Modulating blood pressure, lipids and glucose using old drugs and, GLP-1, SGLT2, DPP4 and PCSK9 for cardiovascular health. What is the evidence?

Karim Meeran

13th June 2019

JAMA | Original Investigation

Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes

A Systematic Review and Meta-analysis

Sean L. Zheng, BM BCh, MA, MRCP; Alistair J. Roddick, BSc; Rochan Aghar-Jaffar, BMedSci, BMBS, MRCP; Matthew J. Shun-Shin, BM BCh, MRCP; Darrel Francis, MB BChir, FRCP, MD; Nick Oliver, MBBS, FRCP; Karim Meeran, MBBS, MD, FRCP, FRCPath

IMPORTANCE The comparative clinical efficacy of sodium-glucose cotransporter 2 (SGLT-2) inhibitors, glucagon-like peptide 1 (GLP-1) agonists, and dipeptidyl peptidase 4 (DPP-4) inhibitors for treatment of type 2 diabetes is unknown.

OBJECTIVE To compare the efficacies of SGLT-2 inhibitors, GLP-1 agonists, and DPP-4

Animated Summary Video

Supplemental content

17th April 2018

236 trials
Outcome was as predicted

https://jamanetwork.com/journals/jama/fullarticle/2678616

What would you do?

- A 76 year old patient with a previous MI has a BP of 140/80 on atenolol.
- LDL is 3.0mmol (120mg/dl) on atorvastatin 80mg

- Is there evidence to lower his BP further?
- To 140/80 (leave on atenolol)
- To 120/80 (add a thiazide diuretic)

ORIGINAL ARTICLE

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group

N Engl J Med 2015; 373:2103-2116 | November 26, 2015 | DOI: 10.1056/NEJMoa1511939

Comments open through December 2, 2015

BACKGROUND

The most appropriate targets for systolic blood pressure to reduce cardiovascular morbidity and mortality among persons without diabetes remain uncertain.

Full Text of Background...

METHODS

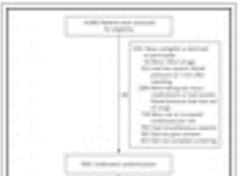
We randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

MEDIA IN THIS ARTICLE

Video

The SPRINT Trial.

FIGURE 1



Endpoints

- Primary: CV death, or an MI (fatal or non fatal) or ACS, Heart Failure

- Secondary: Death from any cause

Optimum medical therapy

- The protocol encouraged, but did not mandate, the use of drug classes with the strongest evidence for reduction in cardiovascular outcomes, including **thiazide**-type diuretics (encouraged as the first-line agent), loop diuretics (for participants with advanced chronic kidney disease), and **beta-adrenergic blockers** (for those with coronary artery disease).5,27 Chlorthalidone was encouraged as the primary thiazide-type diuretic, and **amlodipine** as the preferred calcium-channel blocker

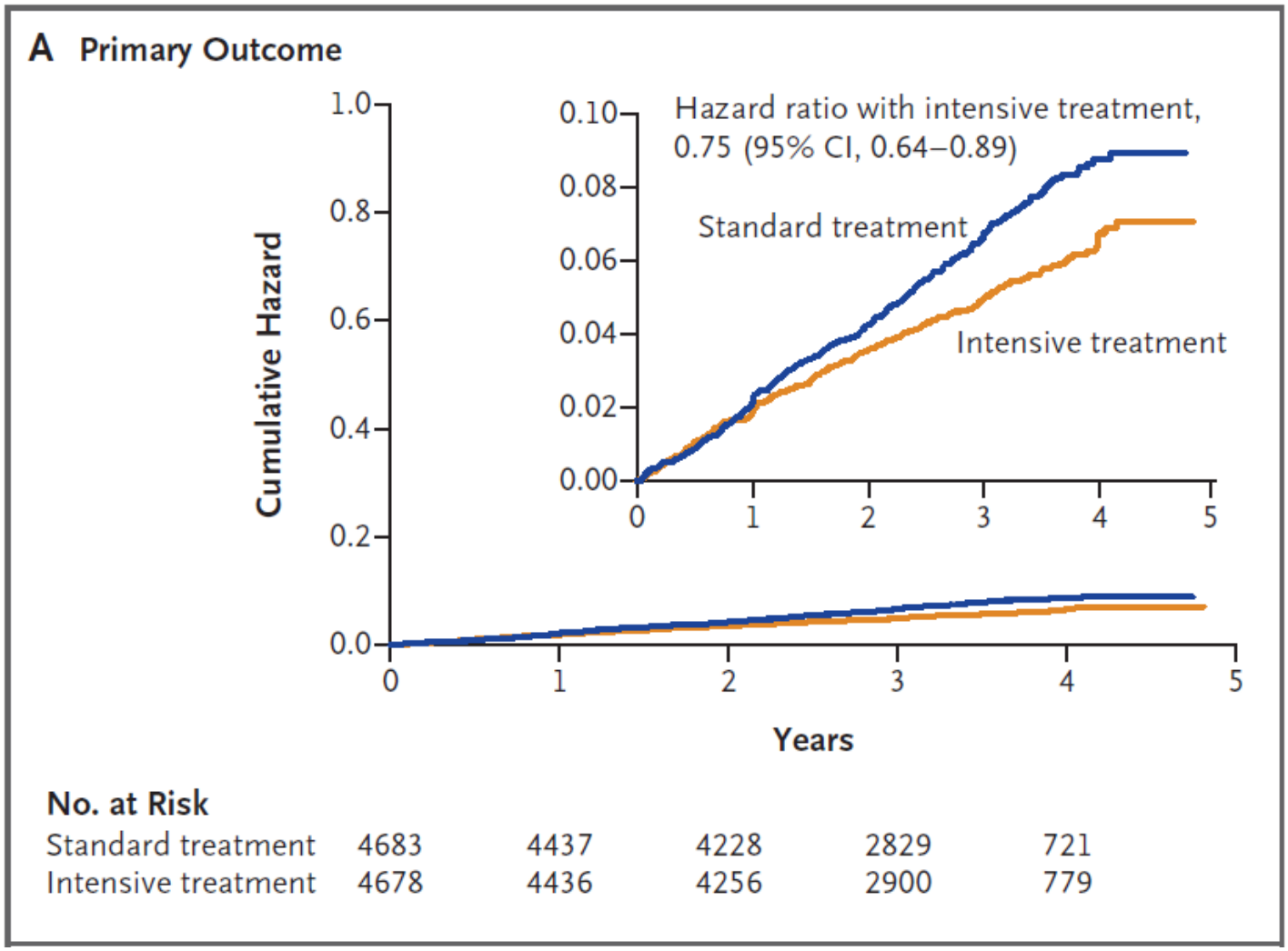
Results

- At 1 year, the mean systolic blood pressure was 121.4 mm Hg in the intensive-treatment group and 136.2 mm Hg in the standard-treatment group. The intervention was stopped early after a median follow-up of 3.26 years owing to a significantly lower rate of the primary composite outcome in the intensive-treatment group than in the standard-treatment group (1.65% per year vs. 2.19% per year; hazard ratio with intensive treatment,

ORIGINAL ARTICLE

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*



10%

8%

(20% relative risk reduction RRR)
Absolute reduction=2%

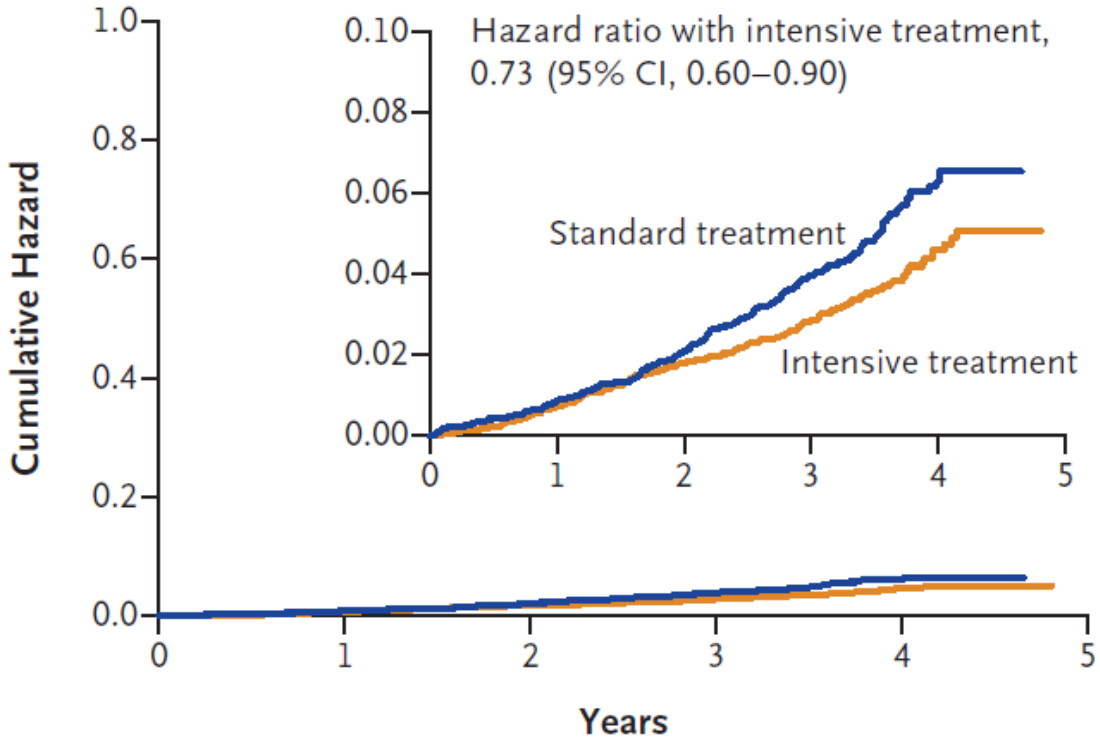
100 get a thiazide, you will reduce 2 events

ORIGINAL ARTICLE

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

B Death from Any Cause



No. at Risk

Standard treatment	4683	4528	4383	2998	789
Intensive treatment	4678	4516	4390	3016	807

7%

5%

(28% RRR (relative risk reduction))
Absolute reduction=2%

100 get a thiazide, you will save 2 lives

Thiazides very cheap

- Using thiazides in 100 people with CAD will save 2 lives over 5 years.

Optimal medical therapy

- Intensive lifestyle modification

- Aspirin
- High dose statin (Atorvastatin 40-80mg od)
- Optimal blood pressure control
- Thiazides are almost free

- Assessment for probable T2D (check HbA1c)

What would you do?

- A 76 year old patient with a previous MI has a BP of 140/80 on atenolol.
- LDL=3.0mmol (120mg/dl) on atorvastatin 80mg

- Is there evidence to lower his BP further?
- To 140/80 (leave on atenolol)
- To 120/80 (add a thiazide diuretic)
- What about further lipid lowering (PCSK9i)?

What do we do about statin intolerance?

Available options for statin intolerant patients?

- Ezetemibe
- Plasma Exchange where available

- Evolocumab (PCSK9 monoclonal antibody)

Until recently none of the above had evidence for prevention of ASCVD

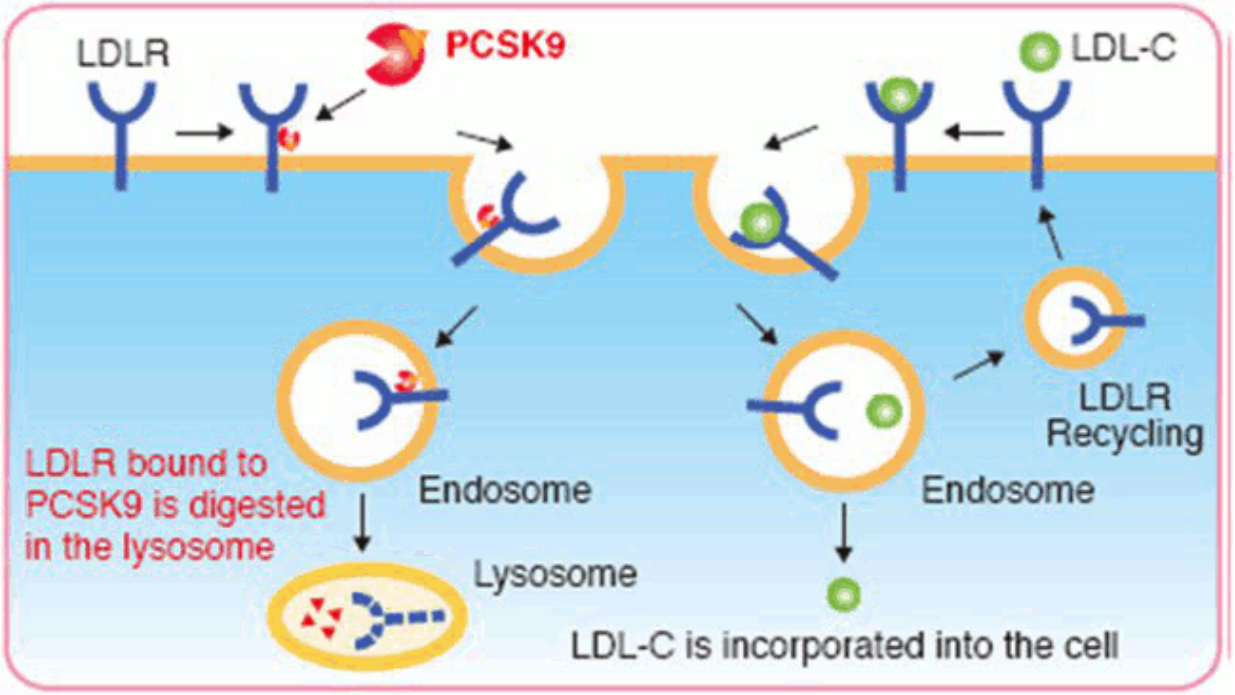
(atherosclerotic CVD)…

proprotein convertase subtilisin kexin 9 (PCSK9)

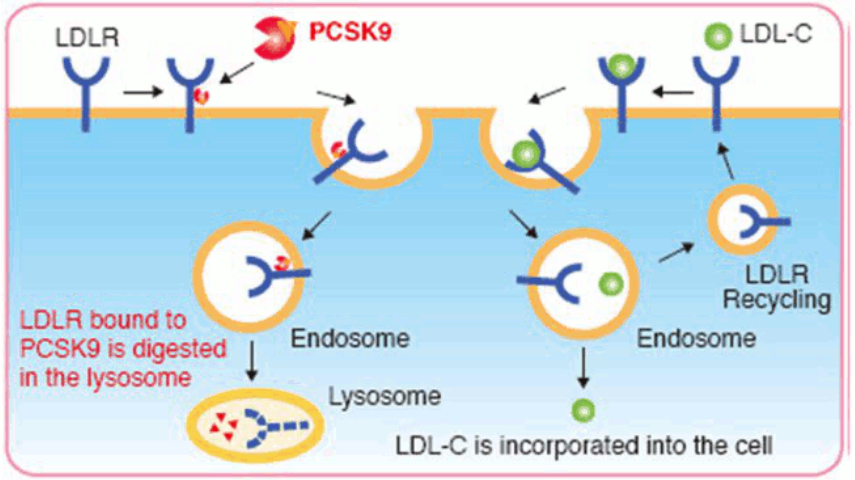
- PCSK9 regulates the levels of the LDL receptor

- Gain-of-function mutations in PCSK9 reduce LDL receptor levels in the liver, resulting in high levels of LDL cholesterol in the plasma and increased susceptibility to coronary heart disease

- Loss-of-function mutations lead to higher levels of the LDL receptor, lower LDL cholesterol levels, and protection from coronary heart disease

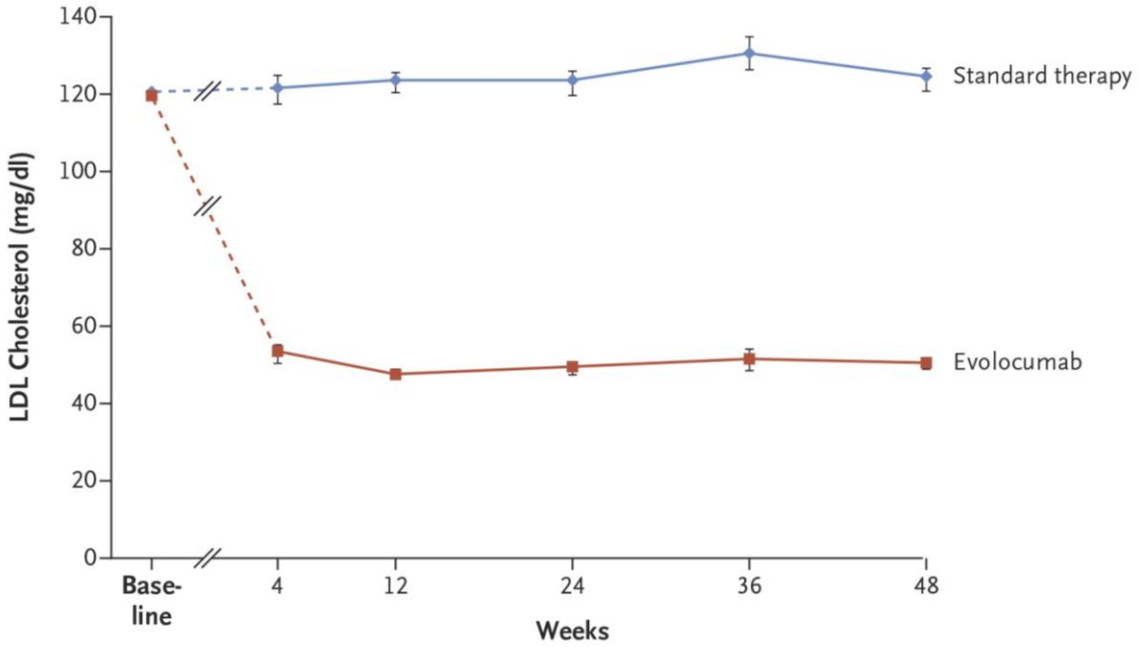


PCSK9 inhibition



3.1 mmol/l

1.3 mmol/l



Further Details

The NEW ENGLAND JOURNAL of MEDICINE

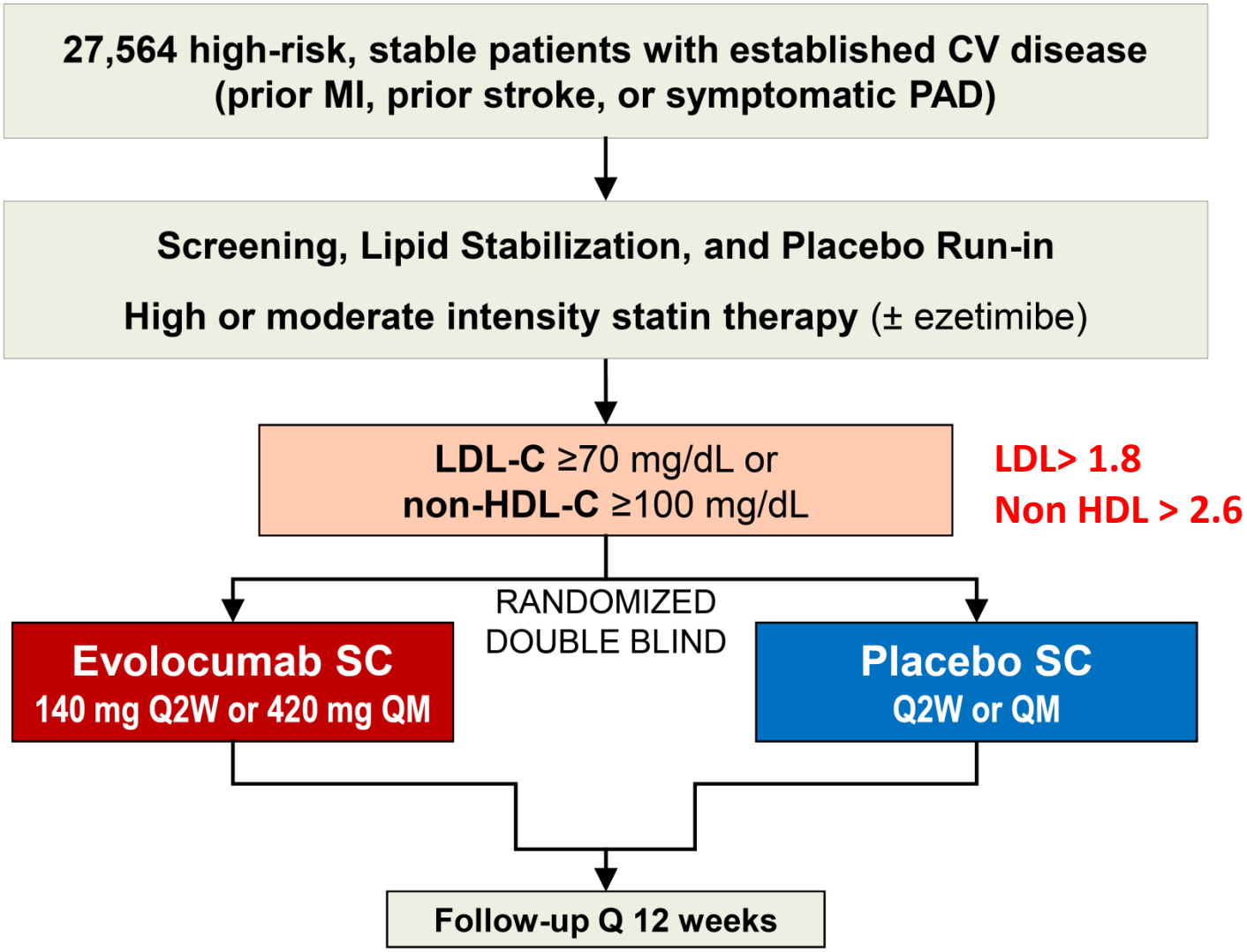
ORIGINAL ARTICLE

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

Article available at www.nejm.org
Slides available at www.TIMI.org

Trial Design



Sabatine MS et al. *Am Heart J* 2016;173:94-101

Lipid Lowering Therapy & Lipid Levels at Baseline

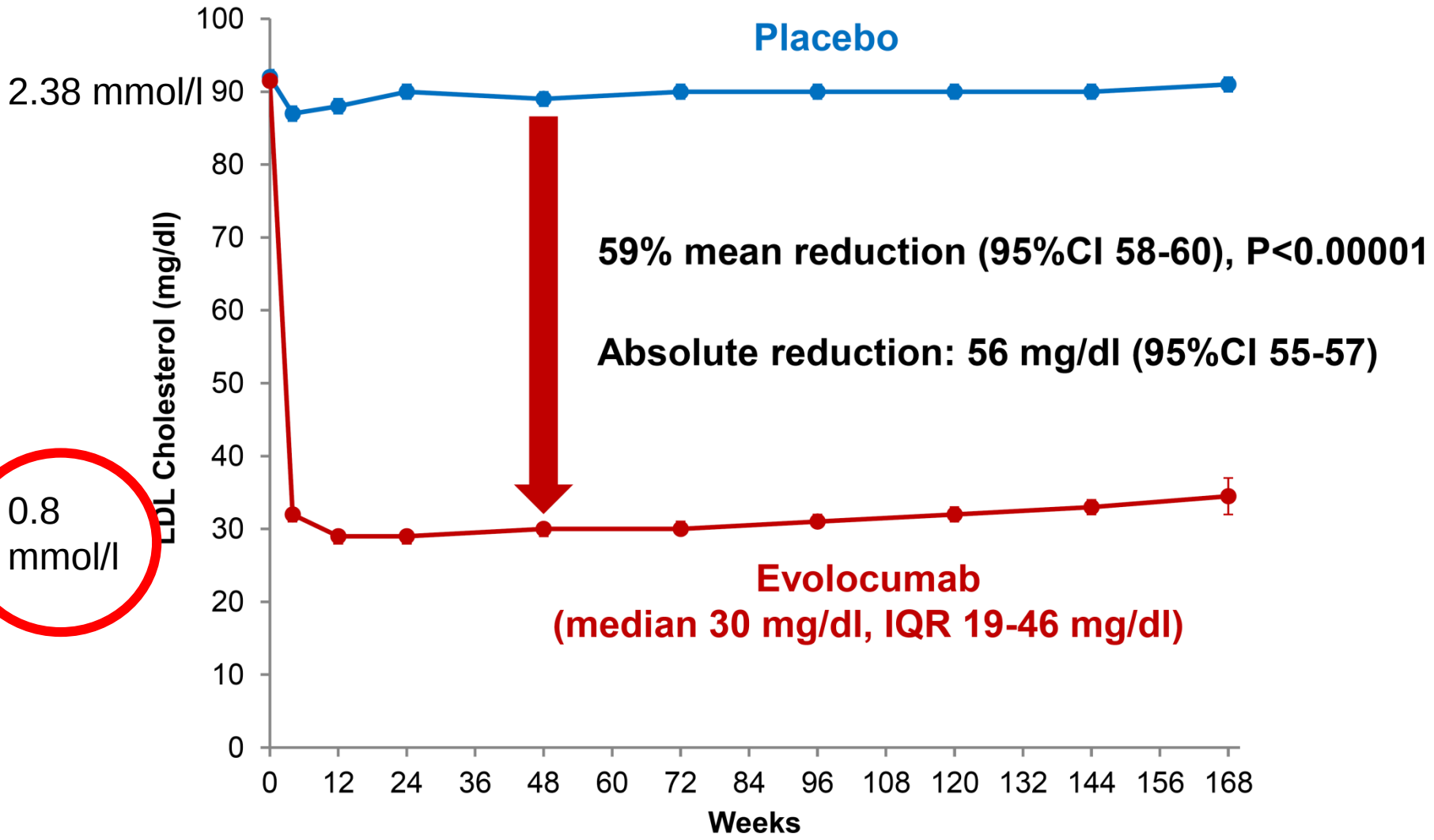
Characteristic	Value
Statin use (%)*	
High-intensity	**69**
Moderate-intensity	**30**
Ezetimibe use (%)	**5**
Median lipid measures (IQR) – mg/dL	
LDL-C	**92 (80-109)**
Total cholesterol	**168 (151-189)**
HDL-C	**44 (37-53)**
Triglycerides	**133 (100-182)**

2.38mM
4.35mM
1.14mM
1.49mM

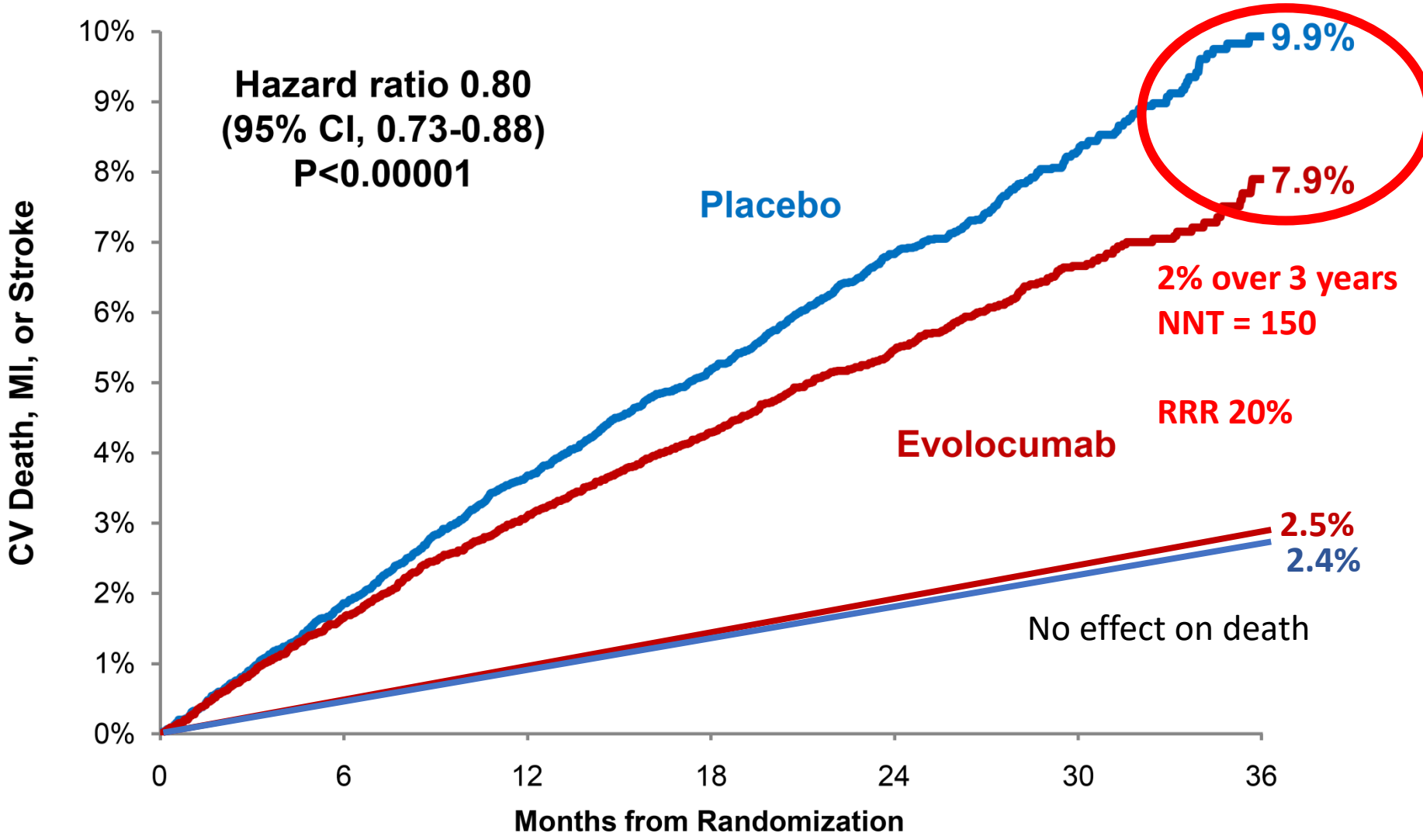
*Per protocol, patients were to be on atorva ≥20 mg/d or equivalent.
1% were on low intensity or intensity data were missing.
Statin intensity defined per ACC/AHA 2013 Cholesterol Guidelines.

Pooled data; no differences between treatment arms

LDL Cholesterol



Key Secondary Endpoint



Conclusions

In patients with known cardiovascular disease:

1. **PCSK9 inhibition with evolocumab significantly & safely ↓ major cardiovascular events when added to statin therapy**

2. **Benefit was achieved with lowering LDL cholesterol well below current targets**

Be aware that:

- Relative risk reduction ~20%.
  - Absolute risk reduction is very small (<0.7% pa)
  - NNT is high (150 = £600,000 to prevent one event!)
  - No effect of mortality
- Low risk, well treated patients on high dose statins (LDL 90 mg/dl)

- Should only really be used in familial hypercholesterolaemia

Does good glucose control prevent complications?

- Is there real evidence that good glucose control prevents complications?

- YES
- NO

Does good glucose control prevent complications?

- Is there real evidence that good glucose control prevents complications?

- YES
- NO

- How long does it take to see benefit from good control?

UK Prospective Diabetes Study (UKPDS)

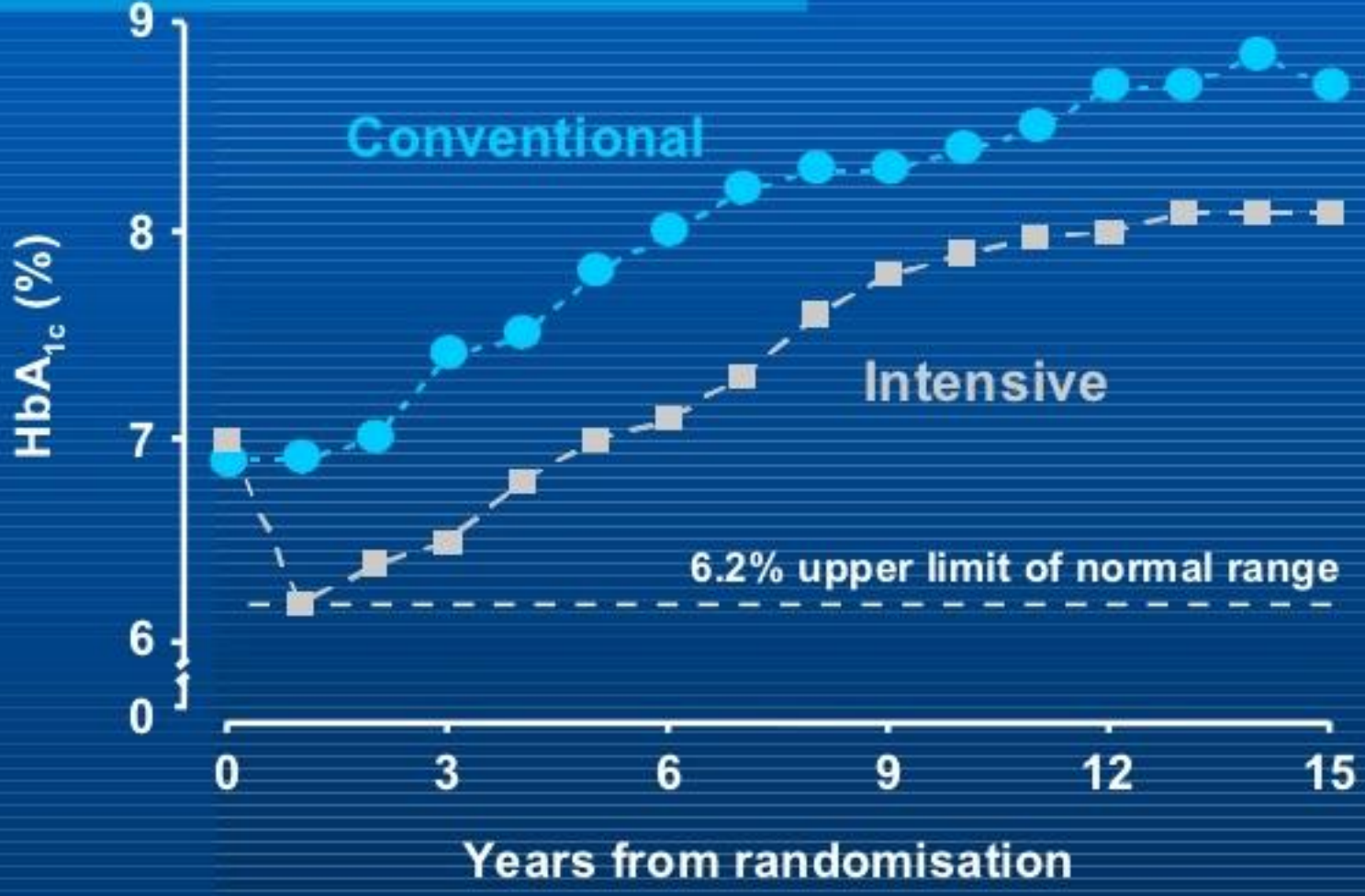
- **20-year Interventional Trial from 1977 to 1997**
- 4,209 patients with *newly-diagnosed type 2 diabetes*
- Received conventional (diet) or intensive glucose control (SU, insulin, or metformin in overweight patients at specific centers)
- Median follow-up 10.0 years, range 6 to 20 years

- **10-year Post-Trial Monitoring from 1997 to 2007**
- Patients returned to community- or hospital-based diabetes care according to their clinical needs
- Clinic-based for first five years; Questionnaire-based for last five years

Median overall follow-up 17.0 years, range 16 to 30 years

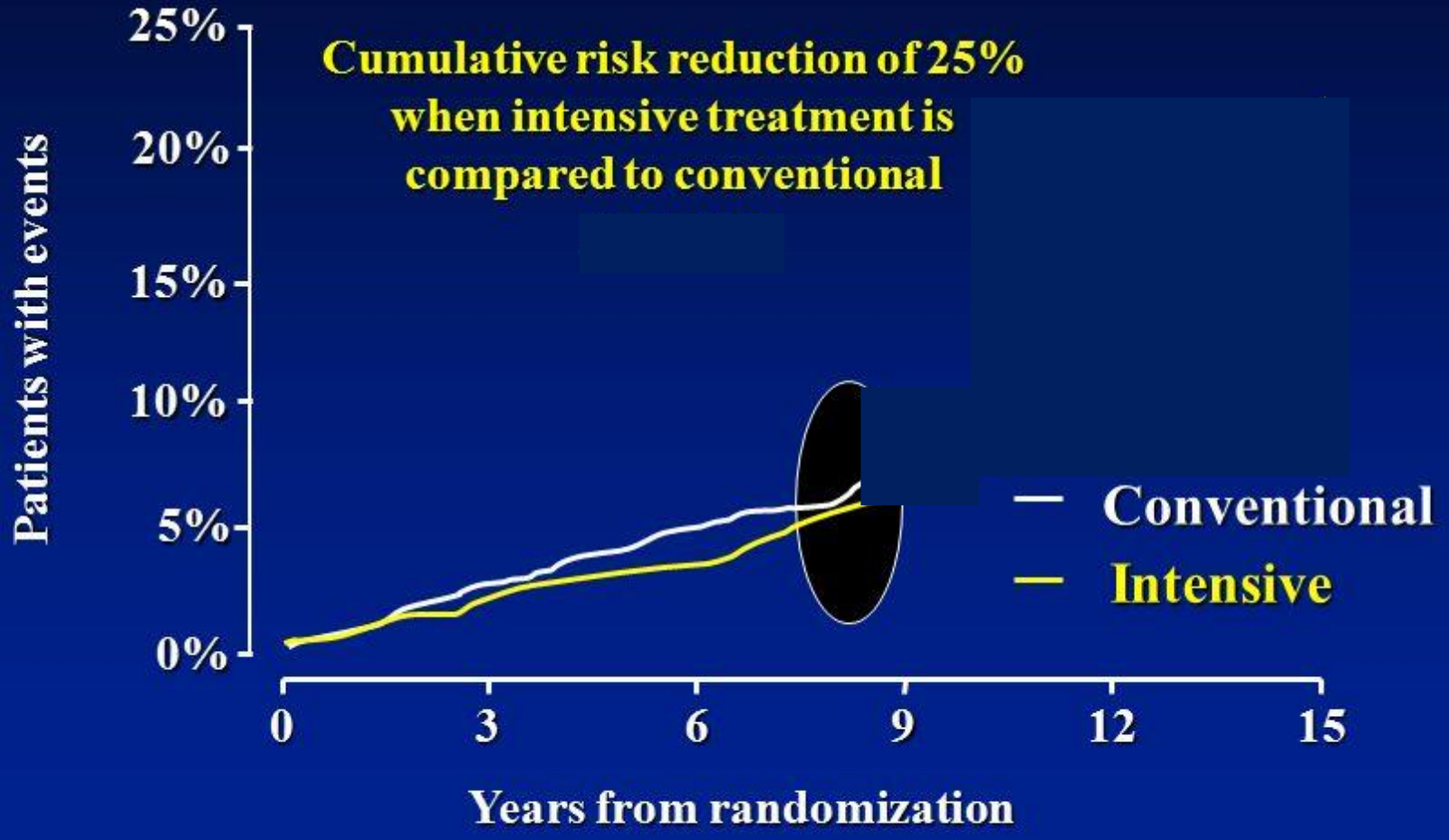
UKPDS 33 Group. *Lancet*. 1998;352(9131):837-853.

UKPDS: Effects of management on HbA_{1c}



UKPDS Group. Lancet. 1998;352:837–853.

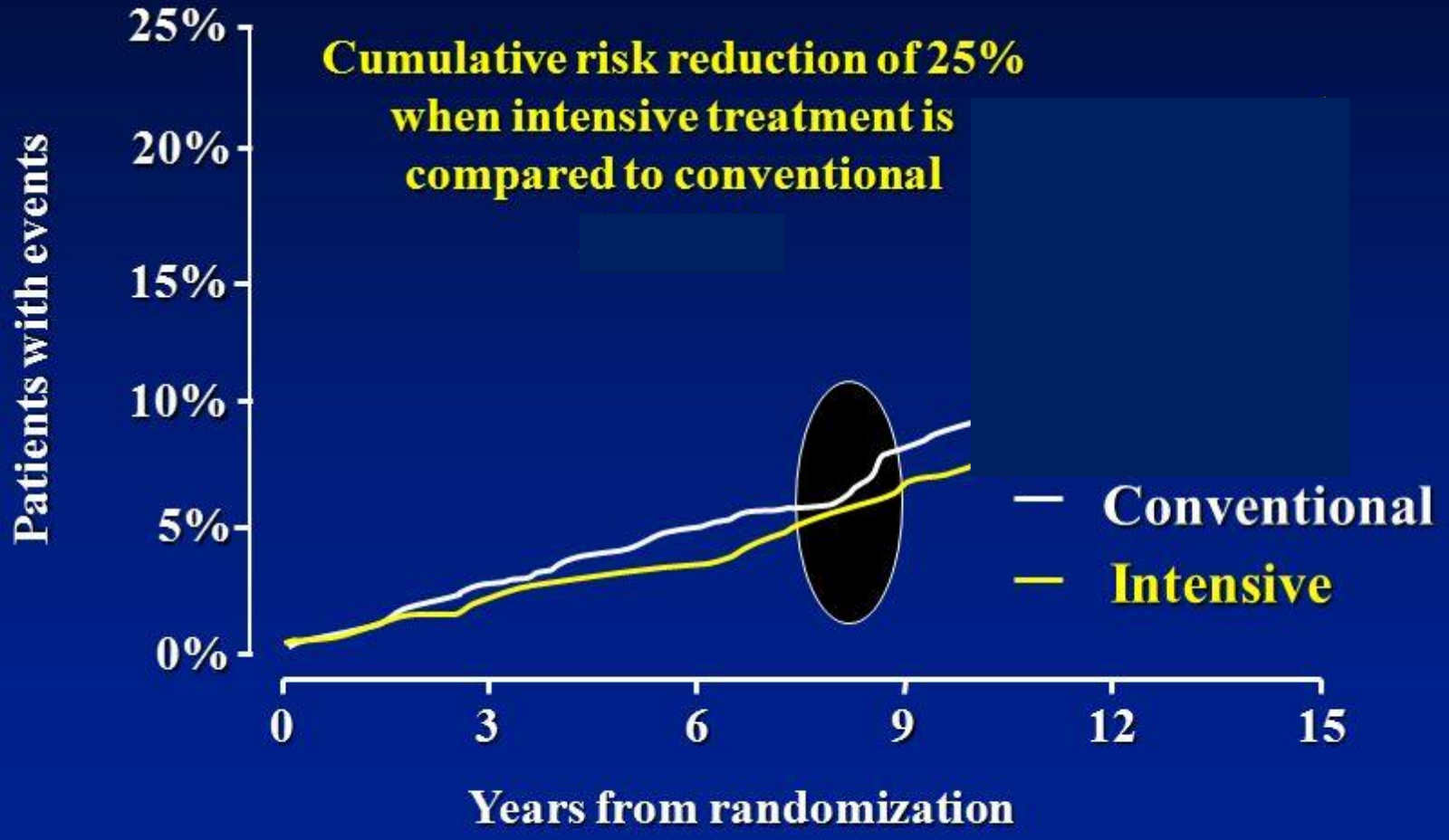
UKPDS:
Effect of Treatment on Microvascular Endpoints



UKPDS Group. *Lancet.* 1998;352:837-853.

IDC

UKPDS:
Effect of Treatment on Microvascular Endpoints



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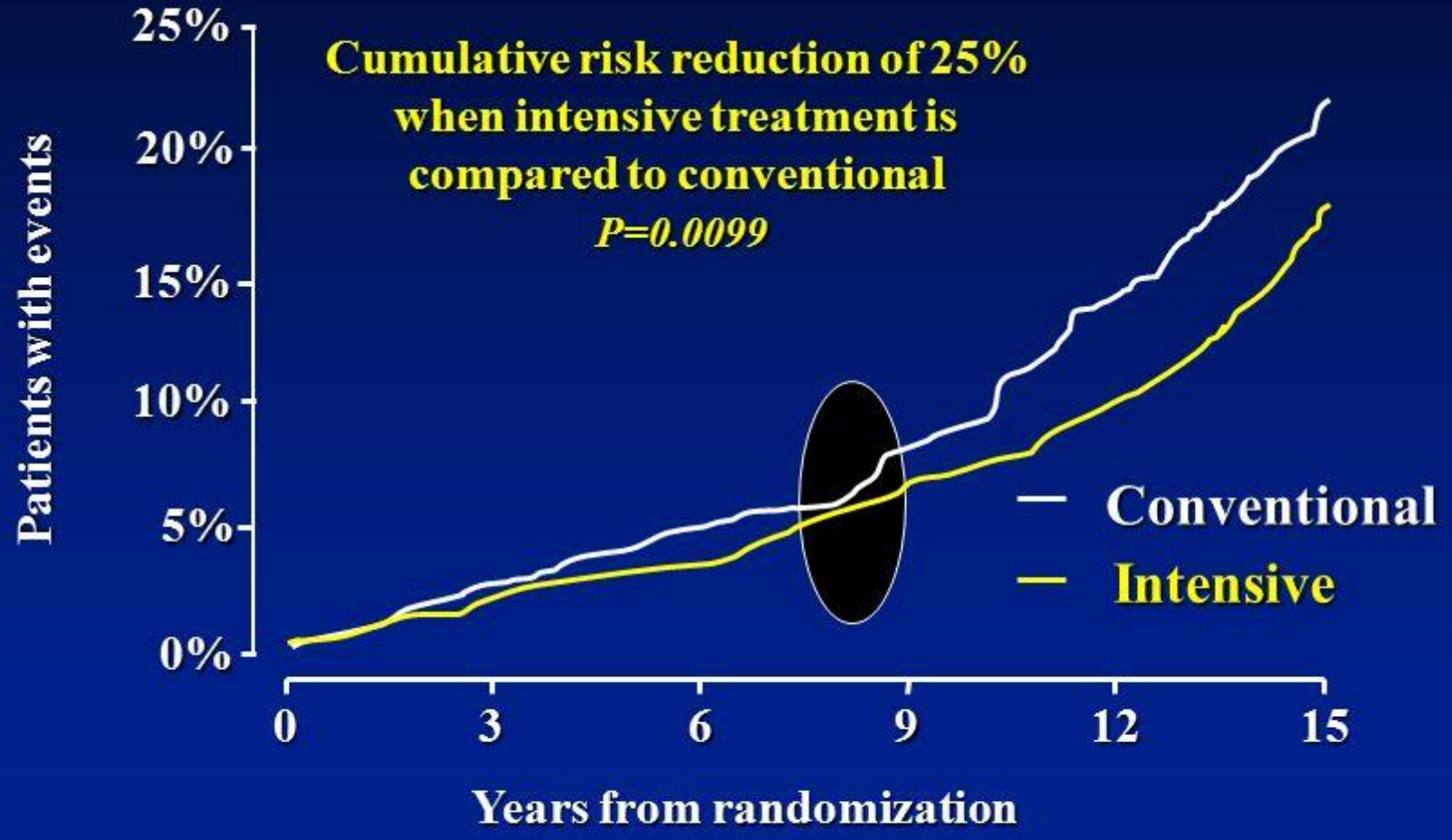


UKPDS Group. *Lancet.* 1998;352:837-853.

IDC

Does good glucose control prevent complications?

- YES (UKPDS published 1998)
- But only after about 15 years in NEWLY diagnosed type 2 diabetes

- And what happened after this?

NEJM 2008 (10 years later)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes

Rury R. Holman, F.R.C.P., Sanjoy K. Paul, Ph.D., M. Angelyn Bethel, M.D., David R. Matthews, F.R.C.P., and H. Andrew W. Neil, F.R.C.P.

ABSTRACT

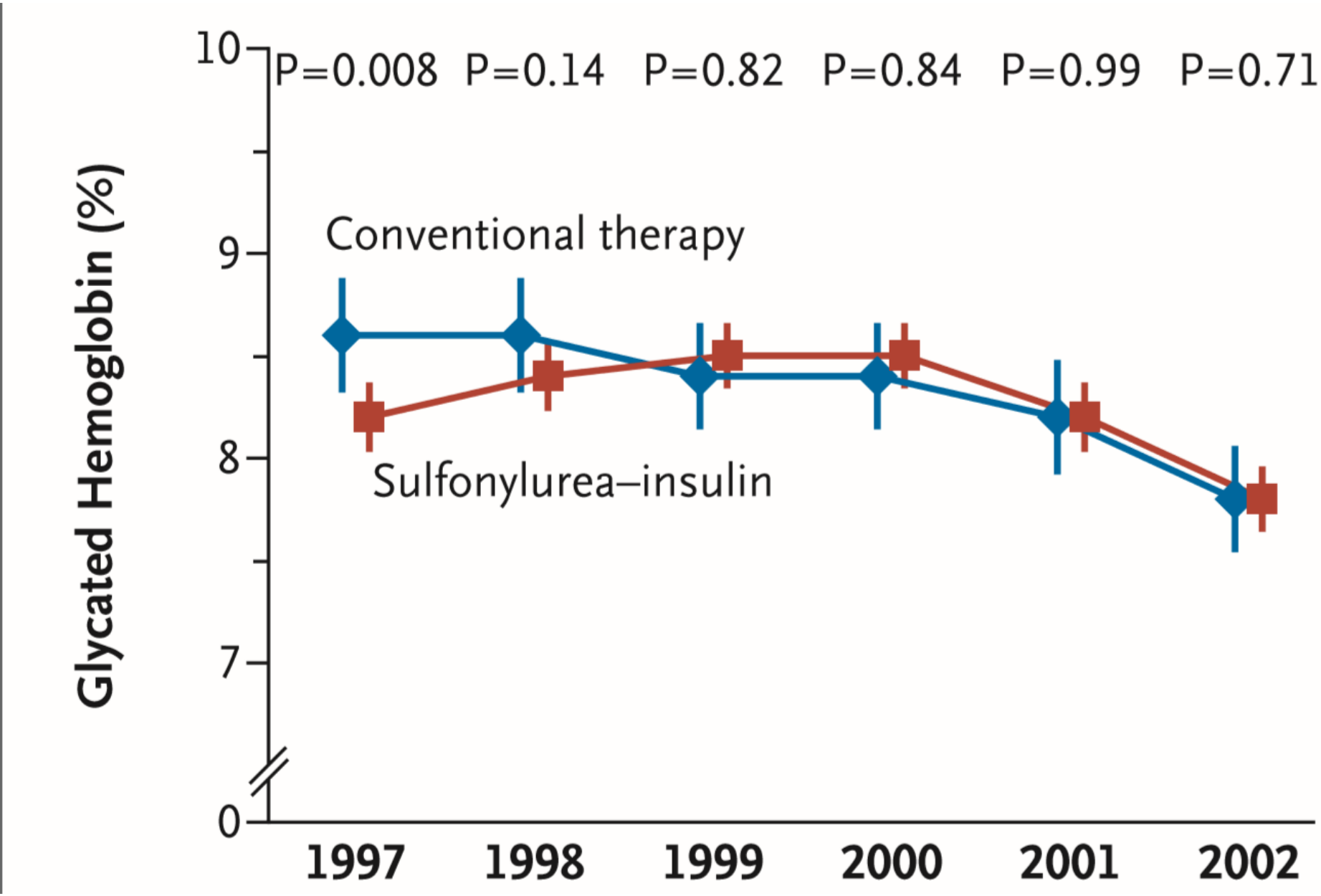
BACKGROUND

During the United Kingdom Prospective Diabetes Study (UKPDS), patients with type 2 diabetes mellitus who received intensive glucose therapy had a lower risk of microvascular complications than did those receiving conventional dietary therapy. We conducted post-trial monitoring to determine whether this improved glucose control persisted and whether such therapy had a long-term effect on macrovascular outcomes.

From the Diabetes Trials Unit (R.R.H., S.K.P., M.A.B.), the Division of Public Health and Primary Health Care (H.A.W.N.), and the National Institute of Health Research (NIHR) School for Primary Care Research (H.A.W.N.), Oxford Centre for Diabetes, Endocrinology, and Metabolism (R.R.H., S.K.P., M.A.B., D.R.M., H.A.W.N.); and the NIHR Oxford Bio-

Follow up 1998 to 2008

- Of 5102 patients with newly diagnosed type 2 diabetes, 4209 were randomly assigned to receive either conventional therapy (dietary restriction) or intensive therapy (either sulfonylurea or insulin or, in overweight patients, metformin) for glucose control.
- In post-trial monitoring, 3277 patients were asked to attend annual UKPDS clinics for 5 years, but no attempts were made to maintain their previously assigned therapies.
- What happened to glucose levels?


P=0.008
P=0.14
P=0.82
P=0.84
P=0.99
P=0.71
Conventional therapy
Sulfonylurea–insulin
Glycated Hemoglobin (%)
10
9
8
7
0
1997
1998
1999
2000
2001
2002

After the UKPDS was over..

- The glucose control became the same as the control group.

- What happened to the patients mortality when they stopped having “good control”?

Table 2. Aggregate Outcomes for Patients during Follow-up.*

Aggregate Outcome	Patients with Clinical Outcome		Absolute Risk†		P Value‡	Risk Ratio for Intensive-Therapy Regimen (95% CI)
	Intensive Therapy	Conventional Therapy	Intensive Therapy	Conventional Therapy		
	no. of patients					
Sulfonyurea–insulin group	2729	1138				
Any diabetes-related end point	1571	686	48.1	52.2	0.04	0.91 (0.83–0.99)
Diabetes-related death	618	297	14.5	17.0	0.01	0.83 (0.73–0.96)
Death from any cause	1162	537	26.8	30.3	0.007	0.87 (0.79–0.96)
Myocardial infarction	678	319	16.8	19.6	0.01	0.85 (0.74–0.97)
Stroke	260	116	6.3	6.9	0.39	0.91 (0.73–1.13)
Peripheral vascular disease	83	40	2.0	2.4	0.29	0.82 (0.56–1.19)
Microvascular disease	429	222	11.0	14.2	0.001	0.76 (0.64–0.89)
Metformin group	342	411				
Any diabetes-related end point	209	262	45.7	53.9	0.01	0.79 (0.66–0.95)
Diabetes-related death	81	120	14.0	18.7	0.01	0.70 (0.53–0.92)
Death from any cause	152	217	25.9	33.1	0.002	0.73 (0.59–0.89)
Myocardial infarction	81	126	14.8	21.1	0.005	0.67 (0.51–0.89)
Stroke	34	42	6.0	6.8	0.35	0.80 (0.50–1.27)
Peripheral vascular disease	13	21	2.3	3.4	0.19	0.63 (0.32–1.27)
Microvascular disease	66	78	12.4	13.4	0.31	0.84 (0.60–1.17)

* Shown are the numbers of patients who were followed for up to 30 years, including up to 10 years of post-trial monitoring, with aggregate clinical outcomes after assignment in the interventional phase of the United Kingdom Prospective Diabetes Study to the sulfonylurea–insulin group or the metformin group or to the corresponding conventional-therapy group.
† The absolute risk is the number of events per 1000 patient-years.
‡ P values were calculated with the use of the log-rank test.

UKPDS 10 years afterwards 2008

- With more than 66,000 person-years of follow up, this large post-trial study showed that benefits of an intensive strategy to control blood glucose levels in patients with type 2 diabetes were sustained for up to 10 years after the cessation of randomized interventions.
- Benefits persisted despite the early loss of within-trial differences in glycated hemoglobin levels between the intensive-therapy group and the conventional-therapy group — a so-called legacy effect.
- The trial showed the extended effects of improved glycemic control in patients with newly diagnosed type 2 diabetes, some of whom were followed for up to 30 years.

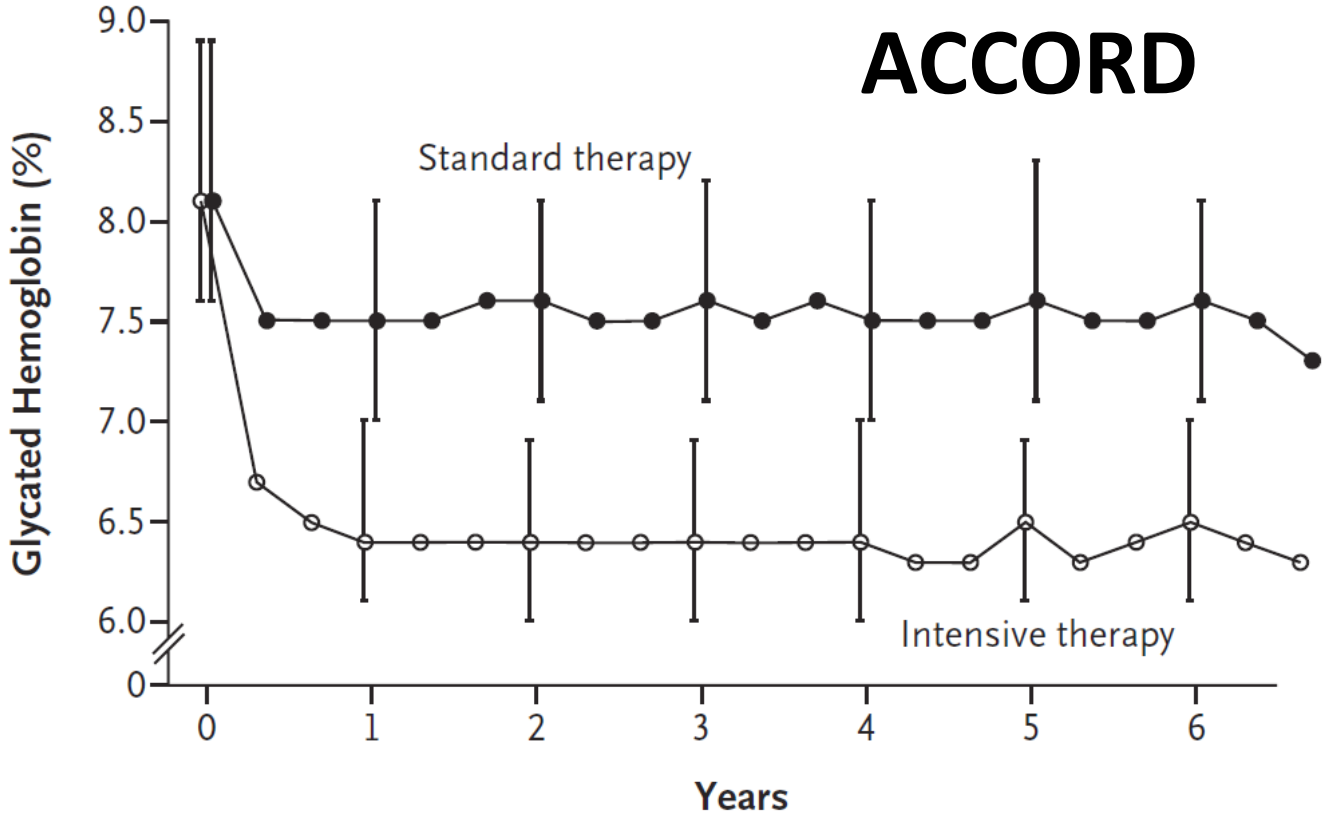
UKPDS summary

- 20 years intervention (1977 to 1997)
- Tight control takes a long time to prevent heart attacks. Heart attacks occur after many years or poor control. NEW ONSET DIABETES in 1977

- 10 years further follow up (1997 to 2007)
- Legacy effect of benefit even after the study is over
- Good control now prevents heart disease in the future

Accord (aim HbA1c=6%) and Advance (6.5%)

- Both sponsored, so need shorter study, so chose patients who already had vascular disease with diabetes (ie high risk of a soon event)
- Accord: United States and Canada.
- Type 2 diabetes mellitus and a glycated haemoglobin level of 7.5% or more over age of 40 and had cardiovascular disease
- Advance: International study, Europe, Asia, Australia and USA
- a history of major macrovascular or microvascular disease or at least one other risk factor for vascular disease



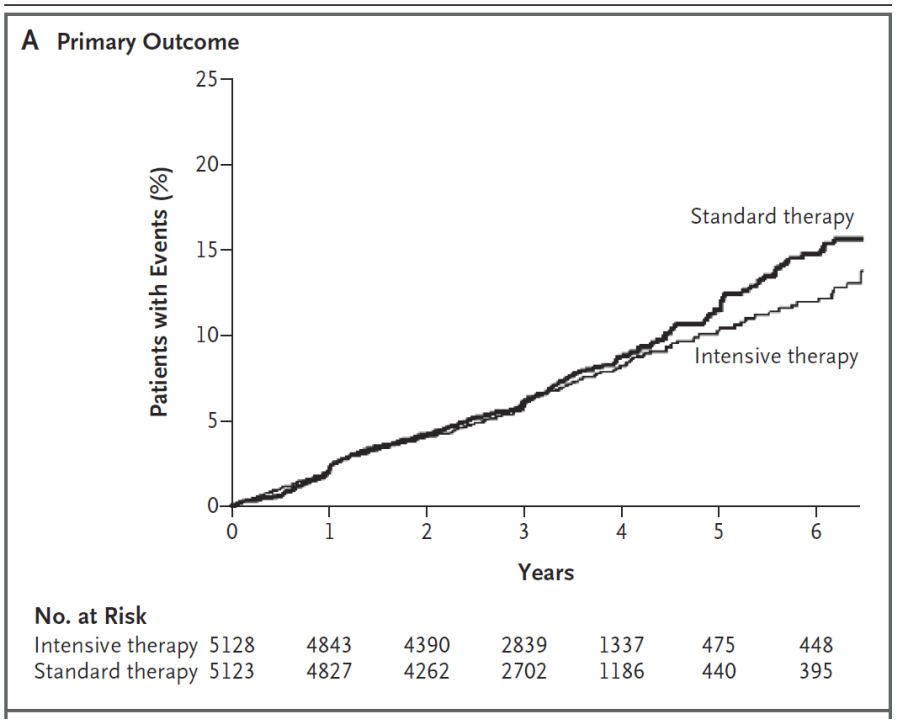
No. at Risk

Standard therapy	5109	4774	4588	3186	1744	455	436
Intensive therapy	5119	4768	4585	3165	1706	476	471

Figure 1. Median Glycated Hemoglobin Levels at Each Study Visit.

I bars denote interquartile ranges.

Accord Primary=stroke, MI or death



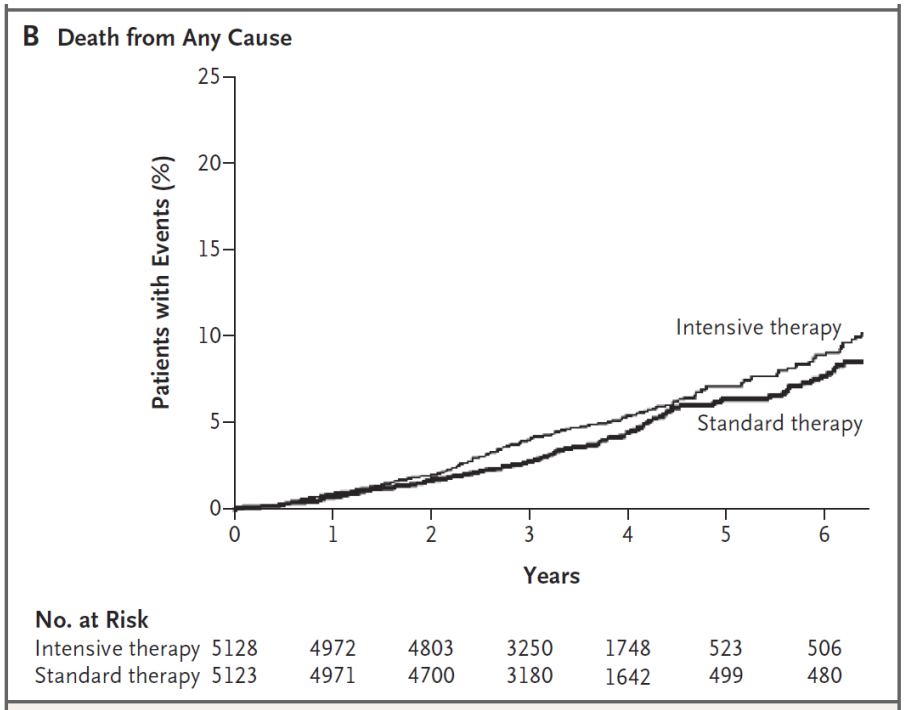


Figure 2. Kaplan–Meier Curves for the Primary Outcome and Death from Any Cause.

Accord (aim HbA1c 6% in high risk)

RESULTS

At 1 year, stable median glycated hemoglobin levels of 6.4% and 7.5% were achieved in the intensive-therapy group and the standard-therapy group, respectively. During follow-up, the primary outcome occurred in 352 patients in the intensive-therapy group, as compared with 371 in the standard-therapy group (hazard ratio, 0.90; 95% confidence interval [CI], 0.78 to 1.04; P=0.16). At the same time, 257 patients in the intensive-therapy group died, as compared with 203 patients in the standard-therapy group (hazard ratio, 1.22; 95% CI, 1.01 to 1.46; P=0.04). Hypoglycemia requiring assistance and weight gain of more than 10 kg were more frequent in the intensive-therapy group (P<0.001).

CONCLUSIONS

As compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. These findings identify a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes. (ClinicalTrials.gov number, NCT00000620.)

SGLT2 Inhibitors:
Lessons Learned from EMPA-REG OUTCOME

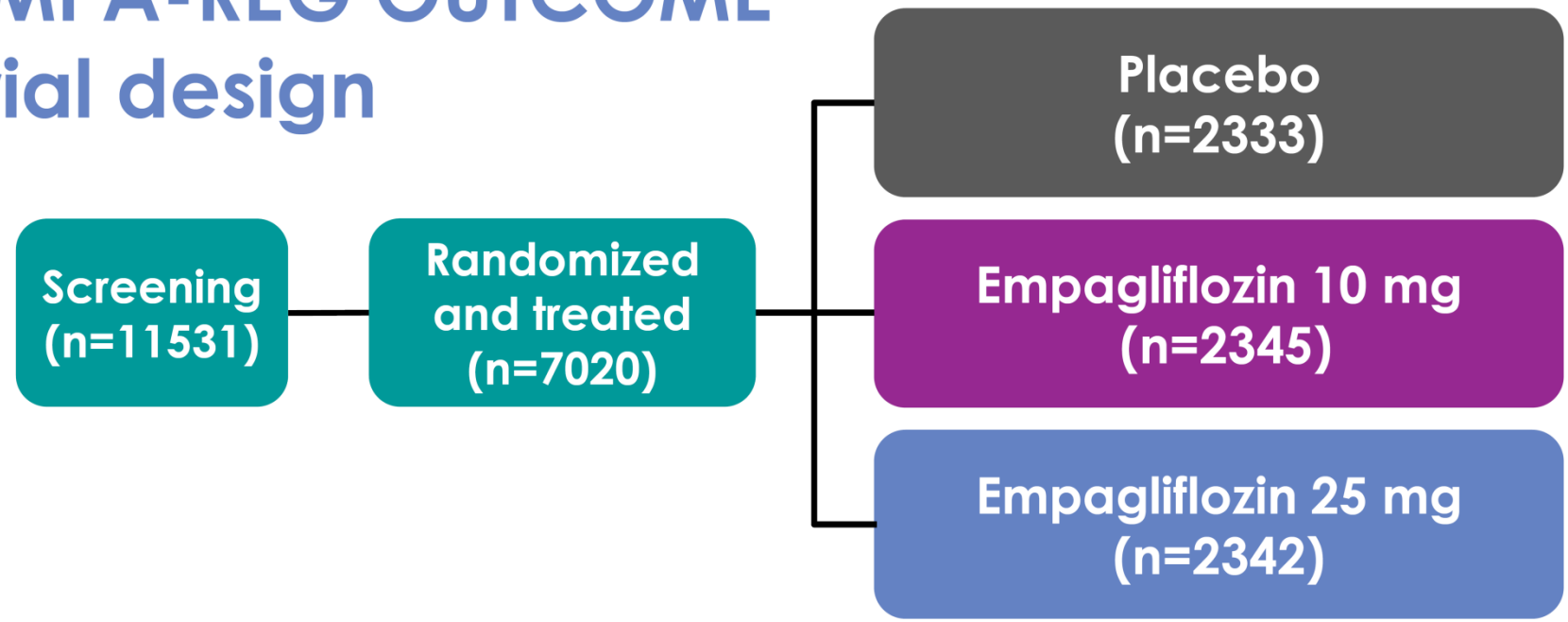
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

EMPA-REG OUTCOME®
Trial design

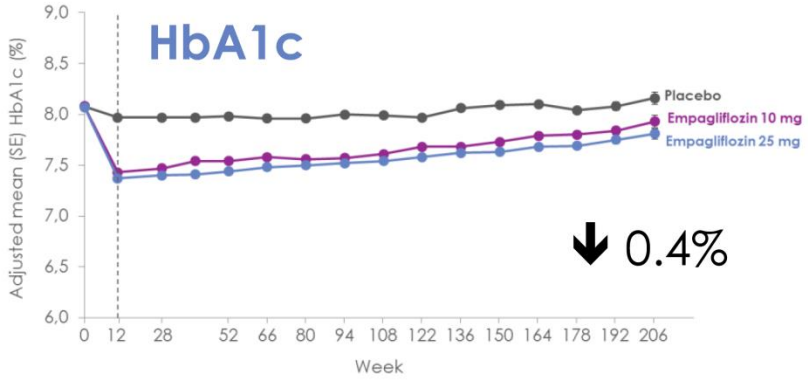


- **Study medication was given in addition to standard of care.**
- **Primary outcome: 3-point MACE**
- **Analysis: Placebo vs. pooled empagliflozin groups**
- **Key inclusion criteria:**
  - Adults with type 2 diabetes and established CVD
  - BMI ≤45 kg/m^2; HbA1c 7–10%; eGFR ≥30 mL/min/1.73m^2 (MDRD)

EMPA-REG OUTCOME®

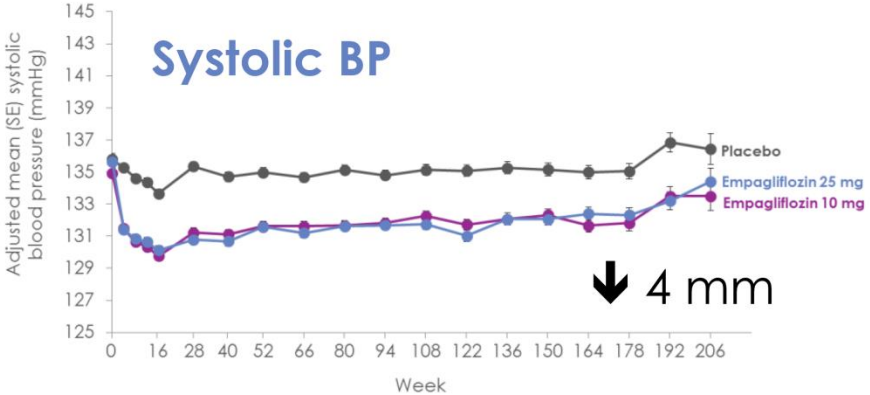
Zinman B *et al. N Engl J Med* 2015;373:2117-28

HbA1c



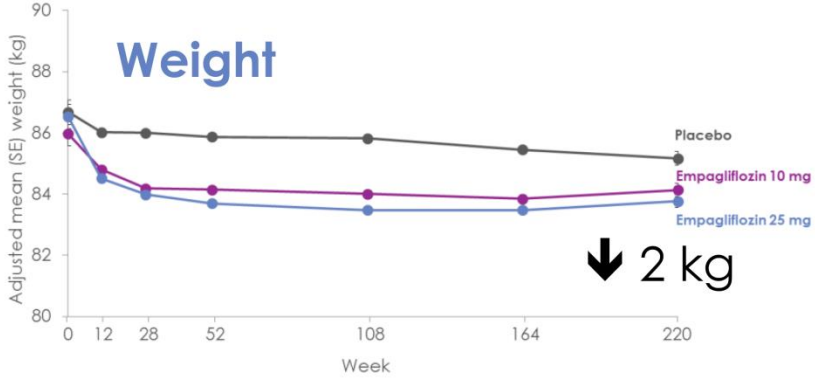
Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

Systolic BP



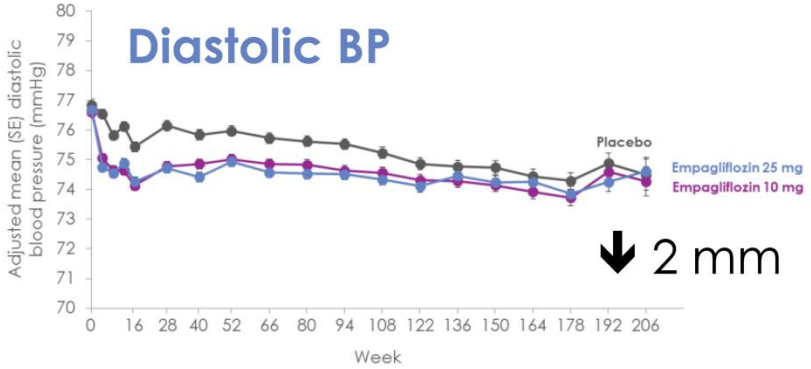
Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
Empagliflozin 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
Empagliflozin 25 mg	2323	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216

Weight



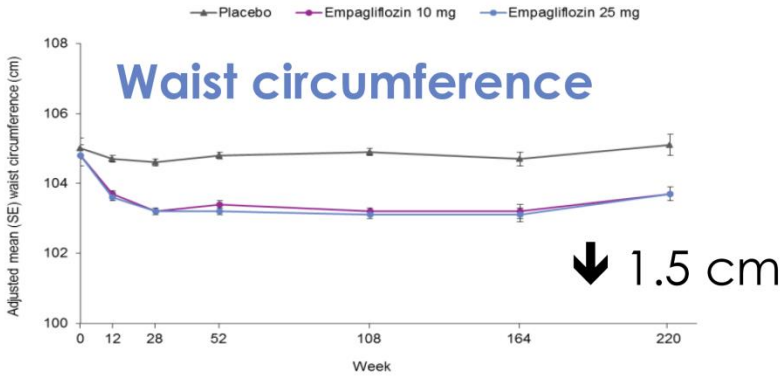
Placebo	2285	1915	2215	2138	1598	1239	425
Empagliflozin 10 mg	2290	1893	2238	2174	1673	1298	483
Empagliflozin 25 mg	2283	1891	2226	2178	1678	1335	489

Diastolic BP



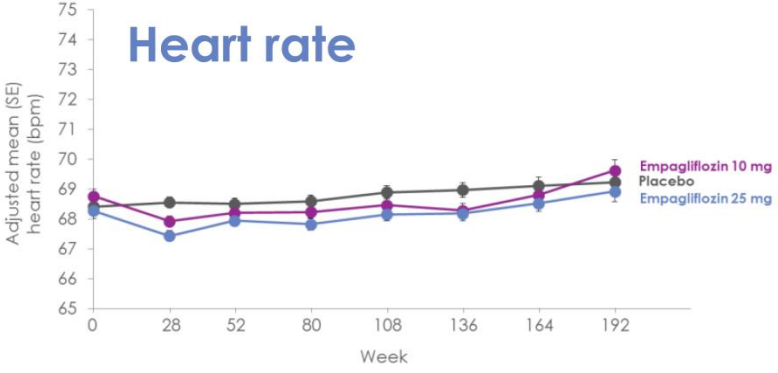
Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
Empagliflozin 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
Empagliflozin 25 mg	2323	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216

Waist circumference



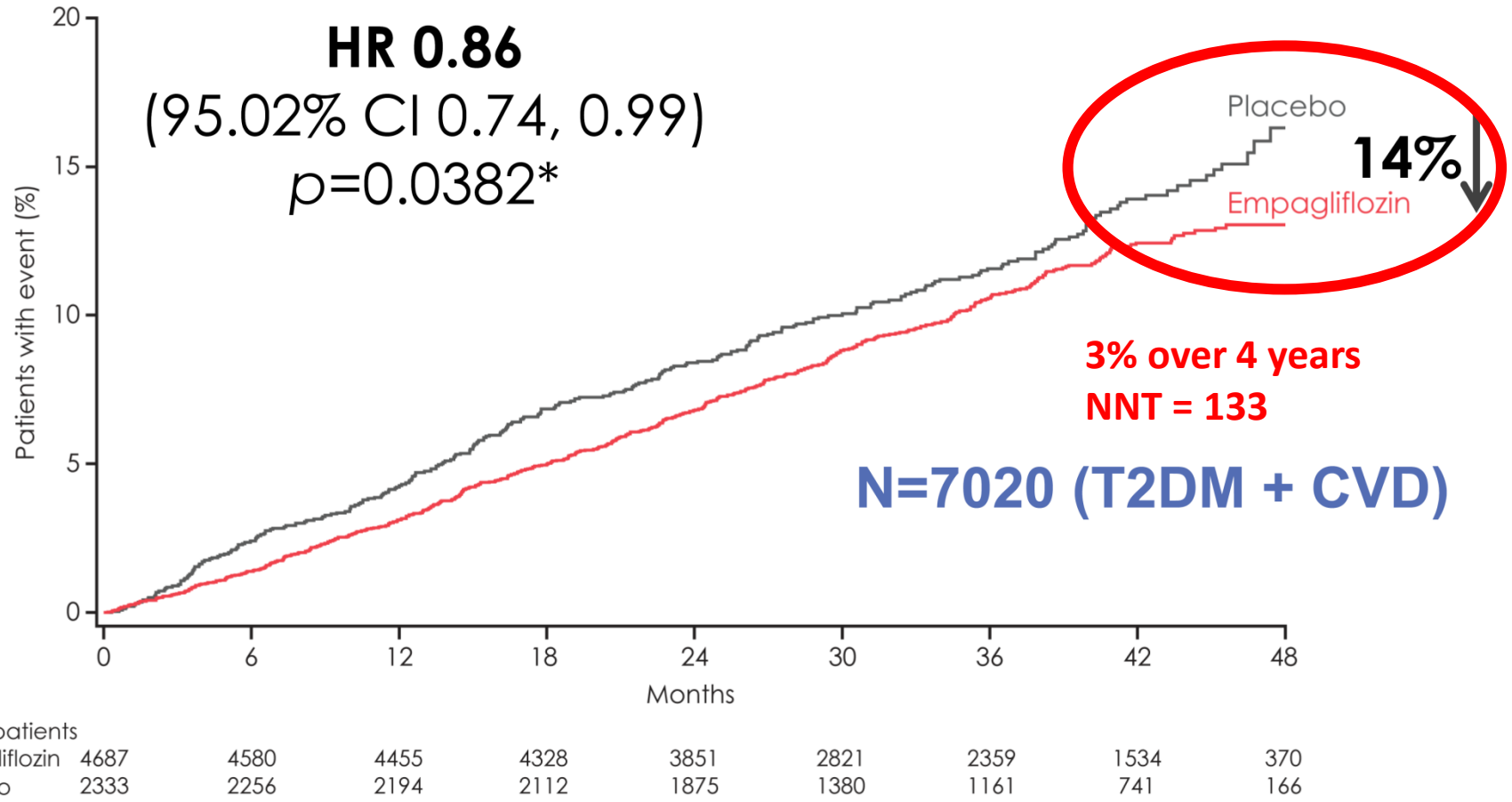
Placebo	2259	1869	2183	2110	1562	1220	418
Empagliflozin 10 mg	2272	1836	2219	2155	1644	1285	475
Empagliflozin 25 mg	2273	1857	2209	2157	1648	1329	486

Heart rate



Placebo	2174	2127	2032	1928	1796	1300	1002	552
Empagliflozin 10 mg	2205	2137	2064	2006	1877	1366	1045	597
Empagliflozin 25 mg	2192	2127	2066	2006	1907	1383	1086	633

EMPA-REG OUTCOME: Primary outcome (3-point MACE)

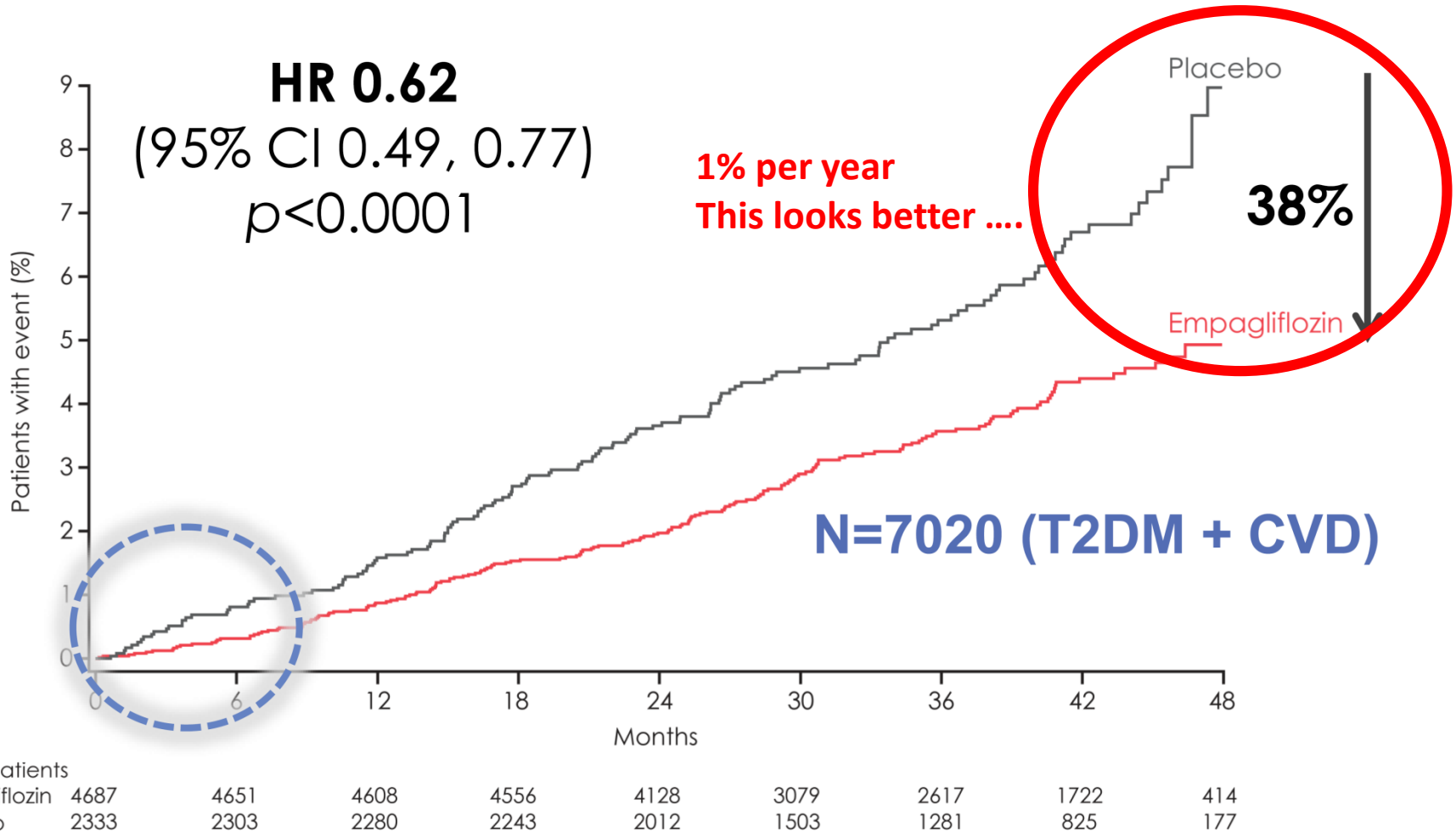


Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.
* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

EMPA-REG OUTCOME®

Zinman B *et al. N Engl J Med* 2015;373:2117-28

EMPA-REG OUTCOME: CV death



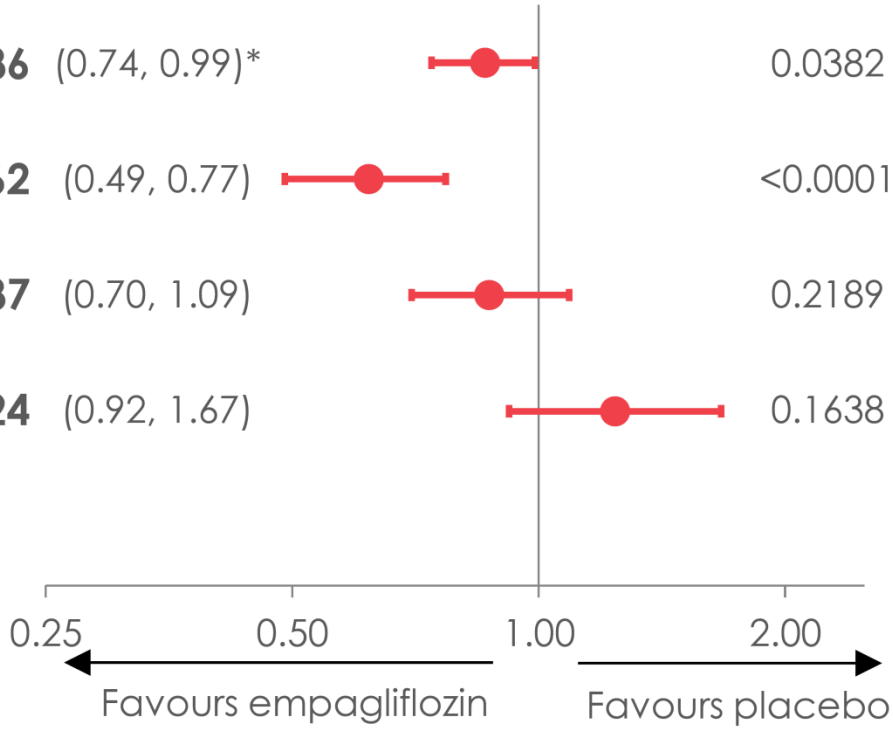
Cumulative incidence function. HR, hazard ratio

All-cause death:
HR 0.68 (95% CI 0.57, 0.82) P<0.0001

Zinman B *et al. N Engl J Med* 2015;373:2117-28

EMPA-REG OUTCOME: Primary Composite Outcome & Its Components

	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	*p*-value
3-point MACE	490/4687	282/2333	**0.86**	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	**0.62**	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	**0.87**	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	**1.24**	(0.92, 1.67)	0.1638

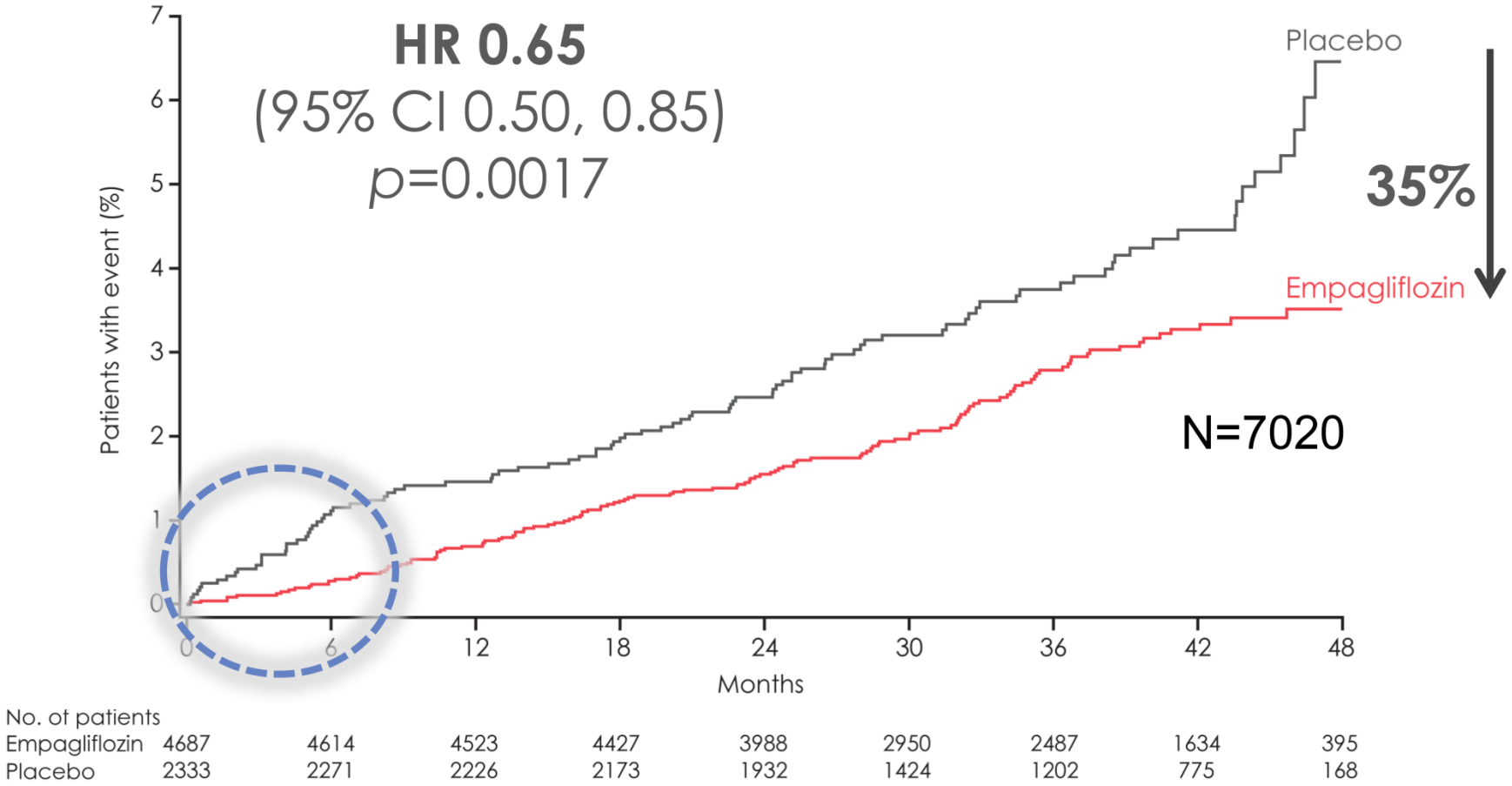


Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction
*95.02% CI

EMPA-REG OUTCOME®

Zinman B *et al. N Engl J Med* 2015;373:2117-28

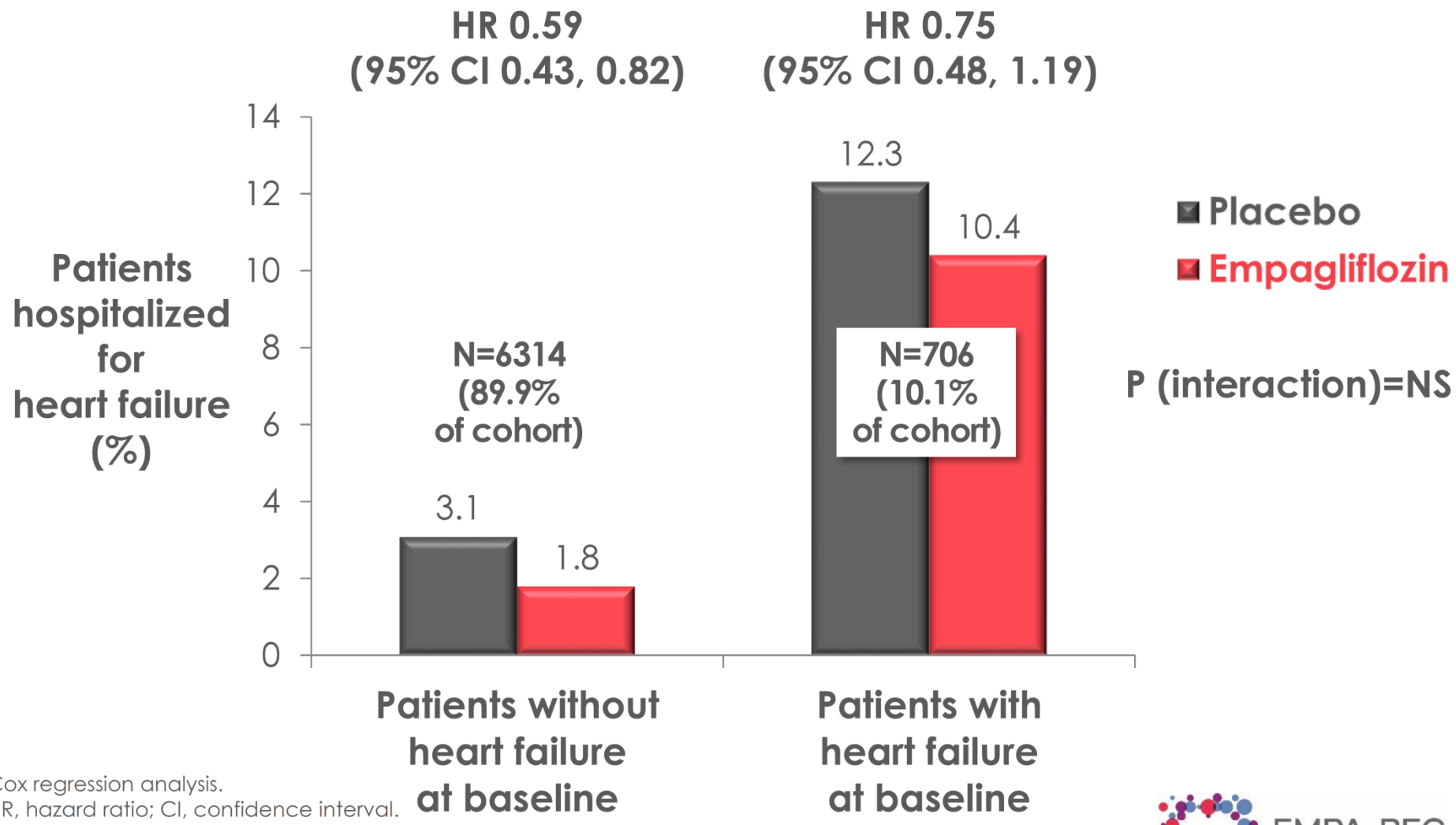
EMPA-REG OUTCOME: Hospitalization for heart failure



Cumulative incidence function. HR, hazard ratio

Zinman B *et al. N Engl J Med* 2015;373:2117-28

Hospitalization for HF in patients with vs. without HF at baseline



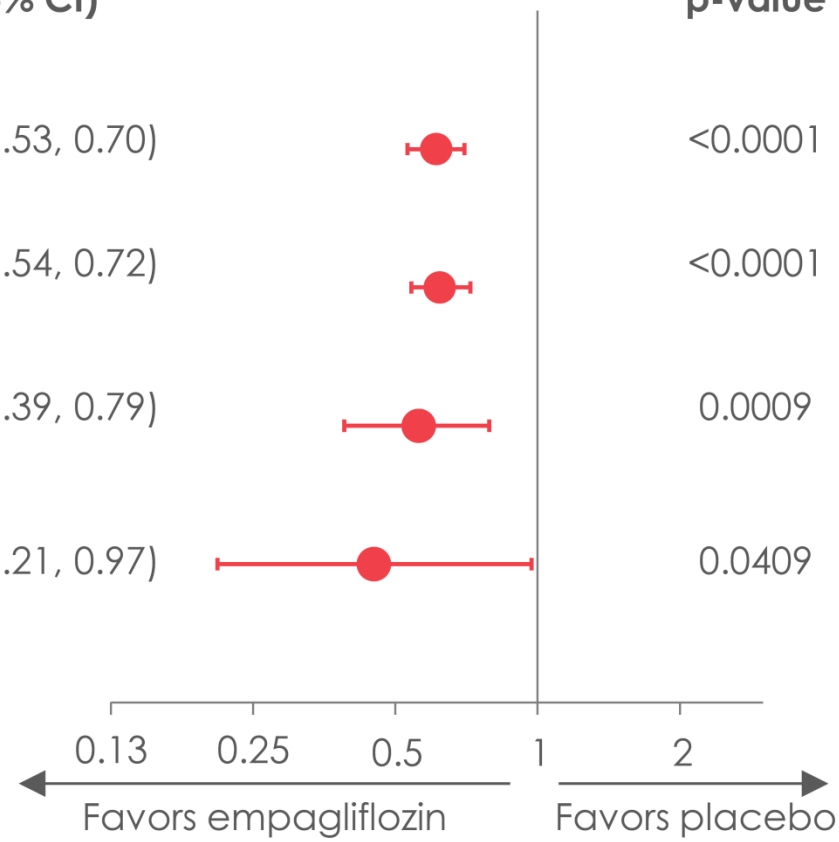
Cox regression analysis.
HR, hazard ratio; CI, confidence interval.

EMPA-REG OUTCOME®

Inzucchi SE, AHA *Scientific Sessions,* Orlando, FL, November 2015

Secondary Outcome: Incident or worsening nephropathy and its components

	Empagliflozin n with event/ N analyzed	Placebo n with event/ N analyzed	Hazard ratio (95% CI)	p-value
Incident or worsening nephropathy	525/4124	388/2061	0.61 (0.53, 0.70)	<0.0001
New onset macroalbuminuria	459/4091	330/2033	0.62 (0.54, 0.72)	<0.0001
Doubling of serum-creatinine*	70/4645	60/2323	0.56 (0.39, 0.79)	0.0009
Initiation of renal replacement therapy	13/4687	14/2333	0.45 (0.21, 0.97)	0.0409

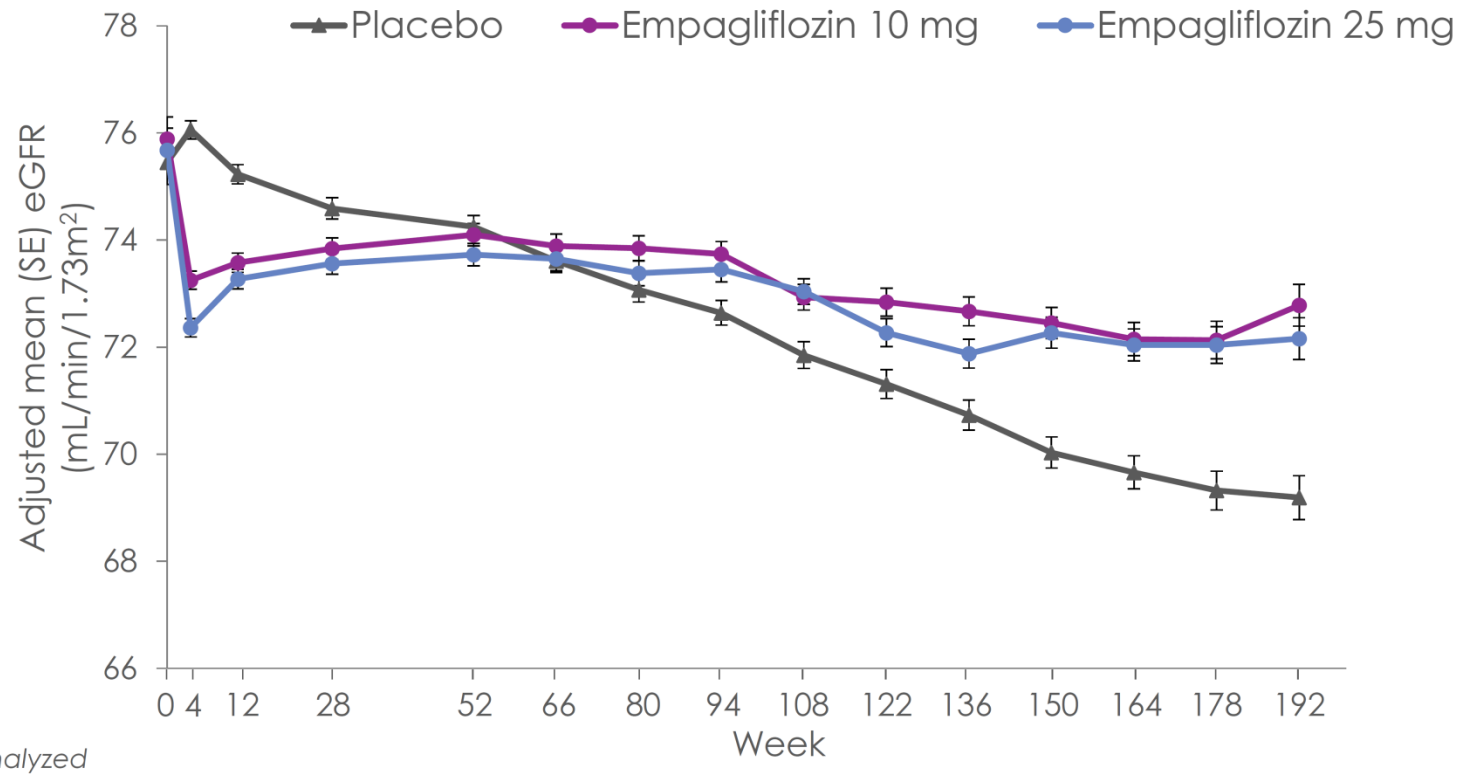


*Accompanied by eGFR (MDRD) ≤45 mL/min/1.73m^2.
Cox regression analyses.

Wanner C *et al. N Engl J Med* 2016;375:323-34

EMPA-REG OUTCOME®

eGFR (CKD-EPI formula) over 192 weeks



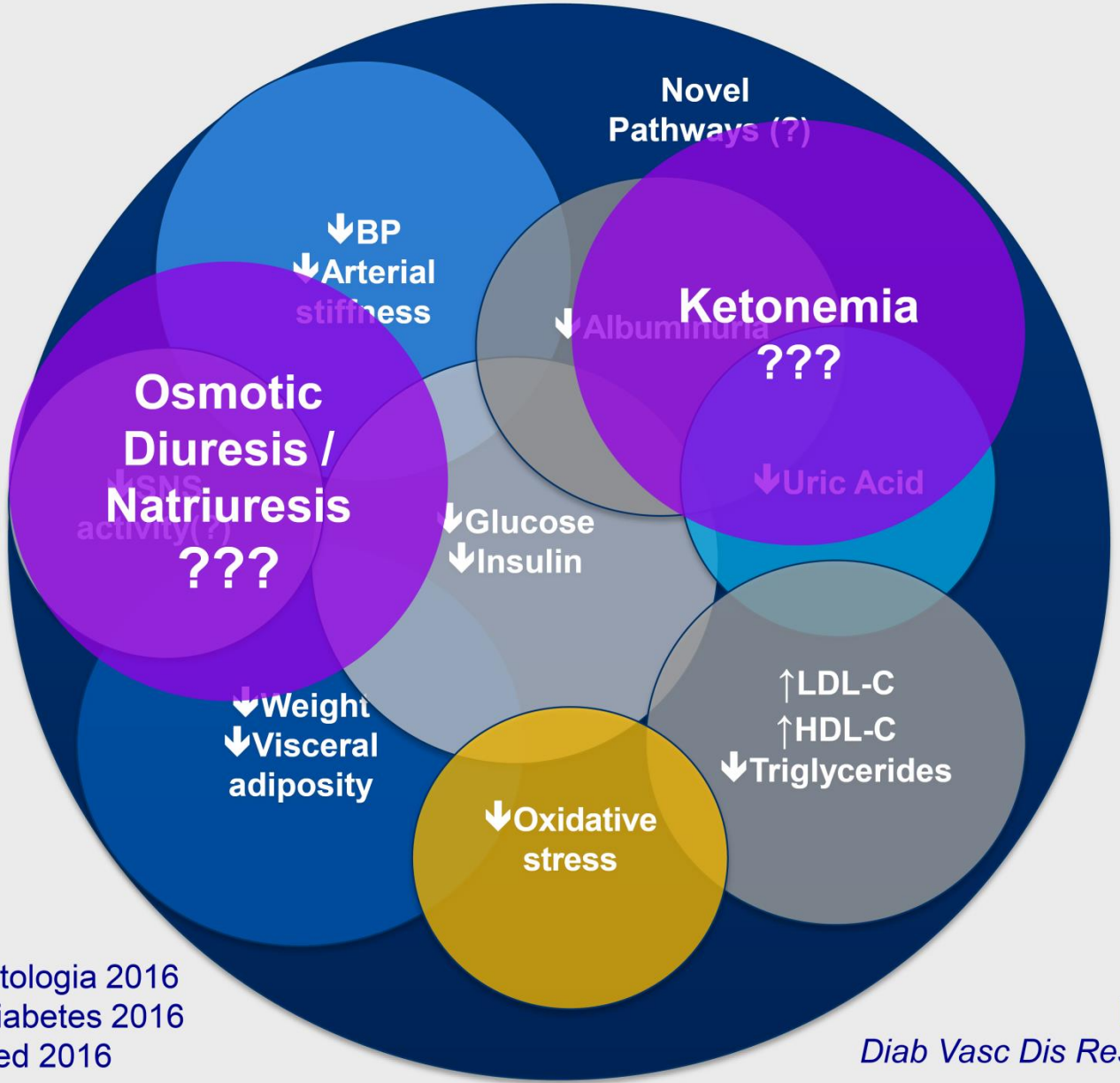
No. analyzed															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in follow-up for adverse/outcome events															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3492	2707	1703

Mixed model repeated measures analysis. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

Wanner C *et al. N Engl J Med* 2016;375:323-34

EMPA-REG OUTCOME®

How does the SGLT2 inhibitor, empagliflozin, exert its cardiovascular benefit?



Sattar N *et al.* Diabetologia 2016
Ferrannini E *et al.* Diabetes 2016
Weir M. Postgrad Med 2016

Inzucchi SE *et al.*
Diab Vasc Dis Res 2015;12:90-100

GLP-1 analogues

- Exanatide
- Liraglutide (Victoza or Saxenda)
- Semaglutide

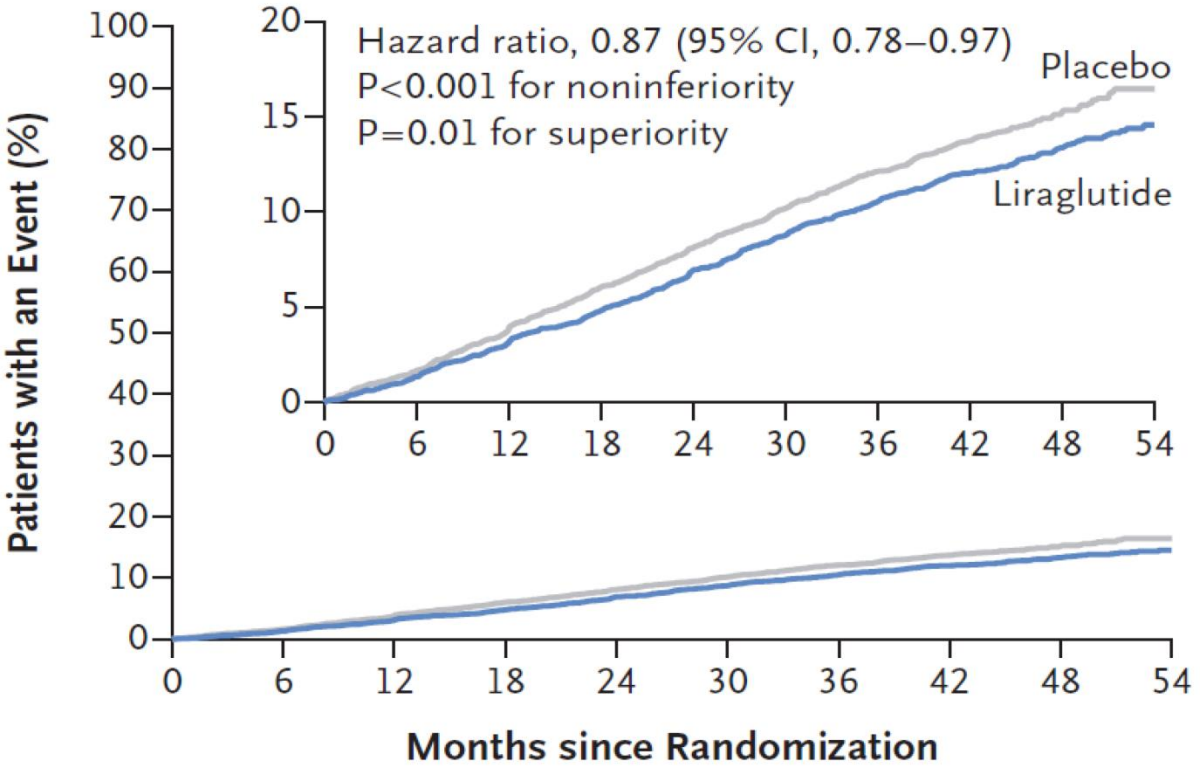
2016

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., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

Primary Outcome



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

LEADER: Primary and secondary outcomes

Outcome	Hazard Ratio (95% CI)	P Value
Primary composite outcome Lira vs plac 608 vs 694 events	0.87 (0.78–0.97)	0.01
All cause death Lira vs plac 381 vs 447 events	0.85 (0.74–0.97)	0.02
CV death Lira vs plac 219 vs 278 events	0.78 (0.66–0.93)	0.007
Myocardial infarction Lira vs plac 292 vs 339 events	0.86 (0.73–1.00)	0.046
Stroke Lira vs plac 173 vs 199 events	0.86 (0.71–1.06)	0.16
Hospitalization for heart failure Liravs plac 218 vs 248 events	0.87 (0.73–1.05)	0.14

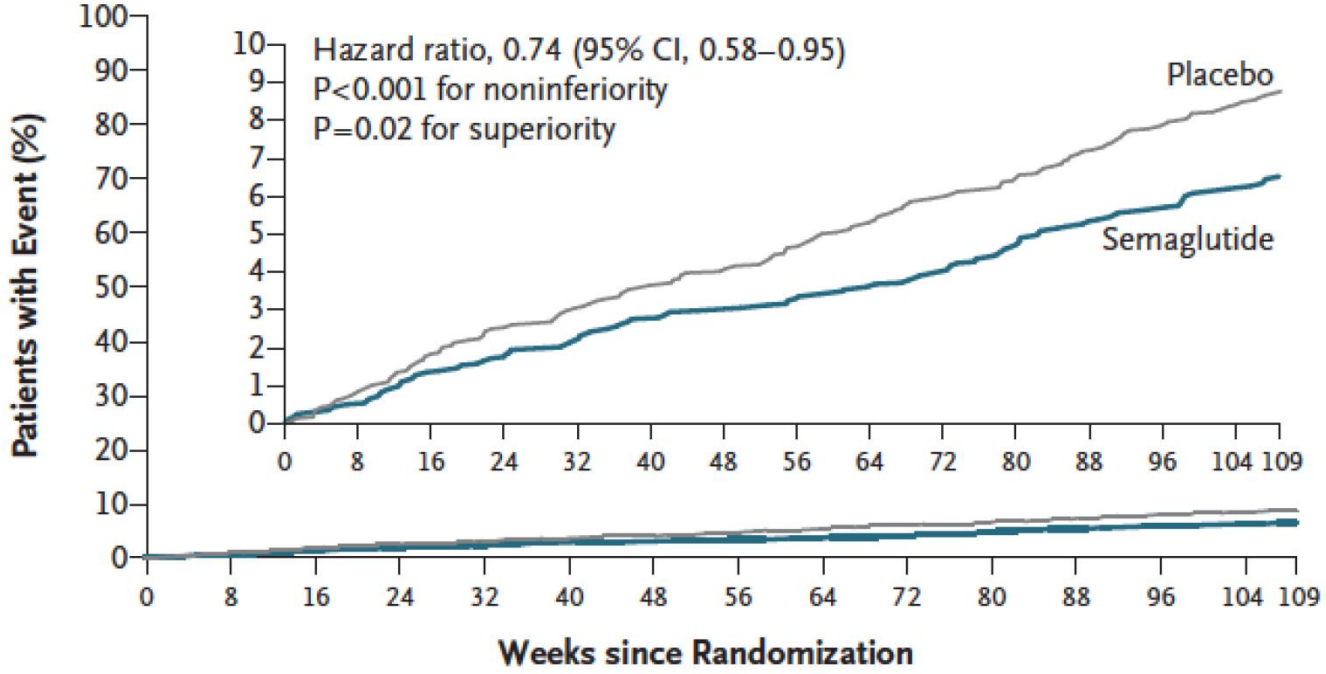
ORIGINAL ARTICLE

2016

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

Primary Outcome



No. at Risk

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

JAMA | Original Investigation

Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes

A Systematic Review and Meta-analysis

Sean L. Zheng, BM BCh, MA, MRCP; Alistair J. Roddick, BSc; Rochan Aghar-Jaffar, BMedSci, BMBS, MRCP; Matthew J. Shun-Shin, BM BCh, MRCP; Darrel Francis, MB BChir, FRCP, MD; Nick Oliver, MBBS, FRCP; Karim Meeran, MBBS, MD, FRCP, FRCPath

IMPORTANCE The comparative clinical efficacy of sodium-glucose cotransporter 2 (SGLT-2) inhibitors, glucagon-like peptide 1 (GLP-1) agonists, and dipeptidyl peptidase 4 (DPP-4) inhibitors for treatment of type 2 diabetes is unknown.

OBJECTIVE To compare the efficacies of SGLT-2 inhibitors, GLP-1 agonists, and DPP-4

Animated Summary Video

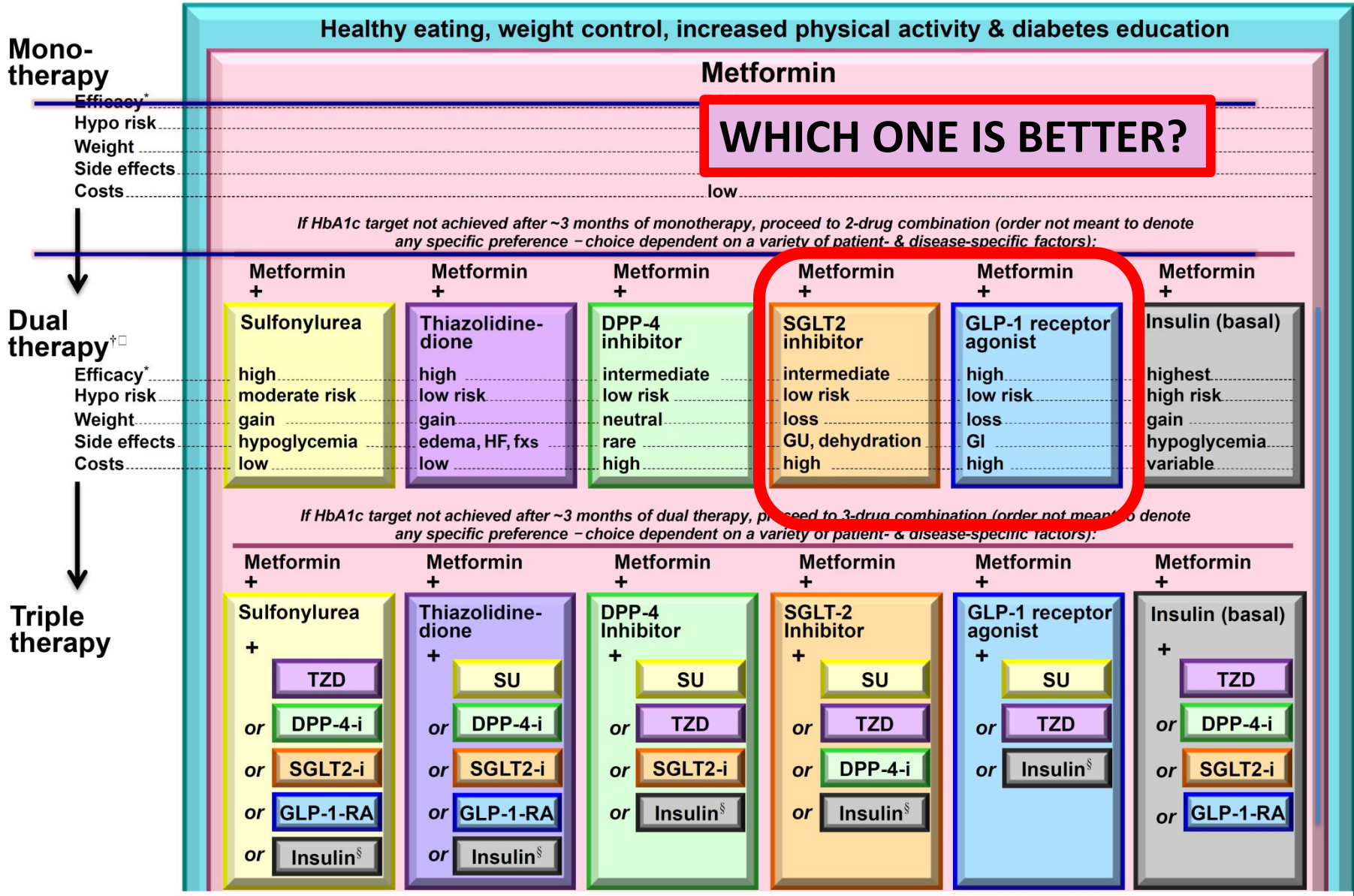
Supplemental content

17th April 2018

236 trials
Outcome was as predicted

https://jamanetwork.com/journals/jama/fullarticle/2678616

Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach



Diabetes Care 2015;38:140 Diabetologia 2015;58:429