Training course:
All About Clinical Trials

Stockholm, 13 December 2019

Clinical Trial Parade: What‘s next - Upcoming and Ongoing Clinical Trials: Diabetes

Heinz Drexel, MD, FESC, FAHA, FRCP (Ed);
Chair, ESC Working Group on Cardiovascular Pharmacotherapy 2018-2020
Feldkirch, A, Bern, CH, Triesen, FL

ESC Working Group Cardiovascular Pharmacotherapy

Conflict of Interest

National PI: ODYSSEY OUTCOMES
Lecture Honoraria, Research Grants, Advisory Boards for:

NovoNordisk, Merck, MSD, Pfizer, Sanofi-Aventis, AstraZeneca, Bayer, Takeda, Daiichi-Sankyo, Novartis, Amgen, Boehringer Ingelheim, BMS, Abbott, Janssen-Cilag, Genericon

ESC Working Group Cardiovascular Pharmacotherapy

Long-term consequences of Diabetes mellitus

- **Microangiopathy:**
  - Glucose-dependent
  - Retinopathy
  - Neuropathy
  - Nephropathy
- **Macroangiopathy – Atherosclerosis**
  - Coronary Artery Disease
  - Peripheral Artery Disease
  - Cerebrovascular Disease

Session Objectives

- Why diabetes in Cardiology?
- Fields of Innovation
- Late breaking trials in 2018 & 2019
- Class effects or not?

ESC Working Group Cardiovascular Pharmacotherapy

Considerations helping to determine whether there is a class effect or not?

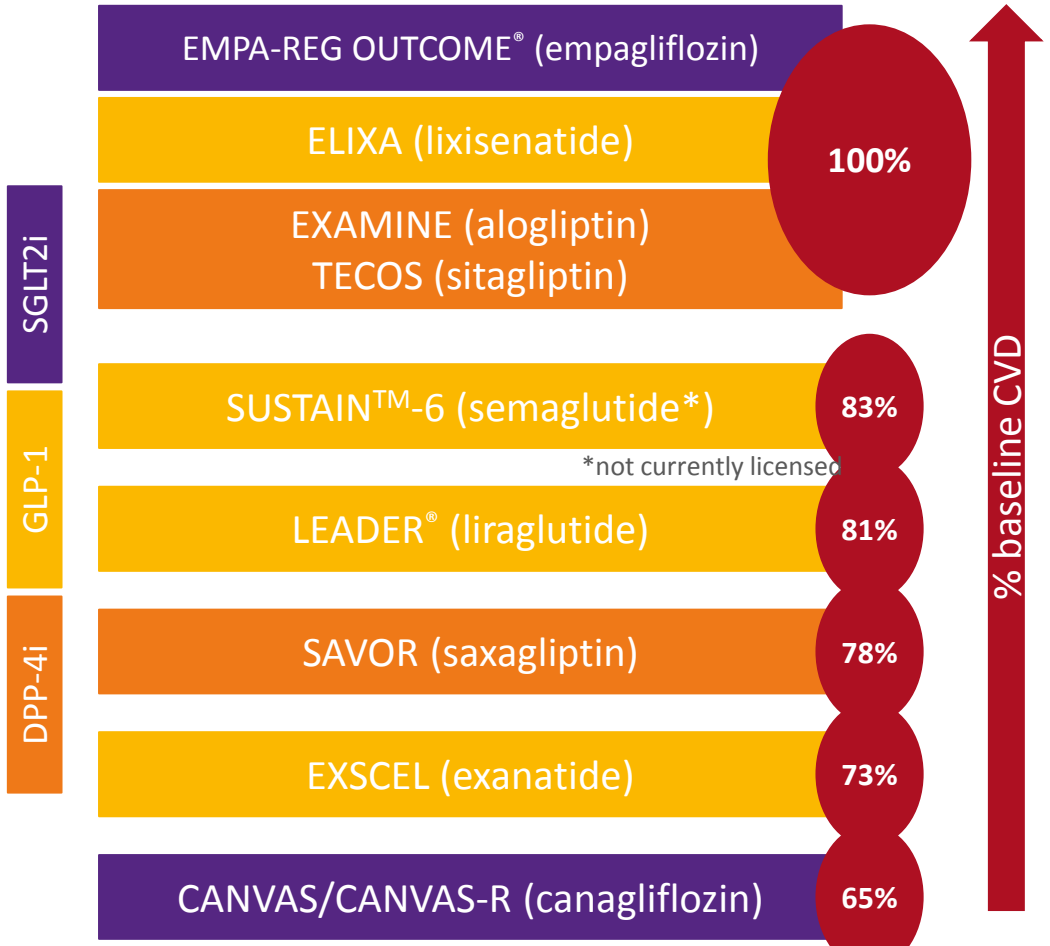
- The drug
- The population
- Look at placebo outcome
- Entry criteria
- Trial size (power)
- Trial duration (safety)

…COMPARABLE?

ESC Working Group Cardiovascular Pharmacotherapy

Baseline criteria of recent CVOTs in T2D

Rates of **baseline established CVD varied substantially between CVOTs**, which may have affected outcomes.



Prior CV history used to define CVD also differed between CVOTs, with varying combinations of the following in inclusion criteria:

- Cardiovascular disease
- Myocardial infarction
- Acute coronary syndrome
- Coronary heart disease
- Chronic kidney disease
- Peripheral vascular disease
- CV risk factor
- Age
- Time since event
- Number of risk factors

CV, cardiovascular; CVD, CV disease; CVOT, CV outcomes trial; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium–glucose transporter 2 inhibitor.

Zinman et al. N Engl J Med 2015;373:2117–28 Neal et al. N Engl J Med 2017;377:644–57 Pfeffer et al. N Engl J Med 2015;373:2247–57 Marso et al. N Eng
Med 2016;375:311–22. Marso et al. N Engl J Med 2016;375:1834–44 Holman et al. N Engl J Med 2017;377:1228–39 Scirica et al. N Engl J Med 2013;369:1317
26 White et al. N Engl J Med 2013;369:1327–35 Green et al. N Engl J Med 2015;373:232–42

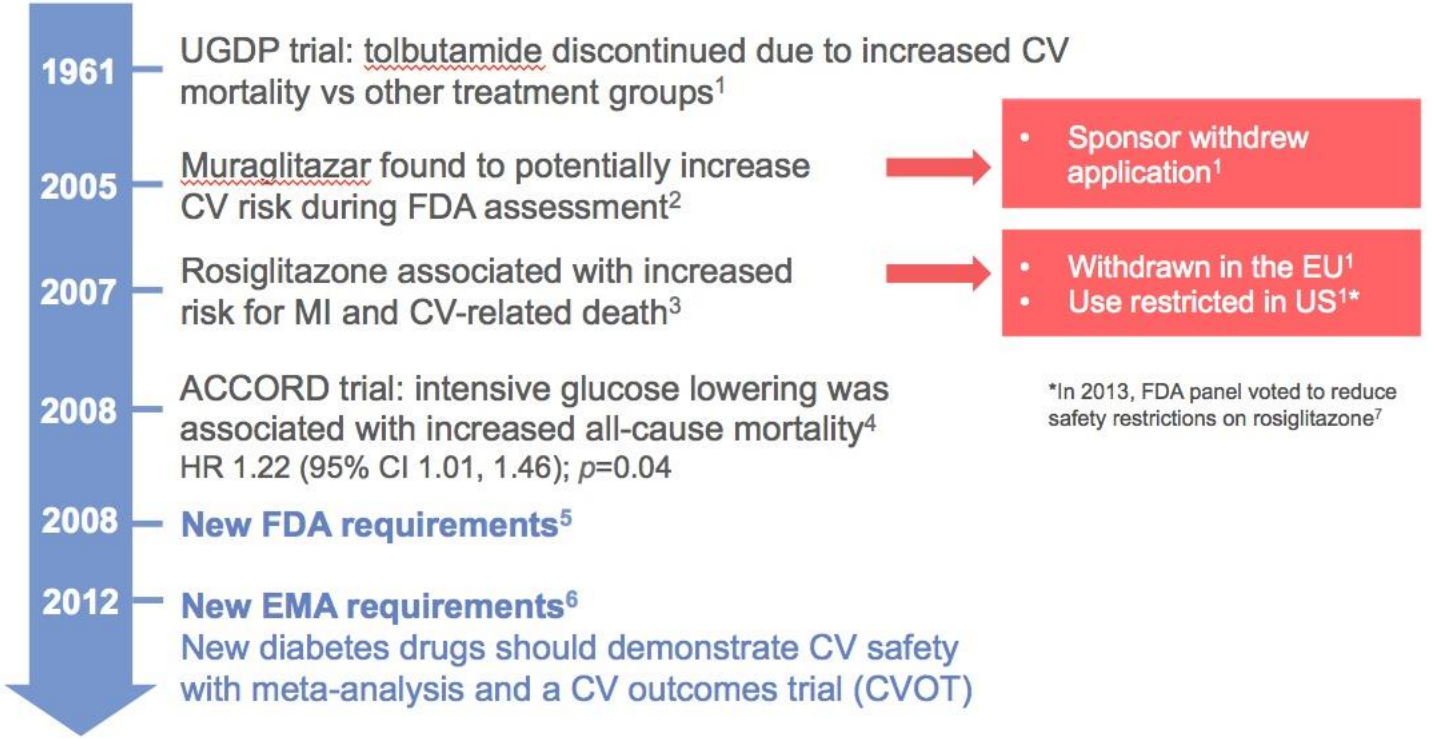
ESC Working Group Cardiovascular Pharmacotherapy

Session Objectives

- Why diabetes in Cardiology?
- Fields of Innovation
- Late breaking trials in 2018 & 2019
- ✓ Class effects or not?

ESC Working Group Cardiovascular Pharmacotherapy

FDA and EMA Demands for CV Safety Data



Nissen S et al. Ann Intern Med 2012;157:671. Nissen S et al. JAMA 2005;294:2581.
Nissen S et al. N Engl J Med 2007;356:2457. ACCORD Study Group. N Engl J Med 2008;358:2545–59.
FDA guidance 2008; EMA scientific guidelines 2012.

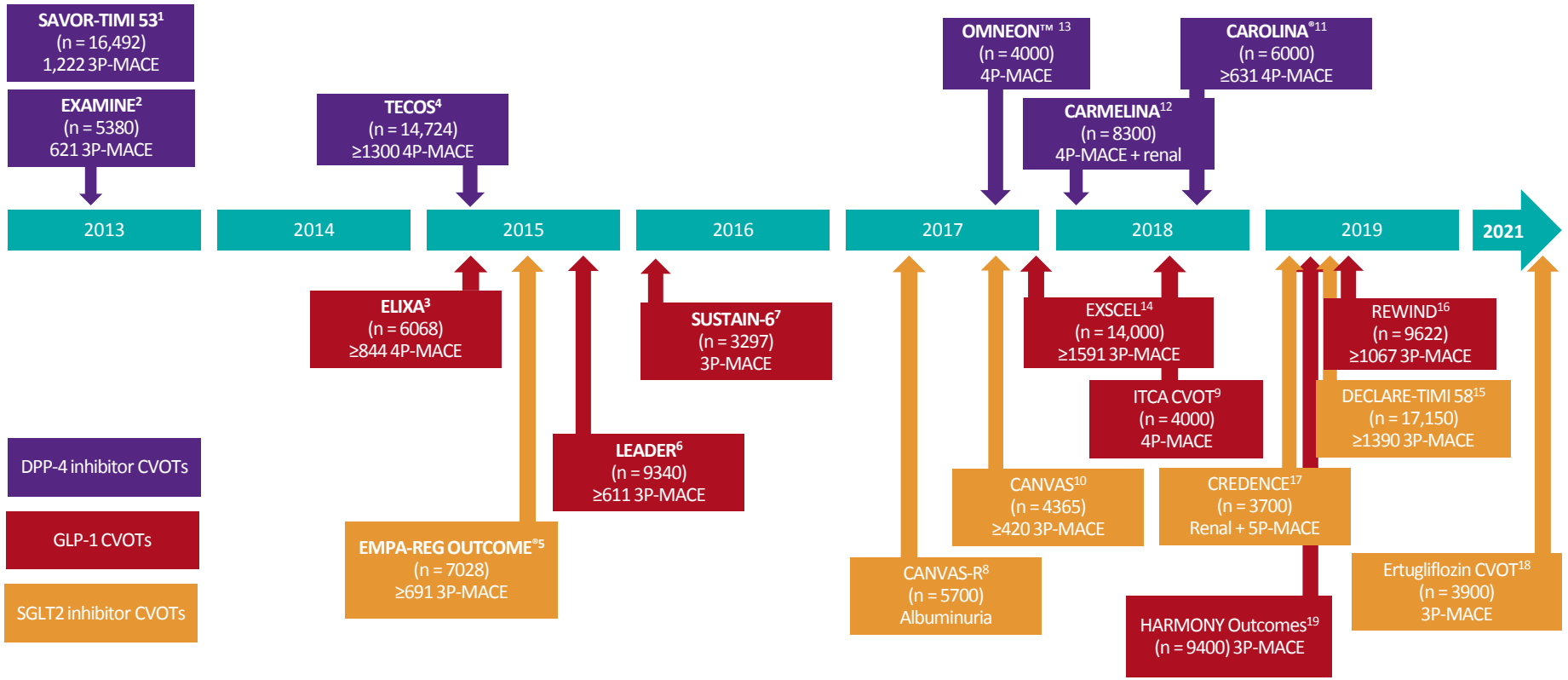
ESC Working Group Cardiovascular Pharmacotherapy

Session Objectives

- ✓ Why diabetes in Cardiology?
- Fields of Innovation
- Late breaking trials in 2018 & 2019
- Class effects or not?

ESC Working Group Cardiovascular Pharmacotherapy

CV Endpoint Trials in Diabetes



Johansen. World J Diabetes 2015;6:1092–96.

ESC Working Group Cardiovascular Pharmacotherapy

Fields of Innovation

- **GLP1 Receptor Agonists**
- **DPP4 Inhibitors**
- **SGLT2 Inhibitors**

ESC Working Group Cardiovascular Pharmacotherapy

Fields of Innovation

- **GLP1 Receptor Agonists**
- **DPP4 Inhibitors**
- **SGLT2 Inhibitors**

ESC Working Group Cardiovascular Pharmacotherapy

Published Trials With GLP1 Receptor Agonists

Study	SUSTAIN-6	LEADER	ELIXA	EXSCEL
Intervention	Semaglutid vs. Placebo	Liraglutid vs. Placebo	Lixisenatid vs. Placebo	Exenatid vs. Placebo
CV Outcome	Positive	Positive	Neutral	Neutral
Population	High risk	High risk	ACS	T2DM
Patient number	3297	9340	6068	14752
Baseline HbA1c	8.7	8.7	7.7	8.0
Follow-up	2[illegible]	3.8 Yr	25 Mo	38 Mo
ΔHbA1c	-0.[illegible]	-0.4%	-0.3%	-0.53%
ΔWeight	-2.9/4.3 kg	-2.3 kg	-0.6 kg	-1.27 kg

No Class Effect?

ESC Working Group Cardiovascular Pharmacotherapy

Marso SP et al. N Engl J Med 2016; 375:1834-1844. Marso SP et al. N Engl J Med 2016;375:311-22.
Pfeffer MA et al. N Engl J Med 2015;373:2247-57. Holman RR et al. N Engl J Med 2017; 377: 1228-1239.

LEADER

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

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*

LEADER trial investigators. N Engl J Med 2016; 375: 311-322.

ESC Working Group Cardiovascular Pharmacotherapy

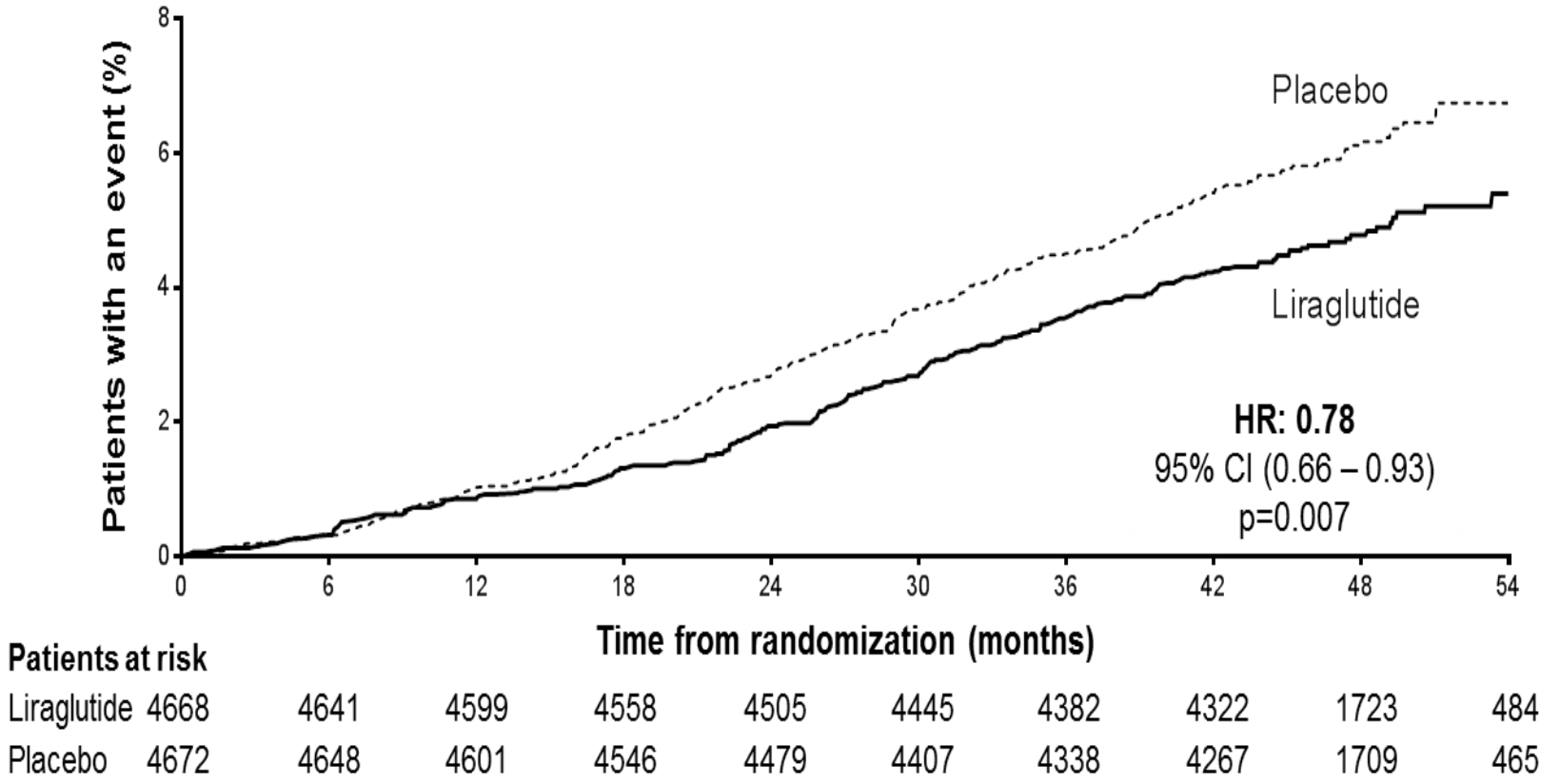
To be Concise

Liraglutide + usual care

versus placebo + usual care

ESC Working Group Cardiovascular Pharmacotherapy

LEADER: Cardiovascular Mortality



LEADER trial investigators. N Engl J Med 2016; 375: 311-322.

ESC Working Group Cardiovascular Pharmacotherapy

Fields of Innovation

- GLP1 Receptor Agonists
- DPP4 Inhibitors
- SGLT2 Inhibitors

ESC Working Group Cardiovascular Pharmacotherapy

Research

JAMA | Original Investigation

Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes

The CAROLINA Randomized Clinical Trial

Julio Rosenstock, MD; Steven E. Kahn, MB, ChB; Odd Erik Johansen, MD, PhD; Bernard Zinman, MD; Mark A. Espeland, PhD; Hans J. Woerle, MD; Egon Pfarr, MSc; Annett Keller, MSc, PhD; Michaela Mattheus, MSc; David Baanstra, MSc, MBA; Thomas Meinicke, MD; Jyothis T. George, MBBS, PhD; Maximilian von Eynatten, MD; Darren K. McGuire, MD, MHSc; Nikolaus Marx, MD; for the CAROLINA Investigators

CAROLINA: Background

Type 2 diabetes is associated with increased cardiovascular risk. In placebo-controlled cardiovascular safety trials, the dipeptidyl peptidase-4 inhibitor linagliptin demonstrated noninferiority, but it has not been tested against an active comparator.

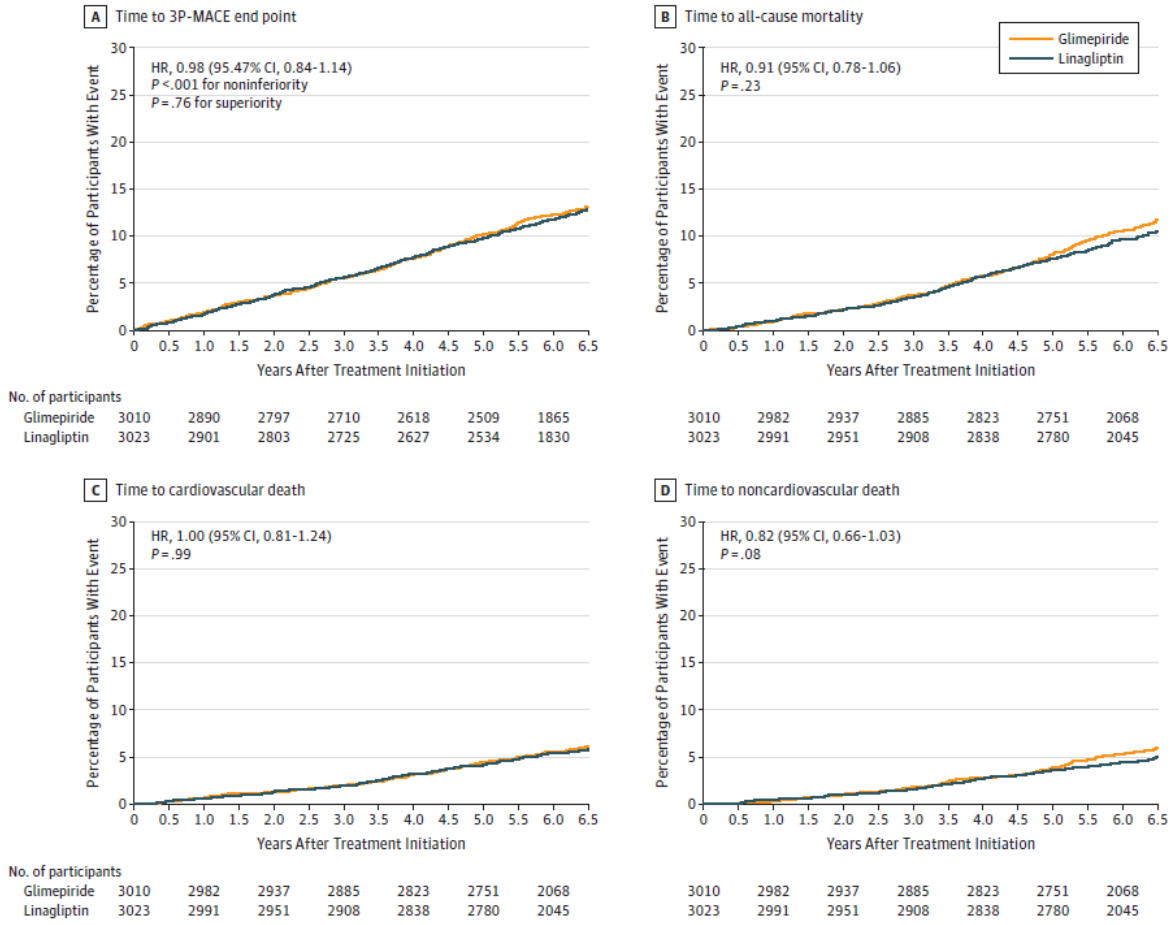
This trial assessed cardiovascular outcomes of linagliptin vs glimepiride (sulfonylurea) in patients with relatively early type 2 diabetes and risk factors for or established atherosclerotic cardiovascular disease.

ESC Working Group Cardiovascular Pharmacotherapy

Rosenstock J et al. JAMA 2019; doi: 10.1001/jama.2019.13772.

CAROLINA: Results

Figure 2. Time to Occurrence of End Points Based on Cox Regression Analyses in Patients Treated With at Least 1 Dose of the Study Drug



A, Composite end point of cardiovascular death, first nonfatal myocardial infarction, or first nonfatal stroke (3-point major cardiovascular event [3P-MACE] outcome). Median (quartile [Q] 1, Q3) follow-up was 6.2 (5.8, 6.6) years in the linagliptin group and 6.2 (5.6, 6.5) years in the glimepiride group. The 95.47% CI for the primary end point was adjusted for multiplicity due to 2 interim analyses and change of the primary end point.

B, Median (Q1, Q3) follow-up was 6.3 (5.9, 6.6) years in the linagliptin group and 6.3 (5.9, 6.6) years in the glimepiride group. C, Median (Q1, Q3) follow-up was 6.3 (5.9, 6.6) years in the linagliptin group and 6.3 (5.9, 6.6) years in the glimepiride group. D, Median (Q1, Q3) follow-up was 6.3 (5.9, 6.6) years in the linagliptin group and 6.3 (5.9, 6.6) years in the glimepiride group. 3P-MACE indicates 3-point major adverse cardiovascular event.

ESC Working Group Cardiovascular Pharmacotherapy

Rosenstock J et al. JAMA 2019; doi: 10.1001/jama.2019.13772.

CAROLINA: Conclusion

Among adults with relatively early type 2 diabetes and elevated cardiovascular risk, the use of linagliptin compared with glimepiride over a median 6.3 years resulted in a noninferior risk of a composite cardiovascular outcome.

OUTCOME:

Linagliptin = Glimepiride = Standard therapy (not placebo!).

ESC Working Group Cardiovascular Pharmacotherapy

Rosenstock J et al. JAMA 2019; doi: 10.1001/jama.2019.13772.

Three Published DPP4 Inhibitor Trials

	SAVOR-TIMI 53	EXAMINE	TECOS
Intervention	Saxagliptin/placebo	Alogliptin/placebo	Sitagliptin/placebo
Main inclusion criteria	History of or multiple risk factors for CV	AC	CVD
No. of patients			14,671
Primary outco			4P-MACE
Key secondary			3P-MACE
Target no. of events		650	1,300
Median follow-up	2.1	1.5	3.0
Completion	Completed	Completed	Completed

Non-Inferiority Met
No CVD Benefit

Scirica et al. N Engl J Med 2013; 369: 1317–26. White et al. N Engl J Med 2013; 369: 1327–35. Green et al. N Engl J Med 2015; 373: 232–42.

ESC Working Group Cardiovascular Pharmacotherapy

Research

JAMA | Original Investigation

Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk

The CARMELINA Randomized Clinical Trial

Julio Rosenstock, MD; Vlado Perkovic, MBBS, PhD; Odd Erik Johansen, MD, PhD; Mark E. Cooper, MBBS, PhD; Steven E. Kahn, MB, ChB; Nikolaus Marx, MD; John H. Alexander, MD, MHSc; Michael Pencina, PhD; Robert D. Toto, MD; Christoph Wanner, MD; Bernard Zinman, MD; Hans Juergen Woerle, MD; David Baanstra, MSc, MBA; Egon Pfarr, MSc; Sven Schnaidt, MSc; Thomas Meinicke, MD; Jyothis T. George, MBBS, PhD; Maximilian von Eynatten, MD; Darren K. McGuire, MD, MHSc; for the CARMELINA Investigators

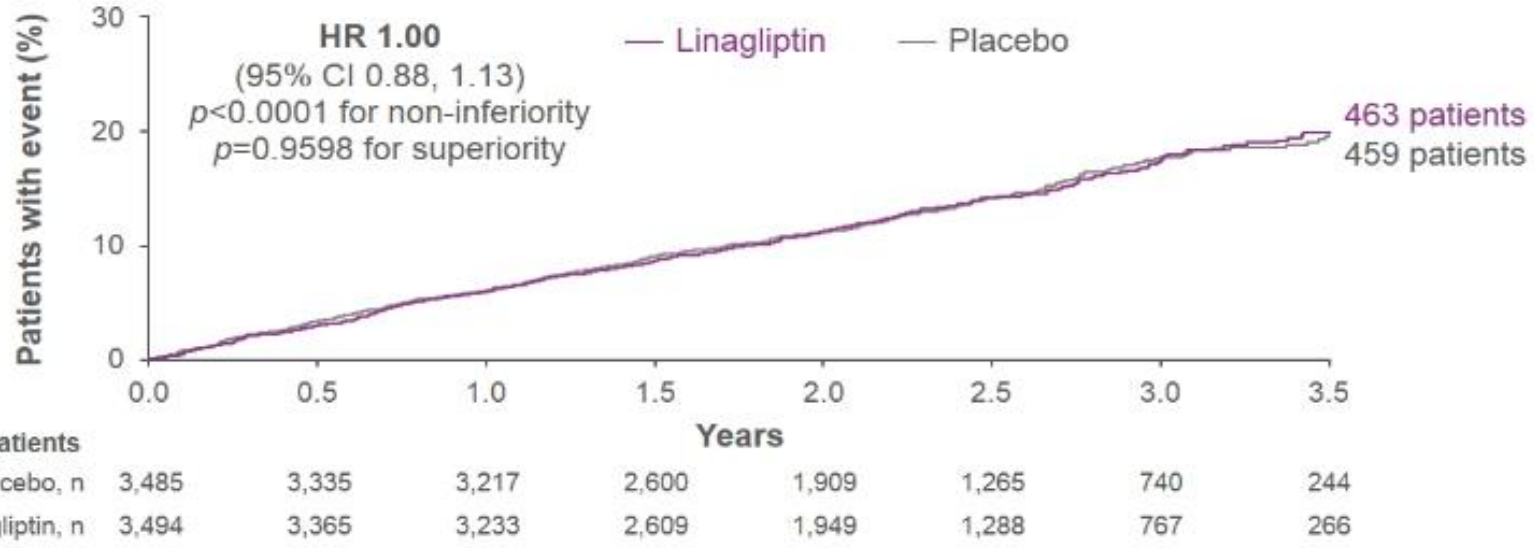
Rosenstock J et al. JAMA 2019; 321: 69-79.

ESC Working Group Cardiovascular Pharmacotherapy

CARMELINA

Time to first occurrence of 4P-MACE

3P-MACE + hospitalization for unstable angina



No. of patients							
Placebo, n	3,485	3,335	3,217	2,600	1,909	1,265	740	244
Linagliptin, n	3,494	3,365	3,233	2,609	1,949	1,288	767	266

Post-hoc analysis
Treated set. Hazard ratios and 95% CIs based on Cox regression models adjusted for region
4P-MACE, 4-point major adverse cardiovascular events

CARMELINA

Rosenstock J et al. JAMA 2019; 321: 69-79.

ESC Working Group Cardiovascular Pharmacotherapy

Session Objectives

- Why diabetes in Cardiology?
- Fields of Innovation
- ✓Late breaking trials in 2018 & 2019
- Class effects or not?

ESC Working Group Cardiovascular Pharmacotherapy

Fields of Innovation

- GLP1 Receptor Agonists
- DPP4 Inhibitors
- SGLT2 Inhibitors

ESC Working Group Cardiovascular Pharmacotherapy

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

ESC Working Group Cardiovascular Pharmacotherapy

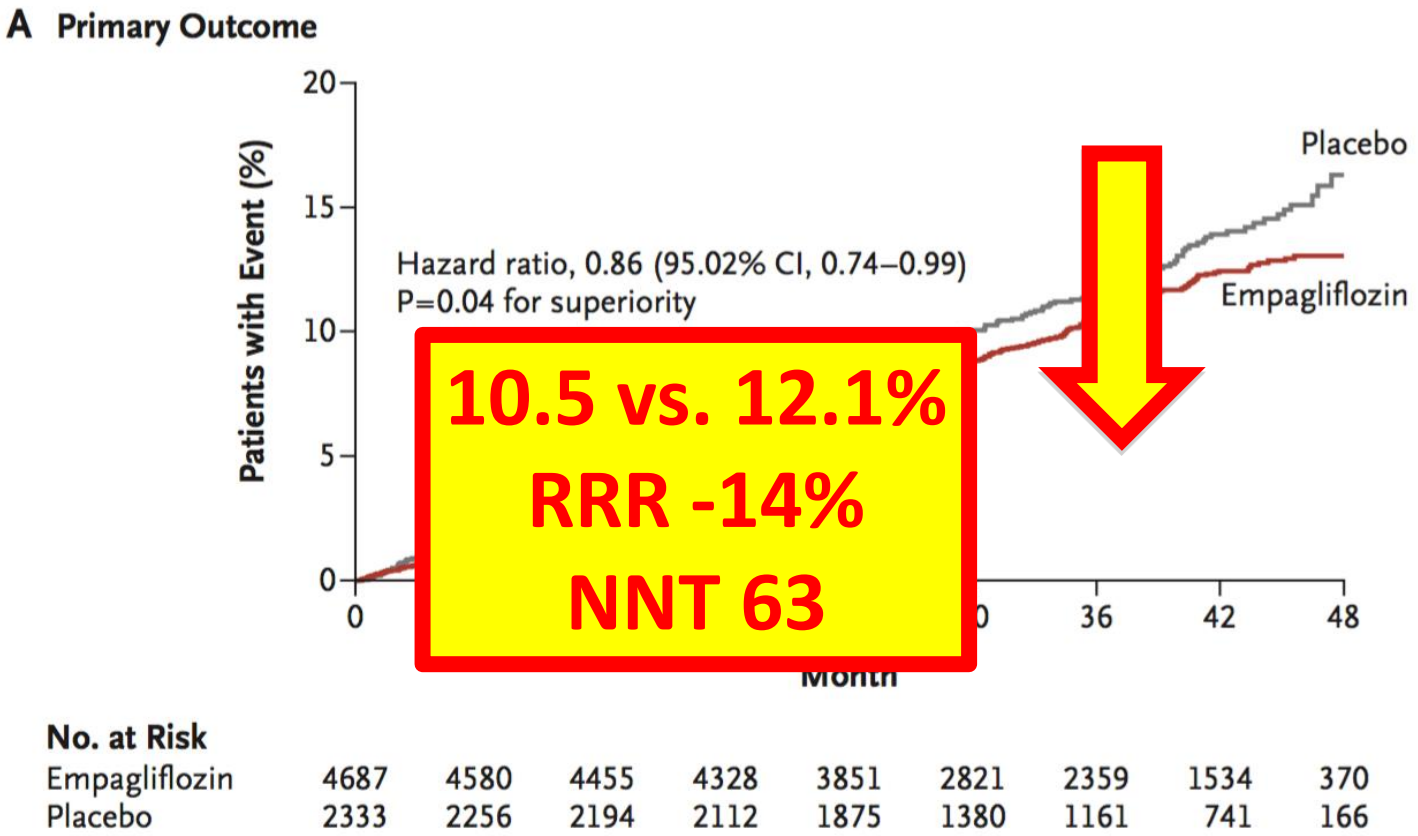
To be Concise

Empagliflozin + usual care

versus placebo + usual care

ESC Working Group Cardiovascular Pharmacotherapy

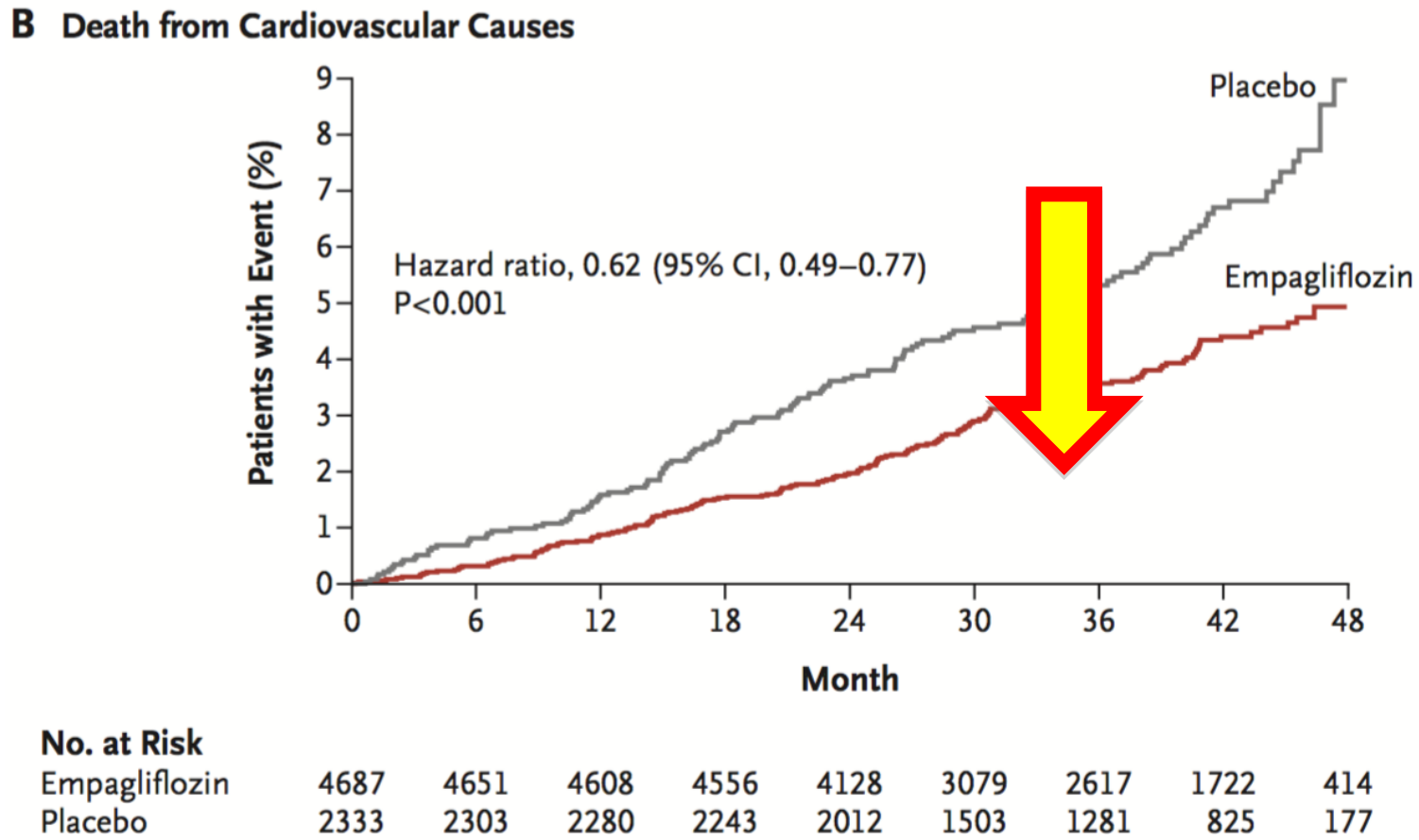
EMPAREG-OUTCOME Primary EP



Zinman B et al. N Engl J Med 2015; 373:2117-2128.

ESC Working Group Cardiovascular Pharmacotherapy

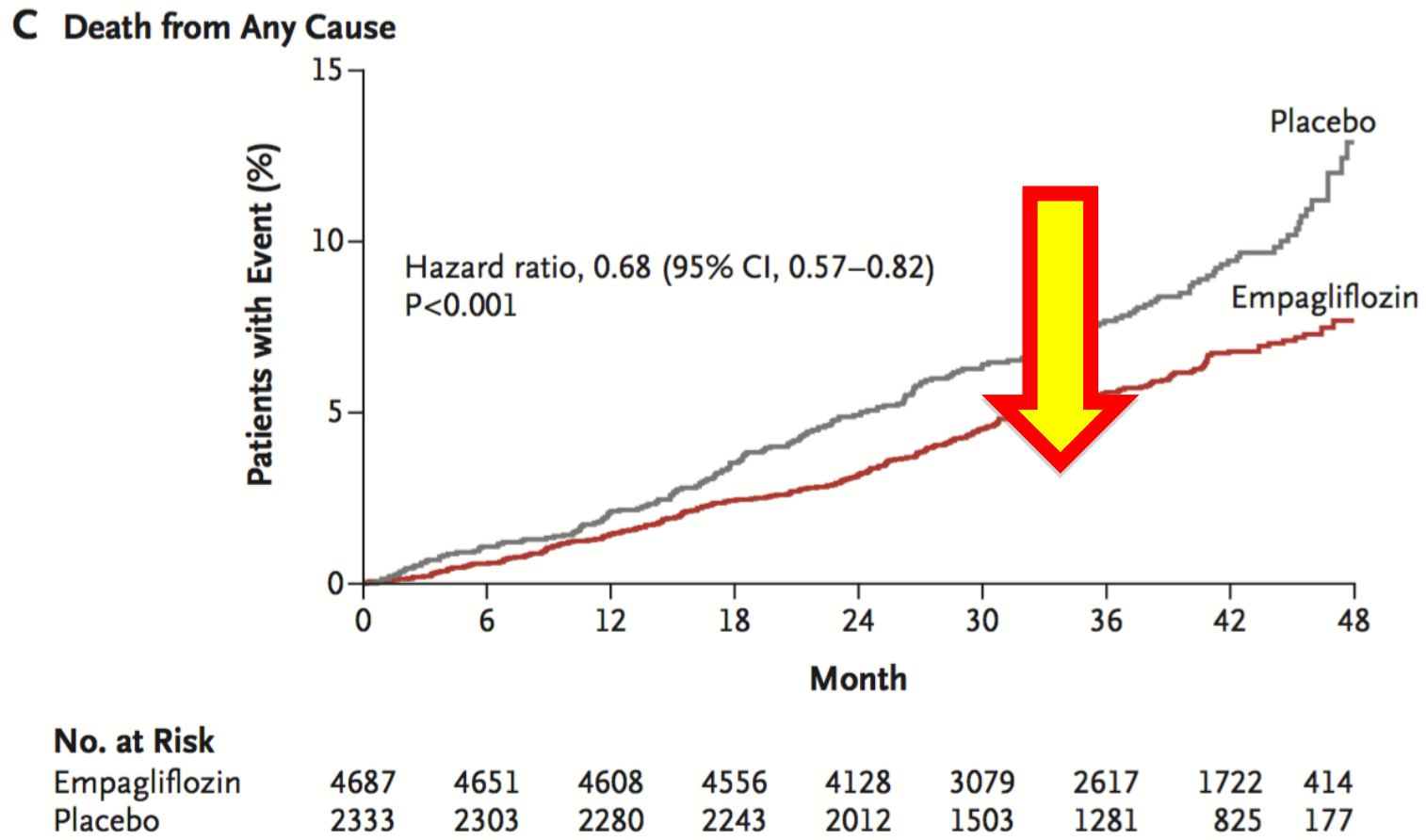
EMPAREG-OUTCOME CV Death



Zinman B et al. N Engl J Med 2015; 373:2117-2128.

ESC Working Group Cardiovascular Pharmacotherapy

EMPAREG-OUTCOME Total Mortality



Zinman B et al. N Engl J Med 2015; 373:2117-2128.

ESC Working Group Cardiovascular Pharmacotherapy

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 21, 2019 VOL. 381 NO. 21

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

ESC Working Group Cardiovascular Pharmacotherapy

DAPA-HF: Background

Inhibitors of sodium–glucose cotransporter 2 (SGLT2) reduce the risk of a first hospitalization for heart failure in patients with T2DM (possibly through glucose-Independent mechanisms).

More data regarding the effects of SGLT2 inhibitors in patients with established heart failure and a reduced EF are needed - regardless of the presence or absence of T2DM.

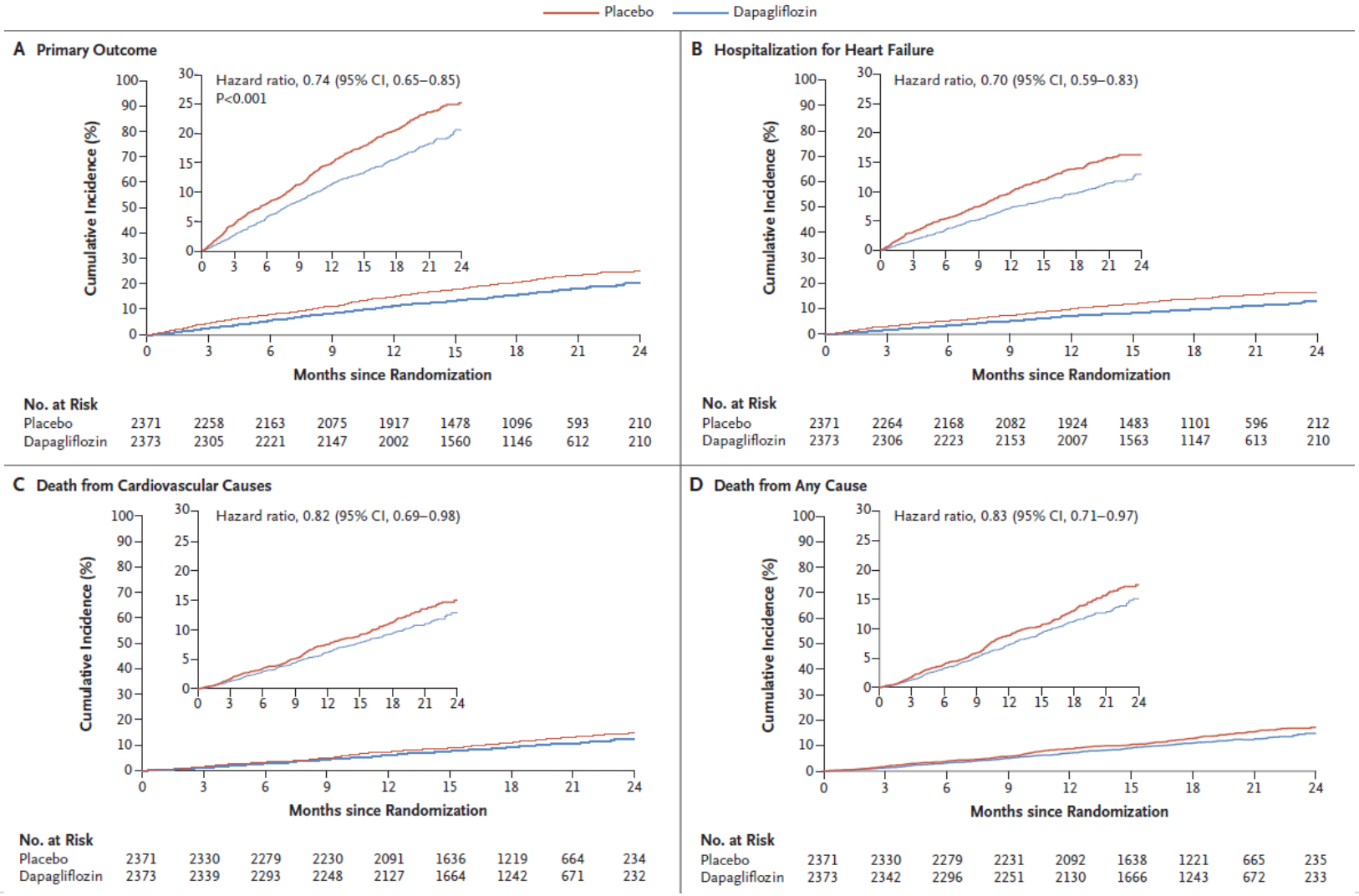
ESC Working Group Cardiovascular Pharmacotherapy

McMurray JJV et al. NEJM 2019; 381: 1995-2008.

DAPA-HF: Methods

- Phase 3, placebo-controlled trial
- 4744 patients with New York Heart Association class II, III, or IV heart failure and an EF of 40% or less
- Either dapagliflozin (10 mg once daily) or placebo, in addition to recommended therapy.
- Primary outcome: composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death.

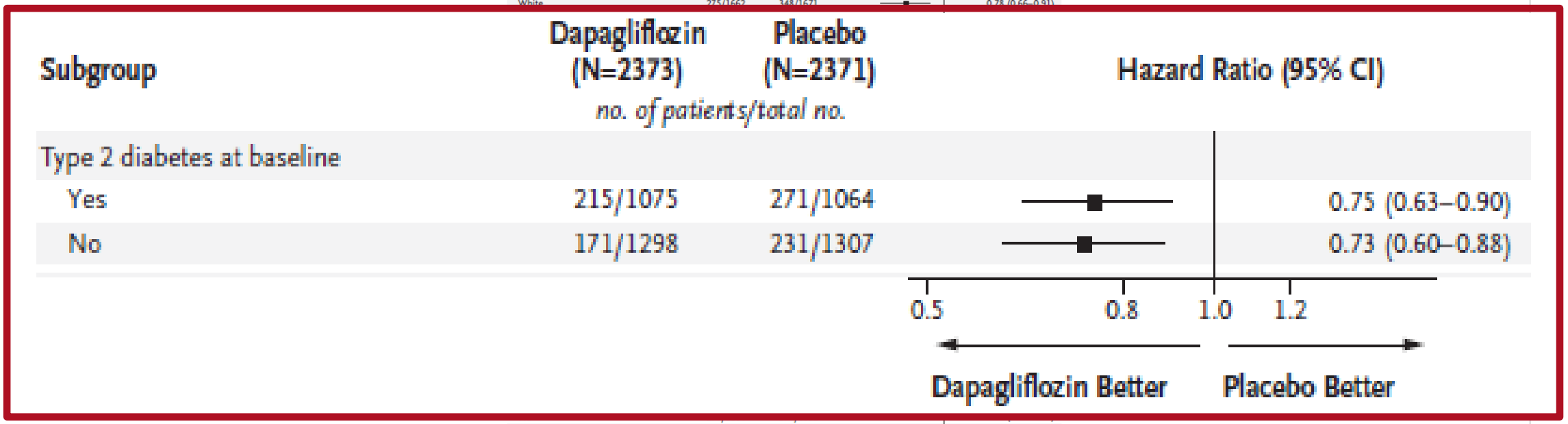
DAPA-HF: Results



McMurray JJV et al. NEJM 2019; 381: 1995-2008.

ESC Working Group Cardiovascular Pharmacotherapy

DAPA-HF: Primary Outcome in Subgroups



McMurray JJV et al. NEJM 2019; 381: 1995-2008.

ESC Working Group Cardiovascular Pharmacotherapy

DAPA-HF: Conclusion

Among patients with heart failure and a reduced EF:

risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than placebo, regardless of the presence of diabetes.

McMurray JJV et al. NEJM 2019; 381: 1995-2008.

Session Objectives

- **Why diabetes in Cardiology?**
- ✓**Fields of Innovation**
- ✓**Late breaking trials in 2018 & 2019**
- **Class effects or not?**

ESC Working Group Cardiovascular Pharmacotherapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

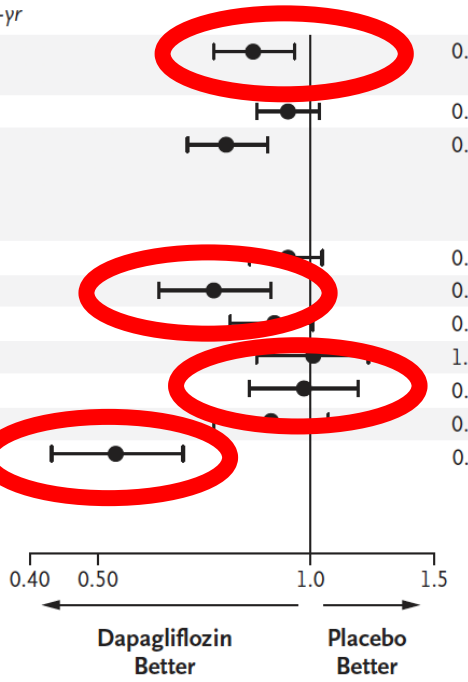
S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI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

Wiviott SD et al.; NEJM 2019; 380; 347-357.

ESC Working Group Cardiovascular Pharmacotherapy

Other Endpoints

Outcome	Dapagliflozin (N=8582) no. (%)	Dapagliflozin (N=8582) rate/1000 patient-yr	Placebo (N=8578) no. (%)	Placebo (N=8578) rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Cardiovascular death or hospitalization for heart failure	417 (4.9)	12.2	496 (5.8)	14.7	0.83 (0.73–0.95)	0.005
MACE	756 (8.8)	22.6	803 (9.4)	24.2	0.93 (0.84–1.03)	0.17
≥40% decrease in eGFR to <60 ml/min/1.73 m², ESRD, or death from renal or cardiovascular cause	370 (4.3)	10.8	480 (5.6)	14.1	0.76 (0.67–0.87)	
Death from any cause	529 (6.2)	15.1	570 (6.6)	16.4	0.93 (0.82–1.04)	
Hospitalization for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61–0.88)	
Myocardial infarction	393 (4.6)	11.7	441 (5.1)	13.2	0.89 (0.77–1.01)	
Ischemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	1.01 (0.84–1.21)	
Death from cardiovascular cause	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82–1.17)	
Death from noncardiovascular cause	211 (2.5)	6.0	238 (2.8)	6.8	0.88 (0.73–1.06)	
≥40% decrease in eGFR to <60 ml/min/1.73 m², ESRD, or death from renal cause	127 (1.5)	3.7	238 (2.8)	7	0.53 (0.43–0.66)	

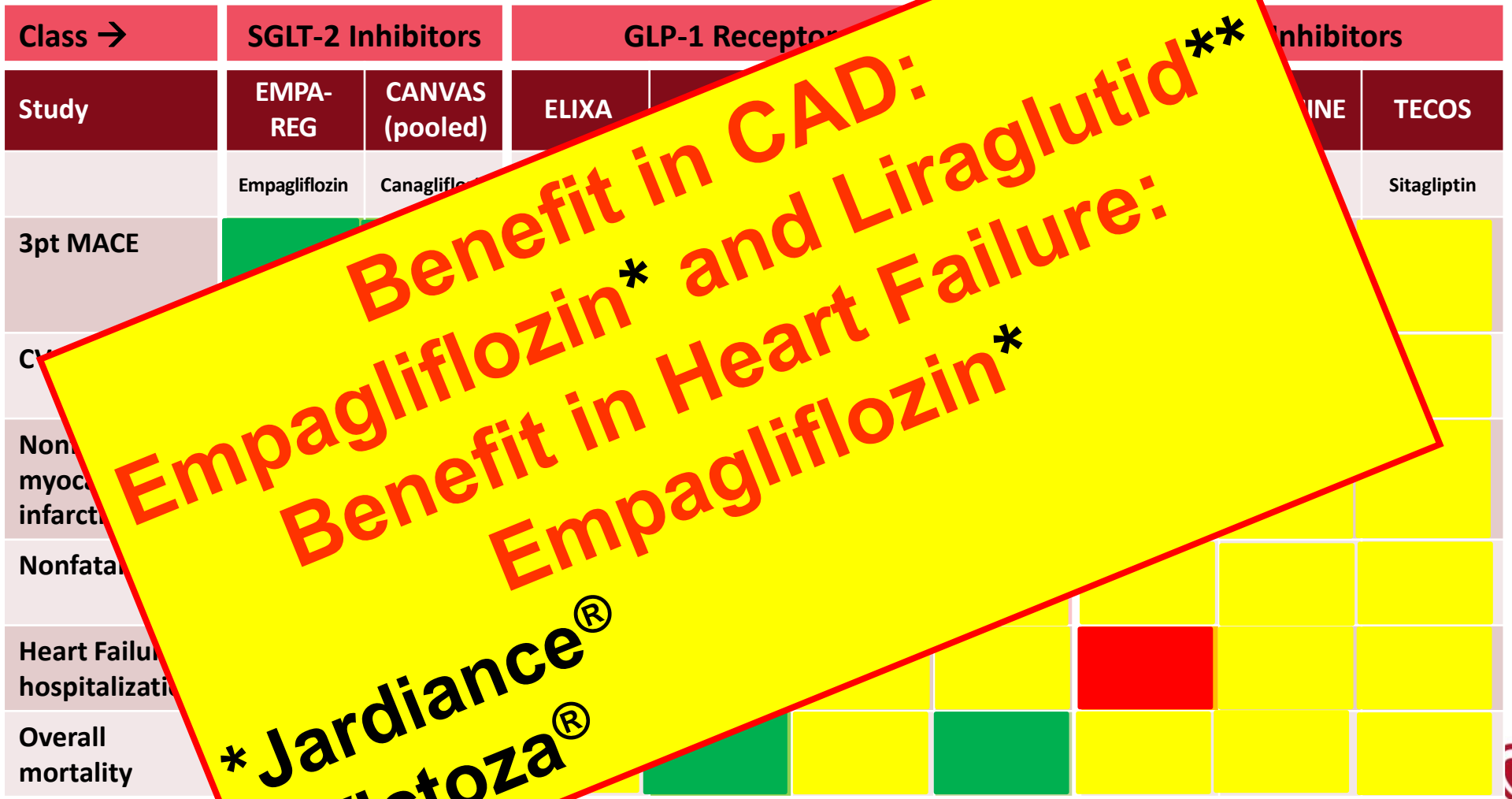


Wiviott SD et al.; NEJM 2019; 380; 347-357.

ESC Working Group Cardiovascular Pharmacotherapy

A Synopsis of Recent Diabetes Outcome-Trials

Significantly improved, neutral, signi ntly worse



Benefit in CAD: Empagliflozin* and Liraglutid Benefit in Heart Failure: Empagliflozin***

*Jardiance®

**Victoza®

ESC Working Group Cardiovascular Pharmacotherapy

Zinman B et al., N Engl J Med ... Neal B et al., N Engl J Med 2017, Pfeffer MA et al., N Engl J Med 2015, Marso SP et al., N Engl J Med 2016, Marso SP et al., N Engl J Med 2016, Holman RR et al., N Engl J Med. DOI: 10.1056/NEJMoa1612917; Scirica BM et al., N Engl J Med 2013, White WB et al., Diabetes Obes Metab 2013, Green JB et al., N Engl J Med 2015

Training course:
All About Clinical Trials

Stockholm, 13 December 2019

Thank you for your attention!

Clinical Trial[illegible]What's next - Upcoming and Ongoing Clinica[illegible] Diabetes

Heinz Drexel, MD, FESC, FAHA, FRCP (Ed);
Chair, ESC Working Group on Cardiovascular Pharmacotherapy 2018-2020

ESC Working Group Cardiovascular Pharmacotherapy

Working Group Cardiovascular Pharmacotherapy