The Dynamic Duo: GLP-1 Receptor Agonists and SGLT2 Inhibitors

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Disclosures

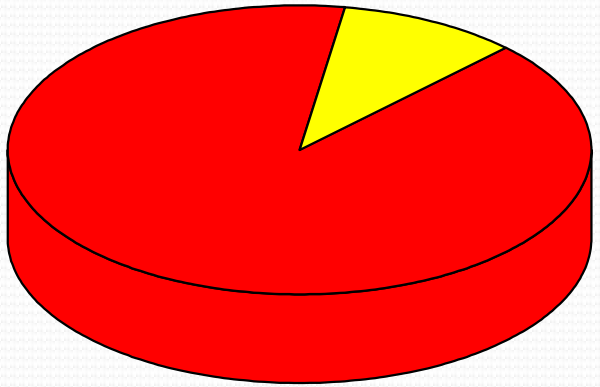
- Eli Lilly – Speaker bureau
- Amgen – Speaker bureau
- Novo Nordisk – Speaker bureau

Prevalence of Diabetes in the United States 2021 CDC Fact Sheet

- Affects 37.3 million Americans (11.3% of the population)
  - Diagnosed: 28.7 million
  - Undiagnosed: 8.6 million
    (Over 1 in 5)
  - Over 4200 people are diagnosed daily

- Pre-Diabetes: 96 million
  - 38% of adults ≥ age 18
  - 48.8% ≥ 65
  - 1 in 7 of these patients know it

Type 1 ~5%
(Approx 2 million)



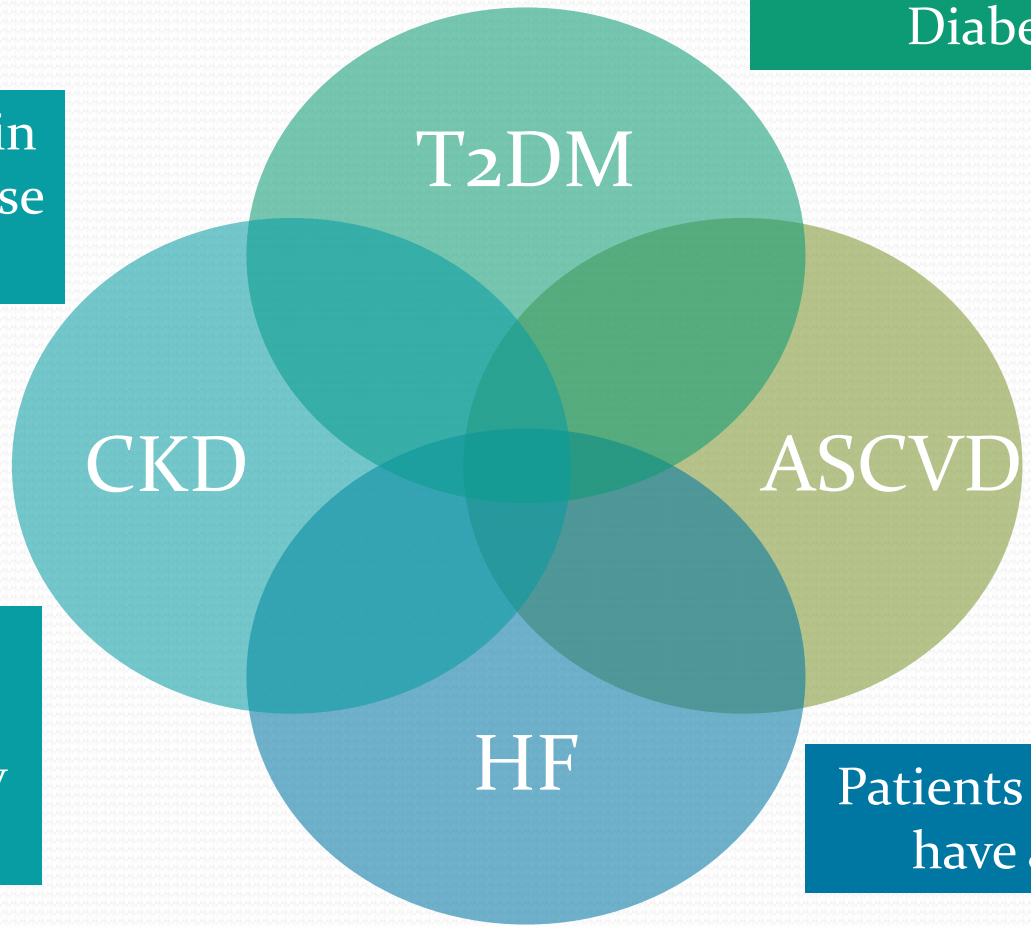
Type 2 ~95%
(Approx 35 million)

Centers for Disease Control and Prevention. National Diabetes Statistics Report website. https://www.cdc.gov/diabetes/data/statistics-report/index.html. Accessed Jan 31, 2023.

Diabetes and Cardiorenal Risk

More than 34 million Americans have diabetes – 95% of whom have Type 2 Diabetes Mellitus (T2DM).

Diabetes and CVD are the main causes of chronic kidney disease (CKD).



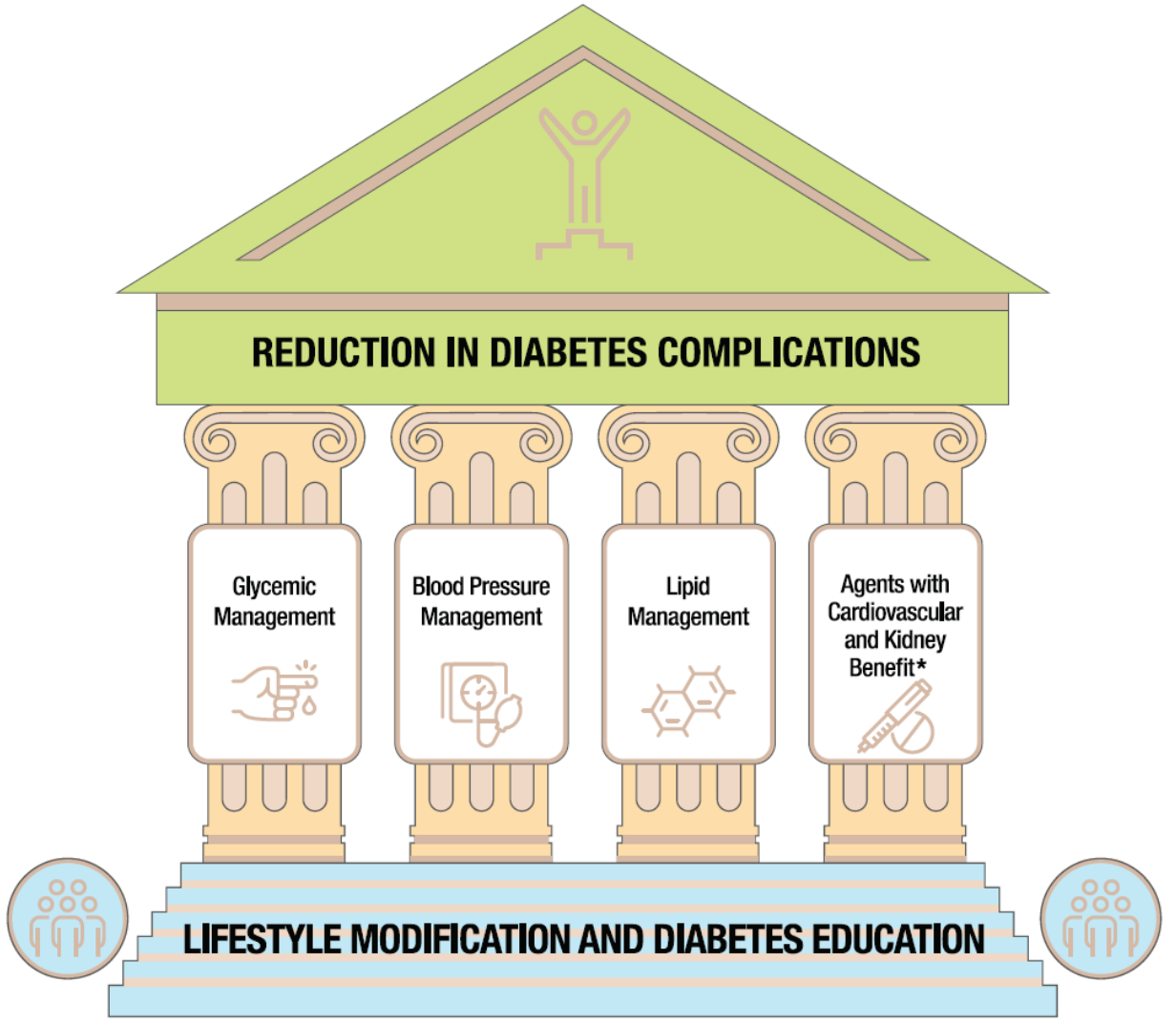
Adults with T2DM are twice as likely to have heart disease, a stroke, or heart failure.

The presence of diabetes and CVD in adults with CKD increases the risk of morbidity and mortality.

Patients with diabetes and heart failure have a 50% 5-year mortality rate.

CDC. Type 2 Diabetes [Internet]. Center for Disease Control [cited 2020 Sep 20]. Available from: https://www.cdc.gov/diabetes/basics/type2.html
National Institute of Diabetes and Digestive and Kidney Diseases. Kidney Disease Statistics for the United States [Internet]. NIH [cited 20 Sep 2020]. Available from: https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease

Multifactorial approach to reduction in risk of diabetes complications



ADA. Standards of Medical Care in Diabetes – 2022. Diabetes Care 2022;45(Suppl. 1):S144–S174.

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

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Diabetes Care®

JANUARY 2023 | VOLUME 46 | SUPPLEMENT 1

Supplement 1

Standards of Care in Diabetes—2023

Major changes for 2023

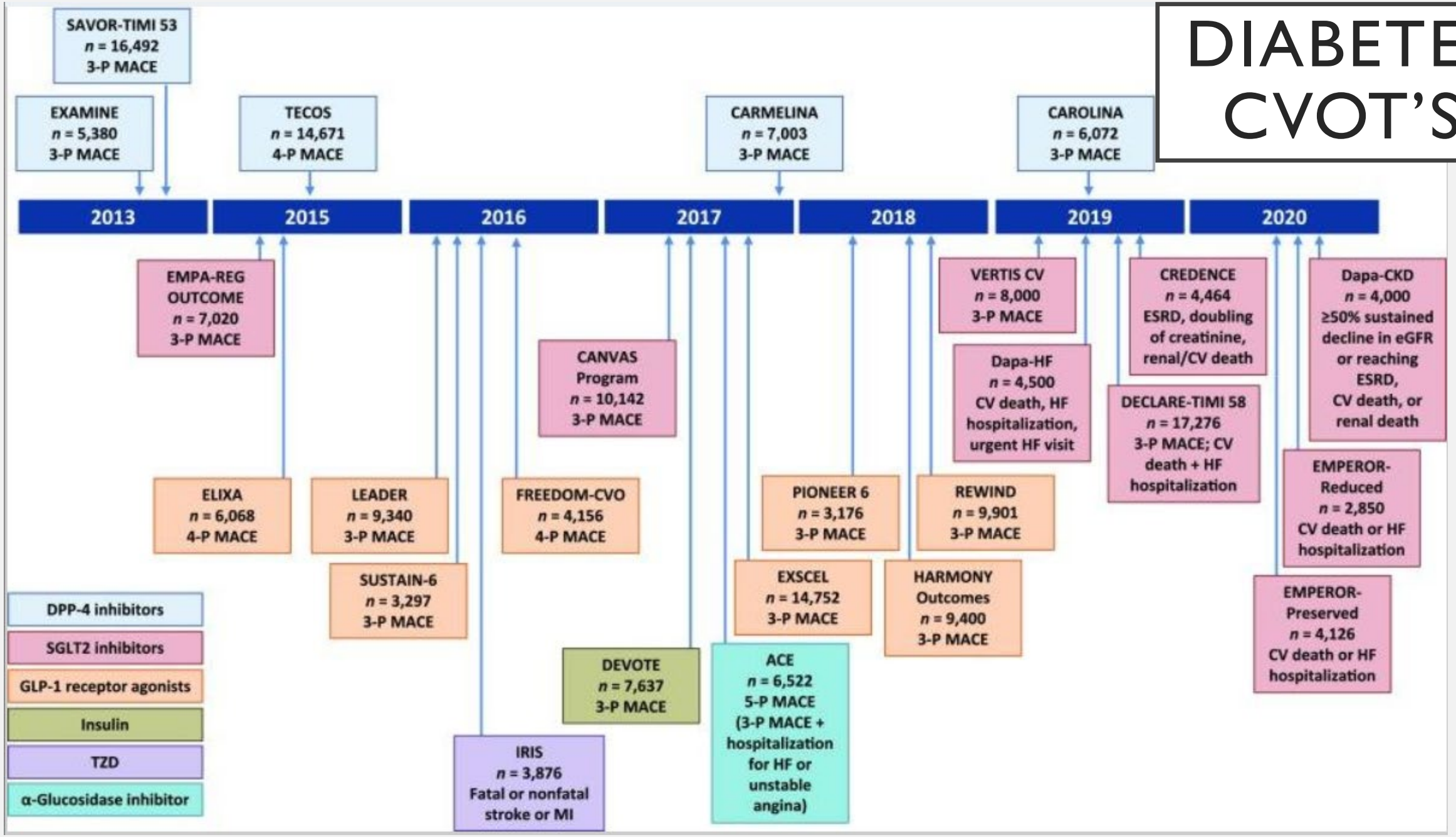
- Even greater Cardio-renal Protection Theme with consideration of glucose-lowering therapies
- Greater emphasis on weight loss in diabetes management
- New LDL-C goal
- New BP goal
- Emphasis on renal protection

The ABC's of Diabetes (Other guideline changes …)

- A1C (and consider ASA)
  - < 7.0% ADA (< 6.5% ACE)
- Blood Pressure
  - < 130/80
- Cholesterol
  - LDL-C < 70 mg/dL (< 55 mg/dL for those with established ASCVD)
    - Statin therapy (moderate to high intensity doses)
  - HDL-C > 40 mg/dL (> 50 mg/dL in women)
  - TG's < 150 mg/dL (the addition of icosapent ethyl can be considered)
- Smoking Cessation

ADA. Standards of Medical Care in Diabetes – 2023. Diabetes Care 2023;46(Suppl. 1):S158–S190.

DIABETES CVOT'S



Cefalu WT et al. Cardiovascular Outcomes Trials in Type 2 Diabetes: Where Do We Go From Here? Reflections From a Diabetes Care Editors' Expert Forum. Diabetes Care 2018;41:14–31.

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

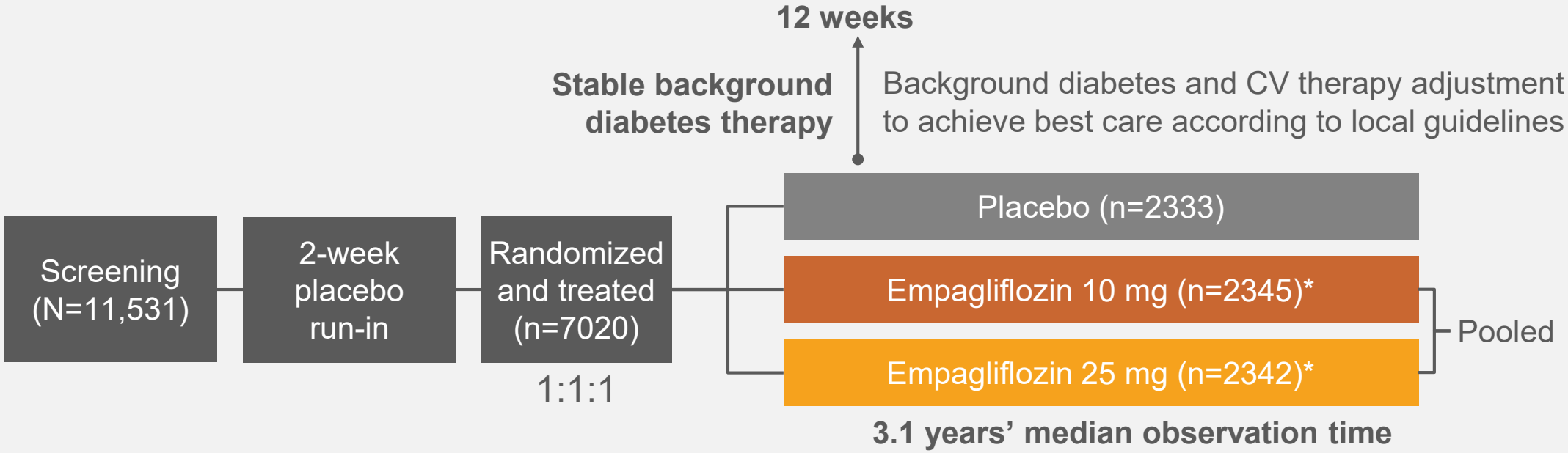
7,020 people with T2DM, 100% with established CVD

Empa 10 or 25 mg vs placebo (all +SOC); Median observation time of 3.1 years

Primary Endpoint: Composite of CV death, non-fatal MI and non-fatal stroke (3-pt MACE)

Zinman B et al. N Engl J Med. 2015;373(22):2117-28.

EMPA-REG OUTCOME® : STUDY DESIGN



Main inclusion criteria

- HbA1c 7–10%
- Established CV disease
  - History of coronary artery disease, peripheral arterial disease, MI or stroke
- eGFR ≥30 ml/min/1.73 m^{2}†

*The two doses have been pooled in the primary analysis; †Initiation of empagliflozin in patients with impaired kidney function should be conducted according to local prescribing information

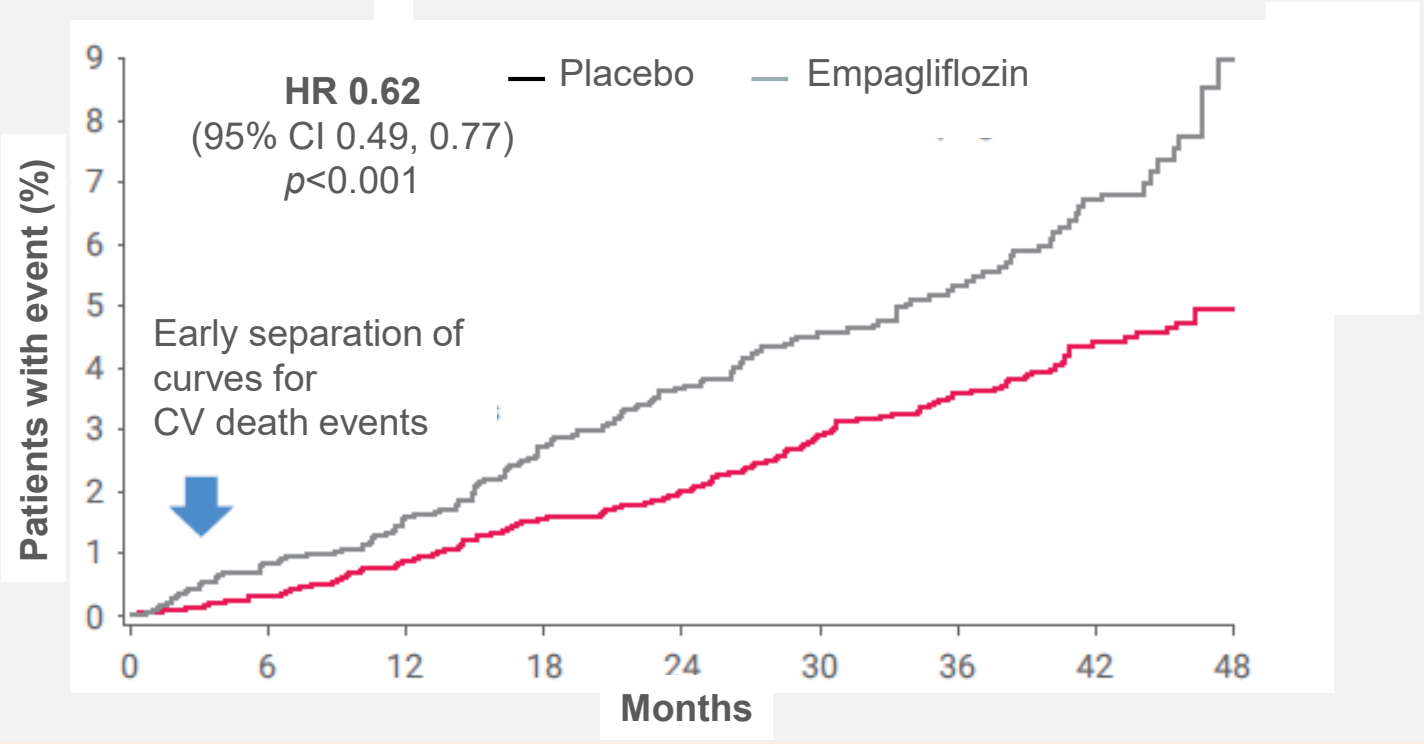
eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; MI, myocardial infarction

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

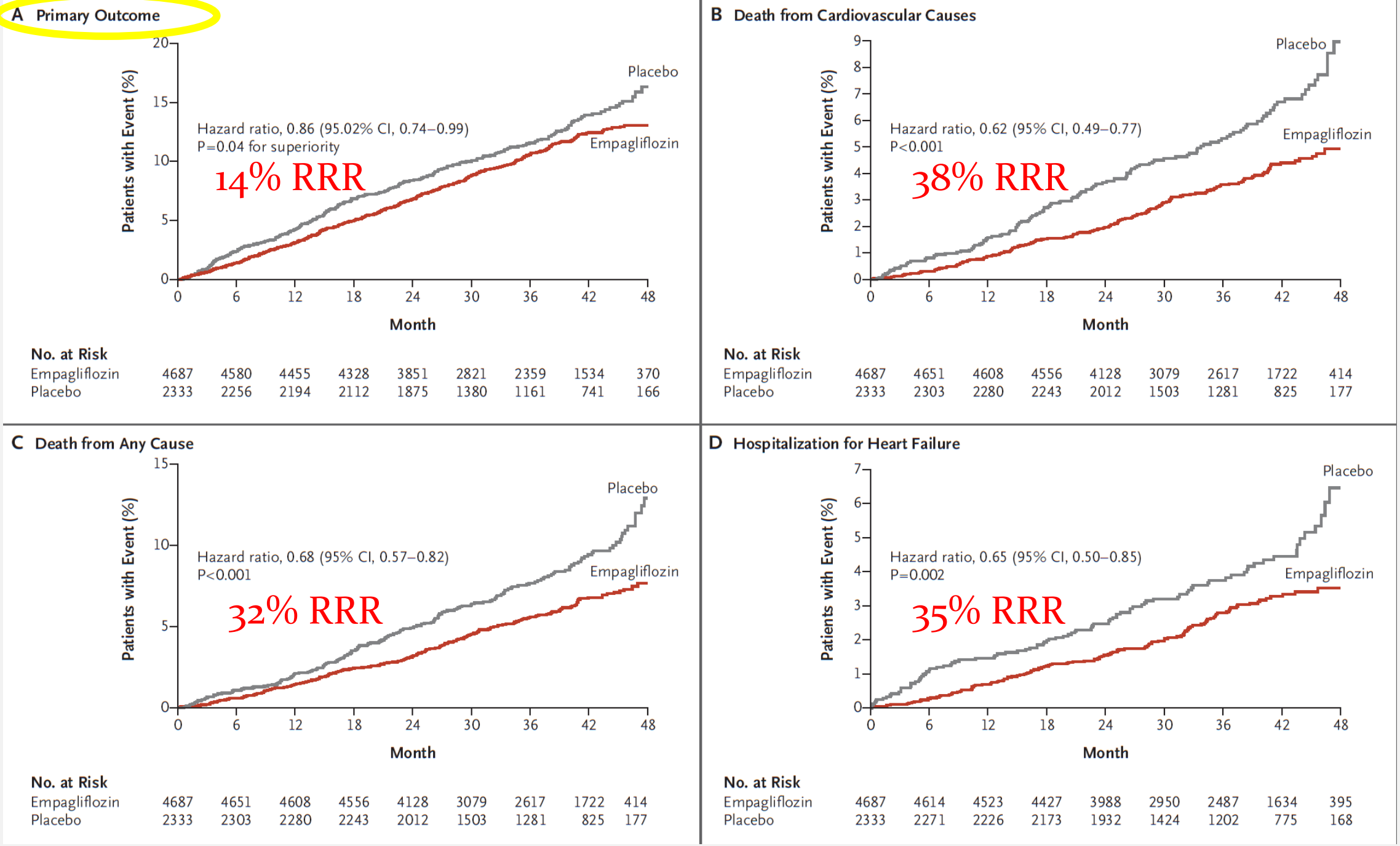
TIME TO OCCURRENCE OF CV DEATH VS PLACEBO ON TOP OF STANDARD OF CARE*† EMPA-REG OUTCOME

CV death

↓38% RRR



Cumulative incidence function. RRR for CV death: 38%; ARR for CV death: 2.2%; rates of CV death: 3.7% (empagliflozin) vs 5.9% (placebo)
*Secondary endpoint; Nominal p-value †Standard of care included CV medications and glucose-lowering agents given at the discretion of physicians
ARR, absolute risk reduction; RRR, relative risk reduction
Zinman B *et al. N Engl J Med* 2015;373:2117



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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*

9,340 people with T2DM at high risk of MACE

Primary Endpoint: Composite of CV death, non-fatal MI and non-fatal stroke: 13% reduction

Secondary Endpoint: 22% reduction of CV mortality
15% decrease in overall mortality

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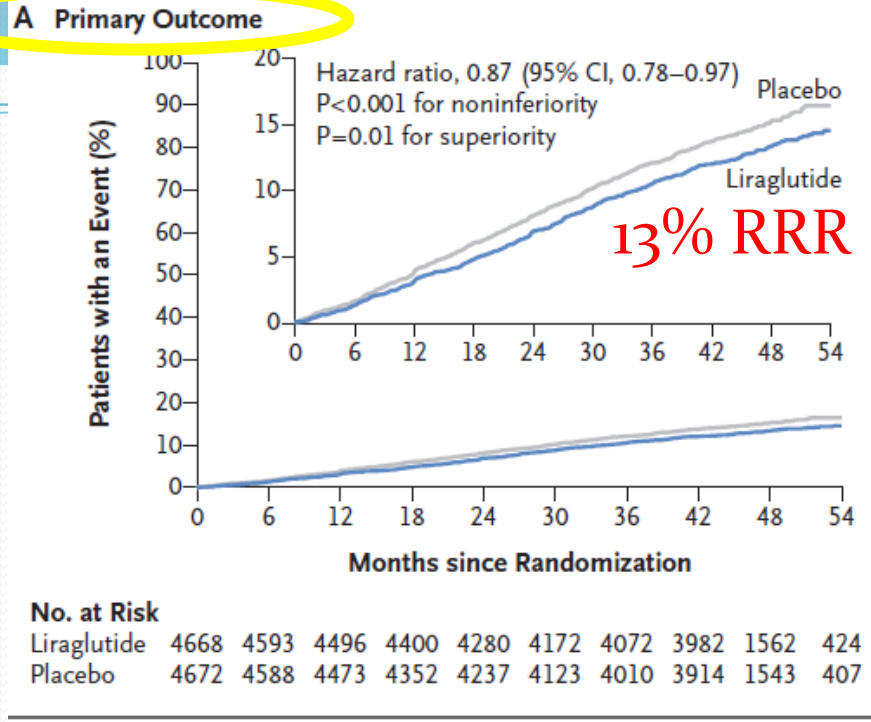
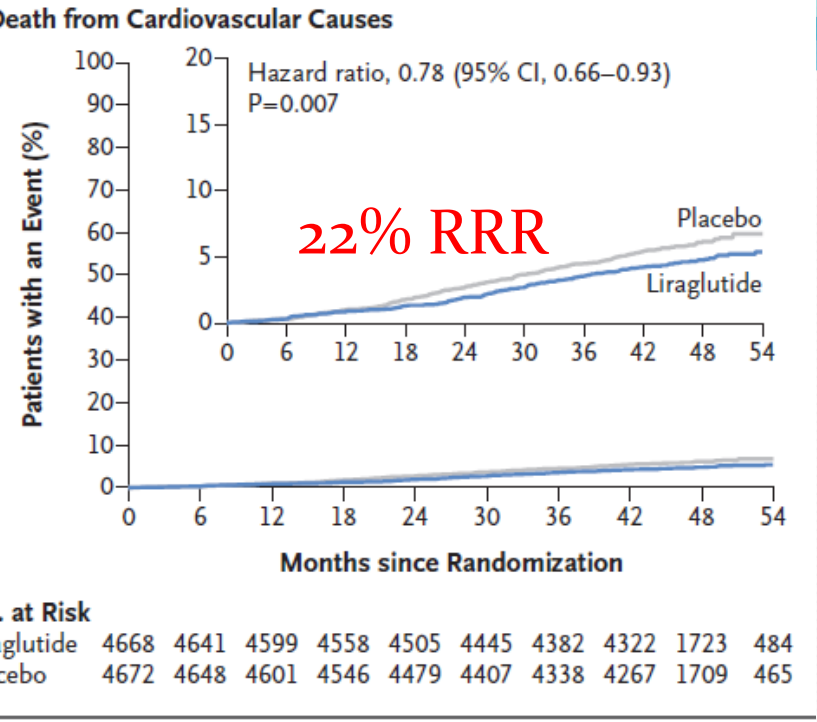
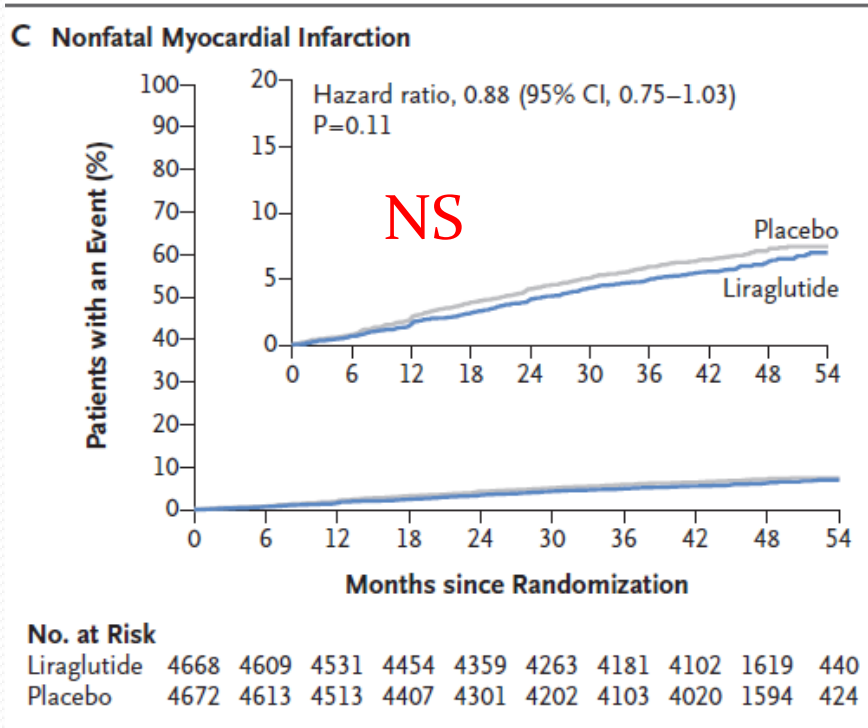
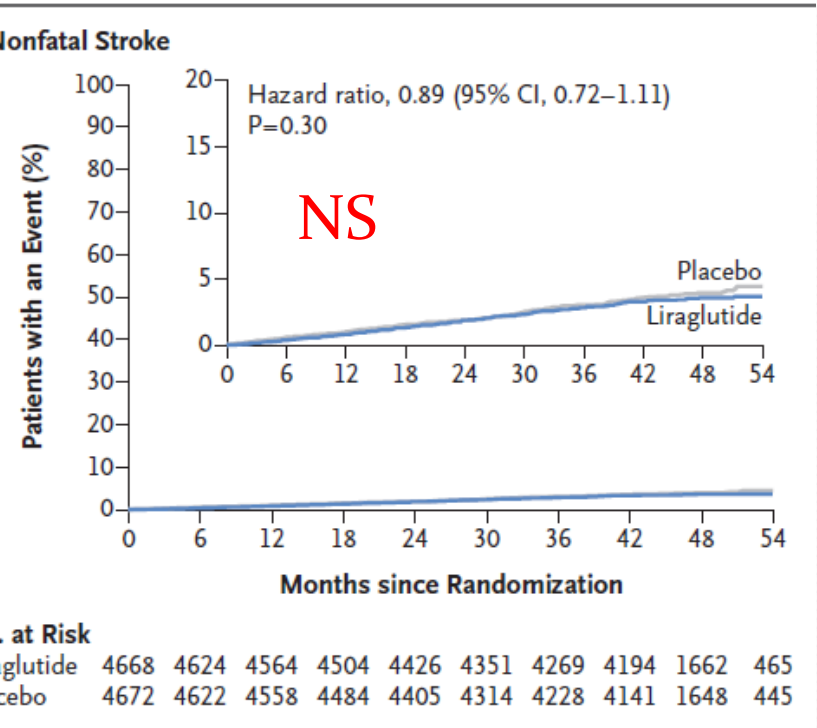
9,340 patients with T2DM at high risk of MACE (81% with CVD)
Liraglutide 1.8 mg; Median 3.8 yrs f/u
Primary Endpoint: Composite of CV death, non-fatal MI and non-fatal stroke









Marso SP et al. N Engl J Med. 2016 Jul 28;375:311-22.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sept 16, 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*

26% reduction of MACE

ABSTRACT

BACKGROUND

Regulatory guidance specifies the need to establish cardiovascular safety of new diabetes therapies in patients with type 2 diabetes in order to rule out excess cardiovascular risk. The cardiovascular effects of semaglutide, a glucagon-like peptide 1 analogue with an extended half-life of approximately 1 week, in type 2 diabetes are unknown.

METHODS

We randomly assigned 3297 patients with type 2 diabetes who were on a standard-care regimen to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks. The primary composite outcome was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. We hypothesized that semaglutide would be noninferior to placebo for the primary outcome. The noninferiority margin was 1.8 for the upper boundary of the 95% confidence interval of the hazard ratio.

From the Research Medical Center, Kansas City, MO (S.P.M.); School of Medicine, Swansea University, Swansea, United Kingdom (S.C.B.); Department of Medicine and Aging Science and Center of Excellence on Aging and Translational Medicine, G. d'Annunzio University, Chieti-Pescara, Italy (A.C.); CPClin Research Center/Hospital Israelita Albert Einstein, São Paulo (F.G.E.); Hospital Universitario Quirón Salud Madrid, Facultad de Ciencias de la Salud, Universidad Europea de Madrid, Madrid (E.J.); Li Ka Shing Knowledge Institute and Keenan Research Centre for Biomedical Science, St. Michael's Hospital, University of Toronto, Toronto (L.A.L.), and the University of Manitoba, Winnipeg (V.W.) —

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3,297 patients with T2DM at high risk of MACE (83% with CVD and/or CKD)
Semaglutide 0.5 or 1 mg; Median 2.1 yrs f/u
Primary Endpoint: 3-point MACE

ABSTRACT

BACKGROUND

Regulatory guidance specifies the need to establish cardiovascular safety of new diabetes therapies in patients with type 2 diabetes in order to rule out excess cardiovascular risk. The cardiovascular effects of semaglutide, a glucagon-like peptide 1 analogue with an extended half-life of approximately 1 week, in type 2 diabetes are unknown.

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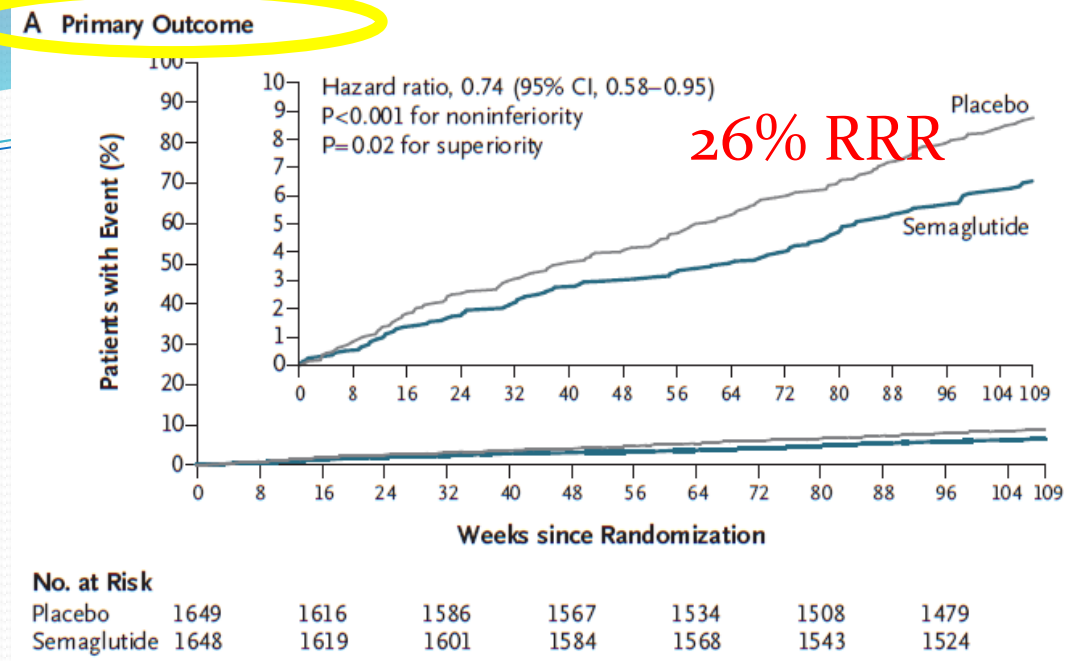

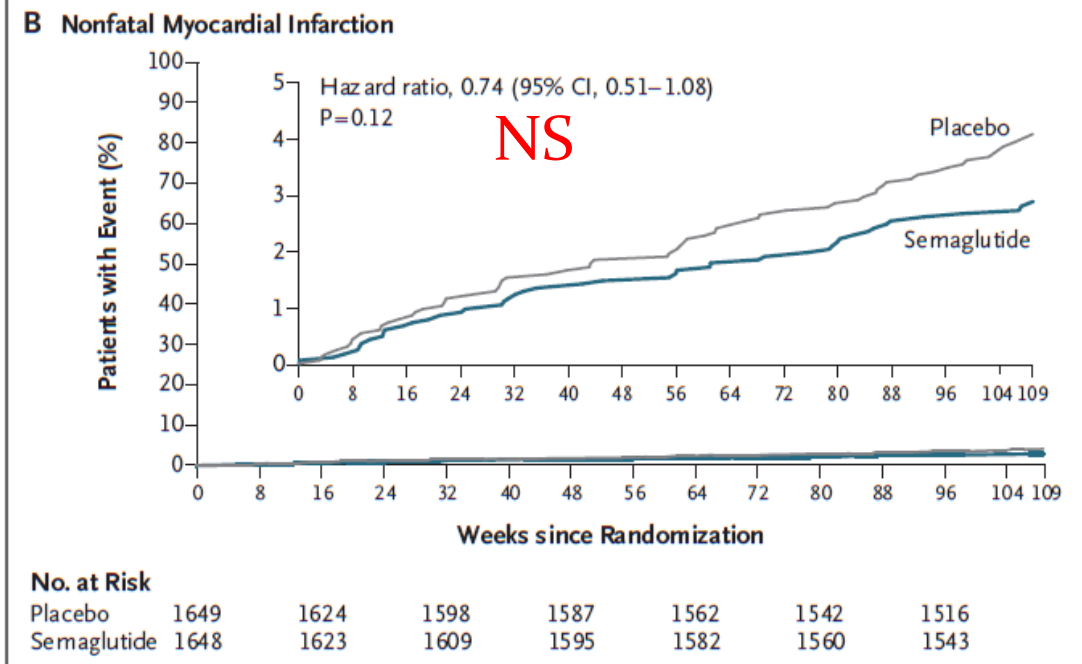

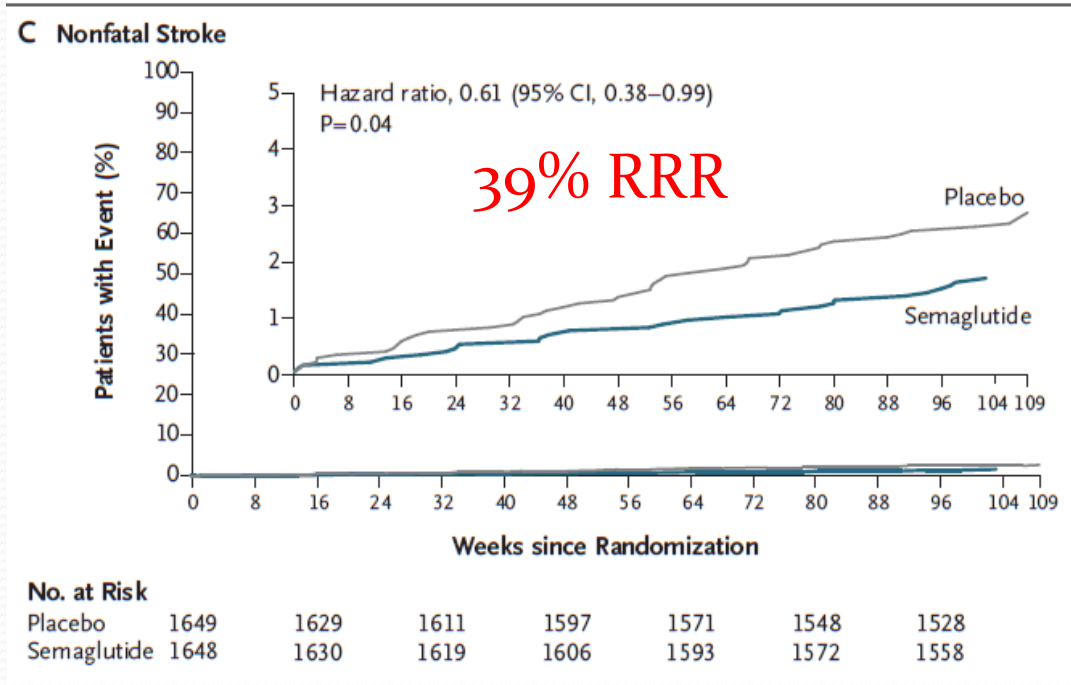

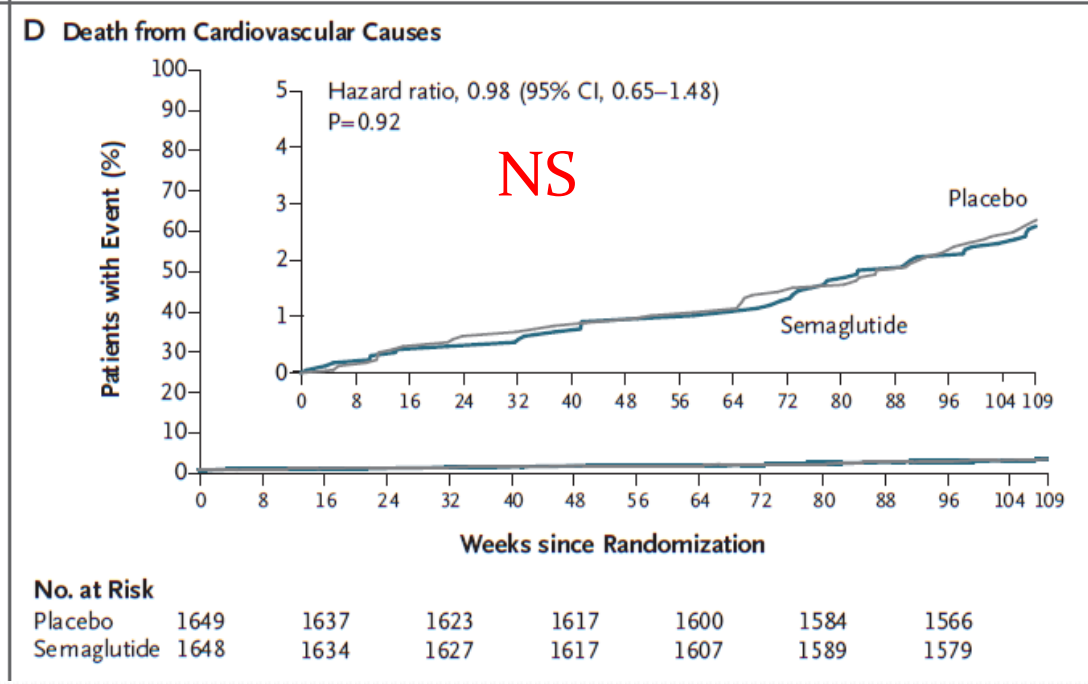

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Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial

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13% reduction in MACE

Summary

Background Three different glucagon-like peptide-1 (GLP-1) receptor agonists reduce cardiovascular outcomes in people with type 2 diabetes at high cardiovascular risk with high glycated haemoglobin A_{1c} (HbA_{1c}) concentrations. We assessed the effect of the GLP-1 receptor agonist dulaglutide on major adverse cardiovascular events when added to the existing antihyperglycaemic regimens of individuals with type 2 diabetes with and without previous cardiovascular disease and a wide range of glycaemic control.

Methods This multicentre, randomised, double-blind, placebo-controlled trial was done at 371 sites in 24 countries. Men and women aged at least 50 years with type 2 diabetes who had either a previous cardiovascular event or cardiovascular risk factors were randomly assigned (1:1) to either weekly subcutaneous injection of dulaglutide (1·5 mg) or placebo. Randomisation was done by a computer-generated random code with stratification by site. All investigators and participants were masked to treatment assignment. Participants were followed up at least every 6 months for incident cardiovascular and other serious clinical outcomes. The primary outcome was the first occurrence of the composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes (including unknown causes), which was assessed in the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT01394952.

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*Investigators listed in the appendix

Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada (Prof H C Gerstein MD, L Dyal MSc, S Hall BA, P Rao-Melacini MSc, G Wong BSc); University of Edinburgh, Edinburgh, UK

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9901 patients with T2DM at high risk of MACE (31% with CVD)

Dulaglutide 1.5 mg; Median 5.4 yrs f/u; Primary Endpoint: 3-point MACE

Summary

Background Three different glucagon-like peptide-1 (GLP-1) receptor agonists reduce cardiovascular outcomes in people with type 2 diabetes at high cardiovascular risk with high glycated haemoglobin A_{1c} (HbA_{1c}) concentrations. We assessed the effect of the GLP-1 receptor agonist dulaglutide on major adverse cardiovascular events when added to the existing antihyperglycaemic regimens of individuals with type 2 diabetes with and without previous cardiovascular disease and a wide range of glycaemic control.

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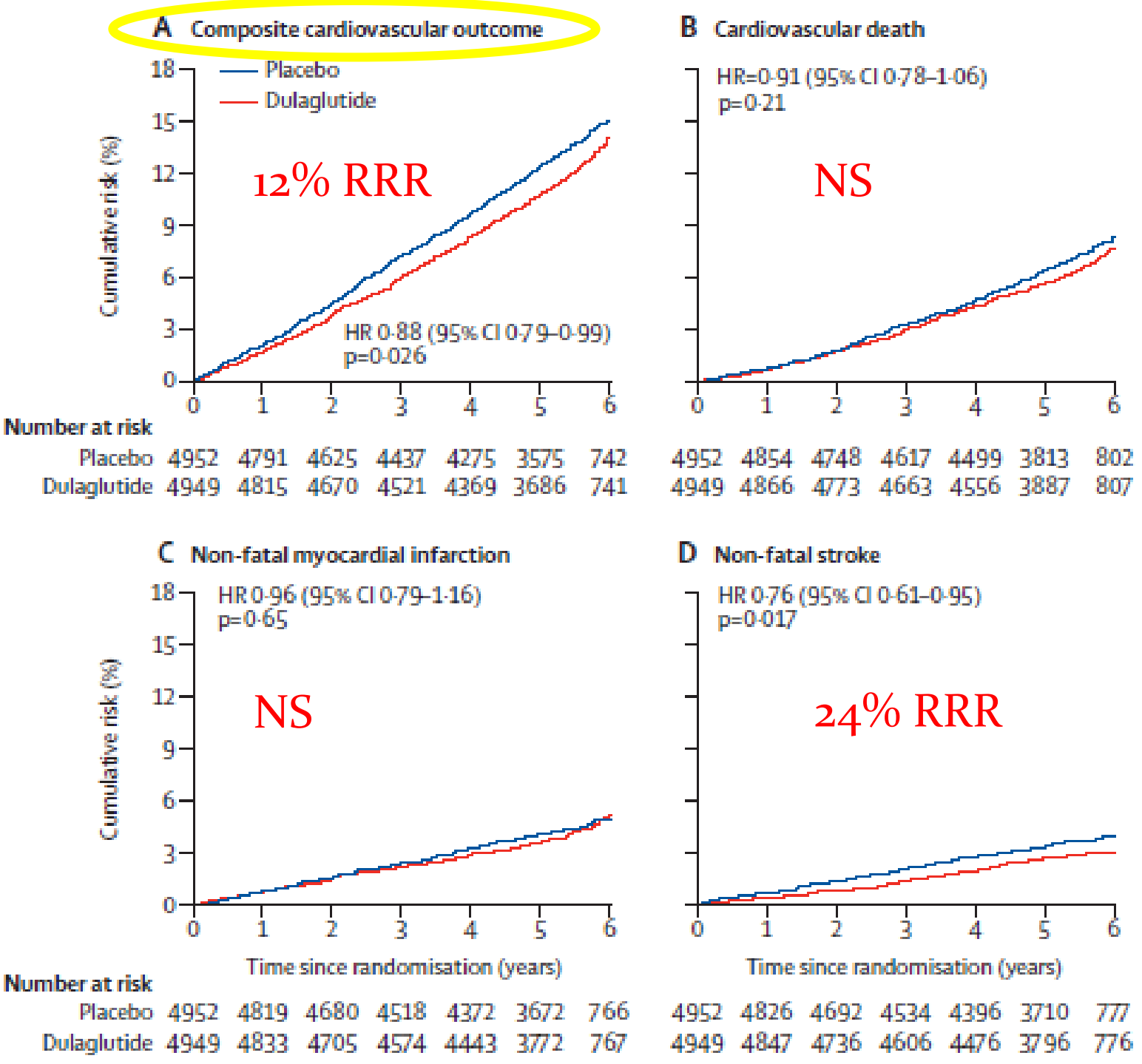
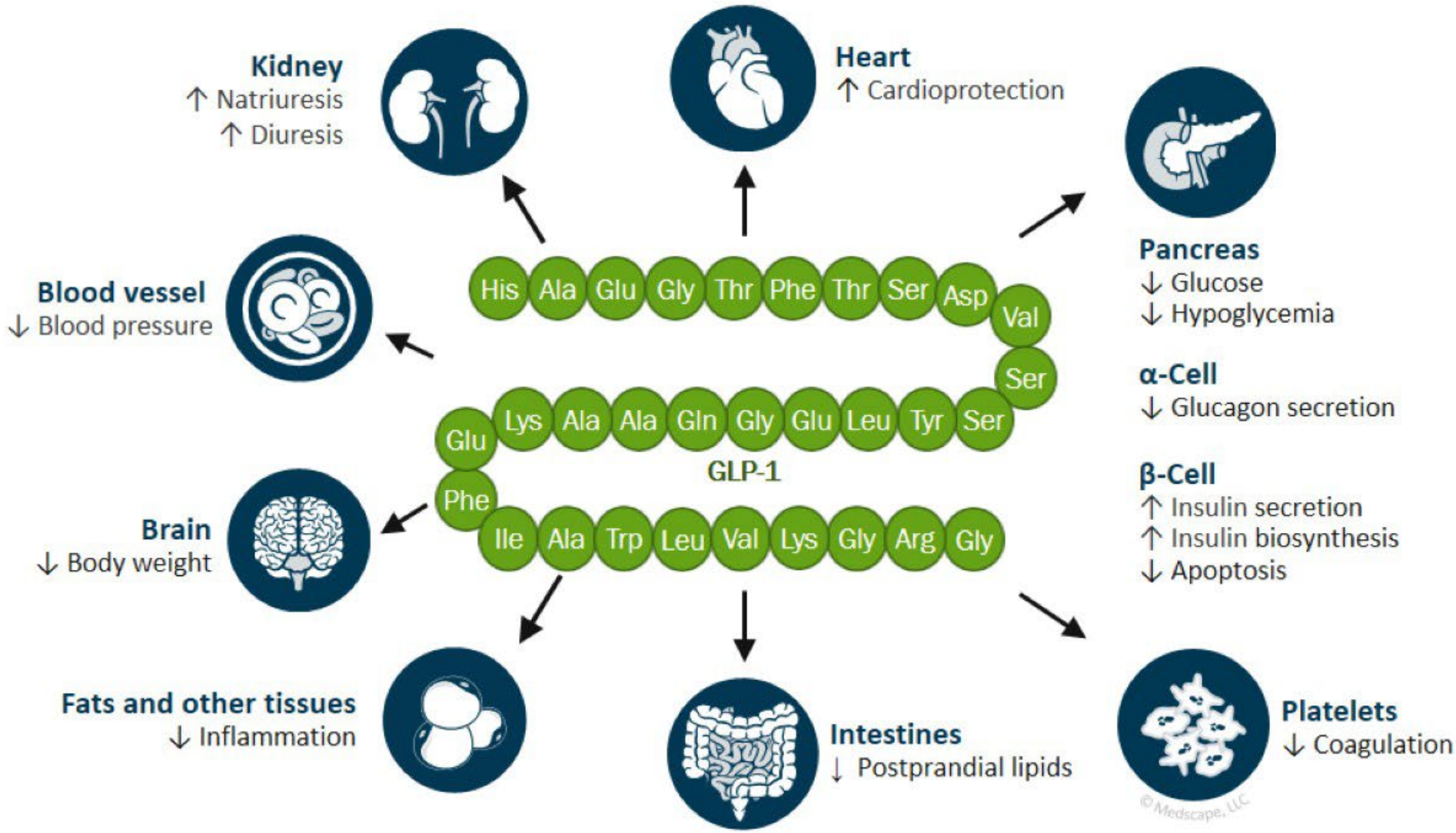


Gerstein HC et al. Lancet. 2019;394:121–30.

CARDIOVASCULAR BENEFIT OF GLP-1 RA'S

- Liraglutide (LEADER) - 13% reduction in MACE (2016)
- Semaglutide (SUSTAIN) - 26% reduction of MACE (2016)
- Albiglutide (Harmony Outcomes) - 22% reduction of MACE (2018)
- Dulaglutide (REWIND) - 12% reduction of MACE (2019)

Potential Mechanisms for CVD Benefit



Adapted from Drucker DJ. *Cell Metab*. 2016;24:15-30.

2019 ACC/AHA CV Disease Primary Prevention Guideline

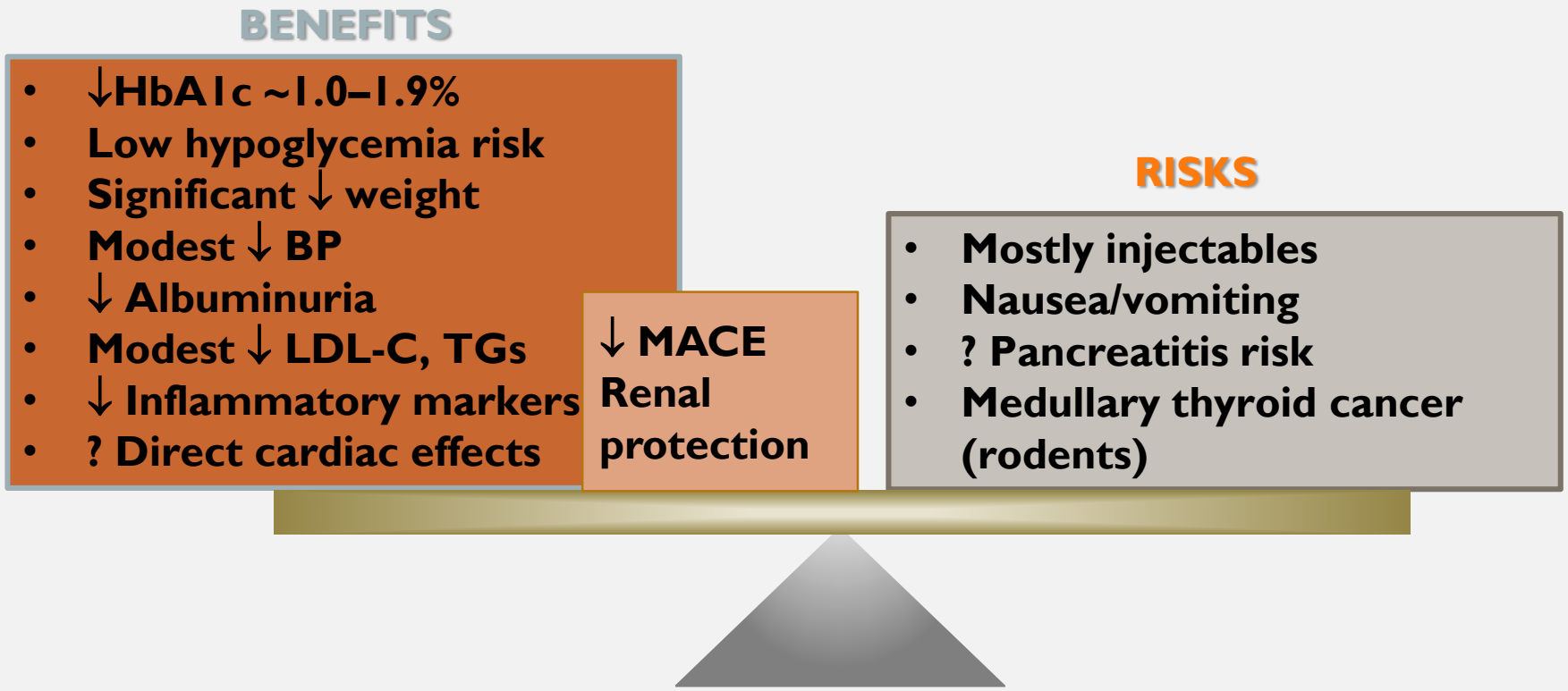
"Three GLP-1R agonists have been found to significantly reduce the risk of ASCVD in adults with T2DM who are at high ASCVD risk."

Recommendation for adults with type 2 diabetes mellitus

- For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk.

Arnett DK, et al. *Circulation.* 2019;140:e596-e646.

GLP-1 RECEPTOR AGONISTS - RISK-TO-BENEFIT RATIO



Kim Y, Babu AR. Diabetes Metab Syndr Obes. 2012;5:313-327.
Inzucchi SE, et al. Diabetes Care. 2015;38:140-149.
Abdul-Ghani M, DeFronzo RA. Diabetes Care. 2017;40:1121-1127.
Lee YS, Jun HS. Mediators of Inflammation. 2016; article ID 3094642.

Glucagon-like Peptide-1 Receptor Agonism

Central Nervous System
- ↑ Satiety
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↓ Glucagon

Stomach
- ↓ Gastric Emptying

Systemic
- ↓ Hyperglycemia

Liver
- ↑ Insulin Sensitivity
- ↓ Hepatic Glucose Production
- ↓ Ectopic Lipid Accumulation

Glucose-dependent Insulinotropic Polypeptide Receptor Agonism

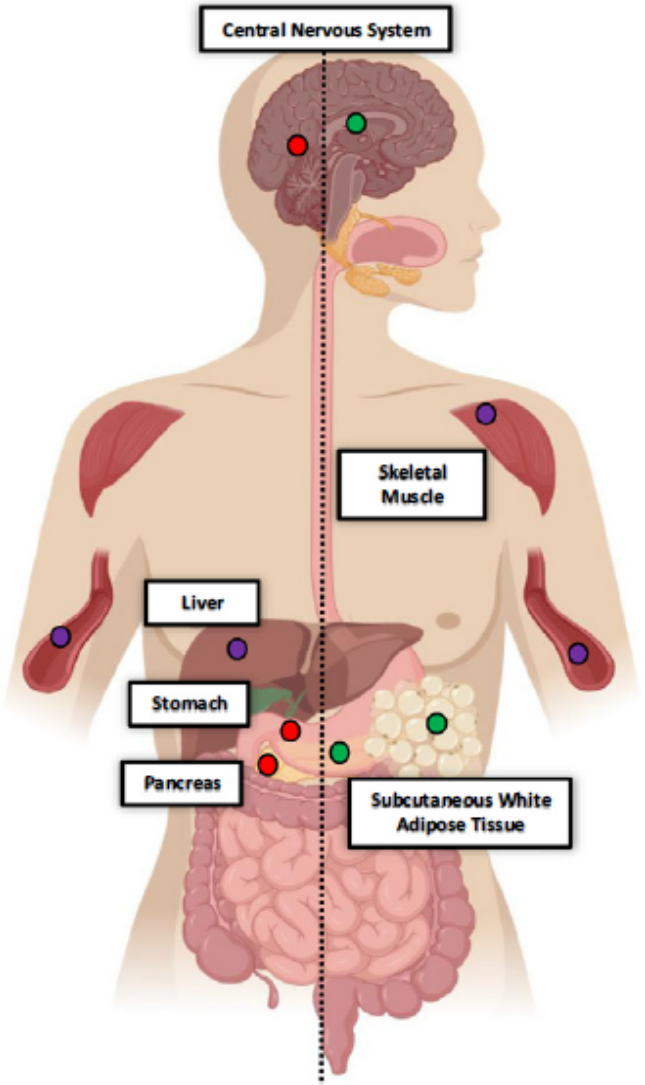
Central Nervous System
- ↓ Food Intake
- ↓ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↑ Glucagon

Subcutaneous White Adipose Tissue
- ↑ Insulin Sensitivity
- ↑ Lipid Buffering Capacity
- ↑ Blood Flow
- ↑ Storage Capacity
- ↓ Proinflammatory Immune Cell Infiltration

Systemic
- ↓ Hyperglycemia
- ↓ Dietary Triglyceride

Skeletal Muscle
- ↑ Insulin Sensitivity
- ↑ Metabolic Flexibility
- ↓ Ectopic Lipid Accumulation



Glucose-dependent Insulinotropic Polypeptide Receptor Agonism

Glucagon-like Peptide 1 Receptor Agonism

Indirect Action

Samms RJ, et al. Trends I Endocrinol Metab 2020;31(6):410-21.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes

Juan P. Frías, M.D., Melanie J. Davies, M.D., Julio Rosenstock, M.D., Federico C. Pérez Manghi, M.D., Laura Fernández Landó, M.D., Brandon K. Bergman, Pharm.D., Bing Liu, Ph.D., Xuewei Cui, Ph.D., and Katelyn Brown, Pharm.D., for the SURPASS-2 Investigators*

ABSTRACT

BACKGROUND

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist that is under development for the treatment of type 2 diabetes. The efficacy and safety of once-weekly tirzepatide as compared with semaglutide, a selective GLP-1 receptor agonist, are unknown.

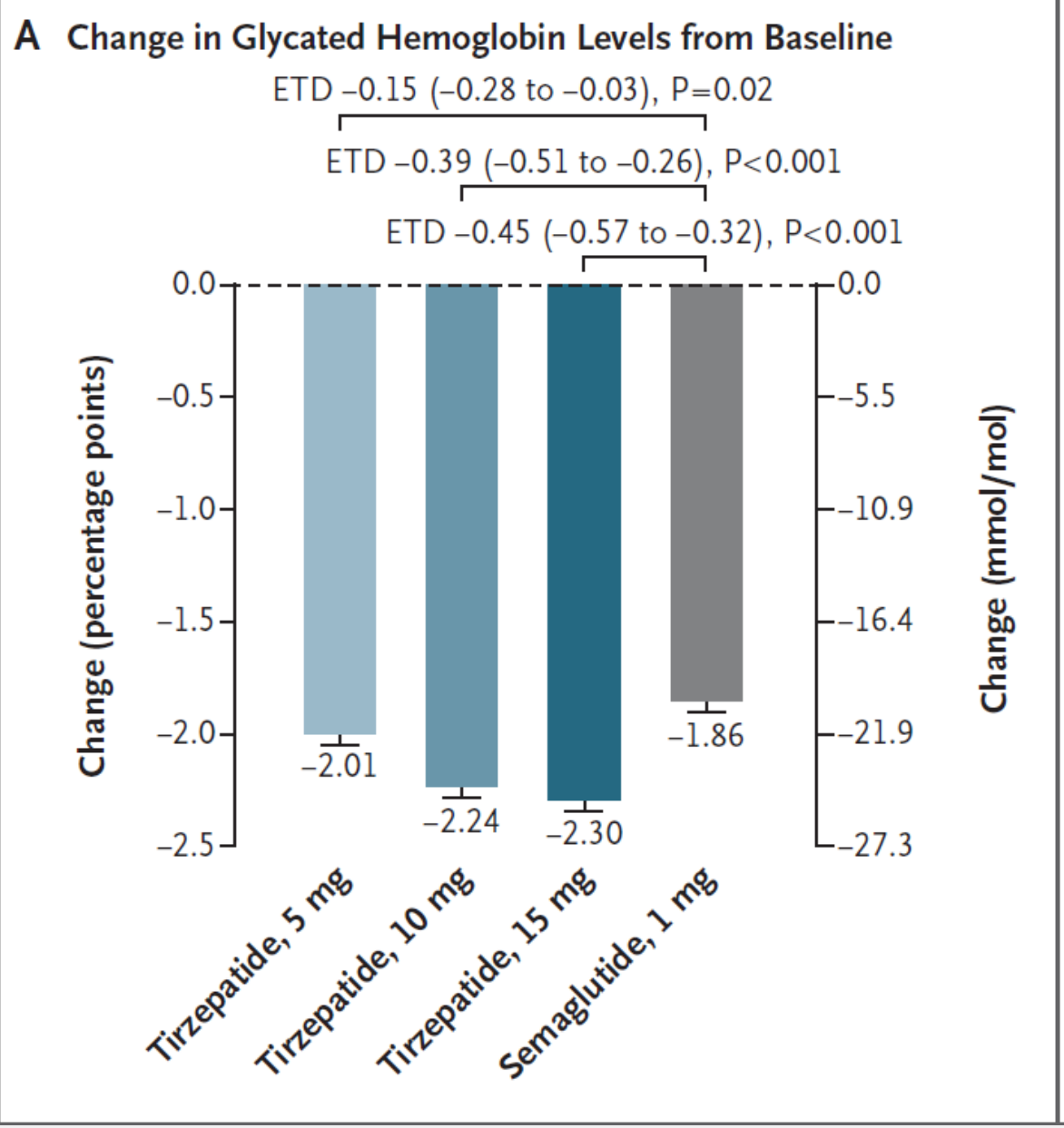
Frías JP, et al. SURPASS-2. NEJM 2021; 385:503-15.

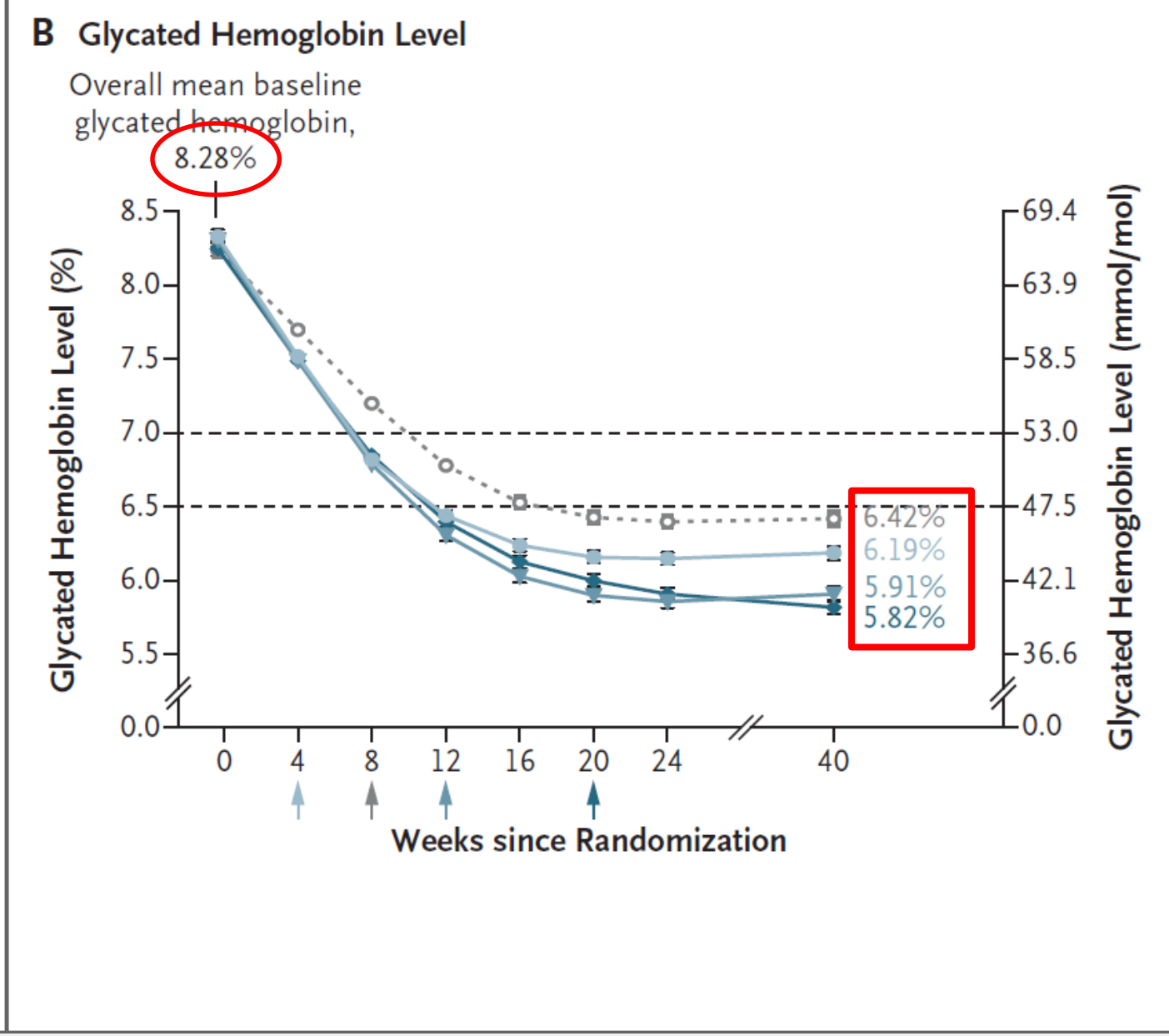
DUAL GLP-1/GIP RECEPTOR AGONISTS SURPASS-2

Drug	Average Δ HbA1C (%) from Baseline	Confidence Interval	Difference in Average Δ HbA1C (%) Relative to Semaglutide 1 mg	P-Value
Tirzepatide 5 mg	-2.01%	(-0.28 to -0.03)	-0.15%	0.02
Tirzepatide 10 mg	-2.25%	(-0.51 to -0.26)	-0.39%	P < 0.001
Tirzepatide 15 mg	-2.30%	(-0.57 to -0.32)	-0.45%	P < 0.001
Semaglutide 1 mg	-1.86%		0 %	-

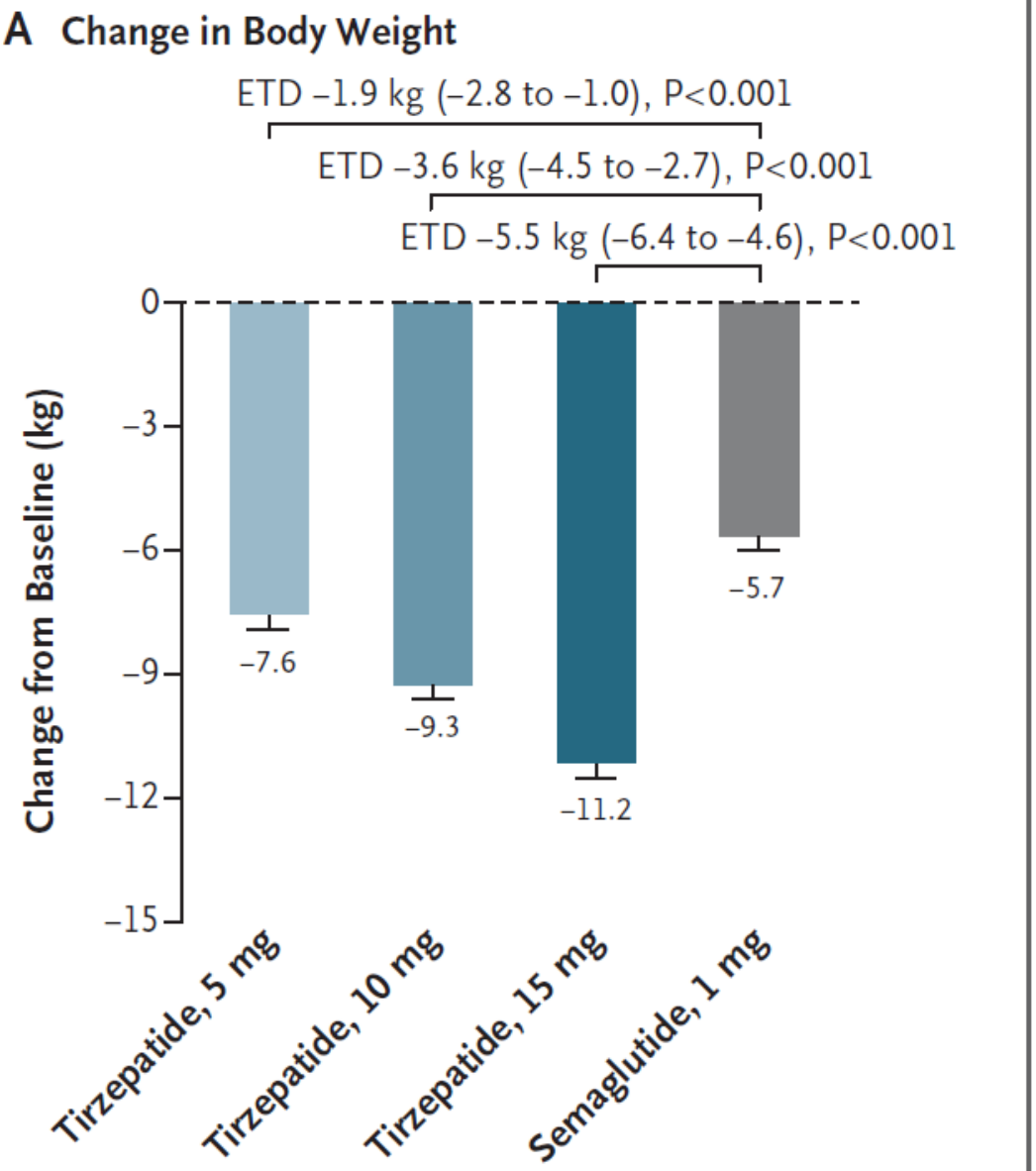
Drug	Average Δ in Body Weight (kg)	P-Value
Tirzepatide 5 mg	-7.6	P < 0.001
Tirzepatide 10 mg	-9.3	P < 0.001
Tirzepatide 15 mg	-11.2	P < 0.001
Semaglutide 1 mg	-5.7	-

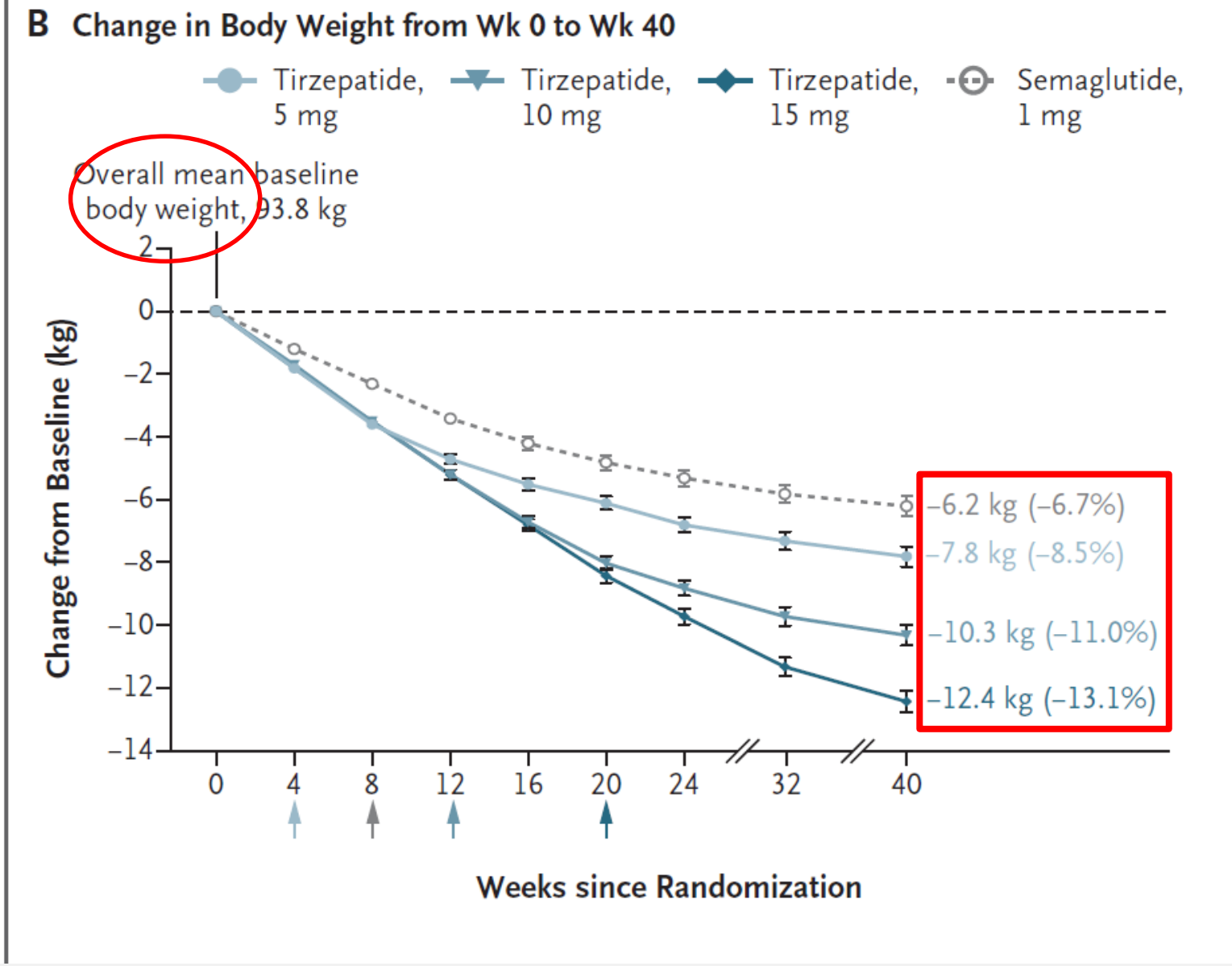
Frías JP, et al. SURPASS-2. N Engl J Med. 2021;385:503-515.





Frías JP, et al. SURPASS-2. NEJM 2021; 385:503-15.

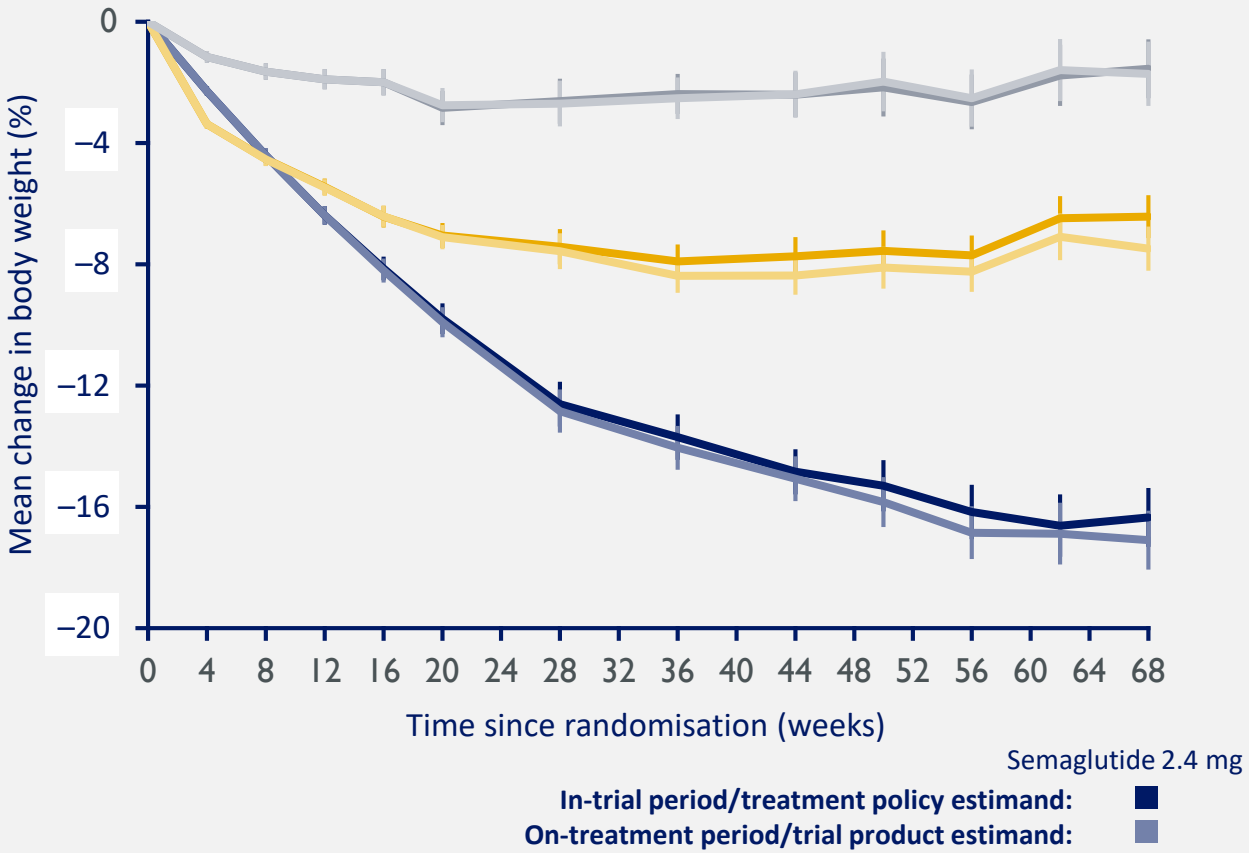




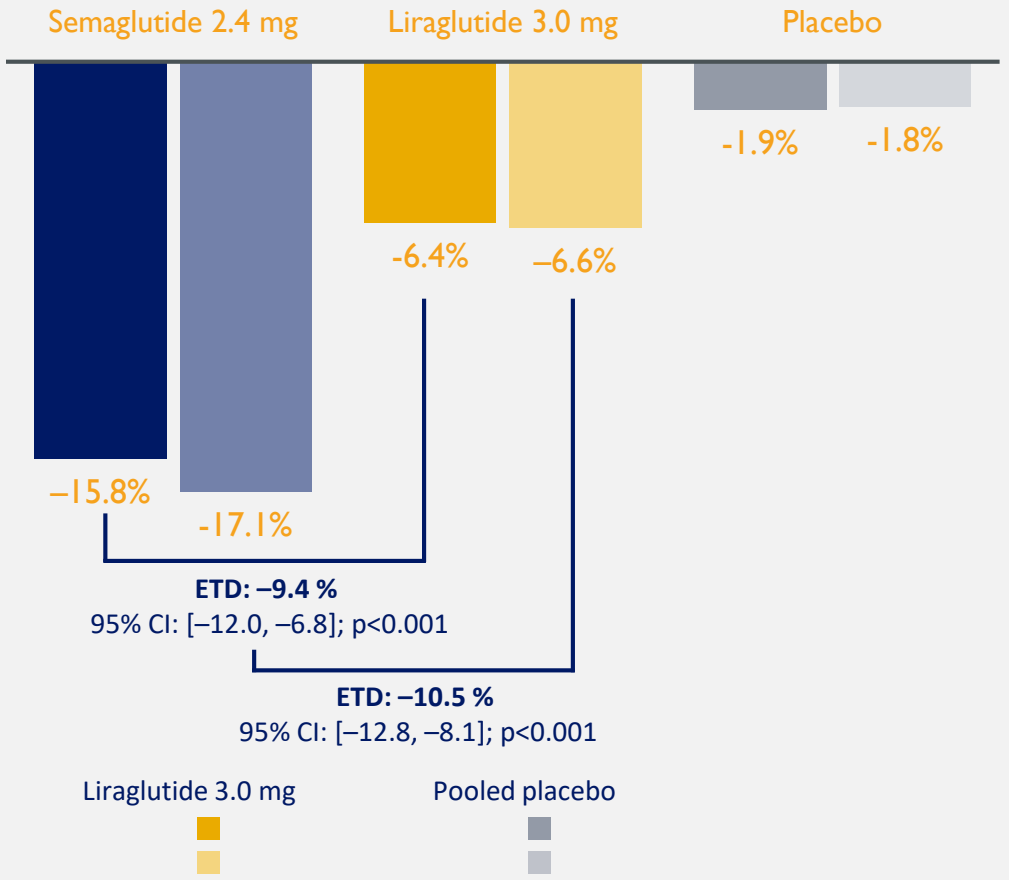
Frias JP. SURPASS-2. NEJM 2021; 385:503-15.

Body Weight % Loss- Semaglutide, Liraglutide

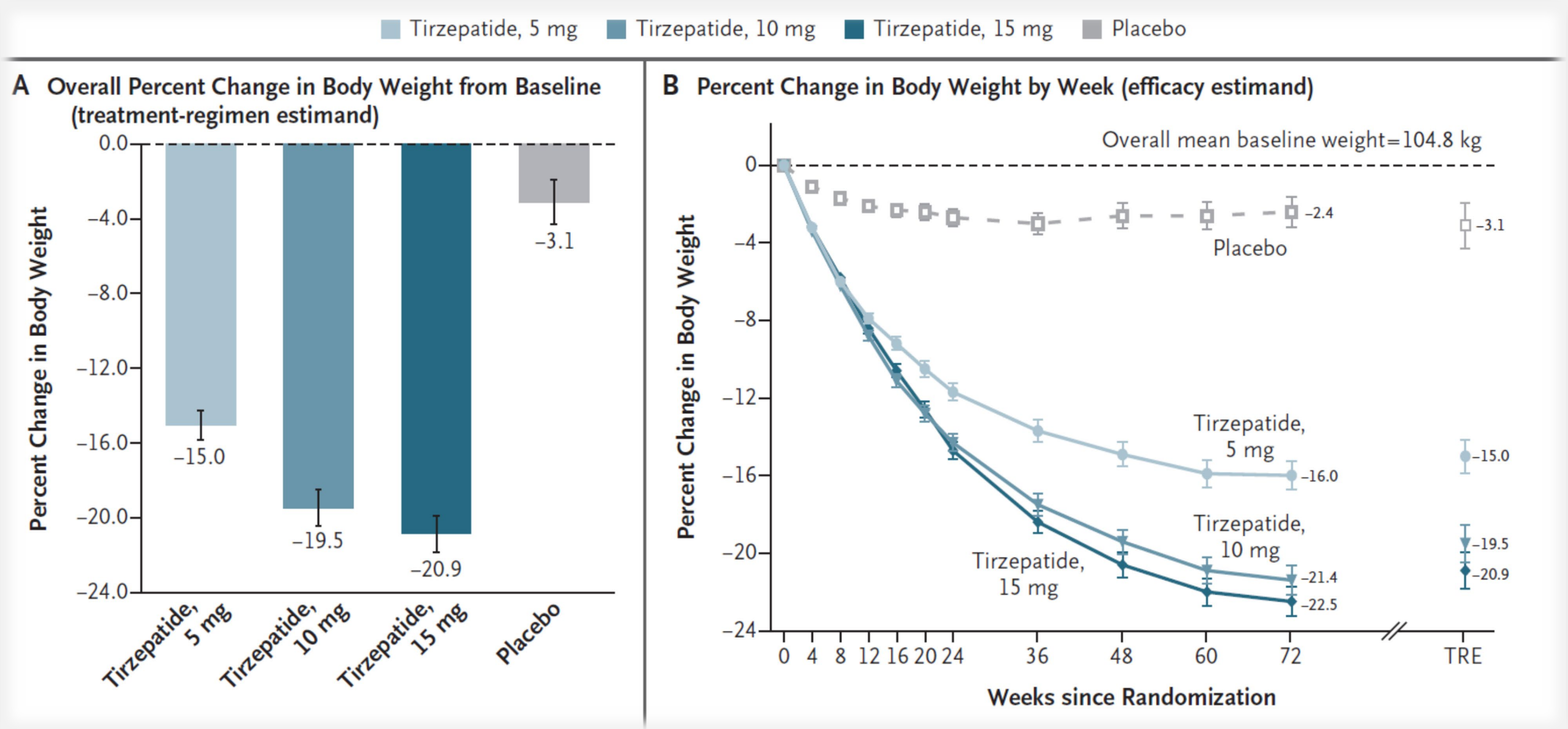
Observed mean change over time*
(Mean at baseline: 104.5 kg)



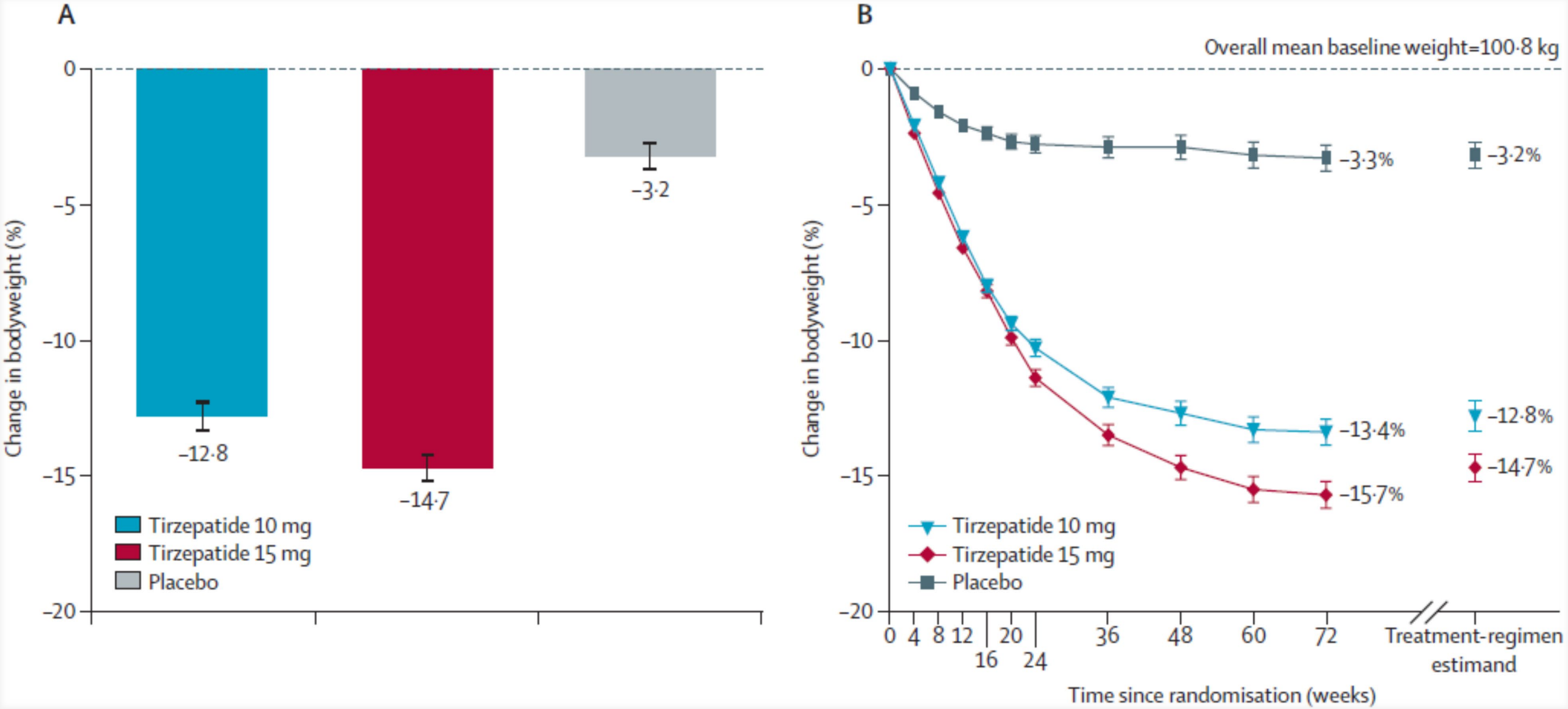
Estimated mean change from baseline to week 68†



Rubino et al. JAMA 2022; 327(2): 138-150

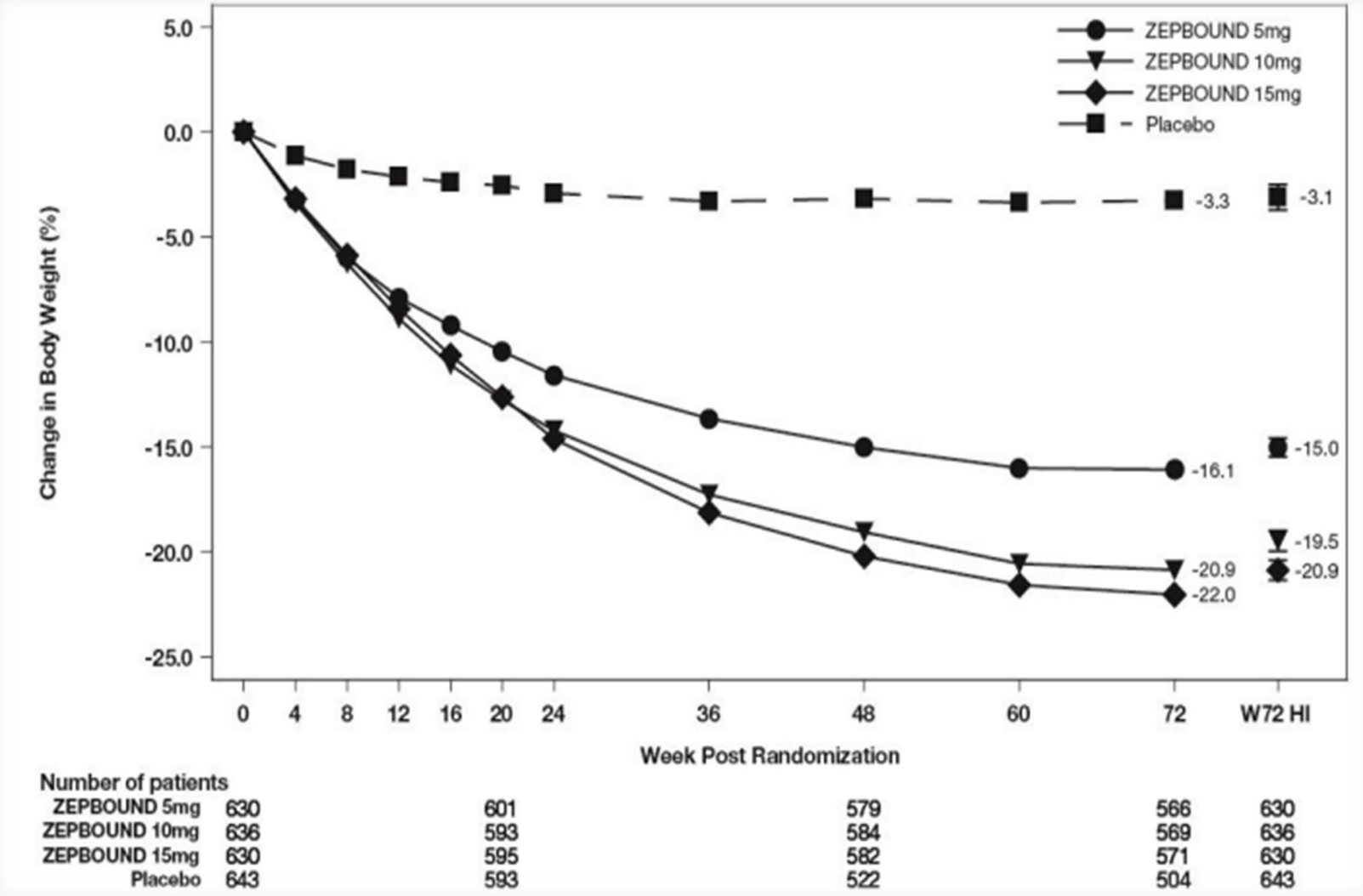


Jastreboff AM et al. N Engl J Med 2022;387:205-16.



Garvey WT et al. Lancet; June 24 2023; https://doi.org/10.1016/S0140-6736(23)01200-X

CHANGE FROM BASELINE (%) IN BODY WEIGHT



Zepbound, prescribing information, Eli Lily 2023.

The NEW ENGLAND JOURNAL of MEDICINE

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*

14% reduction of primary composite outcome: death from CV causes, nonfatal myocardial infarction, or nonfatal stroke

33% relative risk reduction of hospitalization for heart failure

ABSTRACT

BACKGROUND

Canagliflozin is a sodium–glucose cotransporter 2 inhibitor that reduces glycemia as well as blood pressure, body weight, and albuminuria in people with diabetes. We report the effects of treatment with canagliflozin on cardiovascular, renal, and safety outcomes.

NEJM 2017;377:644-57.

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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*

10,142 patients with T2DM, 2/3's with established CVD

Cana 100 or 300 mg or placebo; 2.4 year f/u

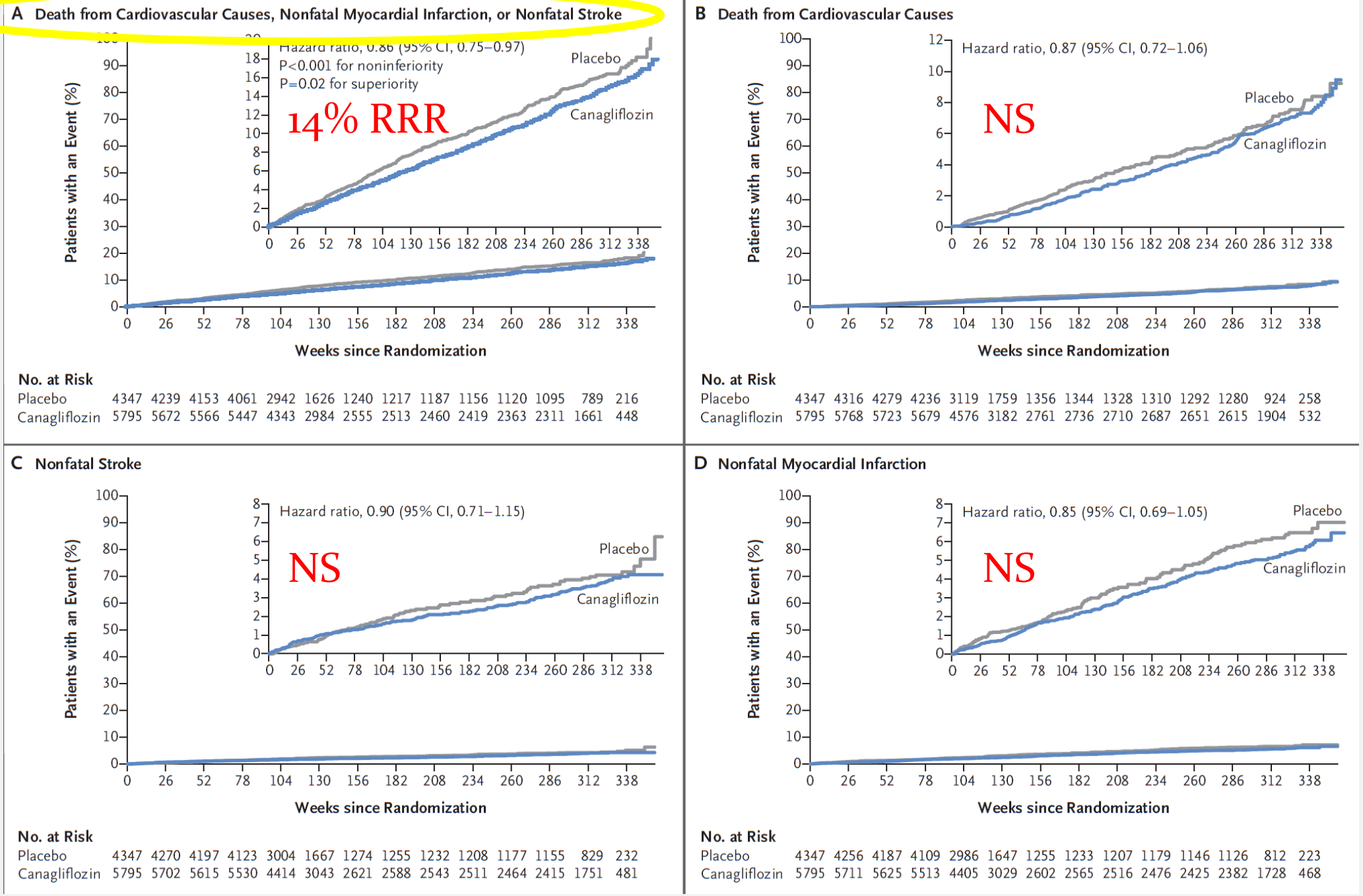
Primary Endpoint: Composite of CV death, non-fatal MI and non-fatal stroke

ABSTRACT

BACKGROUND

Canagliflozin is a sodium–glucose cotransporter 2 inhibitor that reduces glycemia as well as blood pressure, body weight, and albuminuria in people with diabetes. We report the effects of treatment with canagliflozin on cardiovascular, renal, and safety outcomes.

Neal B et al. NEJM 2017;377:644-57.



Neal B et al. NEJM 2017;377:644-57.

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*

No reduction of MACE
17% relative risk reduction of CV death or hospitalization for heart failure

ABSTRACT

BACKGROUND

The cardiovascular safety profile of dapagliflozin, a selective inhibitor of sodium–glucose cotransporter 2 that promotes glucosuria in patients with type 2 diabetes, is undefined.

METHODS

We randomly assigned patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease to receive either dapagliflozin or placebo. The primary safety outcome was a composite of major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction, or ischemic stroke. The primary efficacy outcomes were MACE and a composite of cardiovascular death or hospitalization for heart failure. Secondary efficacy outcomes were a renal composite (≥40% decrease in estimated glomerular filtration rate to <60 ml per minute per 1.73 m^2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) and death from any cause.

RESULTS

We evaluated 17,160 patients, including 10,186 without atherosclerotic cardiovascular disease, who were followed for a median of 4.2 years. In the primary safety outcome

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Wiviott at the TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Hale Building for Transformative Medicine, 60 Fenwood Rd., 7th Fl., Boston, MA 02115, or at swiviott@bwh.harvard.edu.

*A complete list of the DECLARE–TIMI 58 investigators and executive committee and steering committee members is provided in the Supplementary Appendix, available at NEJM.org.

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

DOI: 10.1056/NEJMoa1812389

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*

17,160 patients with T2DM, 39% with established CVD

DAPA 10 mg; 4.2 year median f/u

Two primary efficacy outcomes: MACE or cardiovascular death and HHF

ABSTRACT

BACKGROUND

The cardiovascular safety profile of dapagliflozin, a selective inhibitor of sodium–glucose cotransporter 2 that promotes glucosuria in patients with type 2 diabetes, is undefined.

METHODS

We randomly assigned patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease to receive either dapagliflozin or placebo. The primary safety outcome was a composite of major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction, or ischemic stroke. The primary efficacy outcomes were MACE and a composite of cardiovascular death or hospitalization for heart failure. Secondary efficacy outcomes were a renal composite (≥40% decrease in estimated glomerular filtration rate to <60 ml per minute per 1.73 m^2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) and death from any cause.

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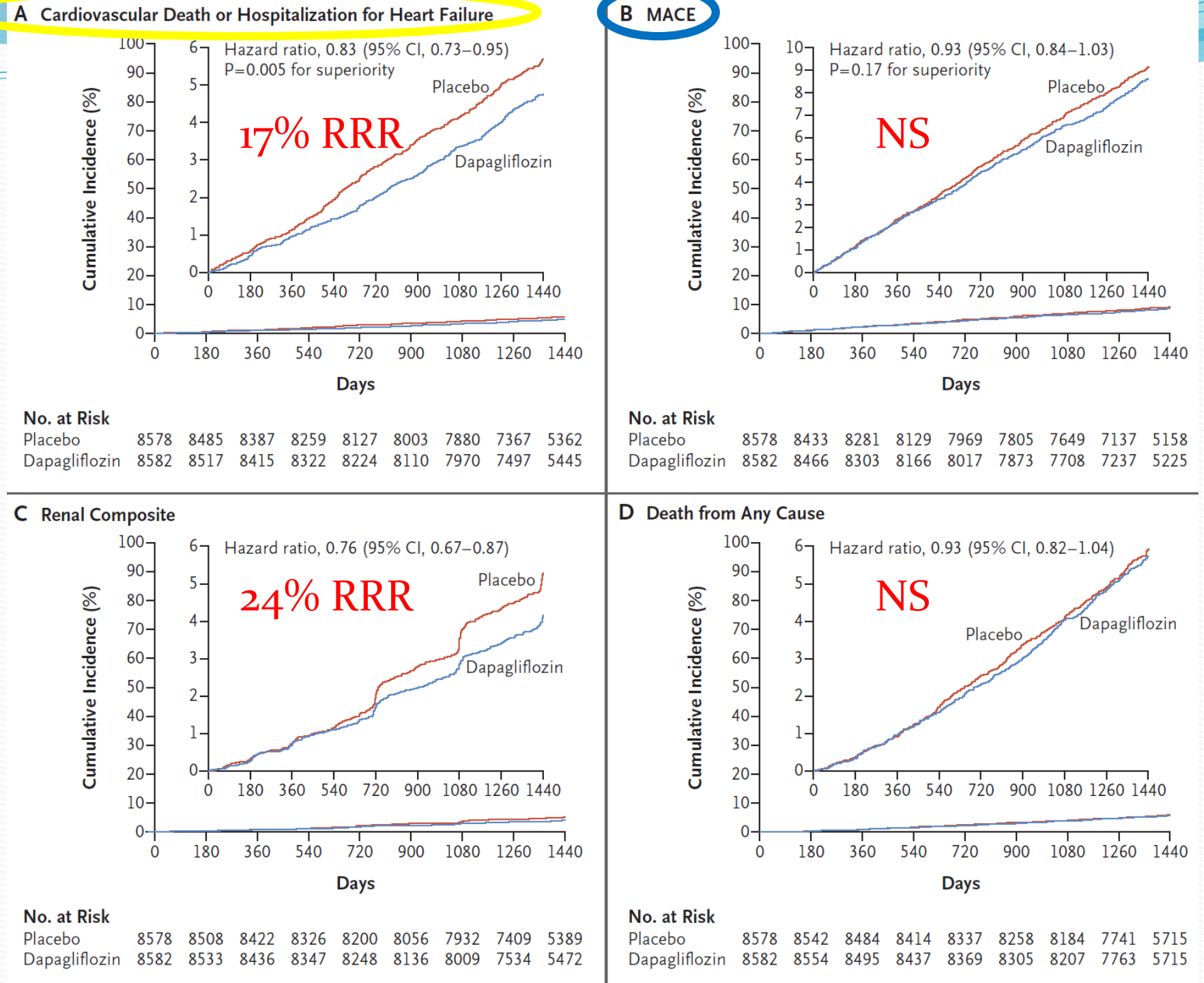


Wiviott SD et al. N Engl J Med. 2019; 280:347-57.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes

C.P. Cannon, R. Pratley, S. Dagogo-Jack, J. Mancuso, S. Huyck, U. Masiukiewicz, B. Charbonnel, R. Frederich, S. Gallo, F. Cosentino, W.J. Shih, I. Gantz, S.G. Terra, D.Z.I. Cherney, and D.K. McGuire, for the VERTIS CV Investigators*

8,238 patients with T2DM; 100% CVD
5 or 15 mg or placebo; 3.0-year median f/u
Primary Endpoint: 3-Point MACE

ABSTRACT

BACKGROUND

The cardiovascular effects of ertugliflozin, an inhibitor of sodium–glucose cotransporter 2, have not been established.

METHODS

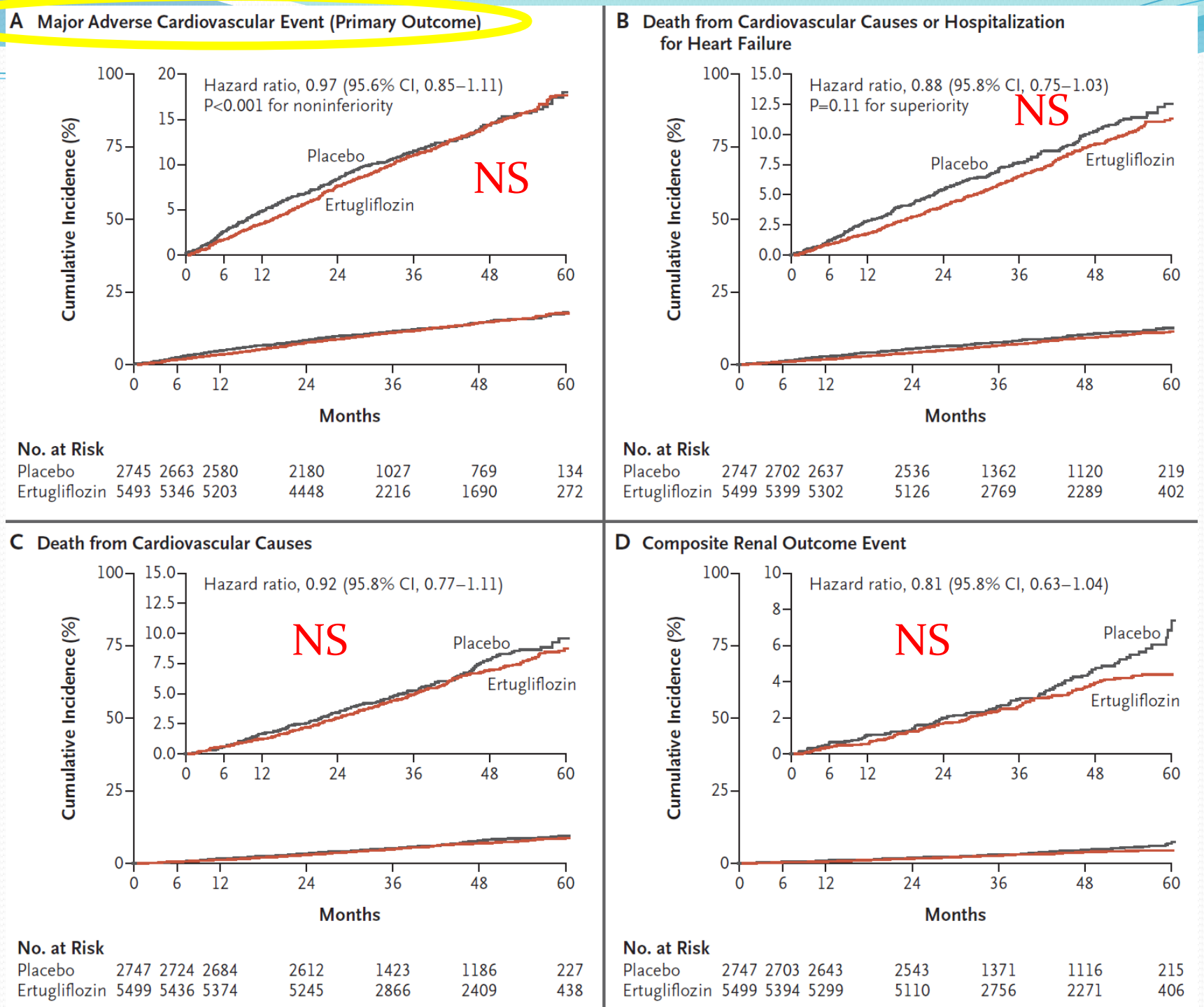
In a multicenter, double-blind trial, we randomly assigned patients with type 2 diabetes and atherosclerotic cardiovascular disease to receive 5 mg or 15 mg of ertugliflozin or placebo once daily. With the data from the two ertugliflozin dose groups pooled for analysis, the primary objective was to show the noninferiority of ertugliflozin to placebo with respect to the primary outcome, major adverse cardiovascular events (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). The noninferiority margin was 1.3 (upper

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Cannon at Brigham and Women's Hospital, 360 Longwood Ave., 7th Fl., Boston, MA 02115, or at cpcannon@bwh.harvard.edu.

*A complete list of the VERTIS CV investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 23, 2020, at NEJM.org.

Cannon CP et al. N Engl J Med 2020; DOI: 10.1056/NEJMoa2004967



Cannon CP et al. N Engl J Med 2020;
DOI: 10.1056/NEJMoa2004967

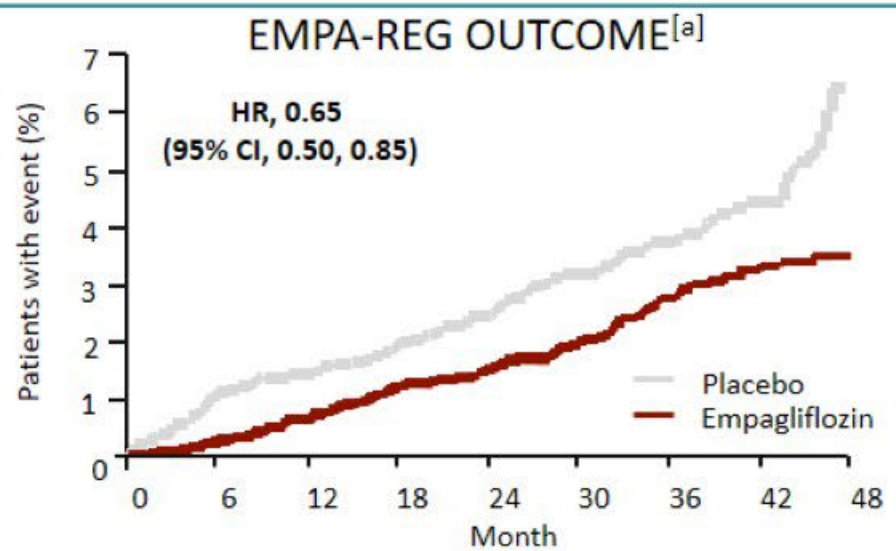
CV Outcomes

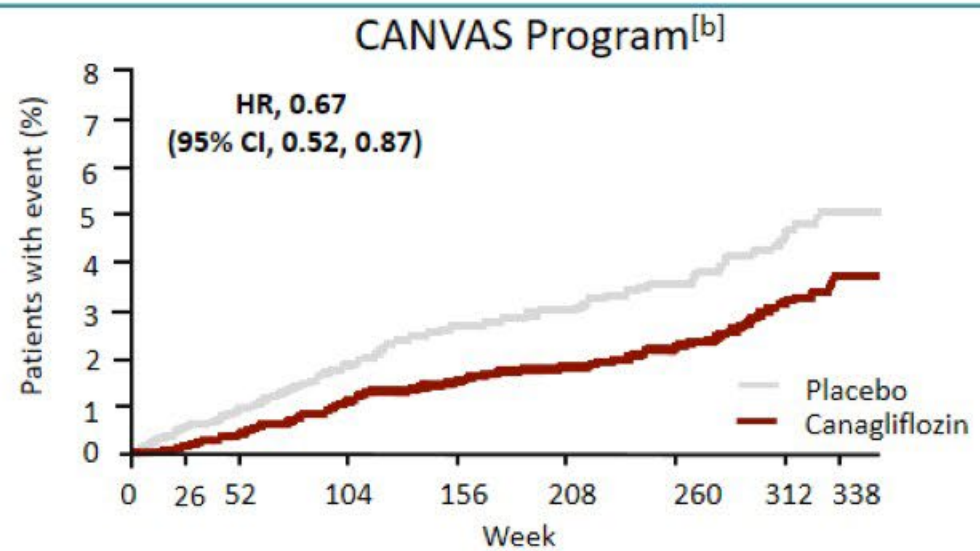
	MACE HR (95% CI)	CV Death HR (95% CI)	HHF HR (95% CI)
EMPA-REG OUTCOME[a]	**0.86** (0.74, 0.99)	**0.62** (0.49, 0.77)	**0.65** (0.50, 0.85)
CANVAS Program[b]	**0.86** (0.75, 0.97)	**0.87** (0.72, 1.06)	**0.67** (0.52, 0.87)
DECLARE-TIMI 58[c]	**0.93** (0.84, 1.03)	**0.98** (0.82, 1.17)	**0.73** (0.61, 0.88)
VERTIS CV[d]	**0.97*** (0.85, 1.11)	**0.92**† (0.77, 1.11)	**0.70** (0.54, 0.90)

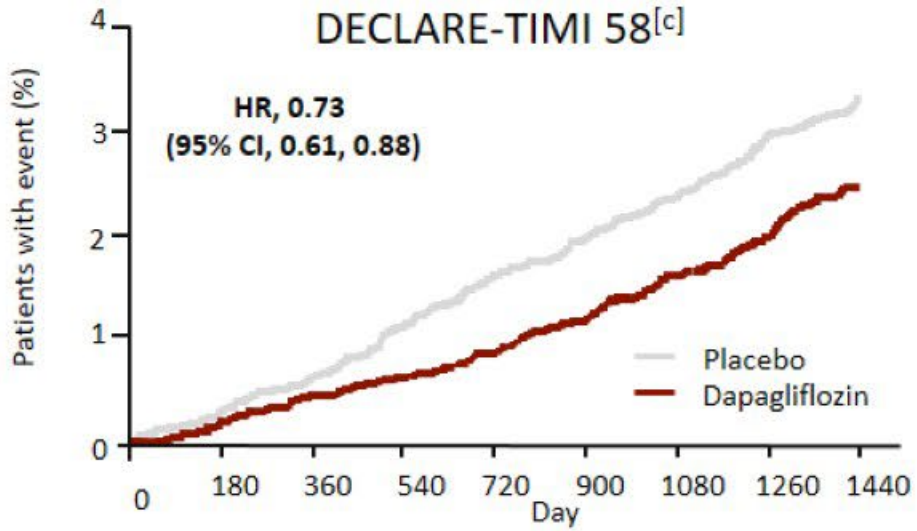
*Full analysis set, 95.6% CI for MACE. †Intention-to-treat analysis set, 95.8% CI.

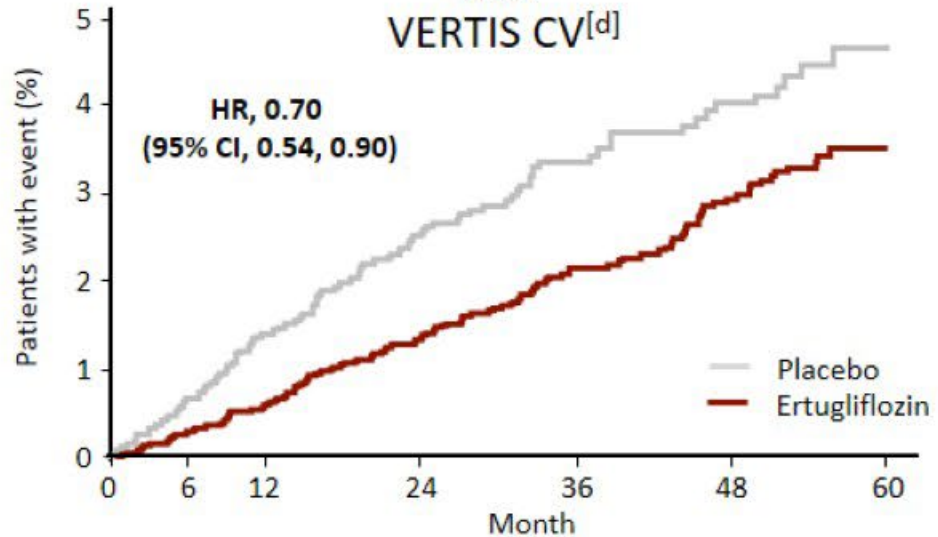
a. Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128; b. Neal B, et al. *N Engl J Med*. 2017;377:644-657; c. Wiviott SD, et al. *N Engl J Med*. 2019;380:347-357; d. McGuire DK. Presented at the EASD Virtual Meeting, 2020.

HHF Outcomes in SGLT2 Inhibitor CV Outcomes Trials









a. Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128; b. Neal B, et al. *N Engl J Med*. 2017;377:644-657; c. Wiviott SD, et al. *N Engl J Med*. 2019;380:347-357; d. McGuire DK. Presented at the EASD Virtual Meeting, 2020. (figure provided by D.K. McGuire, with permission).

SGLT2i's With FDA Indications for Cardiovascular Disease (CVD)

- Empagliflozin
  - Indicated to reduce the risk of cardiovascular (CV) death in adults with type 2 diabetes mellitus and established CV disease.
- Canagliflozin
  - Indicated to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease.
- Dapagliflozin
  - Indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction.

GLP-1 RAs With FDA Indications for Cardiovascular Disease (CVD)

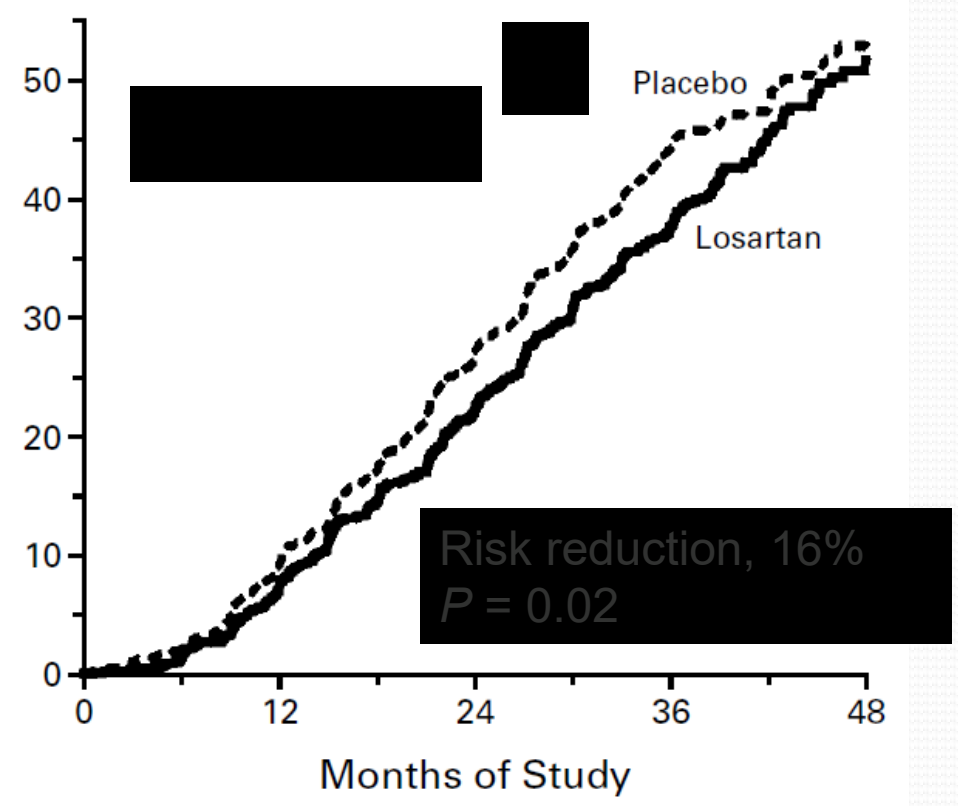
- Liraglutide
  - FDA-approved indication to reduce risk for MACE in adults with T2D and established CVD.
- Semaglutide SQ
  - Indicated to reduce the risk for MACE in adults with T2D with established CVD.
- Dulaglutide
  - Indicated to reduce the risk MACE in adults with T2D with established CVD *or* multiple CV risk factors.

Renal Protection

Proven Renoprotection in T2DM: RENAAL & IDNT

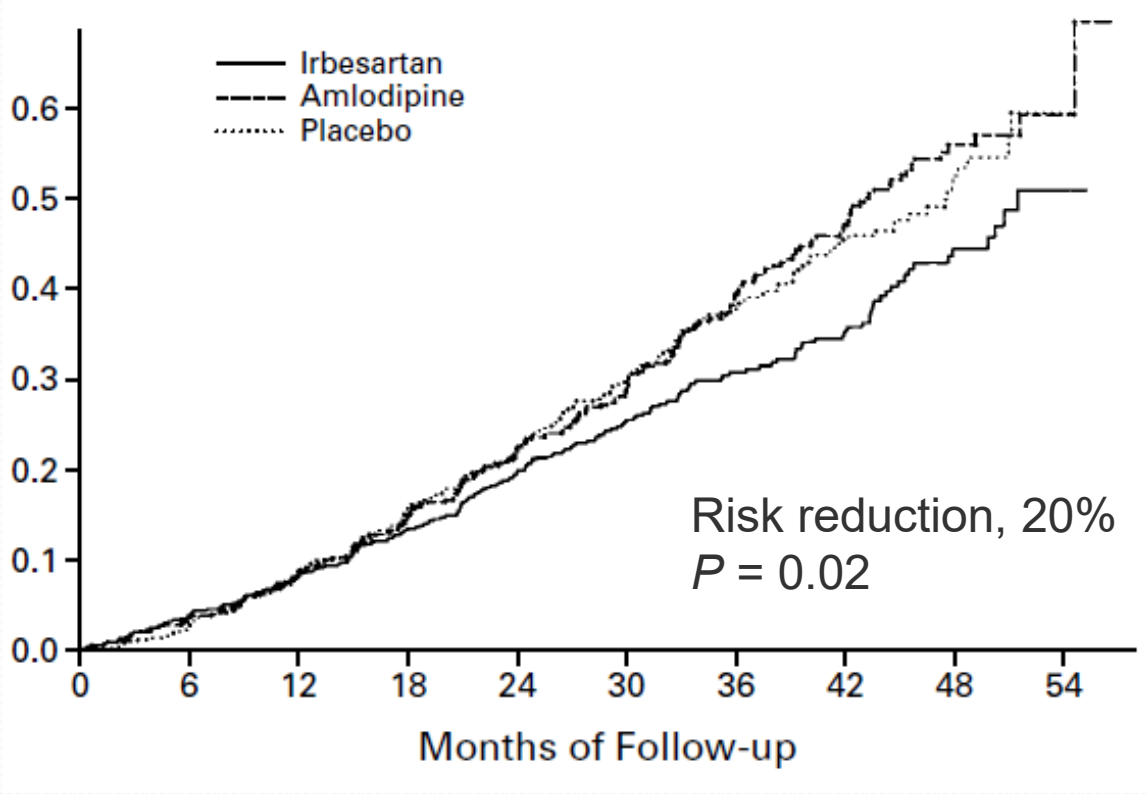
Doubling of serum creatinine, ESKD, or death

RENAAL



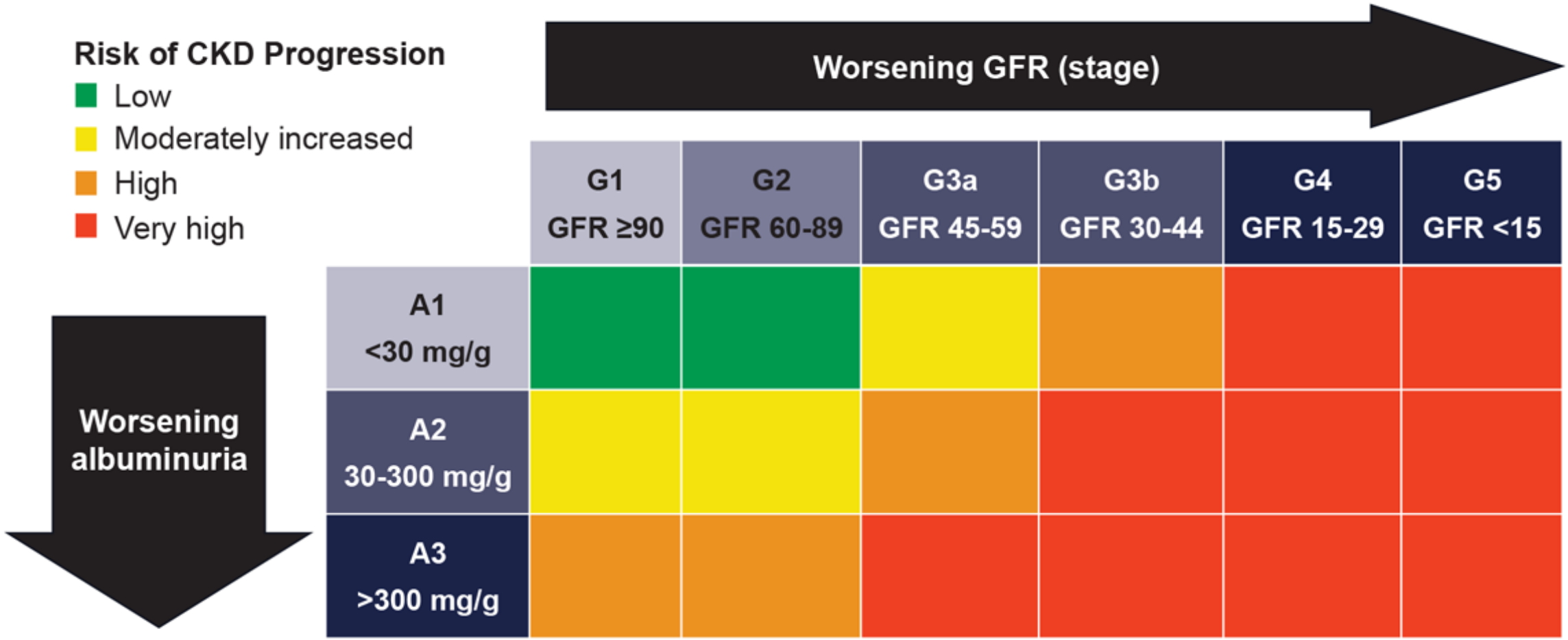
Brenner et al. *N Engl J Med*. 2001; 345:861-869.

IDNT



Lewis et al. *N Eng J Med*. 2001; 345:851-860.

Kidney Disease Outcomes and Quality Improvement (KDOQI) CKD Staging Nomenclature[1]



1. National Kidney Foundation. *Kidney Int Suppl*. 2013;3:i-xiii, 1-150.

Kidney Composite Outcomes

- Generally consistent definitions: sustained ≥ 40% decline in eGFR, ESKD or renal death

		HR (95% CI)
EMPA-REG OUTCOME[a] (post-hoc exploratory)	Sustained ≥ 40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes	**0.55** (0.41, 0.73)
CANVAS Program[b] (prespecified exploratory)	Sustained ≥ 40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes	**0.60** (0.47, 0.77)
DECLARE-TIMI 58[c] (prespecified secondary)	Sustained ≥ 40% decrease in eGFR to < 60 mL/min/1.73 m^2 and/or end-stage renal disease and/or renal death	**0.53** (0.43, 0.66)
VERTIS CV[d]* (prespecified exploratory)	Sustained ≥ 40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes	**0.66** (0.50, 0.88)

*Intention-to-treat analysis set, 95.0% CI.

a. Perkovic V, et al. *Nephrol Dial Transplant.*2019;1–9; b. Neal B, et al. *N Engl J Med*. 2017;377:644-657; c. Wiviott SD, et al. *N Engl J Med*. 2019;380:347-357; d. Cherney D. Presented at the EASD Virtual Meeting, 2020.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 13, 2019 VOL. 380 NO. 24

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

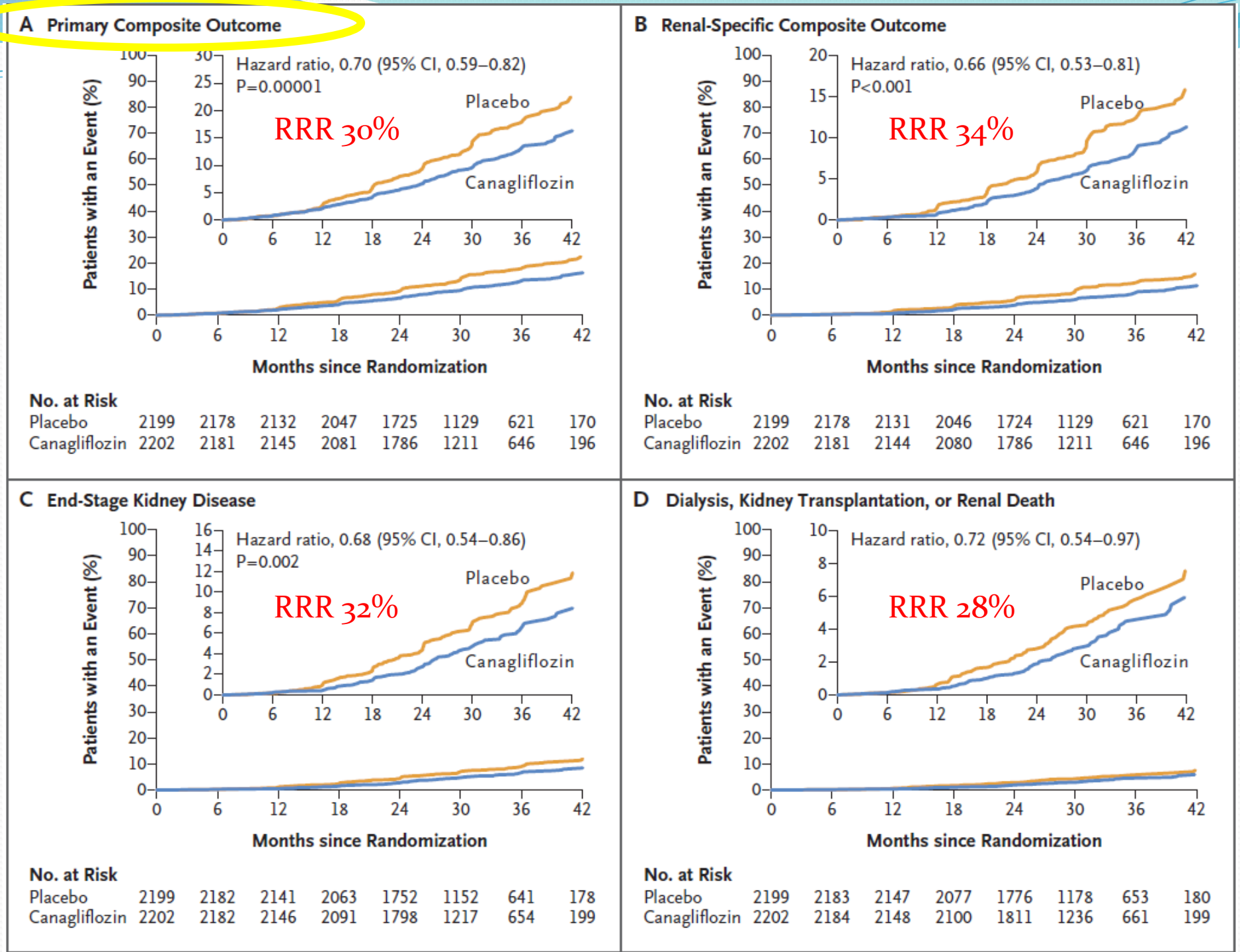
V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

4401 patients with T2DM, eGFR 30-90 ml/min with macro albuminuria (300-5000 mg/g)
Cana 100 mg mg; receiving SOC therapy, Median 2.6 yrs f/u
Primary Endpoint: composite of ESRD, a doubling of the SCr level, or renal or CV death

BACKGROUND

Type 2 diabetes mellitus is the leading cause of kidney failure worldwide, but few effective long-term treatments are available. In cardiovascular trials of inhibitors of sodium–glucose cotransporter 2 (SGLT2), exploratory results have suggested that such drugs may improve renal outcomes in patients with type 2 diabetes.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Perkovic at the George Institute for Global Health, University of New South



Perkovik V et al. N Engl J Med, 2019;380:2295-306.

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.S., Peter Rossing, M.D., G. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

4304 patients **with CKD** (eGFR 25-75 ml/min and urinary Alb:Cr 200-5000 mg/g)
On stable renal protection therapy; Dapa 10 mg; Median 2.4 yrs f/u; 2/3's with T2DM
Primary Endpoint: composite of a sustained decline in the eGFR of at least 50%, ESRD, or death from renal or cardiovascular causes

ABSTRACT

BACKGROUND

Patients with chronic kidney disease have a high risk of adverse kidney and cardiovascular outcomes. The effect of dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes, is not known.

METHODS

We randomly assigned 4304 participants with an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m^2 of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5000 to receive dapagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of a sustained decline in

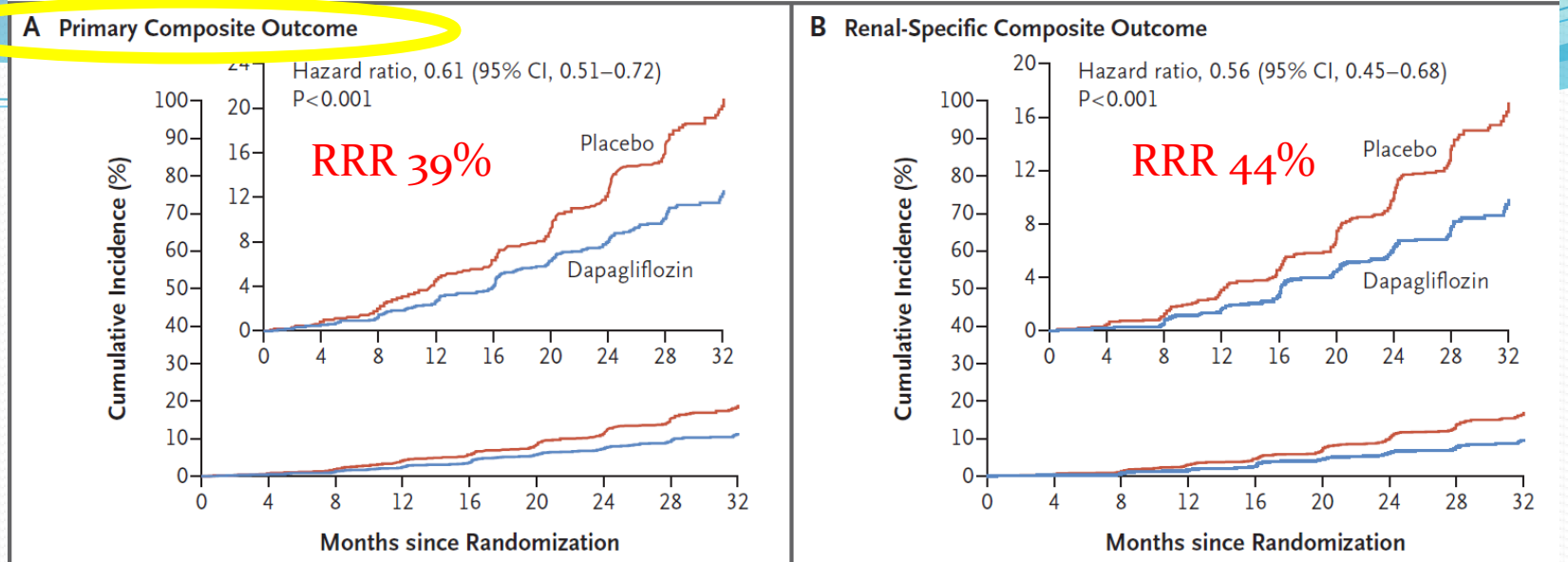
The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Heerspink at the Department of Clinical Pharmacy and Pharmacology, University of Groningen, P.O. Box 30.001, 9700 RB Groningen, the Netherlands, or at h.j.lambers.heerspink@umcg.nl.

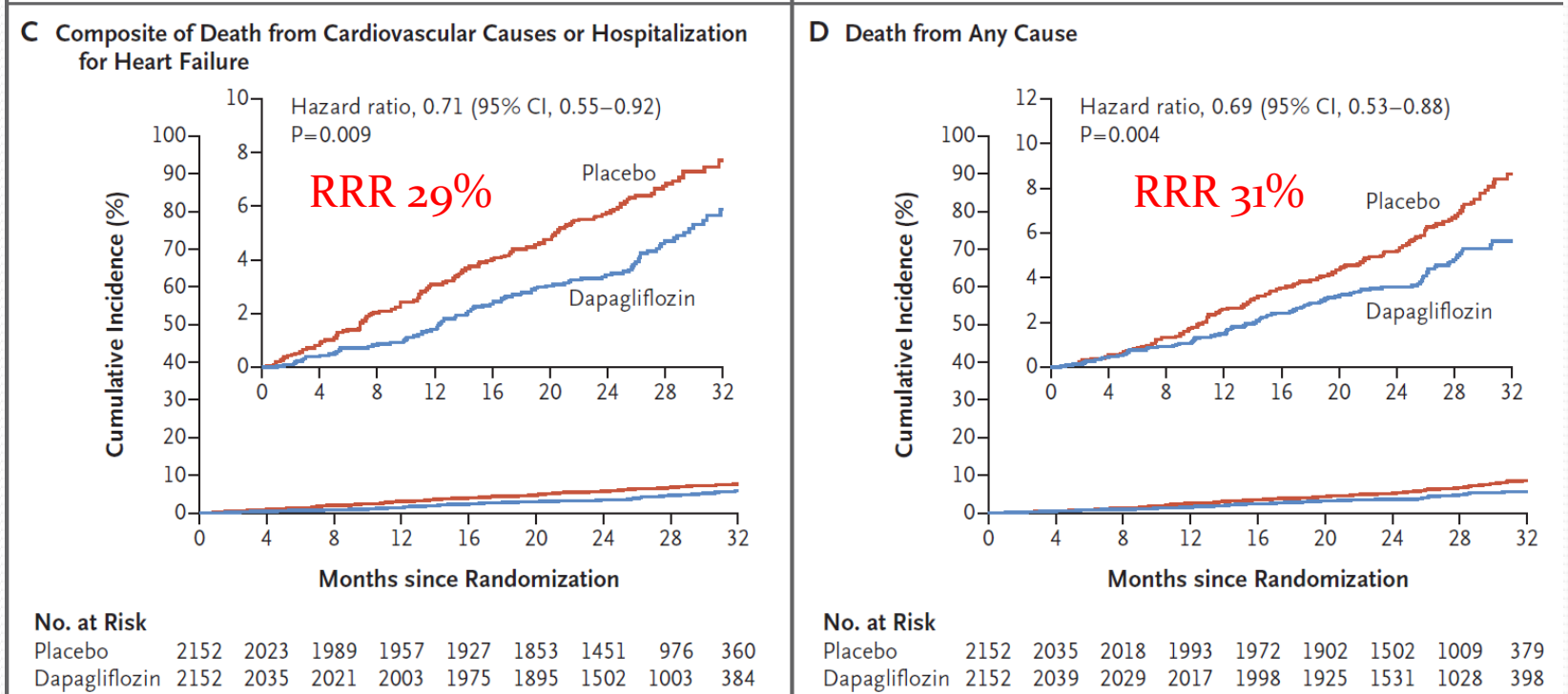
*A complete list of DAPA-CKD committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Dapagliflozin (N=2152)	Placebo (N=2152)
Age — yr	61.8±12.1	61.9±12.1
Female sex — no. (%)	709 (32.9)	716 (33.3)
Race — no. (%)†		
White	1124 (52.2)	1166 (54.2)
Estimated GFR		
Mean — ml/min/1.73 m^2	43.2±12.3	43.0±12.4
Distribution — no. (%)		
≥60 ml/min/1.73 m^2	234 (10.9)	220 (10.2)
45 to <60 ml/min/1.73 m^2	646 (30.0)	682 (31.7)
30 to <45 ml/min/1.73 m^2	979 (45.5)	919 (42.7)
<30 ml/min/1.73 m^2	293 (13.6)	331 (15.4)
Urinary albumin-to-creatinine ratio§		
Median (interquartile range)	965 (472–1903)	934 (482–1868)
>1000 — no. (%)	1048 (48.7)	1031 (47.9)
Type 2 diabetes — no. (%)	1455 (67.6)	1451 (67.4)
Cardiovascular disease — no. (%)¶	813 (37.8)	797 (37.0)
Heart failure — no. (%)	235 (10.9)	233 (10.8)
Previous medication — no. (%)		
ACE inhibitor	673 (31.3)	681 (31.6)
ARB	1444 (67.1)	1426 (66.3)
Diuretic	928 (43.1)	954 (44.3)
Statin	1395 (64.8)	1399 (65.0)

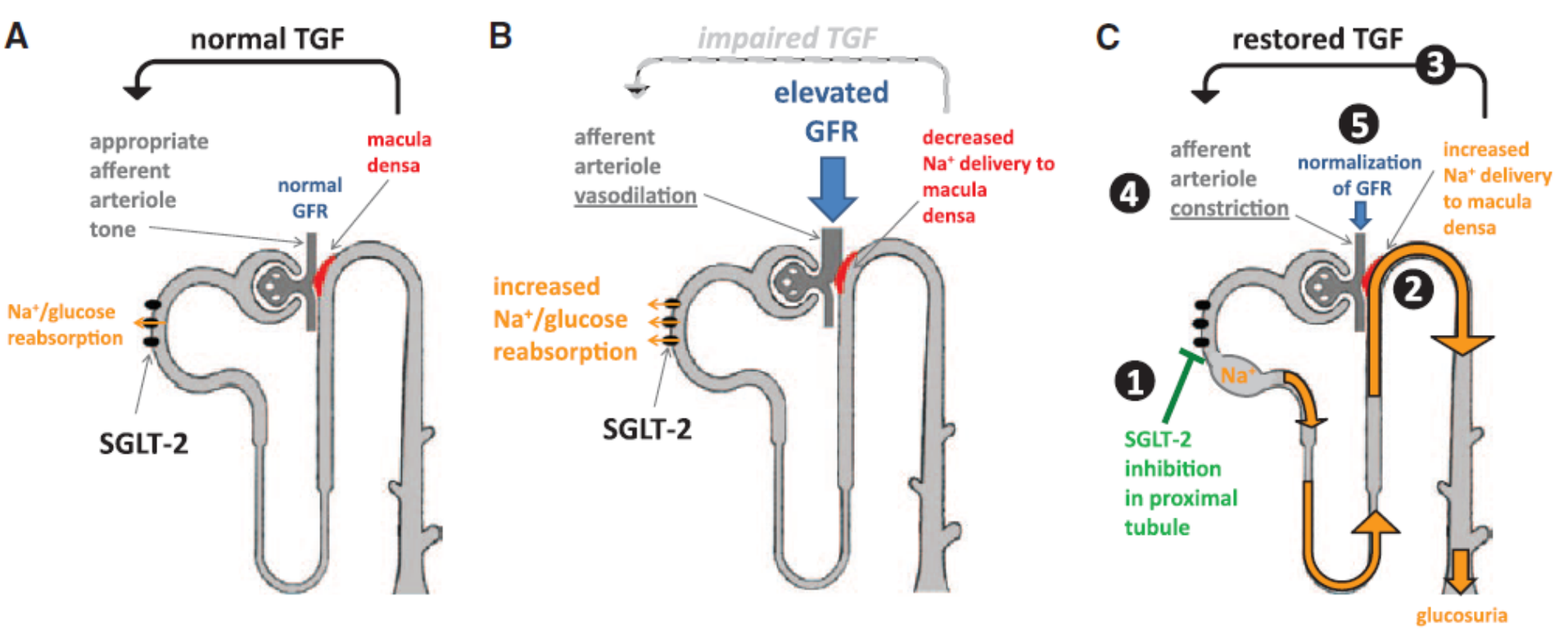
Heerspink HJL et al. NEJM 2020;
DOI: 10.1056/NEJMoa2024816





Heerspink HJL et al. NEJM 2020;
DOI: 10.1056/NEJMoa2024816

Postulated SGLT2i tubuloglomerular feedback (TGF) mechanisms



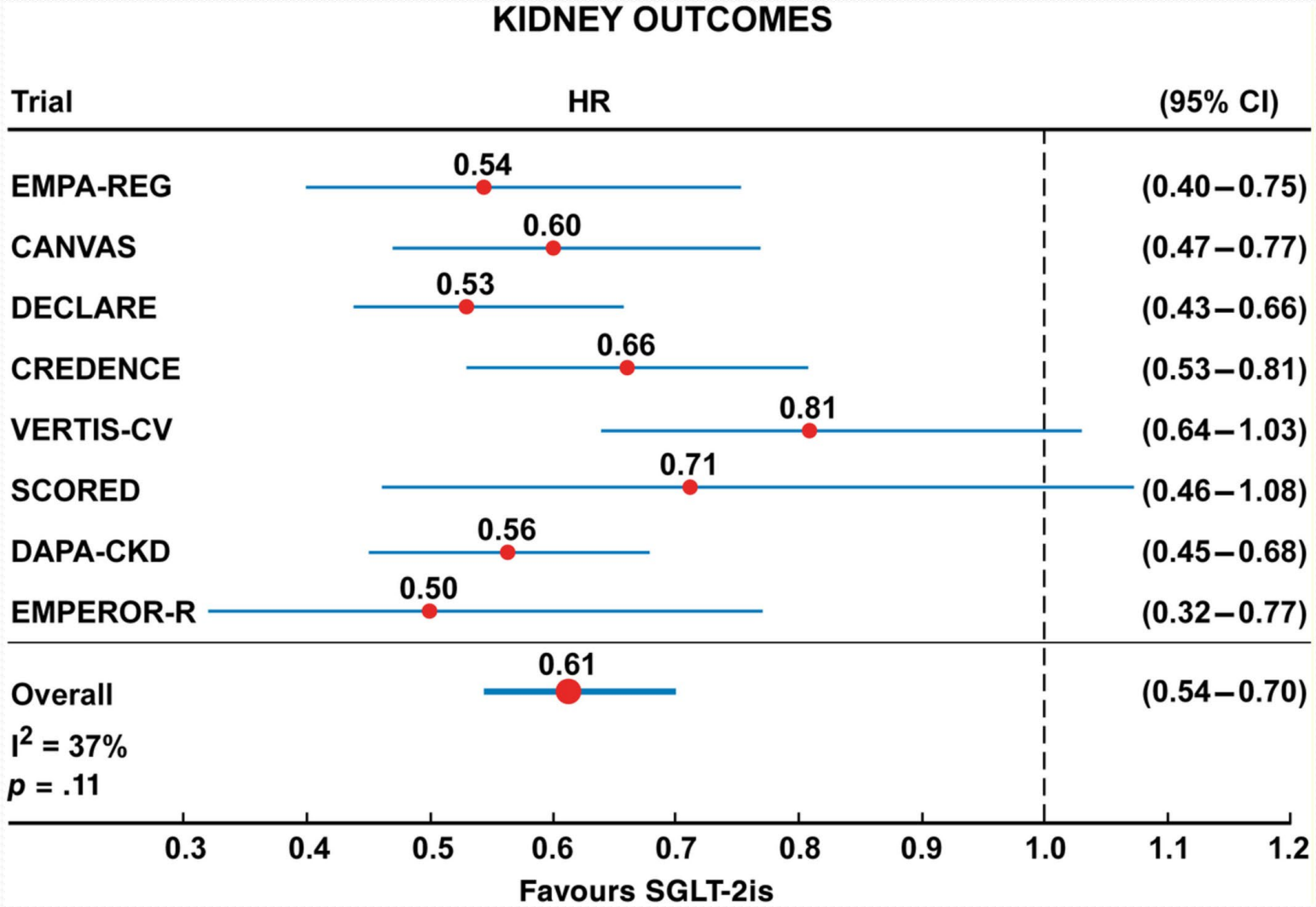
Cherney DZI et al. Circulation. 2014;129:587-97.

SGLT2i's With FDA Indications for Renal Protection

- Canagliflozin
  - Indicated to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria.
- Dapagliflozin
  - FDA granted breakthrough therapy designation (10/2/20) for dapagliflozin for adults with chronic kidney disease **with and without** type 2 diabetes.

(EMPA-Kidney and SCORED results expected in 2022)

Effect of SGLTs on Renal Endpoints



Giugliano et al. Diabetes Obesity Metabolism 2021; Om-line 12 March

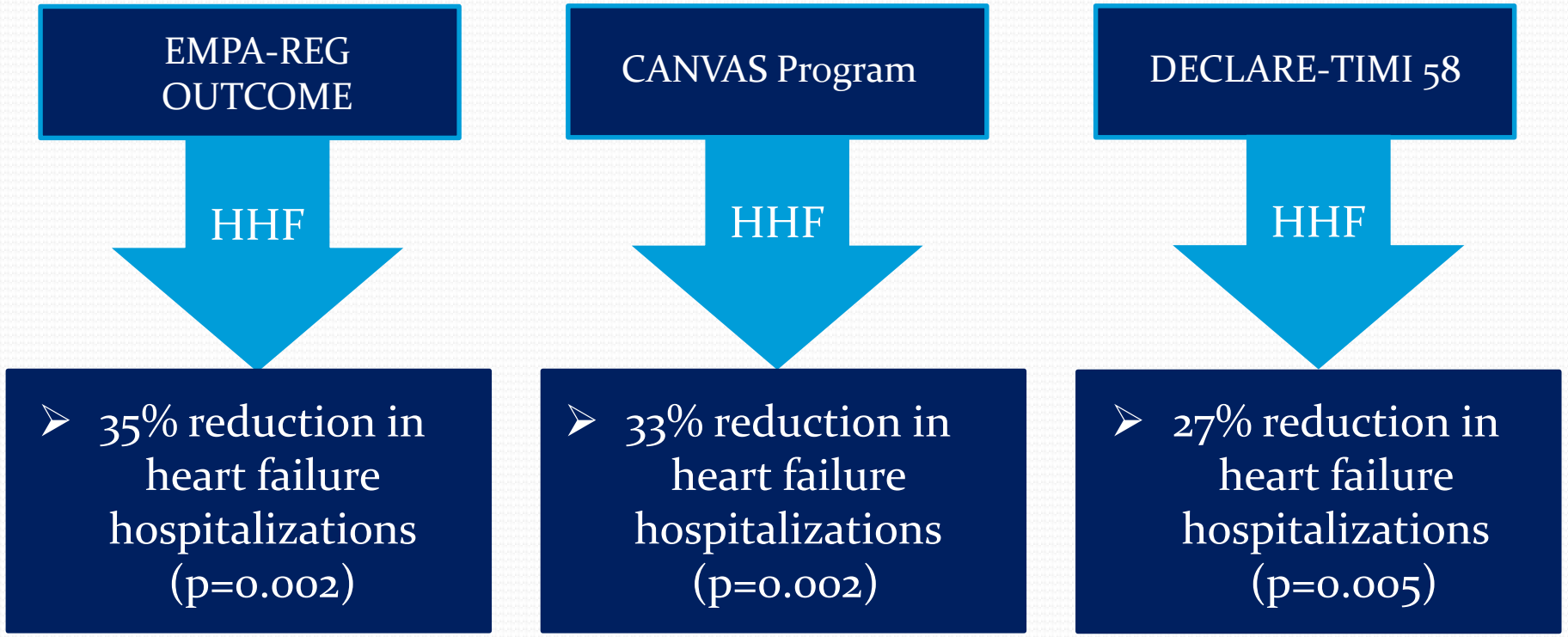
Is the Combined Use of GLP-1 RA and SGLT2 Inhibitor an Option?

	SGLT2I	GLP-1 RA	Combination
Appetite	− (?)	+	+
Body weight	+	+	++
Ischemic CV events	+	+	++
Heart failure events	+	=	+
Insulin levels	−	+	+
Glucagon secretion	−	+	=
Hepatic glucose output	−	+	=
Ketone body production	−	+	=
Muscle glucose uptake	+	+	++
Diuresis, natriuresis	+	+	+
Urinary glucose secretion	+	=	+
Renoprotection	+	=	+

Nauck MA, et al. *Lancet Diabetes Endocrinol*. 2016;963-964; Frías JP, et al. *Lancet Diabetes Endocrinol*. 2016;4:1004-1016; Lundkvist P, et al. *Diabetes Obes Metab*. 2017;19:49-60.

Trials in Heart Failure

Heart failure hospitalizations (HHF) Secondary endpoint of CVOT's



Zinman B et al. N Engl J Med. 2015;373(22):2117-28.
Neal B et al. N Engl J Med. 2017;377:644-57.
Wiviott SD et al. N Engl J Med. 2019; 380:347-357.

Table 2. Cardiovascular Outcome Trials Involving Patients with Heart Failure.*

Variable	DAPA-HF	EMPEROR-Reduced	EMPEROR-Preserved	SOLOIST-WHF
Drug	Dapagliflozin	Empagliflozin	Empagliflozin	Sotagliflozin
No. of patients	4744	3730	5988	1222
Type 2 diabetes — % of patients	41.7	49.8	49.1	100
LVEF — %	31.1	27.4	54.3	35
Median NT-proBNP — pg/ml	1437	1907	970	1864
Mean eGFR — ml/min/1.73 m^2	65.7	62.0	60.6	49.9
Outcomes — hazard ratio (95% CI)				
Cardiovascular death or hospitalization for heart failure	0.74 (0.65–0.85)	0.75 (0.68–0.86)	0.79 (0.69–0.90)	0.67 (0.52–0.85)
Hospitalization for heart failure	0.70 (0.59–0.83)	0.69 (0.59–0.81)	0.73 (0.61–0.88)	0.64 (0.49–0.83)

* Data sources for the trials are as follows: DAPA-HF, McMurray et al.[24]; EMPEROR-Reduced, Packer et al.[25]; EMPEROR-Preserved, Anker et al.[26]; SOLOIST-WHF, Bhatt et al.[27] The abbreviation eGFR denotes estimated glomerular filtration rate, LVEF left ventricular ejection fraction, and NT-proBNP N-terminal pro–B-type natriuretic peptide.

Braunwald E. N Engl J Med. 2022;386:2024-34.

Dapagliflozin is Now Recommended as a First-Line HFrEF Therapy in the 2022 AHA/ACC/HFSA HF Guidelines

Core HFrEF Therapy[1,a]

- ARNI/ ACEI/ARB[b]
- Beta-blocker[c]
- MRA[d]
- SGLT2 inhibitor

Guideline Recommendation[1]

COR	LOE	Recommendation for SGLT2 inhibitors
I	A	In patients with symptomatic chronic HFrEF, SGLT2 inhibitors are recommended to reduce hospitalization for HF and CV mortality, irrespective of the presence of T2D.

Quadruple Therapy Implementation

Early Benefit[2]

- **Simultaneous or rapid sequence initiation** of quadruple therapy is associated with **clinical event reduction within the first 4 weeks**

Projected Event-Free Survival and Overall Survival[3]

- Treatment with the combination of ARNI, beta-blocker, MRA and SGLT2 inhibitor is estimated to afford **2.7 to 8.3 years free from CV death or first hHF** and **1.4 to 6.3 additional years of survival** compared to a combination regimen of ACEI or ARB and beta-blocker

[a]Diuretics are also recommended as needed in patients with fluid retention; [b]ARNI is recommended as de novo or to replace ACEI or ARB in patients with NYHA class II-III. In patients with NYHA class II-IV, ACEI, or ARB when intolerant to ACEI due to cough or angioedema, is recommended when ARNI use is not feasible; [c]One of the 3 beta-blockers proven to reduce mortality; [d]If eGFR >30 mL/min/1.73m^2 and potassium <5.0 mEq/L.

ACC = American College of Cardiology; ACEI = angiotensin-converting enzyme inhibitor; AHA = American Heart Association; ARB = angiotensin-receptor blocker; ARNI = angiotensin-receptor neprilysin inhibitor; CV = cardiovascular; COR = class of recommendation; eGFR = estimated glomerular filtration rate; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; hHF = hospitalization for heart failure; LOE = level of evidence; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter 2 .

1. Heidenreich PA et al. Online ahead of print. *J Am Coll Cardiol*. 2022; 2. McMurray JJV et al. *Circulation*. 2021;143(9):875-877; 3. Vaduganathan M et al. *Lancet*. 2020;396(10244):121-128.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

4744 patients with HFrEF (Class II, III, or IV and EF ≤ 40%); 45% with DM
Dapa 10 mg **in addition to recommended therapy**; Median 18.2 mos f/u
Primary Endpoint: composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death.

ABSTRACT

BACKGROUND

In patients with type 2 diabetes, inhibitors of sodium–glucose cotransporter 2 (SGLT2) reduce the risk of a first hospitalization for heart failure, possibly through glucose-independent mechanisms. More data are needed regarding the effects of SGLT2 inhibitors in patients with established heart failure and a reduced ejection fraction, regardless of the presence or absence of type 2 diabetes.

METHODS

In this phase 3, placebo-controlled trial, we randomly assigned 4744 patients with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either dapagliflozin (at a dose of 10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. McMurray at the British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Pl., Glasgow G12 8TA, United Kingdom, or at john.mcmurray@glasgow.ac.uk.

*A complete list of DAPA-HF committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 19, 2019, at NEJM.org.

The NEW ENGLAND JOURNAL of MEDICINE

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26% relative risk reduction of composite of worsening heart failure or CV death
18% relative risk reduction of CV death
17% relative risk reduction of overall death

ABSTRACT

BACKGROUND

In patients with type 2 diabetes, inhibitors of sodium–glucose cotransporter 2 (SGLT2) reduce the risk of a first hospitalization for heart failure, possibly through glucose-independent mechanisms. More data are needed regarding the effects of SGLT2 inhibitors in patients with established heart failure and a reduced ejection fraction, regardless of the presence or absence of type 2 diabetes.

METHODS

In this phase 3, placebo-controlled trial, we randomly assigned 4744 patients with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either dapagliflozin (at a dose of 10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death.

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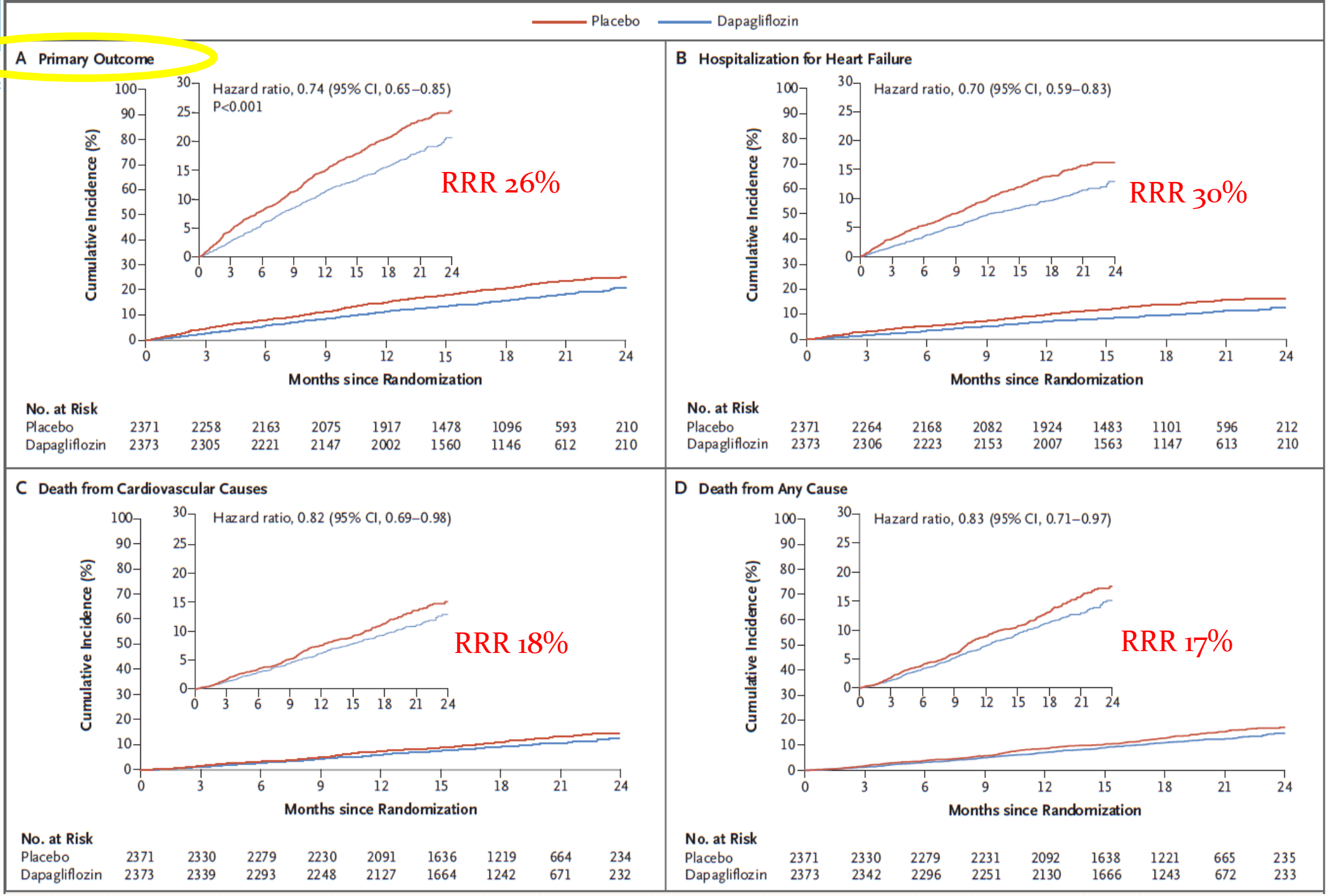
*A complete list of DAPA-HF committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 19, 2019, at NEJM.org.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Dapagliflozin (N=2373)	Placebo (N=2371)
Age — yr	66.2±11.0	66.5±10.8
Female sex — no. (%)	564 (23.8)	545 (23.0)
Body-mass index†	28.2±6.0	28.1±5.9
Race — no. (%)‡		
White	1662 (70.0)	1671 (70.5)
Black	122 (5.1)	104 (4.4)
Asian	552 (23.3)	564 (23.8)
NYHA functional classification — no. (%)		
II	1606 (67.7)	1597 (67.4)
III	747 (31.5)	751 (31.7)
IV	20 (0.8)	23 (1.0)
Heart rate — beats/min	71.5±11.6	71.5±11.8
Systolic blood pressure — mm Hg	122.0±16.3	121.6±16.3
Left ventricular ejection fraction — %	31.2±6.7	30.9±6.9
Median NT-proBNP (IQR) — pg/ml	1428 (857–2655)	1446 (857–2641)
Unknown	200 (8.4)	183 (7.7)
Medical history — no. (%)		
Hospitalization for heart failure	1124 (47.4)	1127 (47.5)
Atrial fibrillation	916 (38.6)	902 (38.0)
Diabetes mellitus§	993 (41.8)	990 (41.8)
Estimated GFR		
Mean — ml/min/1.73 m^2	66.0±19.6	65.5±19.3
Rate of <60 ml/min/1.73 m^2 — no./total no. (%)	962/2372 (40.6)	964/2371 (40.7)
Device therapy — no. (%)		
Implantable cardioverter–defibrillator¶	622 (26.2)	620 (26.1)
Cardiac resynchronization therapy‖	190 (8.0)	164 (6.9)

McMurray JJV et al.
N Engl J Med
2019; 381:1995-2008.



McMurray JJV et al. N Engl J Med 2019; 381:1995-2008.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, H.-P. Brunner-La Rocca, B. Merkely, S.J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M.-F. Seronde, J. Spinar, I. Squire, S. Taddei, C. Wanner, and F. Zannad, for the EMPEROR-Reduced Trial Investigators*

Packer M et al. NEJM 2020;
DOI: 10.1056/NEJMoa2022190.

3730 patients with HFrEF (Class II, III, or IV and EF ≤ 40%); 50% with DM
Empa 10 mg **in addition to recommended HF therapy**; Median 16 mos f/u
Primary Endpoint: composite of CV death or hospitalization for worsening HF

ABSTRACT

BACKGROUND

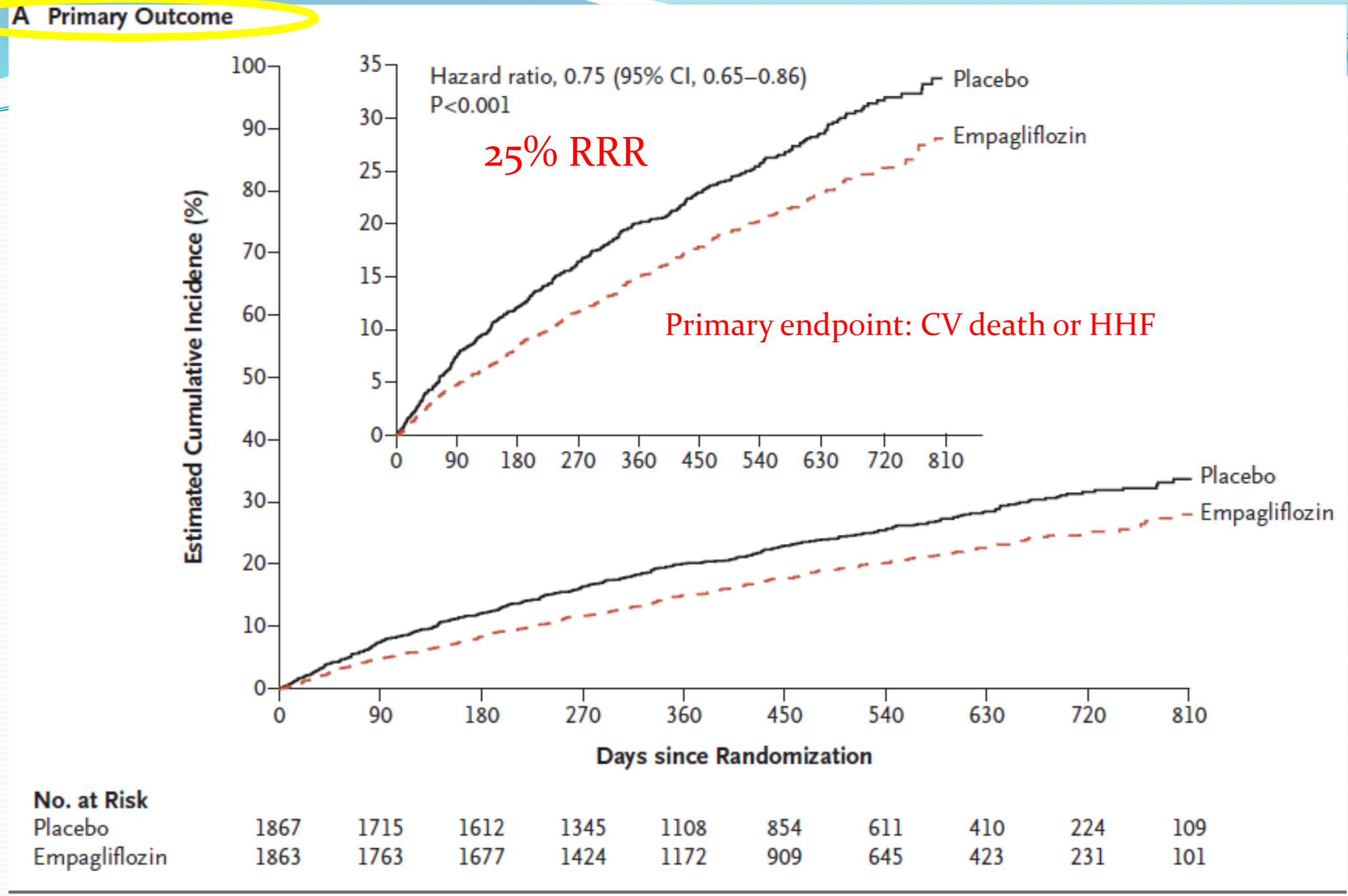
Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure in patients regardless of the presence or absence of diabetes. More evidence is needed regarding the effects of these drugs in patients across the broad spectrum of heart failure, including those with a markedly reduced ejection fraction.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Packer at Baylor Heart and Vascular Institute, 621 N. Hall St., Dallas, TX 75226, or at milton.packer@baylorhealth.edu.

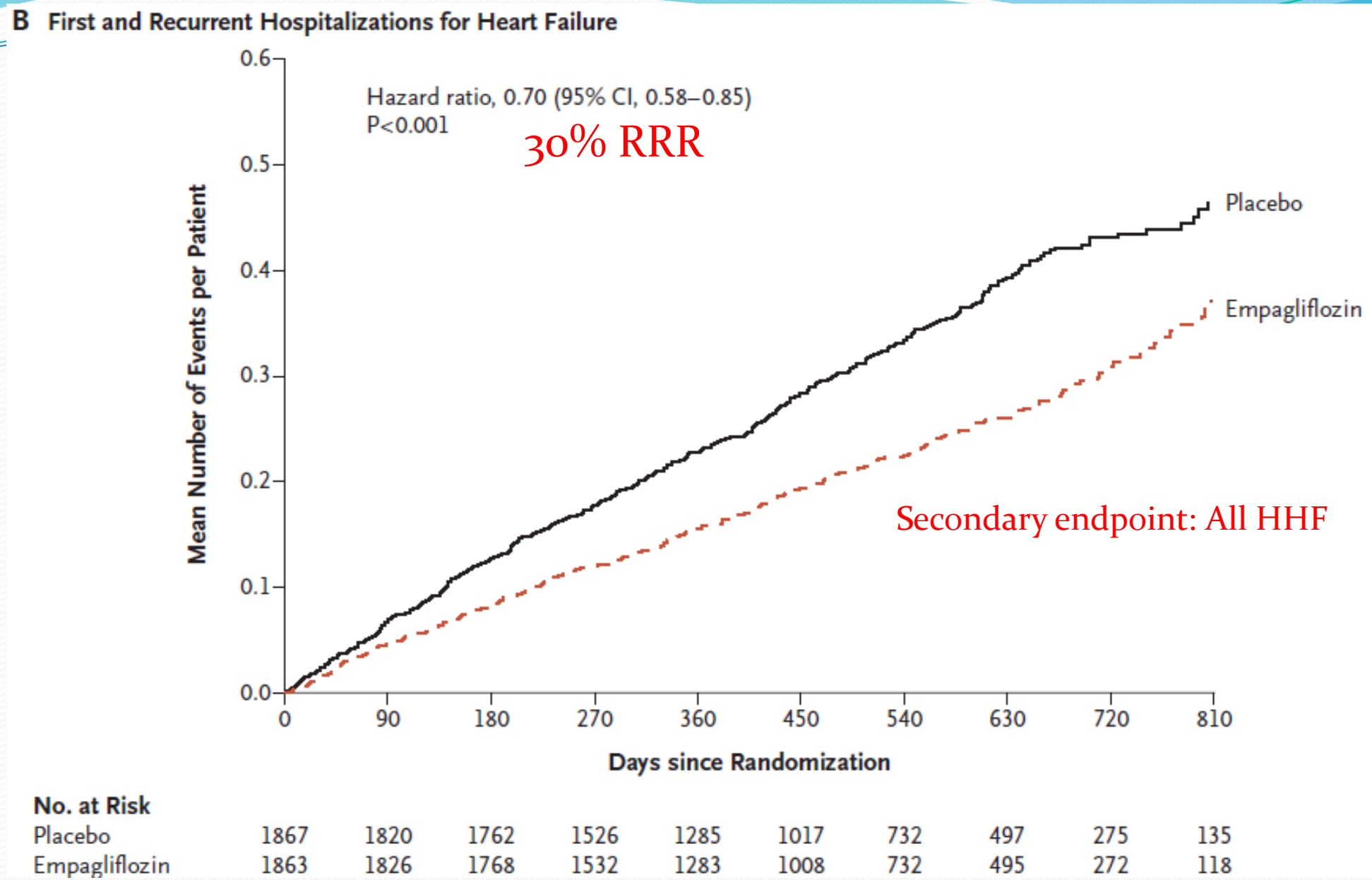
Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Empagliflozin (N = 1863)	Placebo (N = 1867)
Age — yr	67.2±10.8	66.5±11.2
Female sex — no. (%)	437 (23.5)	456 (24.4)
NYHA functional class — no. (%)		
II	1399 (75.1)	1401 (75.0)
III	455 (24.4)	455 (24.4)
IV	9 (0.5)	11 (0.6)
Body-mass index‡	28.0±5.5	27.8±5.3
Heart rate — beats/min	71.0±11.7	71.5±11.8
Systolic blood pressure — mm Hg	122.6±15.9	121.4±15.4
Left ventricular ejection fraction		
Mean value	27.7±6.0	27.2±6.1
Value of ≤30% — no. (%)	1337 (71.8)	1392 (74.6)
NT-proBNP		
Median value (IQR) — pg/ml	1887 (1077–3429)	1926 (1153–3525)
Value of ≥1000 pg/ml — no./total no. (%)	1463/1862 (78.6)	1488/1866 (79.7)
Diabetes mellitus	927 (49.8)	929 (49.8)
Hypertension	1349 (72.4)	1349 (72.3)
Estimated glomerular filtration rate		
Mean value — ml/min/1.73 m^2	61.8±21.7	62.2±21.5
Value of <60 ml/min/1.73 m^2 — no./total no. (%)	893/1862 (48.0)	906/1866 (48.6)

Packer M et al. NEJM 2020;
DOI: 10.1056/NEJMoa2022190.



Packer M et al. NEJM 2020; DOI: 10.1056/NEJMoa2022190.



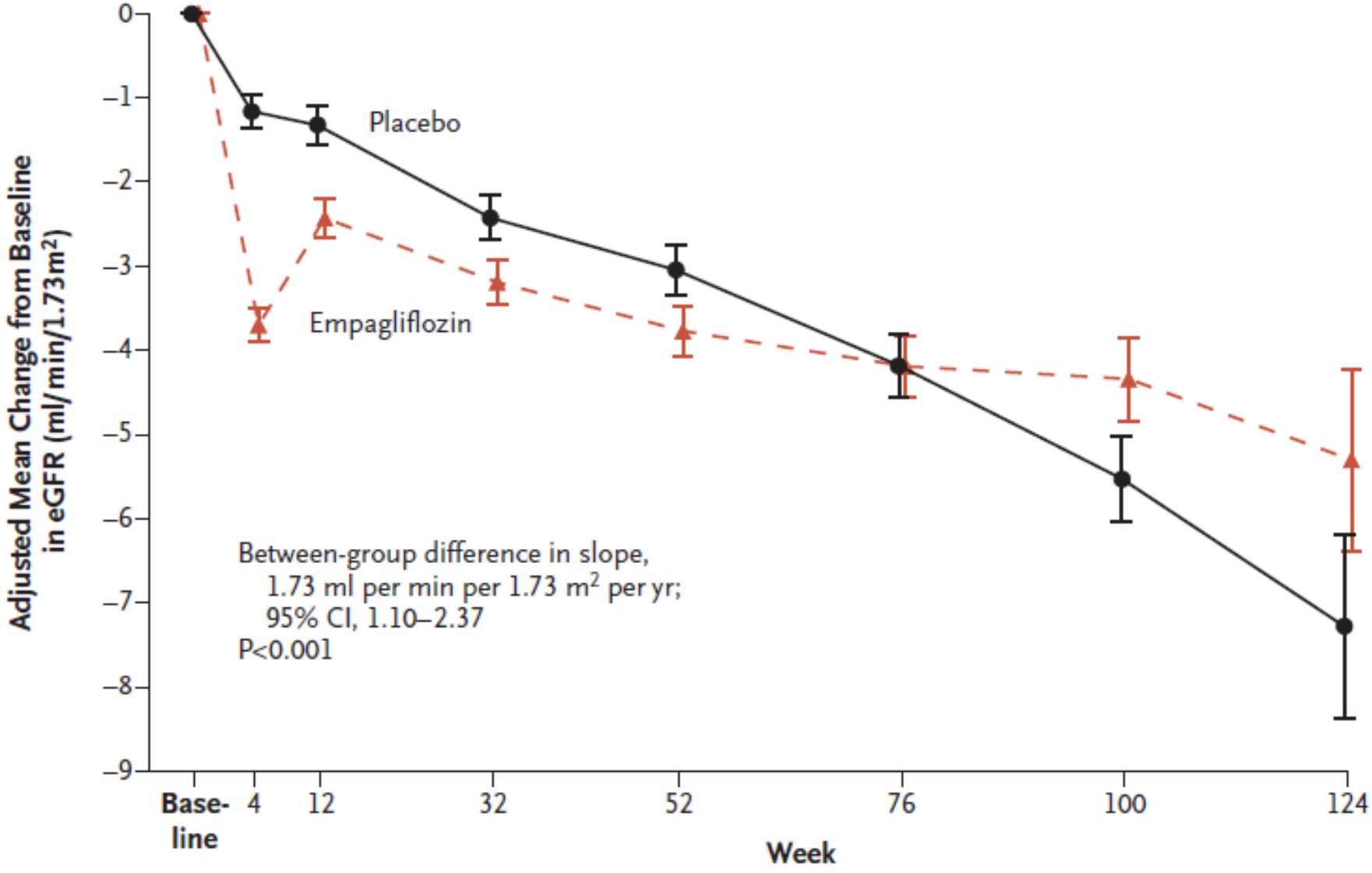
Packer M et al. NEJM 2020; DOI: 10.1056/NEJMoa2022190.

Potential CV and Renal Function Preservation Mechanisms of SGLT2i That May Benefit Heart Failure

Effect	Consequence
Diuresis[a]	Reduced filling pressures, pre/afterload reduction
Natriuresis[b]	Reduced filling pressures, pre/afterload reduction
Blood pressure lowering[c]	Reduced myocardial work, reduced filling pressures, pre/afterload reduction
Weight loss[d]	Improved CV risk profile, lower blood pressure
Reduction in/prevention of albuminuria, slowing of kidney function decline[e]	Reduction in kidney risk profile, possibly lower incident CV events, including less HF
Effects on myocardial and kidney metabolism: shift to more efficient ketone-based metabolism[f]	Improved metabolic efficiency, less myocardial work-load
Blockade of kidney and myocardial sodium-hydrogen co-transporter[g]	Tissue protection: reduction in kidney and myocardial injury

a. Heise T, et al. *Diabetes Obes Metab*. 2013;15:613-621; b. Heise T, et al. *Clin Ther*. 2016;38:2265-2276; c. Heerspink HJ, et al. *Circulation*. 2016;134:752-772; d. Ferrannini G, et al. *Diabetes Care*. 2015;38:1730-1735; e. Wanner Ch, et al. *N Engl J Med*. 2016;375:1801-1802; f. Briand F, et al. *Diabetes*. 2016;6:2032-2038; g. Uthman L, et al. *Front Physiol*. 201821;9:1575.

Changes in the Estimated GFR.

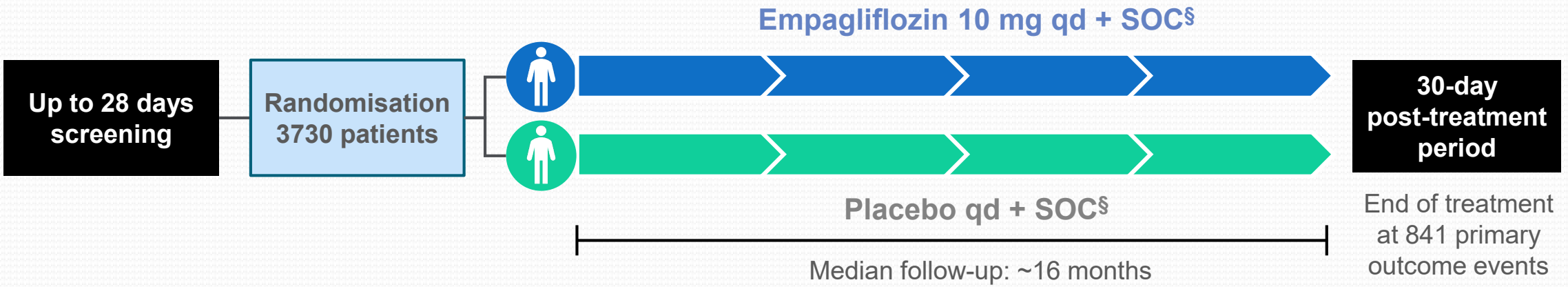


No. at Risk							
Placebo	1792	1765	1683	1500	1146	745	343	76
Empagliflozin	1799	1782	1720	1554	1166	753	356	80

Packer M et al. NEJM 2020; DOI: 10.1056/NEJMoa2022190.

EMPEROR-Reduced

Aim: to investigate the safety and efficacy of empagliflozin versus placebo, on top of SOC, in patients with **HFrEF** with or without diabetes



Key inclusion criteria:

- NYHA class II–IV with LVEF ≤40%*
- Elevated NT-proBNP†
- eGFR ≥20 ml/min/1.73 m^2
- Guideline-recommended medication stable ≥1 week prior to first visit

Primary endpoint: time to first event of adjudicated CV death or adjudicated HHF

Key secondary endpoints (Confirmatory):

- First and recurrent adjudicated HHF events
- Slope of change in eGFR (CKD-EPI) from baseline

Secondary endpoints

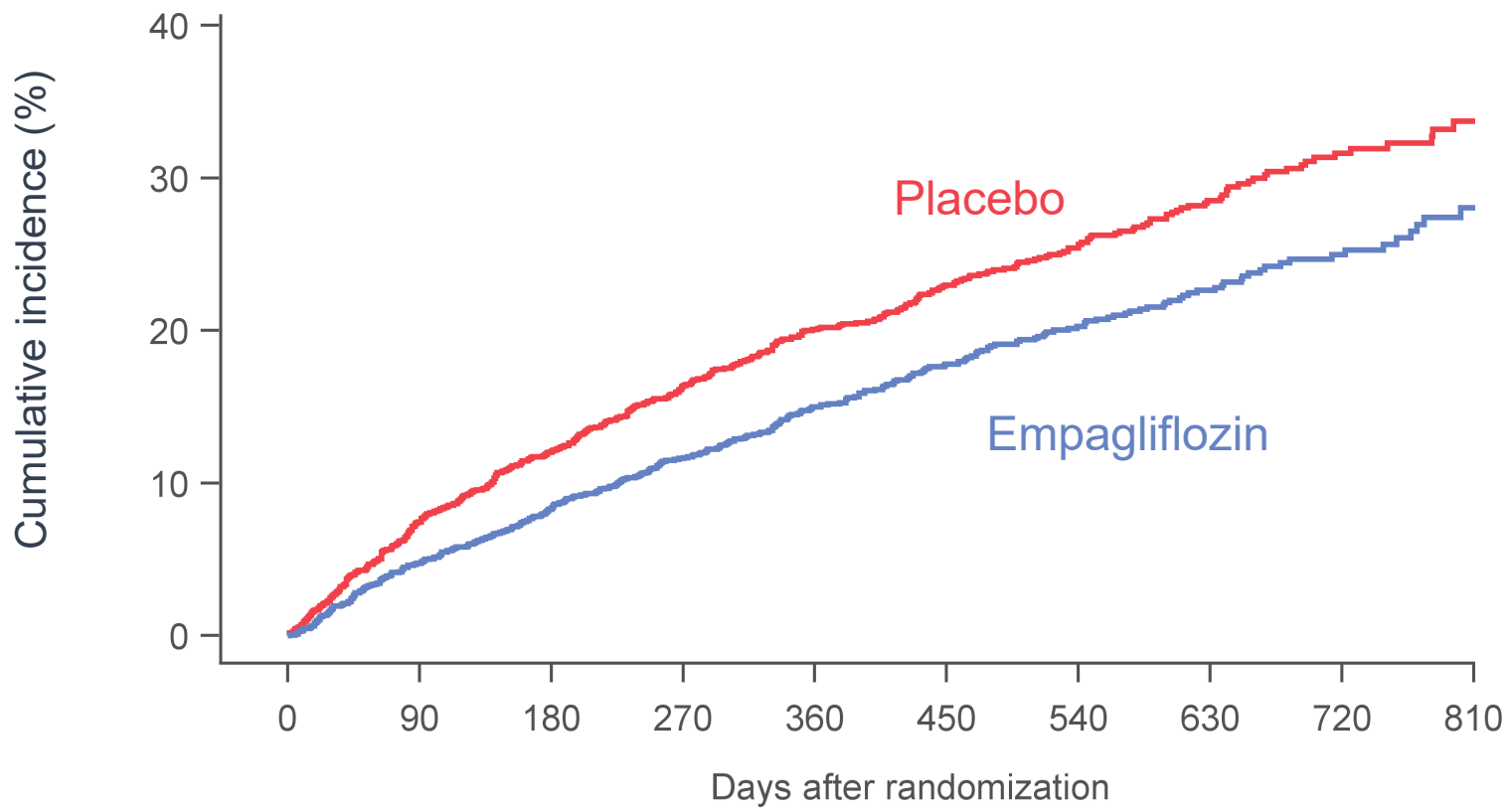
- Change from baseline KCCQ-CSS at week 52
- HHF (First event)
- CV Death
- All-cause mortality
- Composite kidney endpoint‡

Empagliflozin is not approved to reduce the risk for progression of kidney disease or to slow kidney function decline in adults with heart failure with reduced ejection fraction.

§Guideline-directed medical therapy. *For ≥3 months; †NT-proBNP-based enrichment of the population: patients with a higher ejection fraction require a higher NT-proBNP level for inclusion); ‡Occurrence of chronic dialysis, kidney transplant or sustained reduction in eGFR ≥40%

ClinicalTrials.gov. NCT03057977 (accessed Jan 2021); Packer M et al. Eur J Heart Fail 2019;21:1270

EMPEROR-Reduced: Time to Cardiovascular Death or Hospitalization for Heart Failure (Primary Endpoint)



462 patients with event
Rate: 21.0/100 patient-years

361 patients with event
Rate: 15.8/100 patient-years

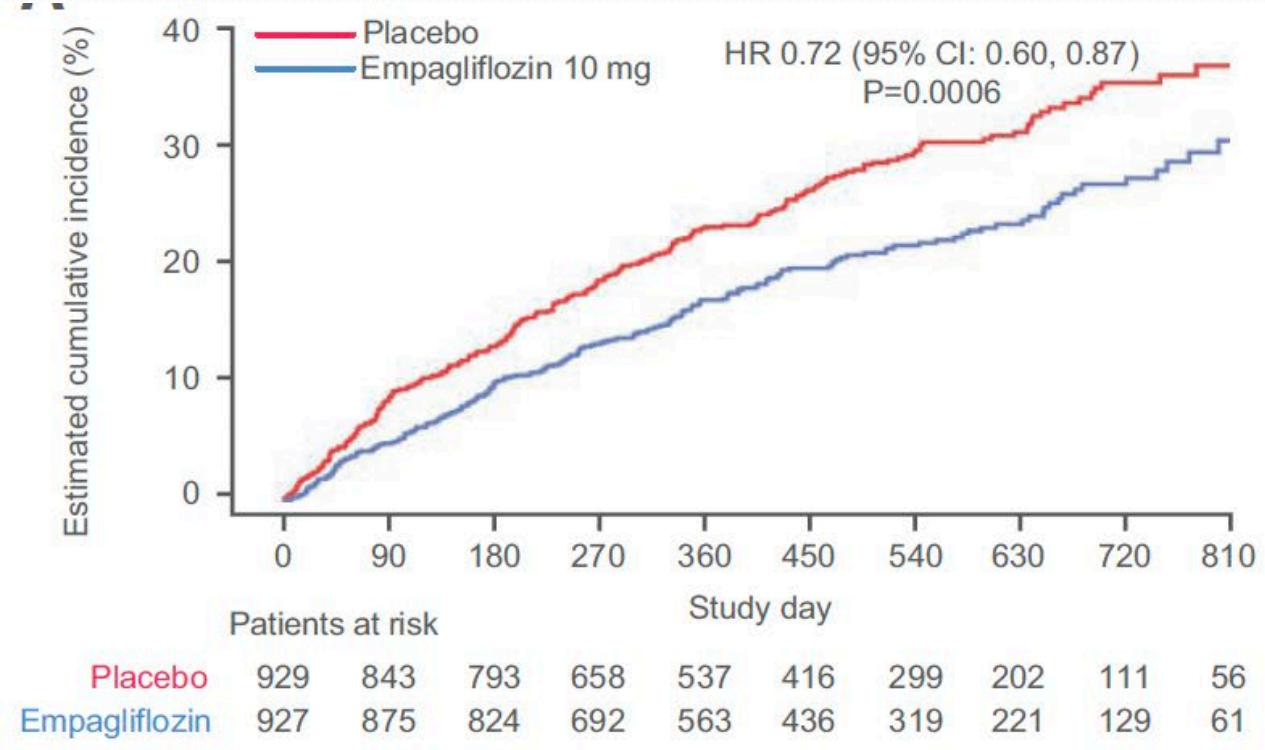
HR 0.75
(95% CI 0.65, 0.86)
P < 0.0001

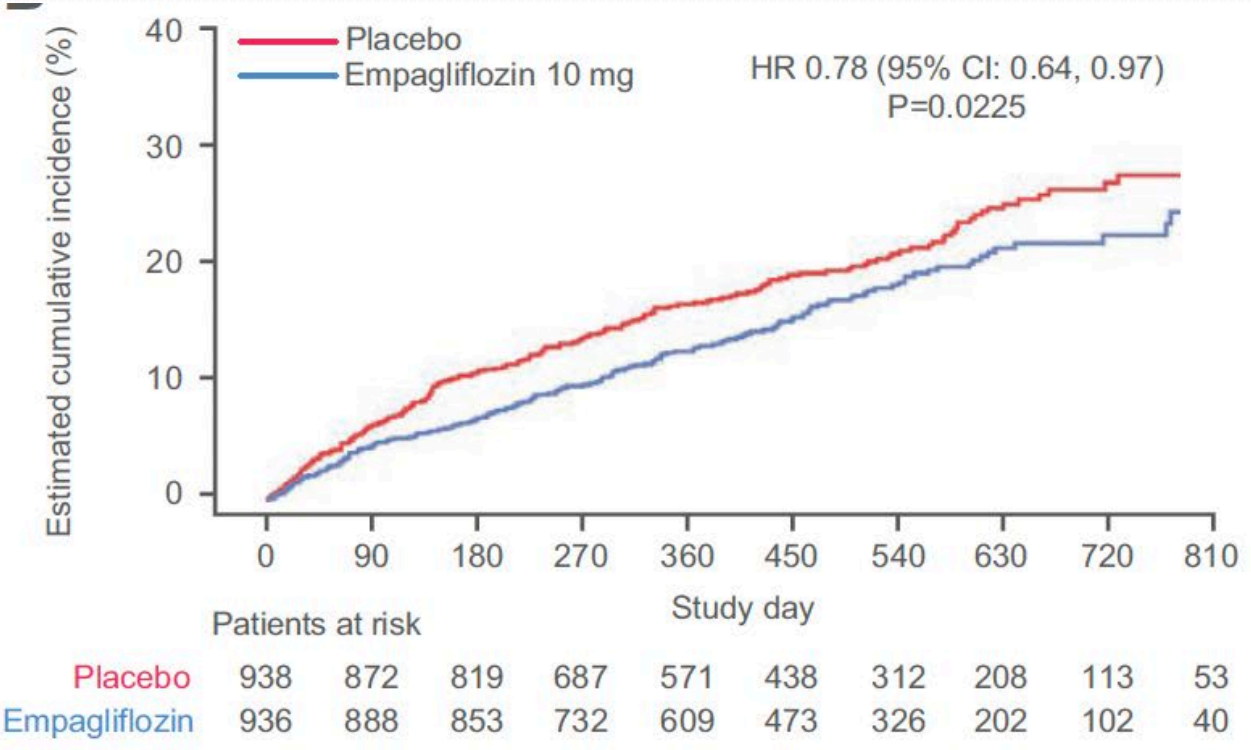
Patients at risk

Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

Packer et al. N Engl J Med. 2020; 383:1413-1424

EMPEROR-Reduced Primary Outcome With and Without Type 2 Diabetes

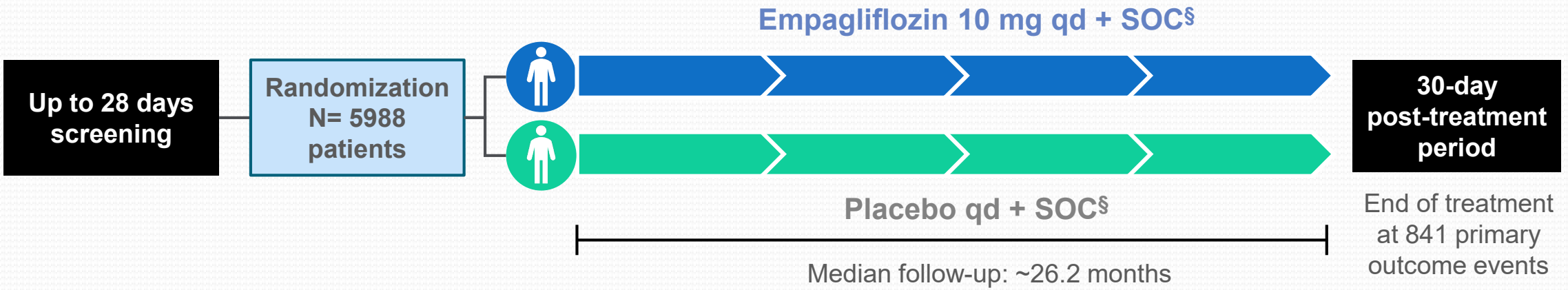




Anker et al. Circulation 2021; 143: 337-349

EMPEROR-Preserved

Aim: to investigate the safety and efficacy of empagliflozin versus placebo, on top of SOC, in patients with **HFpEF** with or without diabetes



Key inclusion criteria:

- NYHA class II–IV with LVEF >40%*
- Elevated NT-proBNP†
- Structural heart changes or HHF within 12 months of screening
- eGFR ≥20 ml/min/1.73 m²
- Guideline-recommended medication stable ≥1 week prior to first visit

Primary endpoint: time to first event of adjudicated CV death or adjudicated HHF

Key secondary endpoints (Confirmatory):

- First and recurrent adjudicated HHF events
- Slope of change in eGFR (CKD-EPI) from baseline

Secondary endpoints

- Change from baseline KCCQ-CSS at week 52
- HHF (First event)
- CV Death
- All-cause mortality
- Composite kidney endpoint‡

Empagliflozin is not approved to reduce the risk for progression of kidney disease or to slow kidney function decline in adults with heart failure with preserved ejection fraction.

§Guideline-directed medical therapy. *Most recent assessment prior to enrollment and no prior LVEF ≤40%.†NT-proBNP >300 pg/ml w/o AF or > 900 pg/ml with AF; ‡Occurrence of chronic dialysis, kidney transplant or sustained reduction in eGFR ≥40%

ClinicalTrials.gov. NCT03057977; Anker SD et al. Eur J Heart Failure 2019; doi:10.1002/ejhf.1596. Anker S et al. N Engl J Med. 2021; DOI: 10.1056/NEJMoa2107038

EMPEROR-Preserved: Main Inclusion and exclusion criteria

Main Inclusion criteria	Main Exclusion criteria

• Age ≥18 years
• Chronic HF NYHA class II–IV
• **LVEF >40%**
• **NT-proBNP:**
  • **>300 pg/mL** in patients without AF
  • **>900 pg/mL** in patients with AF
• **Structural changes in the heart** (increases in left atrial size or left ventricular mass) **or HHF within 12 months of screening**
	• MI, coronary artery bypass graft surgery or other major CV surgery, stroke or TIA ≤90 days before visit
	• Heart transplant recipient, or listed for heart transplant
	• Acute decompensated HF
	• SBP ≥180 mmHg at randomization
	• Symptomatic hypotension and/or SBP <100 mmHg
	• eGFR <20 mL/min/1.73 m² or requiring dialysis

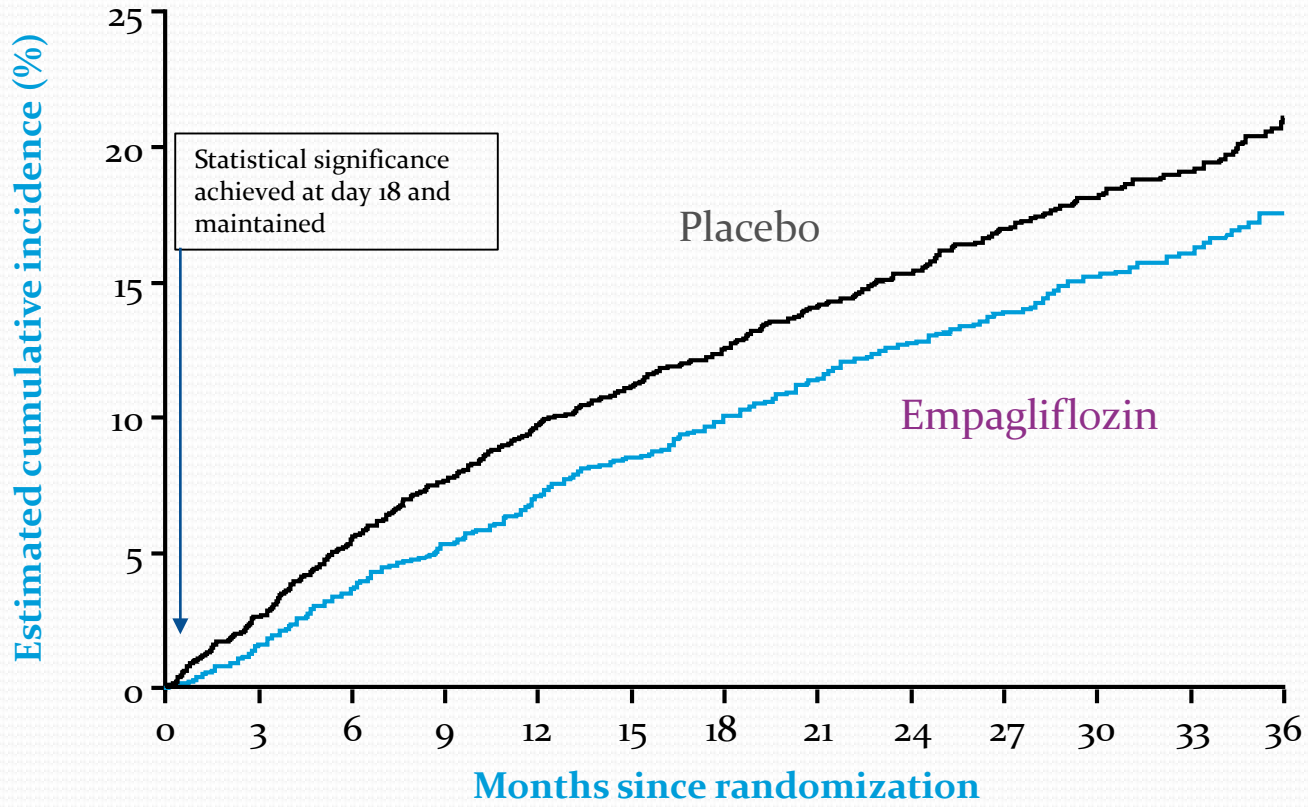
Further criteria apply

Empagliflozin is not approved to reduce the risk for progression of kidney disease or to slow kidney function decline in adults with heart failure with preserved ejection fraction.

SBP, systolic blood pressure; TIA, transient ischemic attack.

Anker S *et al. N Engl J Med*. 2021; DOI: 10.1056/NEJMoa2107038

Primary composite endpoint: Time to first adjudicated CV death or hospitalization for heart failure



Patients at risk

Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

RRR 21%

ARR 3.3%

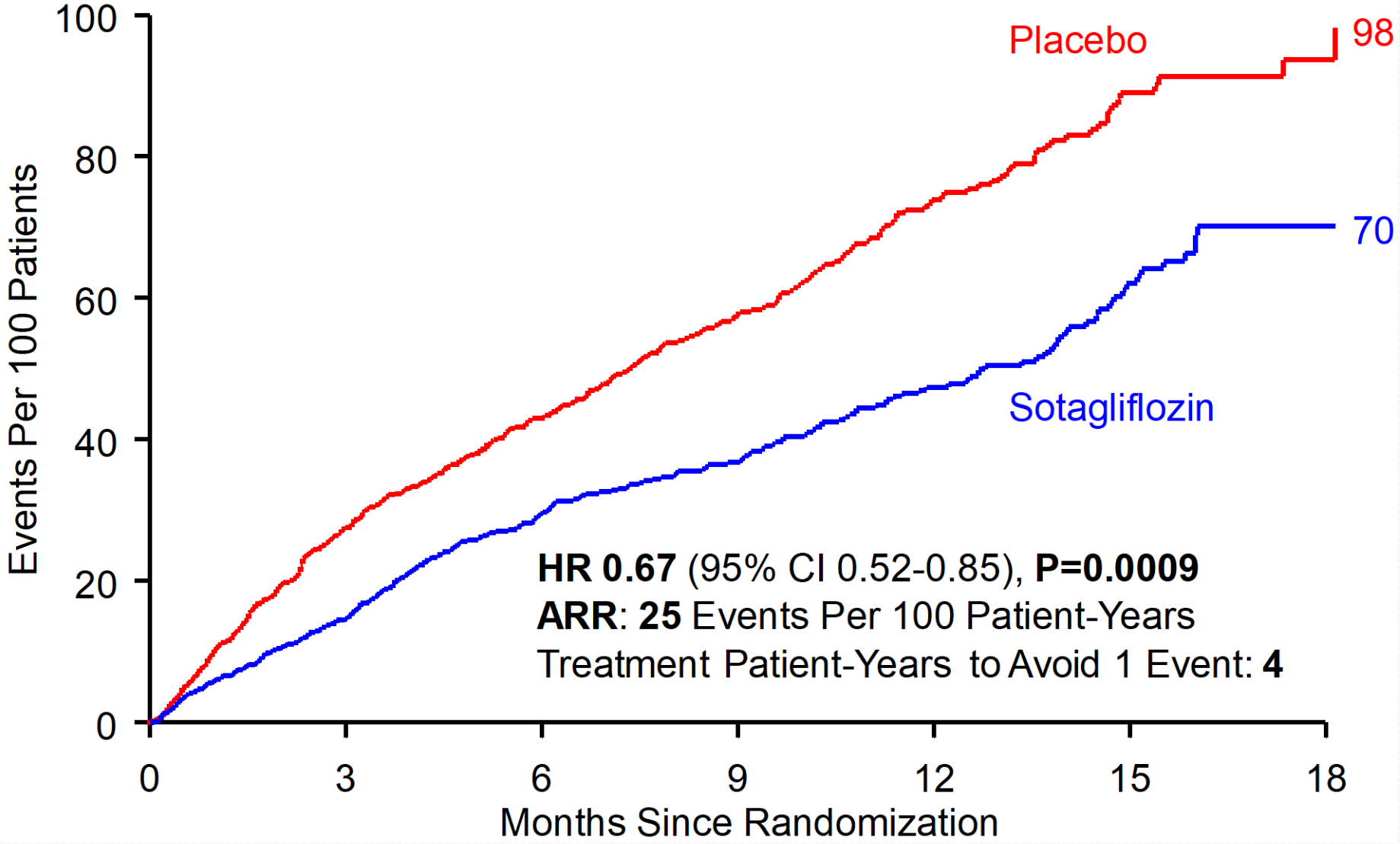
NNT*=31

HR: 0.79
(95% CI: 0.69, 0.90)
p<0.001

Empagliflozin:
415 (13.8%) patients with event
Rate: 6.9/100 patient-years
Placebo:
511 (17.1%) patients with event
Rate: 8.7/100 patient-years

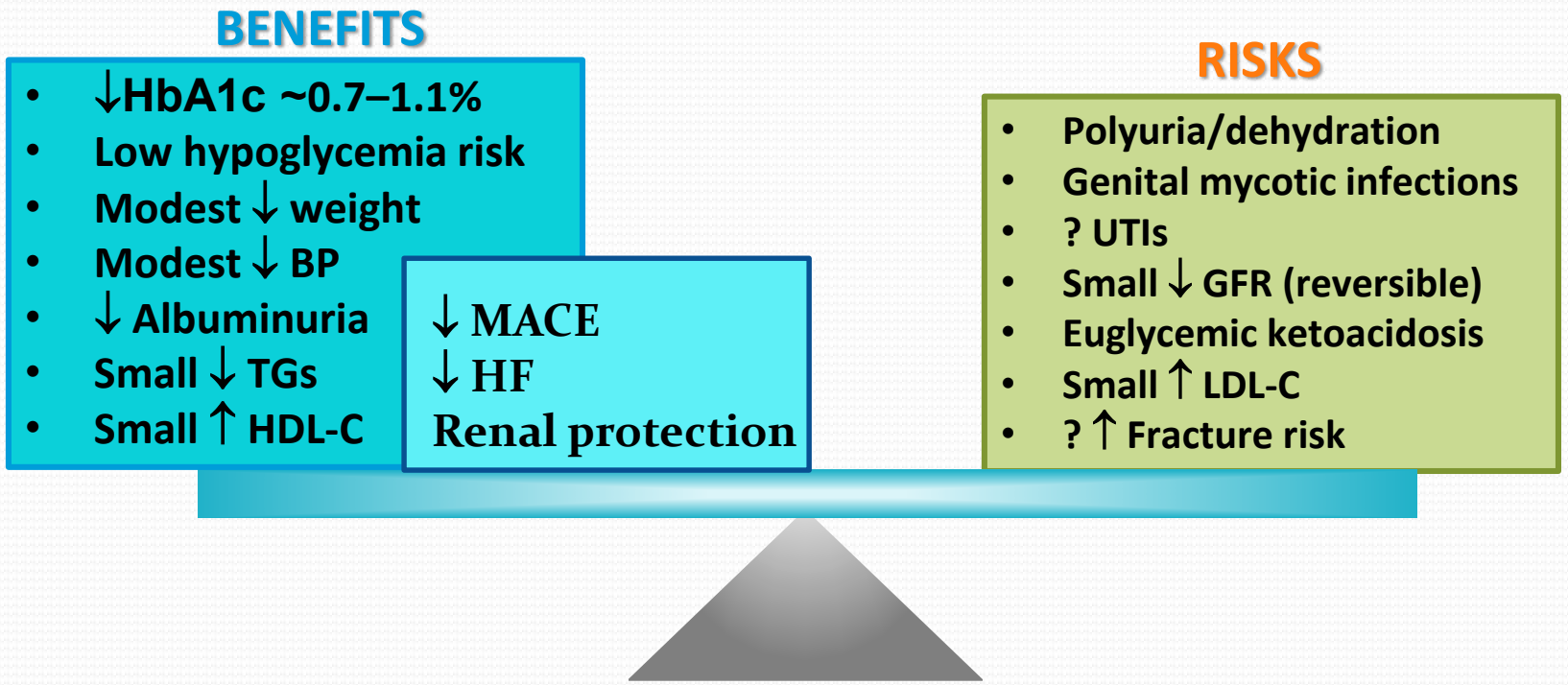
Empagliflozin is not approved to reduce the risk for progression of kidney disease or to slow kidney function decline in adults with heart failure with preserved ejection fraction.
Cox proportional hazards model, with adjustment for prespecified baseline covariates of age, sex, geographical region, diabetes status, left ventricular ejection fraction and eGFR.
*During a median trial period of 26 months. ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; NNT, number needed to treat; RRR, relative risk reduction.
Anker S *et al. N Engl J Med*. 2021; DOI: 10.1056/NEJMoa2107038. Packer M. HFSA Emperor-Preserved presentation.

SOLOIST-WHF
Primary Efficacy: Total CV Death, HHF, and Urgent HF Visit



Bhatt et al. *N Engl J Med.* 2021; 384: 117-128

SGLT2 Inhibitors - Risk-to-Benefit Ratio



TG = triglycerides; UTI = urinary tract infection; GFR = glomerular filtration rate; LDL-C = low-density lipoprotein-cholesterol

Kim Y, Babu AR. *Diabetes Metab Syndr Obes*. 2012;5:313-327.
Inzucchi SE, et al. *Diabetes Care*. 2015;38:140-149.
Burke KR, et al. *Pharmacotherapy*. 2017;37:187-194.

Bottom Line – Diabetes management

- If a patient has known ASCVD, HF, or CKD, or is at high risk, the addition of an SGLT2 inhibitor or GLP-1 receptor agonist with proven efficacy should be provided irrespective of A1C!

ADA/EASD 2022; AACE/ACE 2020.

SGLT-2 Inhibitors: The Gift that keeps on Giving (to the Heart and Kidneys)

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Questions?