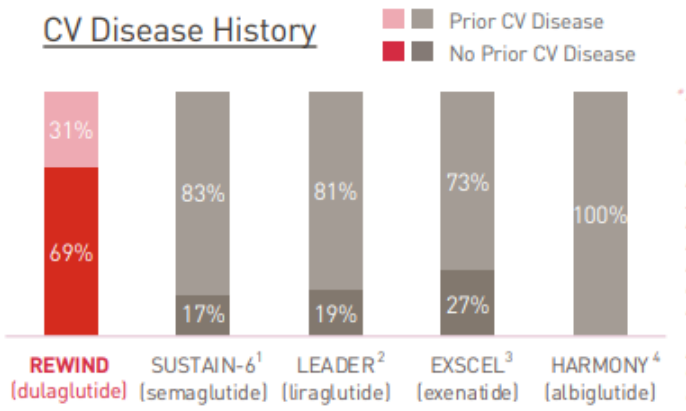
CV, cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular event; MI, myocardial infarction; OR, odds ratio.
Bain SC et al. Diabetes Obes Metab. 2018; 1-10. doi: 10.1111/dom.13553. Novo Nordisk company announcement: www.novonordisk.com/media.

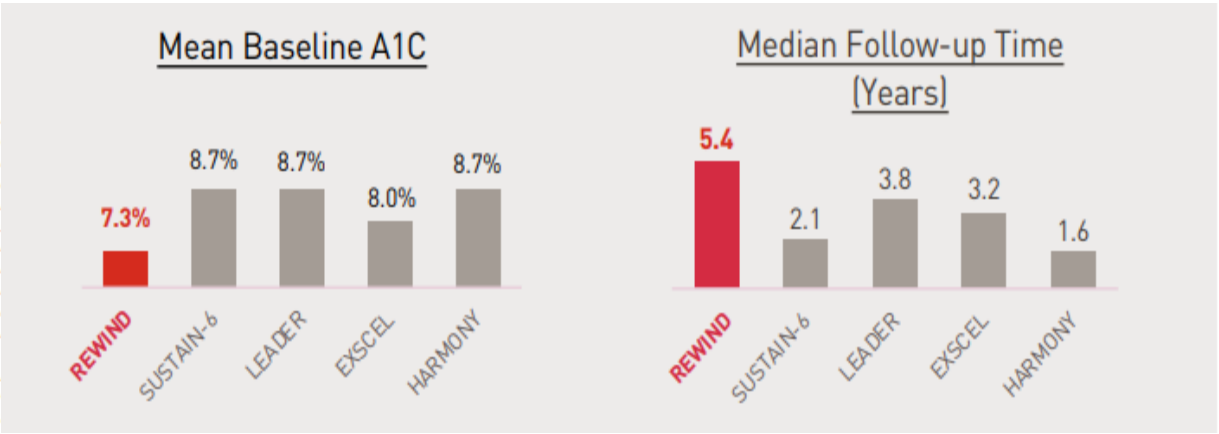
Pressenotiz zur Rewind-Studie

(dulaglutide) demonstrates superiority in reduction of cardiovascular events for broad range of people with type 2 diabetes

Only 31 percent of REWIND trial participants had established CV disease

INDIANAPOLIS, November 5, 2018 – (dulaglutide) significantly reduced major adverse cardiovascular events (MACE), a composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction (heart attack) or non-fatal stroke, meeting the primary efficacy objective in the precedent-setting REWIND trial. Eli Lilly and Company's (NYSE: LLY) once-weekly Trulicity is the first type 2 diabetes medicine to demonstrate superiority in the reduction of MACE events in a clinical trial that included a majority of participants who did not have established CV disease.





Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial

Juan Pablo Frias, Michael A Nauck, Joanna Van, Mark E Kutner, Xuewei Cui, Charles Benson, Shweta Urva, Ruth E Gimeno, Zvonko Milicevic, Deborah Robins, Axel Haupt

Summary

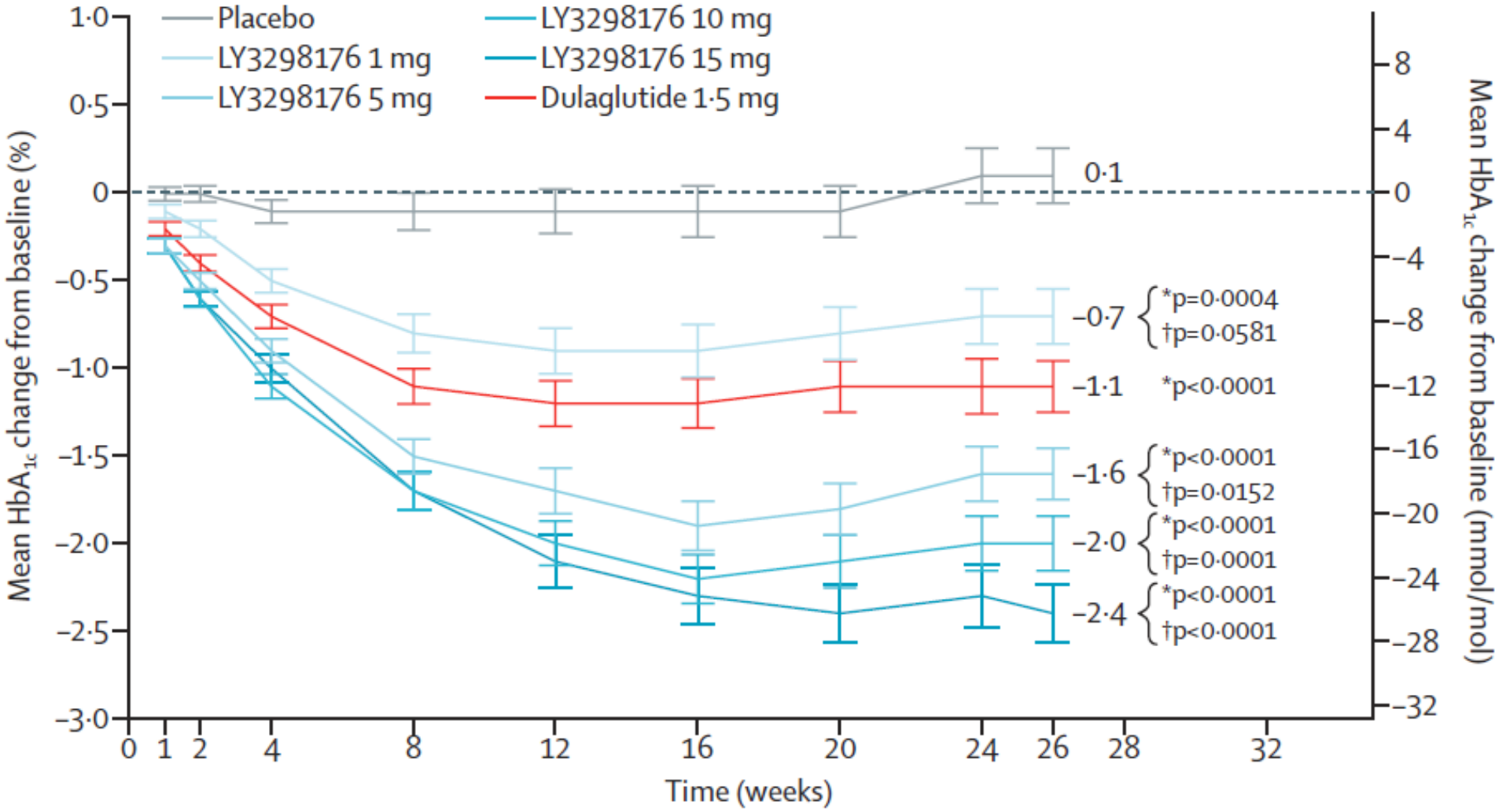
Background LY3298176 is a novel dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist that is being developed for the treatment of type 2 diabetes. We aimed to examine the efficacy and safety of co-stimulation of the GLP-1 and GIP receptors with LY3298176 compared with placebo or selective stimulation of GLP-1 receptors with dulaglutide in patients with poorly controlled type 2 diabetes.

Interpretation The dual GIP and GLP-1 receptor agonist, LY3298176, showed significantly better efficacy with regard to glucose control and weight loss than did dulaglutide, with an acceptable safety and tolerability profile. Combined GIP and GLP-1 receptor stimulation might offer a new therapeutic option in the treatment of type 2 diabetes.

October 4, 2018
http://dx.doi.org/10.1016/
S0140-6736(18)32260-8

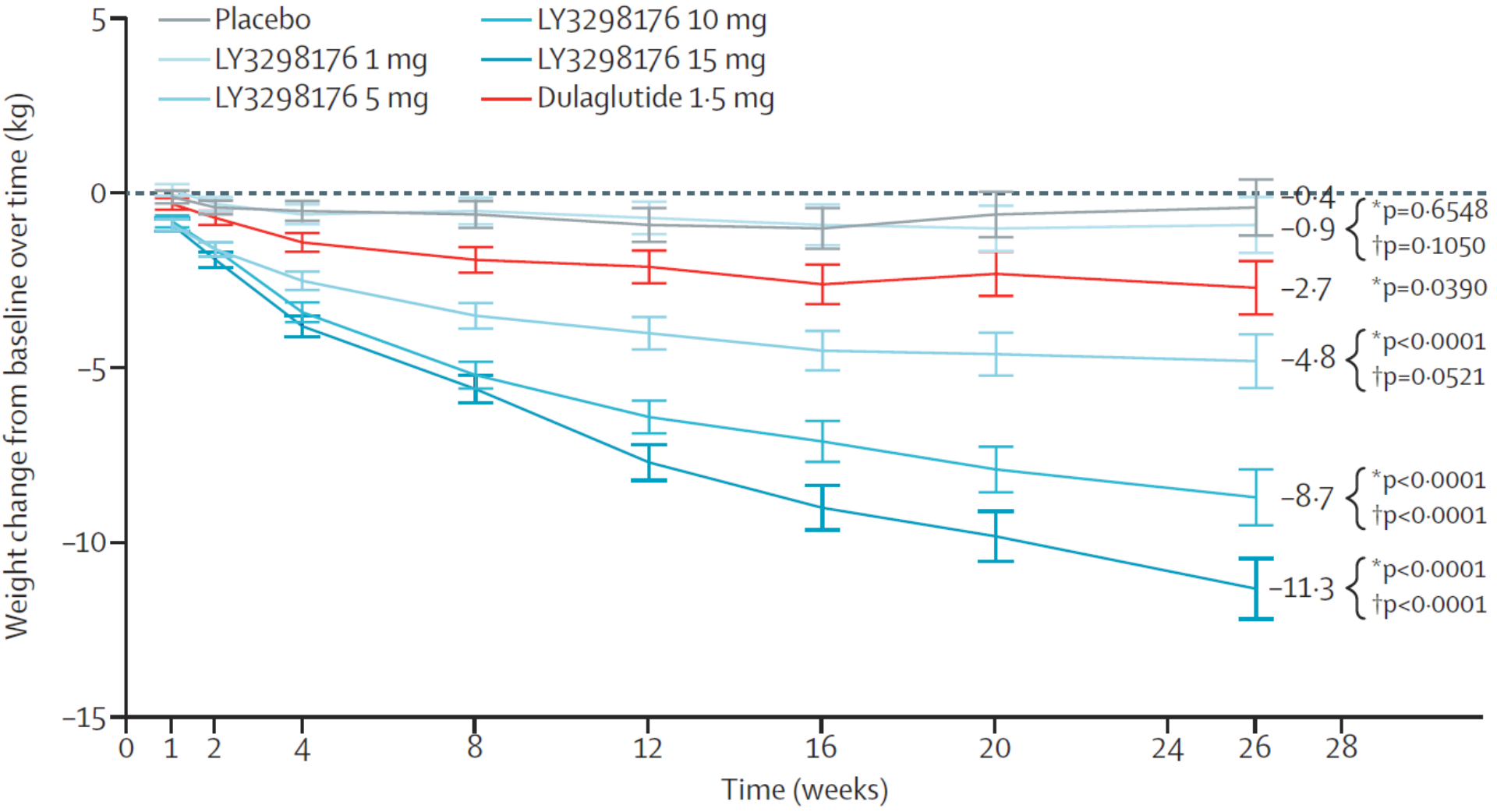
LY32981761, vs Dulaglutide vs Placebo 1x/Woche s.c.: HbA1c nach 26 Wochen

October 4, 2018
http://dx.doi.org/10.1016/
S0140-6736(18)32260-8

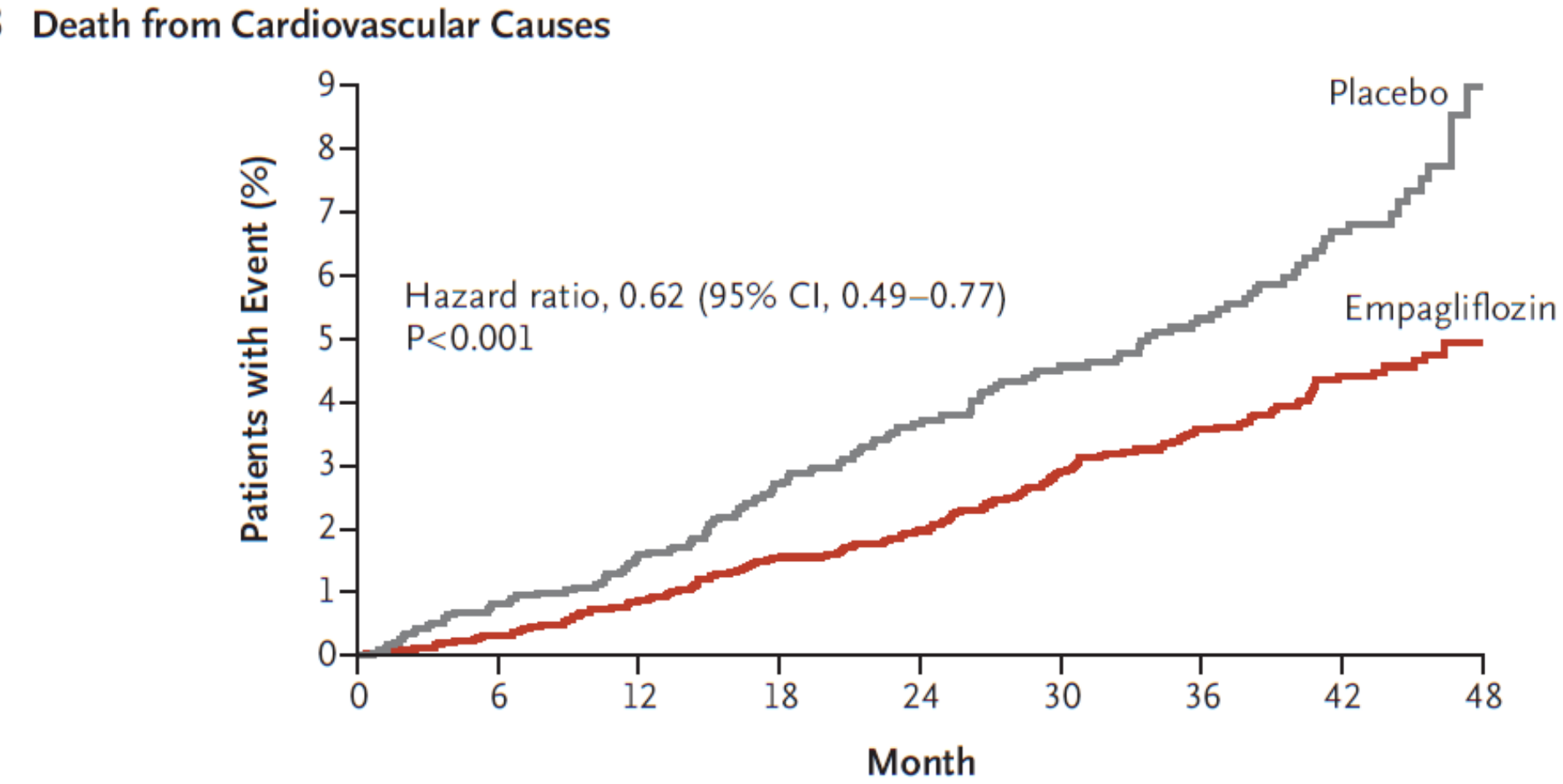


LY32981761, vs Dulaglutide vs Placebo 1x/Woche s.c.: Gewichtswreduktion nach 26 Wochen

October 4, 2018
http://dx.doi.org/10.1016/
S0140-6736(18)32260-8

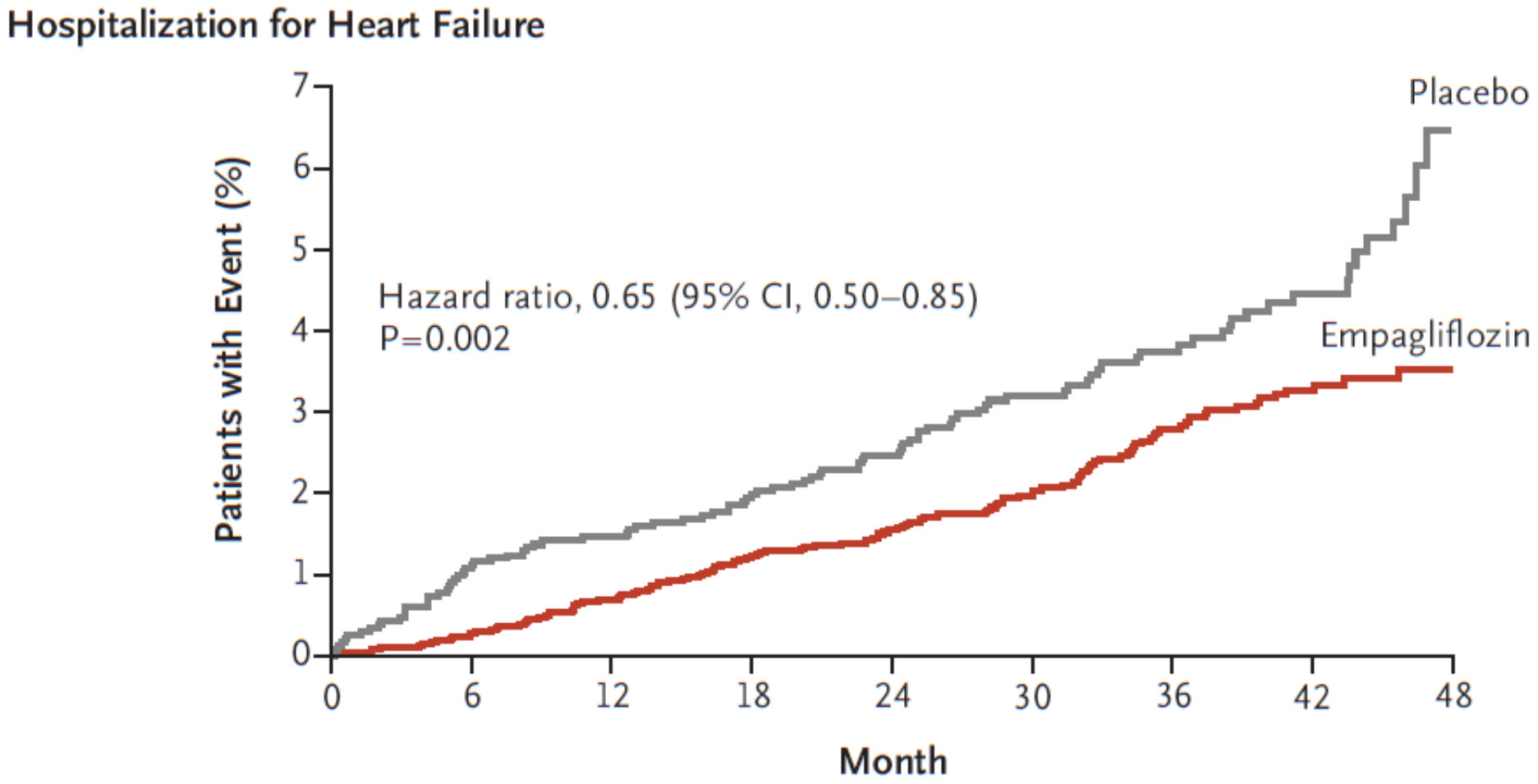


EMPA-REG Outcome: Kardiovaskuläre Mortalität



N Engl J Med 2015; 373:2117-2128

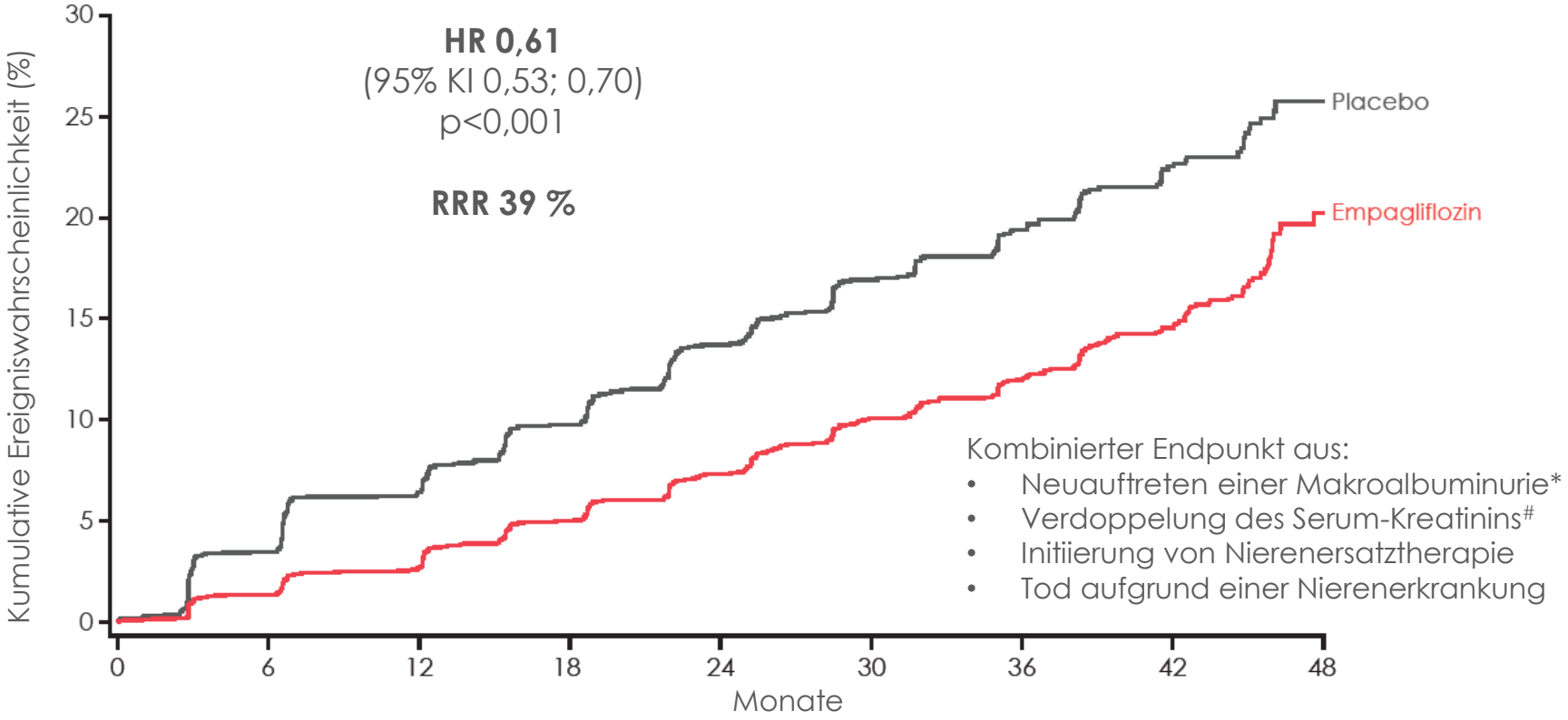
EMPA-REG Outcome: Herzinsuffizienz-Hospitalisation



No. at Risk									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

N Engl J Med 2015; 373:2117-2128

Neuauftreten oder Verschlechterung einer Nierenerkrankung



Anzahl Patienten

Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

*Albumin: Kreatinin Verhältnis ≥ 300 mg/g
#Zusammen mit einer eGFR [MDRD] ≤45 ml/min/1,73m^2.
Kaplan-Meier-Kurve. Patienten, die ≥1 Dosis der Studienmedikation erhielten. Hazard Ratios basierend auf Cox-Regressions-Analysen.
HR, Hazard Ratio; KI, Konfidenzintervall; RRR, relative Risikoreduktion. Präspezifizierte Analysen.
Referenz: Wanner C et al. N Engl J Med. 2016; DOI: 10.1056/NEJMoa1515920 [Epub ahead of print].

N Engl J Med 2015; 373:2117-2128

1.000 HochrisikoTyp-2 Diabetiker 3 J. Empagliflozin:

- 25 Tote (Gesamtmortalität)

- 14 Herzinsuffizienz-Hospitalisationen

+ 53 Genitalinfektionen

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2017; 377:644-657

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

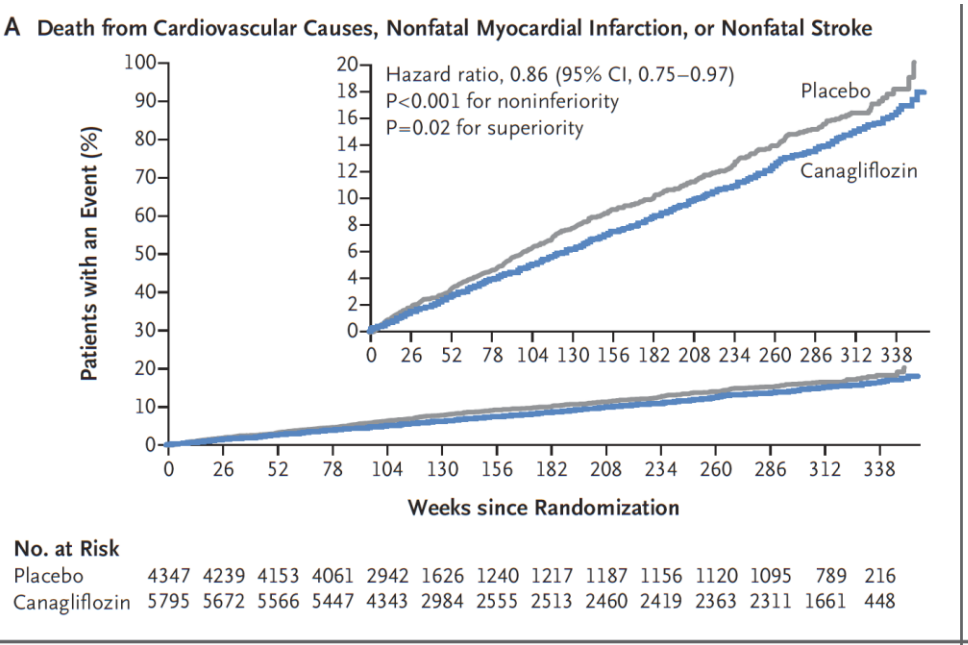
Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

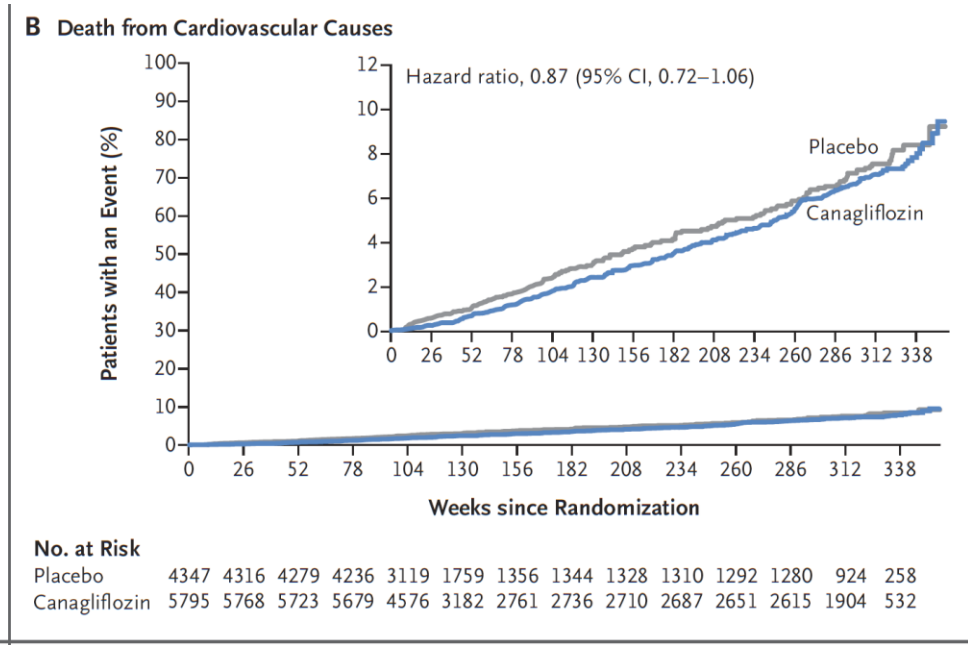
CONCLUSIONS

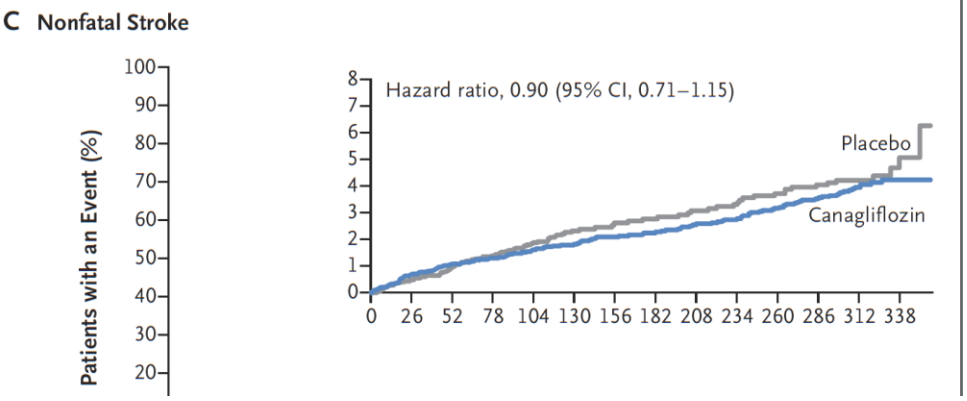
In two trials involving patients with type 2 diabetes and an elevated risk of cardiovascular disease, patients treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo but a greater risk of amputation, primarily at the level of the toe or metatarsal. (Funded by Janssen Research and

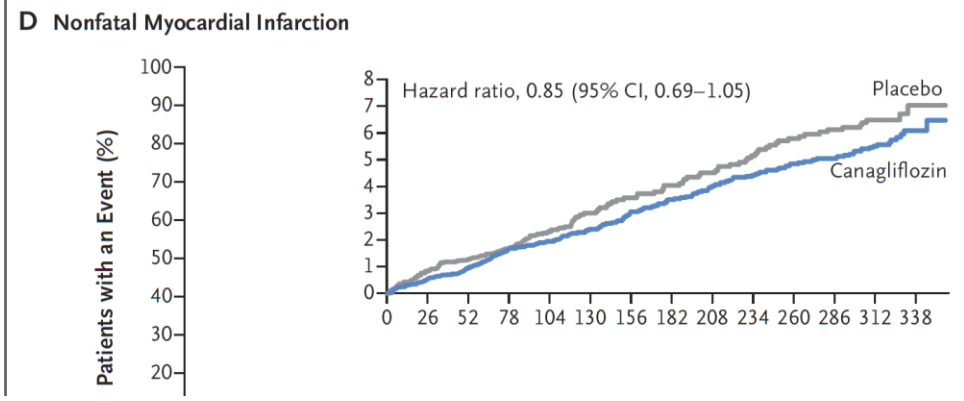
N Engl J Med 2017; 377:644-657

CANVAS: Endpunkte





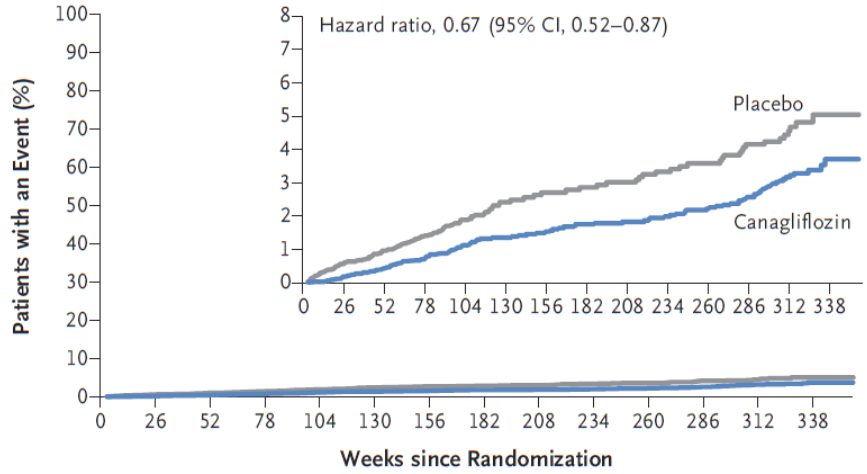




CANVAS: Endpunkte

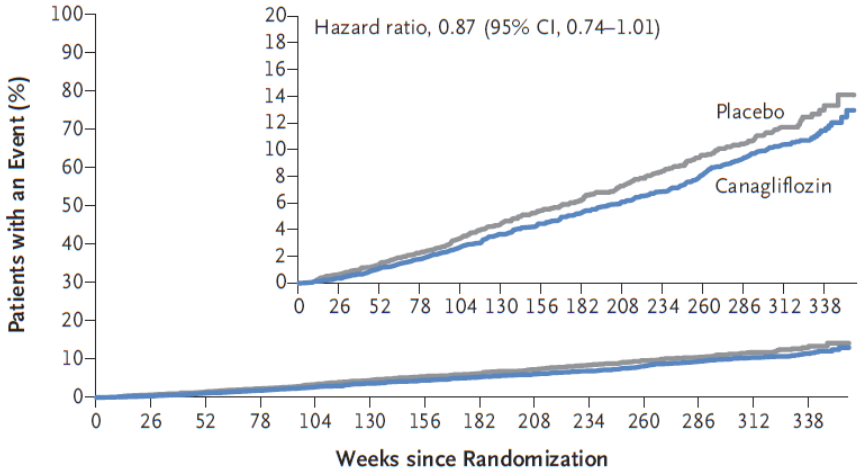
N Engl J Med 2017; 377:644-657

A Hospitalization for Heart Failure



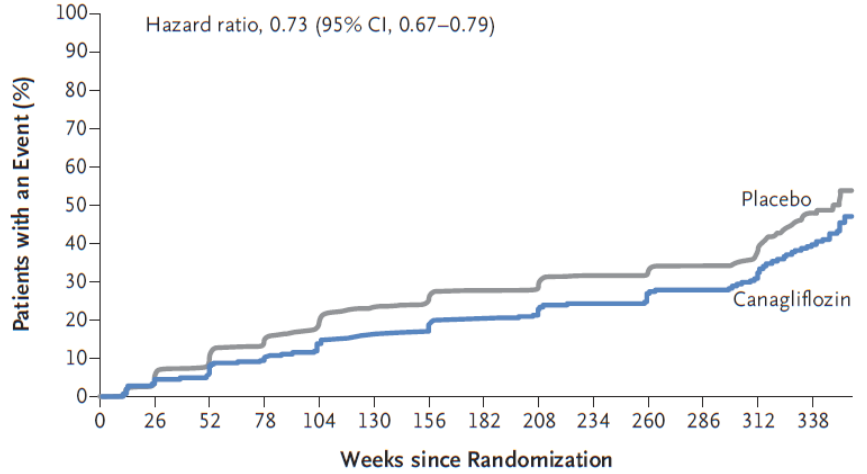
No. at Risk														
Placebo	4347	4267	4198	4123	3011	1667	1274	1256	1236	1210	1180	1158	829	233
Canagliflozin	5795	5732	5653	5564	4437	3059	2643	2610	2572	2540	2498	2451	1782	490

B Death from Any Cause



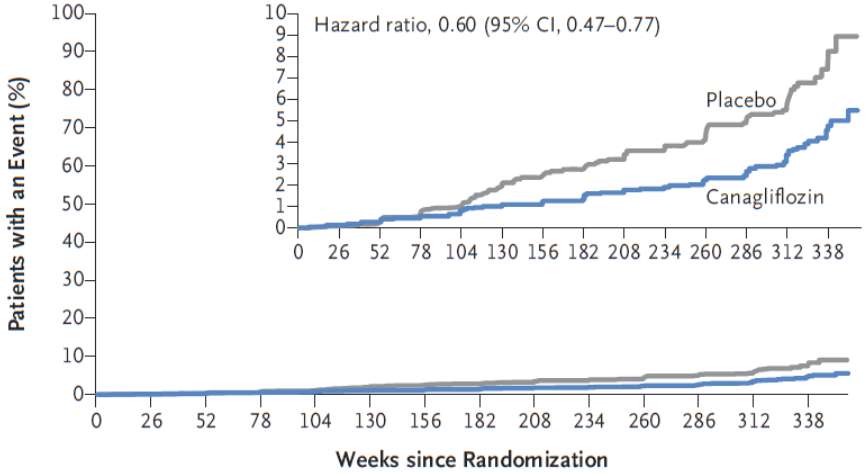
No. at Risk														
Placebo	4347	4316	4279	4236	3119	1759	1356	1344	1328	1310	1292	1280	924	258
Canagliflozin	5795	5768	5723	5679	4576	3182	2761	2736	2710	2687	2651	2615	1904	532

C Progression of Albuminuria



No. at Risk														
Placebo	3819	3473	3096	2700	1690	877	724	652	626	565	548	485	303	67
Canagliflozin	5196	4791	4475	4027	2968	1951	1730	1593	1528	1408	1354	1213	775	185

D Composite of 40% Reduction in eGFR, Requirement for Renal-Replacement Therapy, or Death from Renal Causes



No. at Risk														
Placebo	4347	4287	4227	4151	3029	1674	1274	1253	1229	1202	1173	1148	819	229
Canagliflozin	5795	5737	5664	5578	4454	3071	2654	2623	2576	2542	2495	2450	1781	493

N Engl J Med 2017; 377:644-657

CANVAS: Adverse Events

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
All serious adverse events	104.3	120.0	0.04
Adverse events leading to discontinuation	35.5	32.8	0.07
Serious and nonserious adverse events of interest recorded in the CANVAS Program			
Acute pancreatitis (adjudicated)	0.5	0.4	0.63
Cancer			
Renal cell	0.6	0.2	0.17
Bladder	1.0	1.1	0.74
Breast	3.1	2.6	0.65
Photosensitivity	1.0	0.3	0.07
Diabetic ketoacidosis (adjudicated)	0.6	0.3	0.14
Amputation	6.3	3.4	<0.001
Fracture (adjudicated)‡			
All	15.4	11.9	0.02
Low-trauma	11.6	9.2	0.06
Venous thromboembolic events	1.7	1.7	0.63
Infection of male genitalia§	34.9	10.8	<0.001
Serious and nonserious adverse events of interest collected in CANVAS alone¶			
Osmotic diuresis	34.5	13.3	<0.001
Volume depletion	26.0	18.5	0.009
Hypoglycemia	50.0	46.4	0.20
Acute kidney injury	3.0	4.1	0.33
Hyperkalemia	6.9	4.4	0.10
Urinary tract infection	40.0	37.0	0.38
Mycotic genital infection in women	68.8	17.5	<0.001
Severe hypersensitivity or cutaneous reaction	8.5	6.1	0.17
Hepatic injury	7.4	9.1	0.35
Renal-related (including acute kidney injury)	19.7	17.4	0.32

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ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*

17.000 Typ 2 Diabetiker:

- 7.000 mit CVD
- 10.000 ohne CVD

DECLARE: Patienten

7.000 mit CVD
10.000 ohne CVD

This article was published on November 10, 2018, at NEJM.org.
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Characteristic	Dapagliflozin (N=8582)	Placebo (N=8578)
Age — yr	63.9±6.8	64.0±6.8
Female sex — no. (%)	3171 (36.9)	3251 (37.9)
Race — no. (%)†		
White	6843 (79.7)	6810 (79.4)
Black	295 (3.4)	308 (3.6)
Asian	1148 (13.4)	1155 (13.5)
Other	296 (3.4)	305 (3.6)
Region — no. (%)		
North America	2737 (31.9)	2731 (31.8)
Europe	3806 (44.3)	3823 (44.6)
Latin America	946 (11.0)	931 (10.9)
Asia–Pacific	1093 (12.7)	1093 (12.7)
Body-mass index‡	32.1±6.0	32.0±6.1
Median duration of type 2 diabetes (IQR) — yr	11.0 (6.0–16.0)	10.0 (6.0–16.0)
Glycated hemoglobin — %	8.3±1.2	8.3±1.2
Systolic blood pressure — mm Hg	135.1±15.3	134.8±15.5
Estimated glomerular filtration rate — ml/min/1.73 m^2	85.4±15.8	85.1±16.0
Established atherosclerotic cardiovascular disease — no. (%)	3474 (40.5)	3500 (40.8)
History of coronary artery disease — no. (%)	2824 (32.9)	2834 (33.0)
History of peripheral artery disease — no. (%)	522 (6.1)	503 (5.9)
History of cerebrovascular disease — no. (%)	653 (7.6)	648 (7.6)
History of heart failure — no. (%)	852 (9.9)	872 (10.2)
Glucose-lowering therapies — no. (%)		
Insulin	3567 (41.6)	3446 (40.2)
Metformin	7020 (81.8)	7048 (82.2)
Sulfonylurea	3615 (42.1)	3707 (43.2)
DPP-4	1418 (16.5)	1470 (17.1)
GLP-1 receptor agonist	397 (4.6)	353 (4.1)
Cardiovascular therapies — no. (%)		
Antiplatelet agents	5245 (61.1)	5242 (61.1)
ACE inhibitor or ARB	6977 (81.3)	6973 (81.3)
Beta-blocker	4498 (52.4)	4532 (52.8)
Statin or ezetimibe	6432 (74.9)	6436 (75.0)
Diuretics	3488 (40.6)	3479 (40.6)

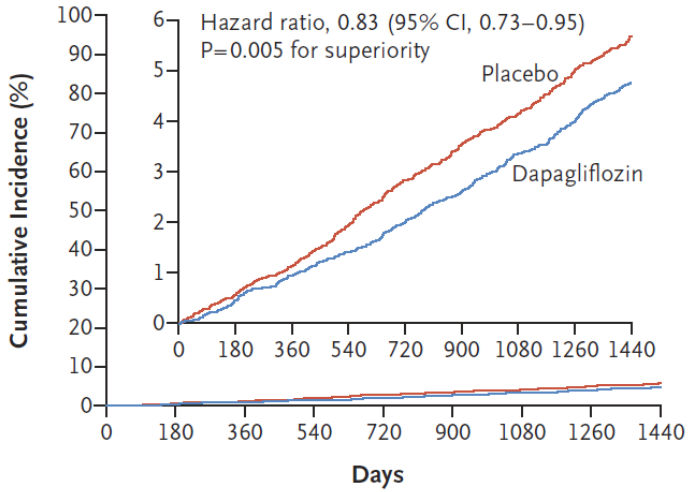
Einschlusskriterien der SGLT2-Hemmer-Endpunktstudien im Vergleich zur allgemeinen TDM2 Population

	DECLARE-TIMI 58	CANVAS	EMPA-REG OUTCOME	VERTIS-CV	T2DM-Gesamtpopulation
Substanz	**Dapagliflozin**	**Canagliflozin**	**Empagliflozin**	**Ertugliflozin**	
Patienten, n	17.160	10.142	7.020	8.237	564.351
Alter, Jahre	63,8	63,3	63,1	64,4	67,2
Weiblich, %	37	36	29	30	42
CV-Erkrankung, %	41	66	99	99	30
Herzinsuffizienz, %	10	14	10	22	9

Modifiziert nach: 1. Birkeland KI, et al. Präsentiert auf dem European Association for the Study of Diabetes 54th Annual Meeting, Berlin, 1.-5. Oktober 2018; 1137-P. [https://www.easd.org/virtualmeeting/home.html#!resources/differences-in-external-validity-of-sglt2-i-cardiovascular-outcome-trials-in-general-type-2-diabetes-populations-a-large-observational-study-in-european-countries-6beeb24d-309e-4d52-b042-f739ae8f65f4; abgerufen am: 08.10.2018];

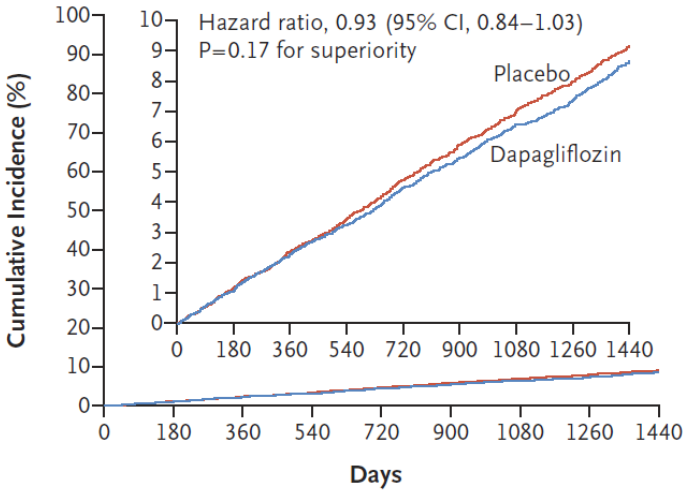
DECLARE: Endpunkte

A Cardiovascular Death or Hospitalization for Heart Failure



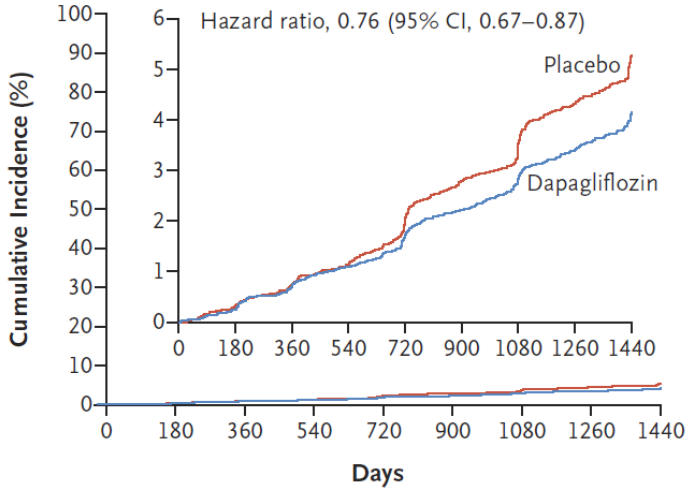
No. at Risk									
Placebo	8578	8485	8387	8259	8127	8003	7880	7367	5362
Dapagliflozin	8582	8517	8415	8322	8224	8110	7970	7497	5445

B MACE



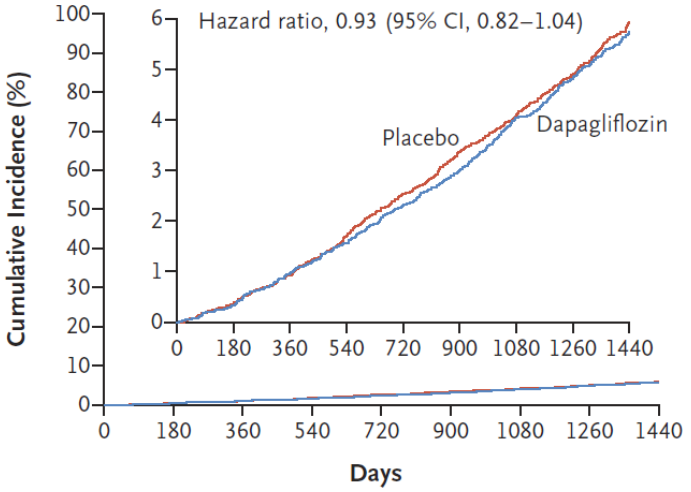
No. at Risk									
Placebo	8578	8433	8281	8129	7969	7805	7649	7137	5158
Dapagliflozin	8582	8466	8303	8166	8017	7873	7708	7237	5225

C Renal Composite



No. at Risk									
Placebo	8578	8508	8422	8326	8200	8056	7932	7409	5389
Dapagliflozin	8582	8533	8436	8347	8248	8136	8009	7534	5472

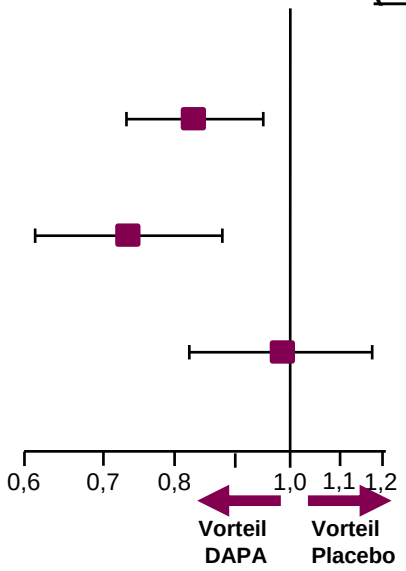
D Death from Any Cause



No. at Risk									
Placebo	8578	8542	8484	8414	8337	8258	8184	7741	5715
Dapagliflozin	8582	8554	8495	8437	8369	8305	8207	7763	5715

DOI: 10.1056/NEJMoa1812389

DECLARE
Primärer Endpunkt: HHI oder CV-Tod und einzelne Komponenten



	Anzahl der Ereignisse DAPA 10 mg (n=8.582)	Placebo (n=8.578)	HR (95 %-KI)	P-Wert*
Kombination aus HHI/CV-Tod	417	496	0,83 (0,73; 0,95)	0,005
HHI	212	286	0,73 (0,61; 0,88)	
CV-Tod	245	249	0,98 (0,82; 1,17)	

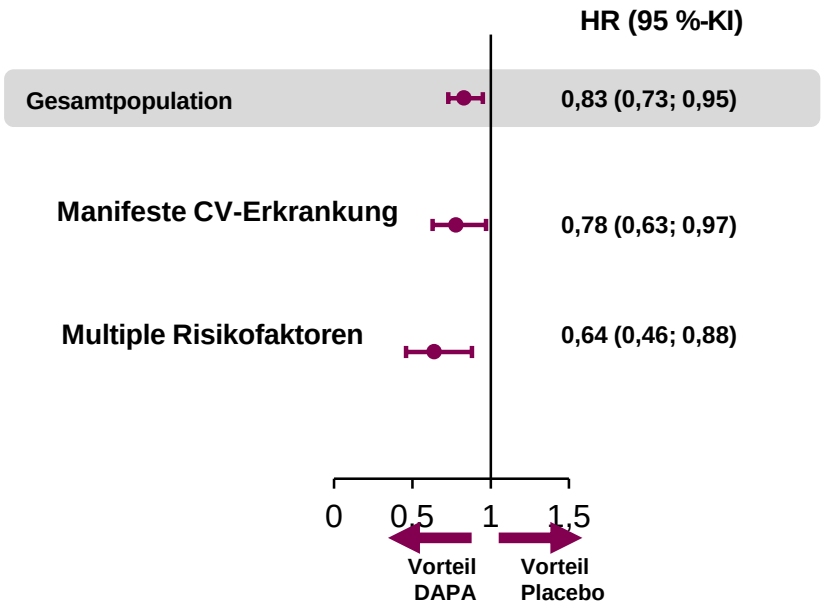
Dapagliflozin ist nicht zugelassen zur Reduktion des kardiovaskulären Risikos.
*Zweiseitiger P-Wert für den primären Wirksamkeitsendpunkt CV-Tod oder HHI.
CV, kardiovaskulär; DAPA, Dapagliflozin; HHI, Hospitalisierung aufgrund von Herzinsuffizienz; HR, Hazard-Ratio; KI, Konfidenzintervall.

Modifiziert nach: Wiviott SD, et al. N Engl J Med 2018; doi 10.1056/NEJMoa1812389; [Epub ahead of print].

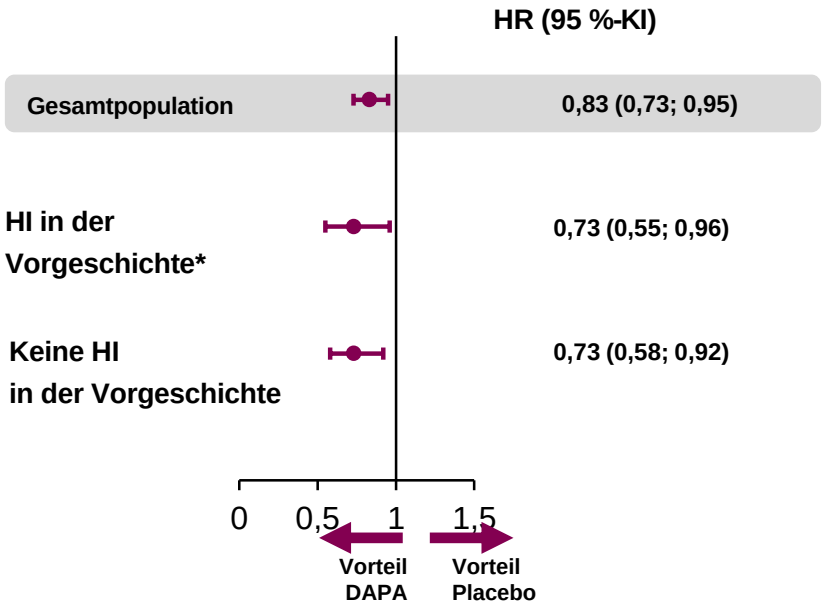
DECLARE

HHI in Abhängigkeit von CV-Risiko und HI in der Vorgeschichte

HHI in Abhängigkeit von CV-Risiko



HHI in Abhängigkeit von HI in der Vorgeschichte

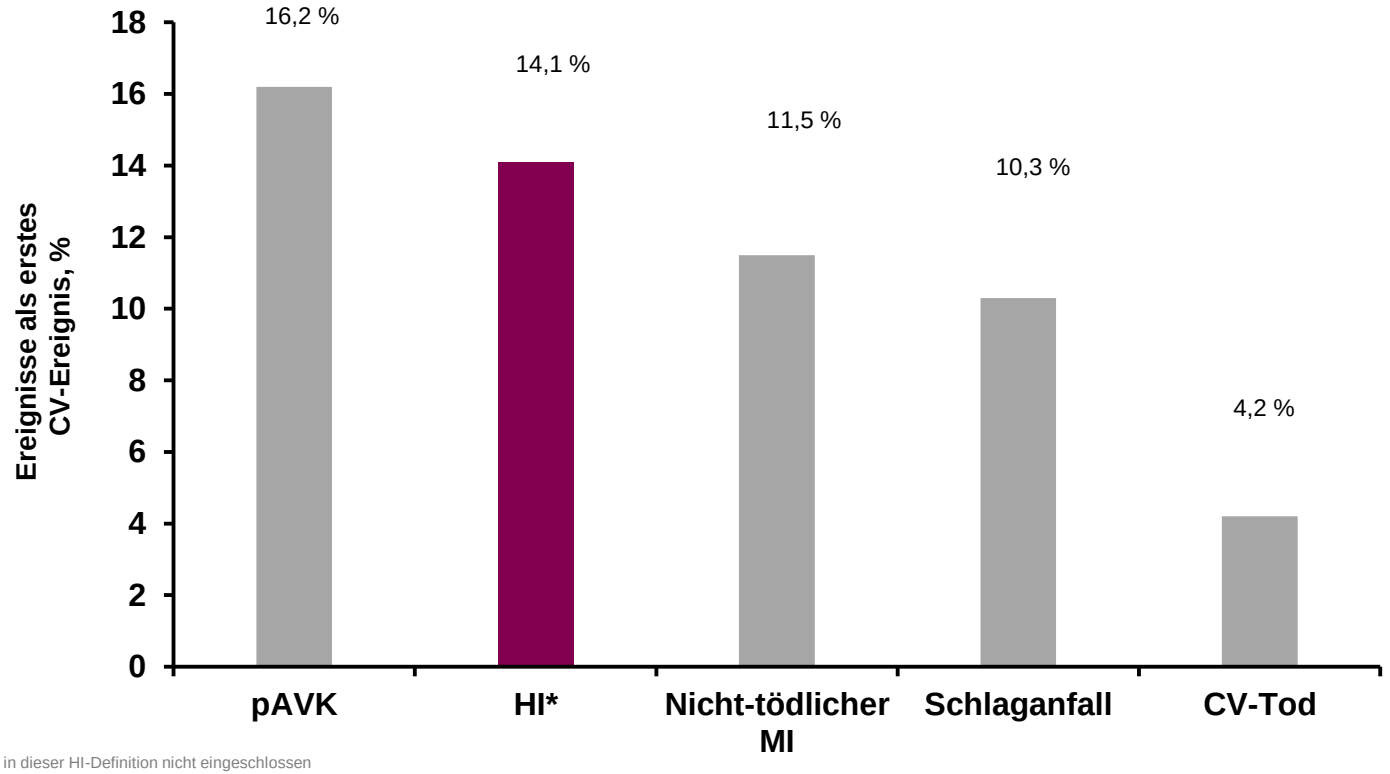


Dapagliflozin ist nicht zugelassen zur Reduktion des kardiovaskulären Risikos.
*10 % der Patienten in der DECLARE-Studie wiesen eine HI in der Vorgeschichte auf.
CV, kardiovaskulär; HI, Herzinsuffizienz; HHI, Hospitalisierung aufgrund von Herzinsuffizienz.

Modifiziert nach: Wiviott SD, et al. N Engl J Med 2018; doi 10.1056/NEJMoa1812389; [Epub ahead of print]. Artikel und Supplementary Appendix.

Häufigkeit kardiovaskulärer Erkrankungen bei Typ 2 Diabetes

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



*HI nach MI wurde in dieser HI-Definition nicht eingeschlossen
CV, kardiovaskulär; HI, Herzinsuffizienz; MACE; schwerwiegendes unerwünschtes kardiovaskuläres Ereignis (*major adverse cardiovascular event*); MI, Myokardinfarkt; pAVK, periphere arterielle Verschlusskrankheit; T2DM, Typ 2 Diabetes mellitus.

Modifiziert nach: Shah AD, et al. Lancet Diabetes Endocrinol. 2015;3:105-113, Appendix.

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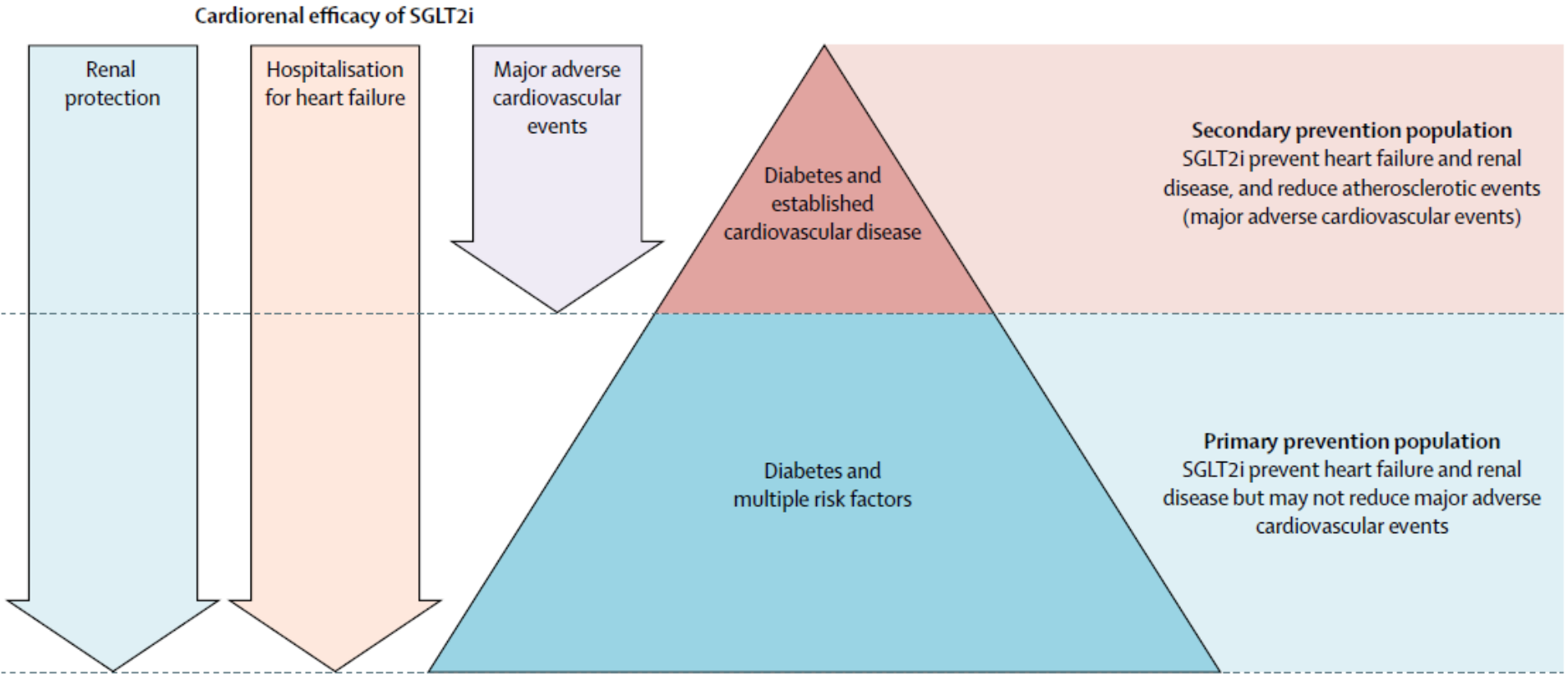
CONCLUSIONS

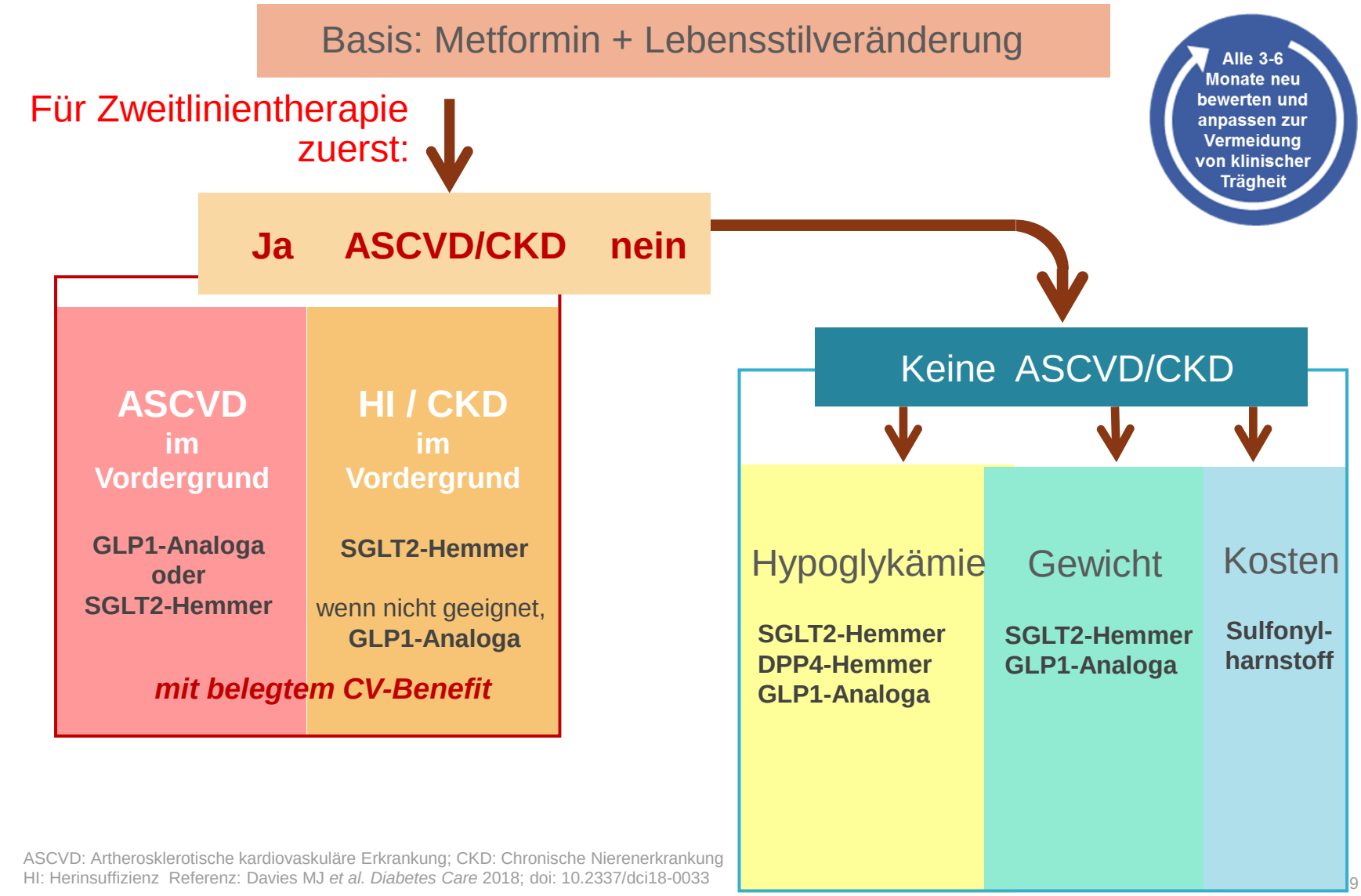
In patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease, treatment with dapagliflozin did not result in a higher or lower rate of MACE than placebo but did result in a lower rate of cardiovascular death or hospitalization for heart failure, a finding that reflects a lower rate of hospitalization for heart failure. (Funded by AstraZeneca; DECLARE–TIMI 58 ClinicalTrials.gov

Nutzen der SGLT2-Hemmer bei Typ 2 Diabetikern unterschiedlicher Risikoklassen



November 10, 2018
http://dx.doi.org/10.1016/
S0140-6736(18)32824-1

ADA/EASD Consensus Report 2018: Wahl von Antidiabetika bei Typ-2-Diabetes



ASCVD: Artherosklerotische kardiovaskuläre Erkrankung; CKD: Chronische Nierenerkrankung
HI: Herinsuffizienz Referenz: Davies MJ *et al. Diabetes Care* 2018; doi: 10.2337/dci18-0033

Kardiovask. Risikosenkung mit neuen Antidiabetika

Empagliflozin (EMPA-REG)	Gesamtmortalität	- 32%
[Canagliflozin (CANVAS)	3-MACE	-14%]
Dapagliflozin (DECLARE)	Herzinsuff.-Hospit.	- 27%
Liraglutid (LEADER):	Gesamtortalität	-15%
[Semaglutid (SUSTAIN-6):	3-MACE	-26%]
[Albiglutid (HARMONY)	3-MACE	-22%]
Dulaglutid (REWIND)	3-MACE	(?%)

3-MACE: kardiovask. Tod + MI + Stroke

TDM2: Take Home Messages

- ASS nicht in der Primärprävention
- Omega-3 FS ohne Wirkung
- Eicosapentaensäure: Mortalitätssenkung bei ASCVD
- Insulin Degludec: weniger Hypoglykämien als Glargin, wieder verfügbar

EASD, ADA, Praxis-LL DDG: Welches Zweitmedikament nach Metformin?

- erstrangige Kriterien: ASCVD, HI, CNI (SGLT2-Hemmer, GLP1-RA bevorzugt)
- zweitrangig: Hypoglykämievermeidung, Gewichtsreduktion, (Kosten)

- SGLT2-Hemmer
  - ohne ASCVD: Herzinsuffizienzvermeidung, Nephroprotektion
  - mit ASCVD: zusätzlich kardiovaskuläre Risikoreduktion
- GLP1-Rezeptor-Agonisten
  - Alternative für SGLT2-Hemmer (z.B.bei Niereninsuffizienz, Genitalinfektionen)
  - Add on zu SGLT2-Hemmer (+ Metformin)
- Hypoglykämievermeidung: bevorzugt SGLT2-Hemmer, DPP4-Hemmer, (GLP1-RA)
- Gewichtsreduktion: GLP1-RA, SGLT2-Hemmer, Kombination aus beiden
- Insulin erst bei Versagen der anderen Kombinationstherapien incl. GLP1-RA