Diabetes medications: The expansion of nonglycemic benefits

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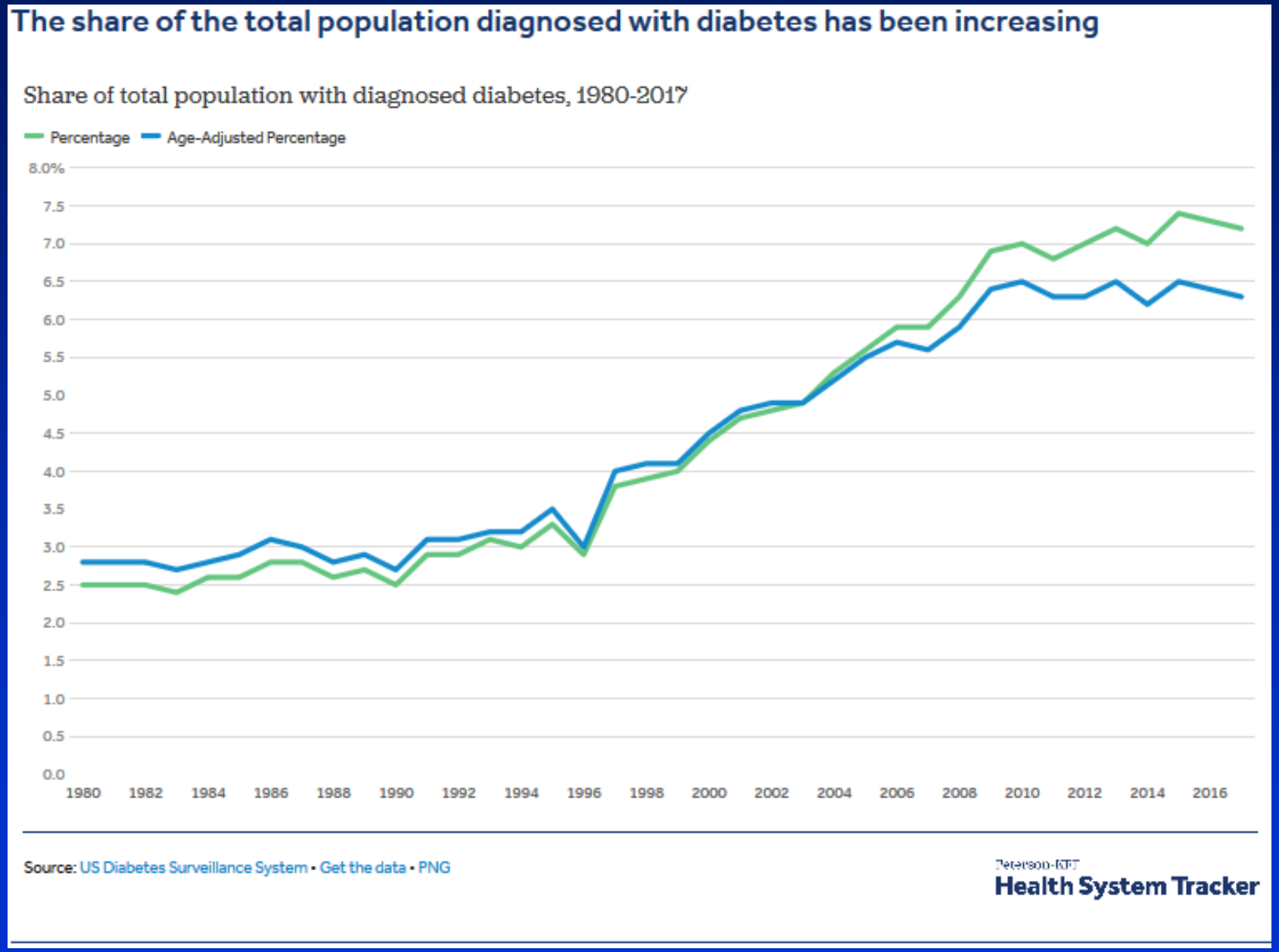
Chairman Division of Endocrinology and Metabolism
Philadelphia College of Osteopathic Medicine

Diabetes on the Rise in the U.S.

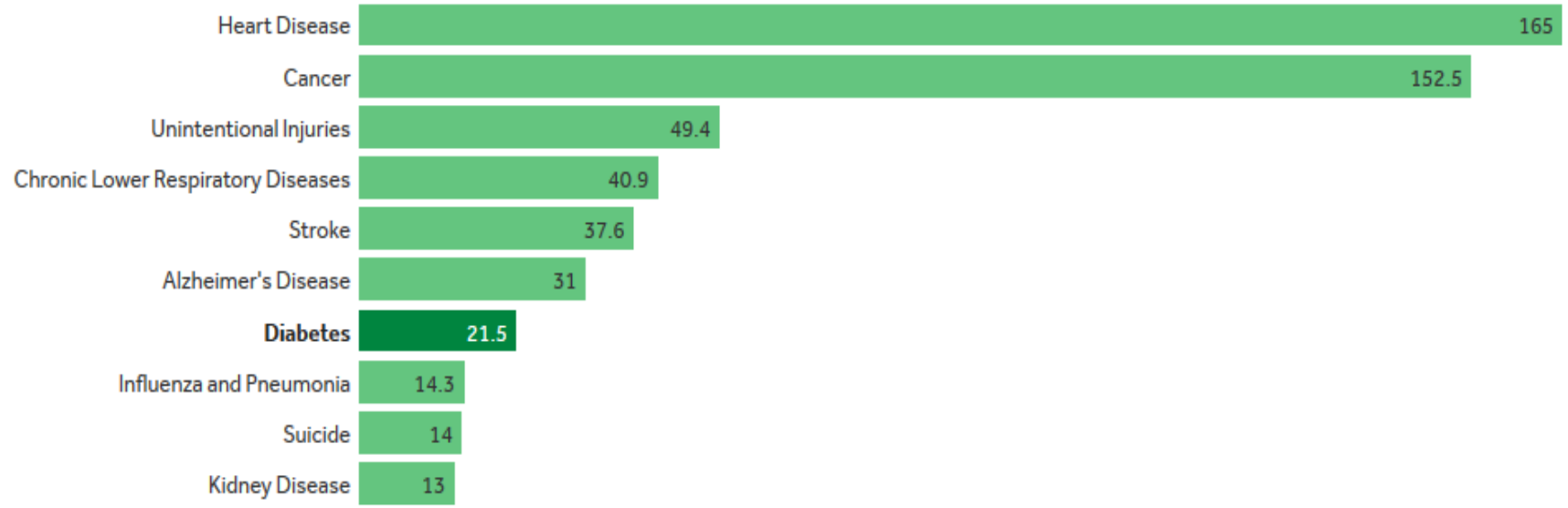


Top 10 Causes of Death in the U.S.

Prevalence and Mortality

Diabetes is the seventh leading cause of death in the United States

Age-adjusted death rates for the 10 leading causes of death per 100,000 population, 2017



Source: CDC WONDER • Get the data • PNG

Peterson-KFF
Health System Tracker

Case 1 T2DM

- 47 year old male assessed for T2DM control. DM x 6 years treated with metformin and sitagliptin. Current A1C 7.8 %.
- Hx hypertension, mixed hyperlipidemia,
- BMI 33, bp 132/84

eGFR 64, lytes normal, urine micro 28 lipids LDL C 76, TG 178, HDLC 42

Concerned about glycemic control and wt reduction.

- Recommendations?

Pharmacologic Therapy for Type 2 Diabetes (continued)

9.6 Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure. E

9.7 The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels ($300 mg/dL [16.7 mmol/L]) are very high. A

Pharmacologic Therapy for Type 2 Diabetes

.4a First-line therapy depends on comorbidities, patient-centered treatment factors, and management needs and generally includes metformin and comprehensive lifestyle modification. A

.4b **Other medications (glucagonlike peptide 1 receptor agonists, sodium–glucose cotransporter 2 inhibitors), with or without metformin based on glycemic needs, are appropriate initial therapy for individuals with type 2 diabetes with or at high risk for atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease (Fig. 9.3). A**

.5 Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. A

GLP-1 RA and SGLT-2i

A1C reduction

Primary initial role in T2DM management

Semiglutide weekly, dulaglutide, efpegenatide

tirzepatide

Semiglutide oral

SGLT-2i

canagliflozin,dapagliflozin,empagliflozin,sotogliflozin,

Comparison of glucose lowering with GLP-RA and SGLT-i

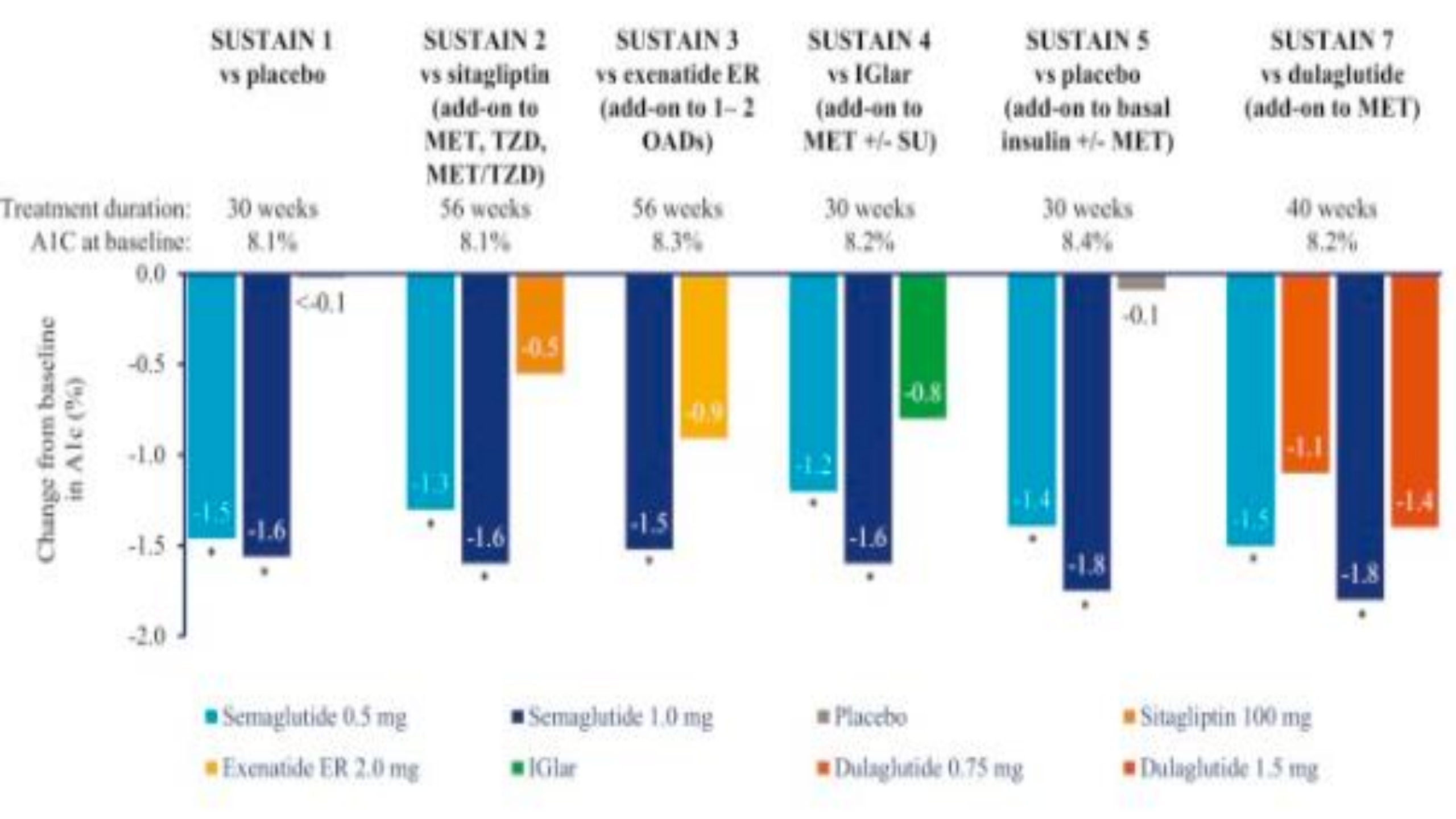
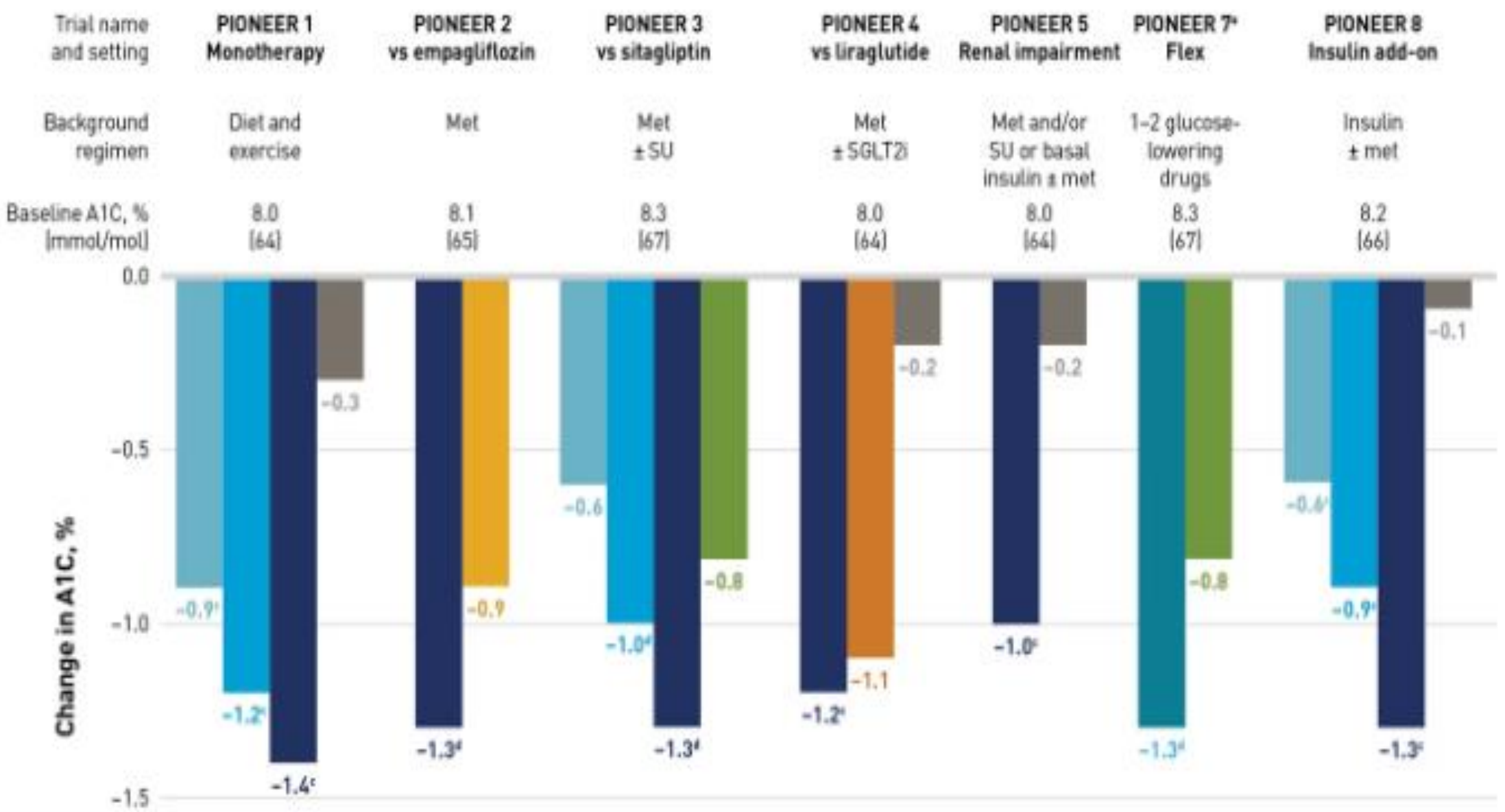
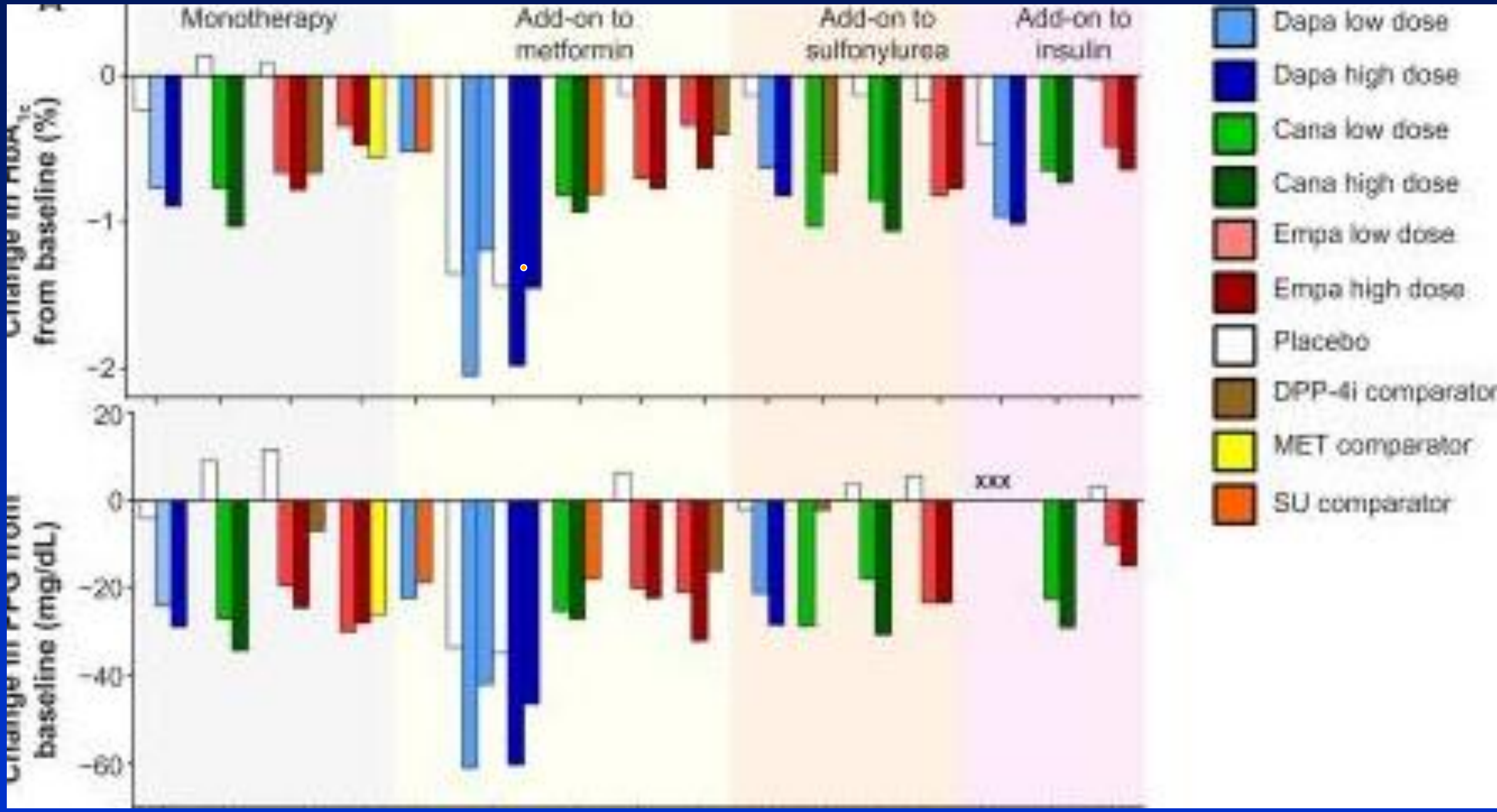

SUSTAIN 1
vs placebo
SUSTAIN 2
vs sitagliptin (add-on to MET, TZD, MET/TZD)
SUSTAIN 3
vs exenatide ER (add-on to 1– 2 OADs)
SUSTAIN 4
vs IGlar (add-on to MET +/- SU)
SUSTAIN 5
vs placebo (add-on to basal insulin +/- MET)
SUSTAIN 7
vs dulaglutide (add-on to MET)
Treatment duration: 30 weeks 56 weeks 56 weeks 30 weeks 30 weeks 40 weeks
A1C at baseline: 8.1% 8.1% 8.3% 8.2% 8.4% 8.2%
Change from baseline in A1c (%)
0.0
-0.5
-1.0
-1.5
-2.0
-1.5
-1.6
<-0.1
-1.3
-1.6
-0.5
-1.5
-0.9
-1.2
-1.6
-0.8
-1.4
-1.8
-0.1
-1.5
-1.1
-1.8
-1.4
*
Semaglutide 0.5 mg
Semaglutide 1.0 mg
Placebo
Sitagliptin 100 mg
Exenatide ER 2.0 mg
IGlar
Dulaglutide 0.75 mg
Dulaglutide 1.5 mg

FIGURE 2. Reduction in A1C Levels With Oral Semaglutide and Comparators at the Primary Analysis Time Point (26 Weeks, Except for PIONEER 7[a,b])[15-21]




Monotherapy
Add-on to metformin
Add-on to sulfonylurea
Add-on to insulin
0
−1
−2
from baseline (%)
20
0
−20
−40
−60
baseline (mg/dL)
xxx
Dapa low dose
Dapa high dose
Cana low dose
Cana high dose
Empa low dose
Empa high dose
Placebo
DPP-4i comparator
MET comparator
SU comparator

Outline

- Clinical trial results of GIP/GLP-1 coagonist, tirzepatide (SURPASS studies) in T2D
- Glycemic control
- Weight
- Cardiovascular risk factors
- Cardiovascular outcome studies

List of GIP/GLP-1 Receptor Coagonists

GIP/GLP-1 Receptor Coagonists	Phase
LY3298176 (tirzepatide)	Late phase III
NN9709	Discontinued
SAR438335	Discontinued
RG-7697	Discontinued
CPD-86	Preclinical
TAK-094	Preclinical
ZP-I-98	Preclinical

Tirzepatide: A Novel Dual GIP and GLP-1 Receptor Agonist

- **Molecular Attributes[1]**
  - Tirzepatide is a multifunctional peptide based on the native GIP peptide sequence, modified to bind to GIP or GLP-1 receptors
  - Tirzepatide is a 39–amino acid linear peptide and includes a C20 fatty diacid moiety
  - Tirzepatide has a mean half-life of ~5 days, enabling once-weekly dosing
  - Is in late phase III clinical trial program (SURPASS)[2-7]

* Participants had T2D with inadequate glycemic control on diet and exercise alone or on a stable dose of metformin monotherapy.

1. Coskun. Molecular Metab. 2018;18:3. 2. Rosenstock. Lancet. 2021;398:143. 3. Frias. NEJM. 2021;[Epub].
4. Ludvik. ADA 2021. Abstr 78-LB. 5. Lily news release. investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-achieves-all-primary-and-key-secondary-study. 6. Dahl. ADA 2021. Abstr 80-LB. 7. NCT04255433.

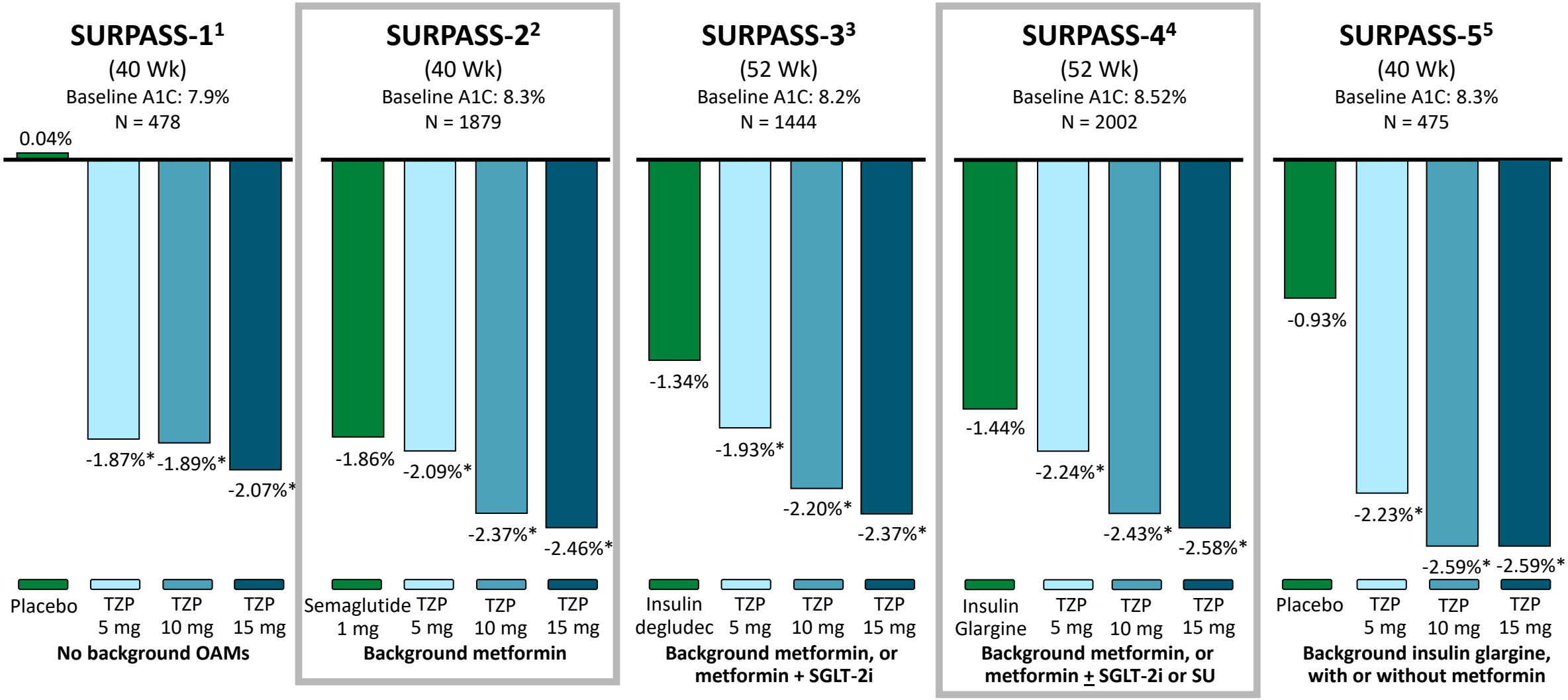
The NEW ENGLAND JOURNAL of MEDICINE

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*

SURPASS: Tirzepatide Reduces A1C in Type 2 Diabetes

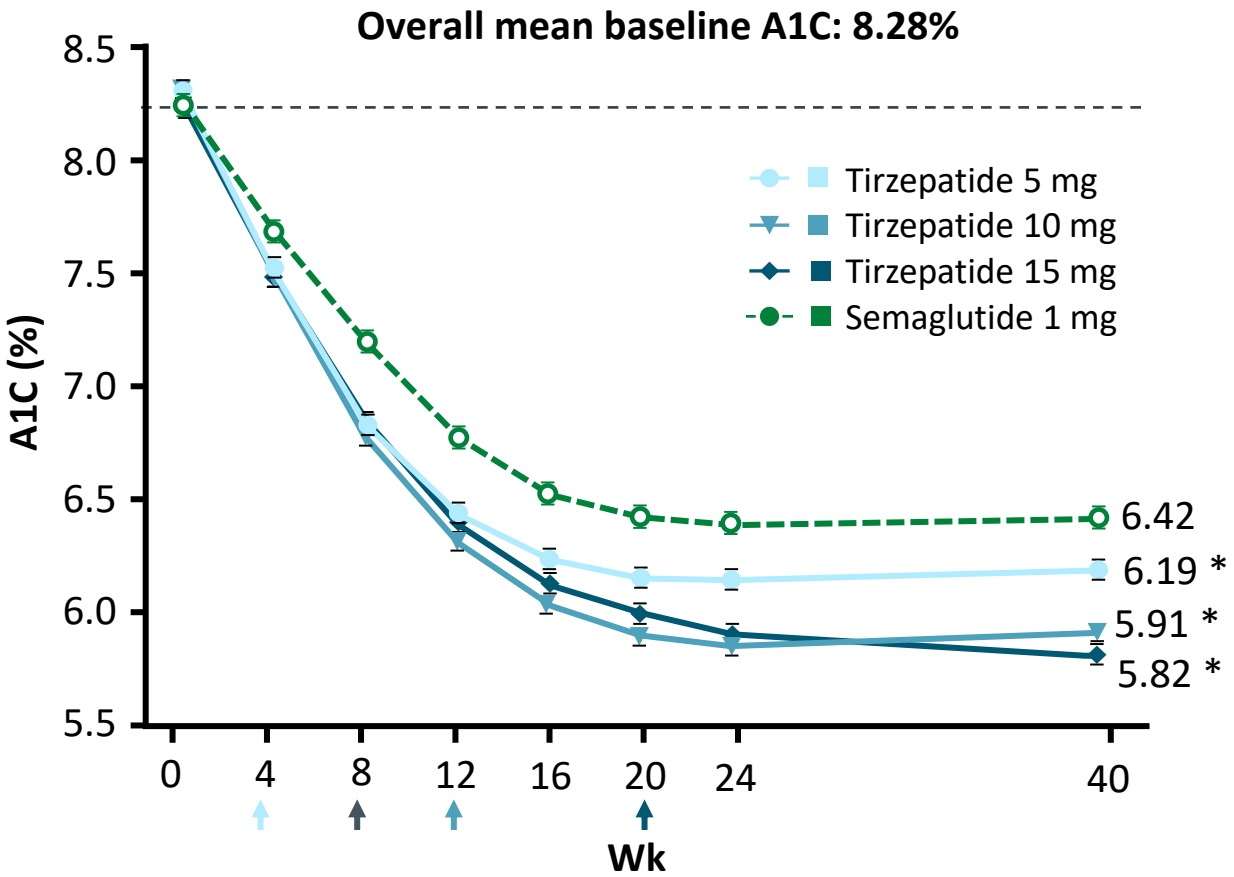


1. Rosenstock. Lancet. 2021;398:143. 2. Frias. NEJM. 2021;385:503. 3. Giorgino. ADA 2021. Abstr 78-LB. 4. Lily news release. investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-achieves-all-primary-and-key-secondary-study.
5. Dahl. ADA 2021. Abstr 80-LB.

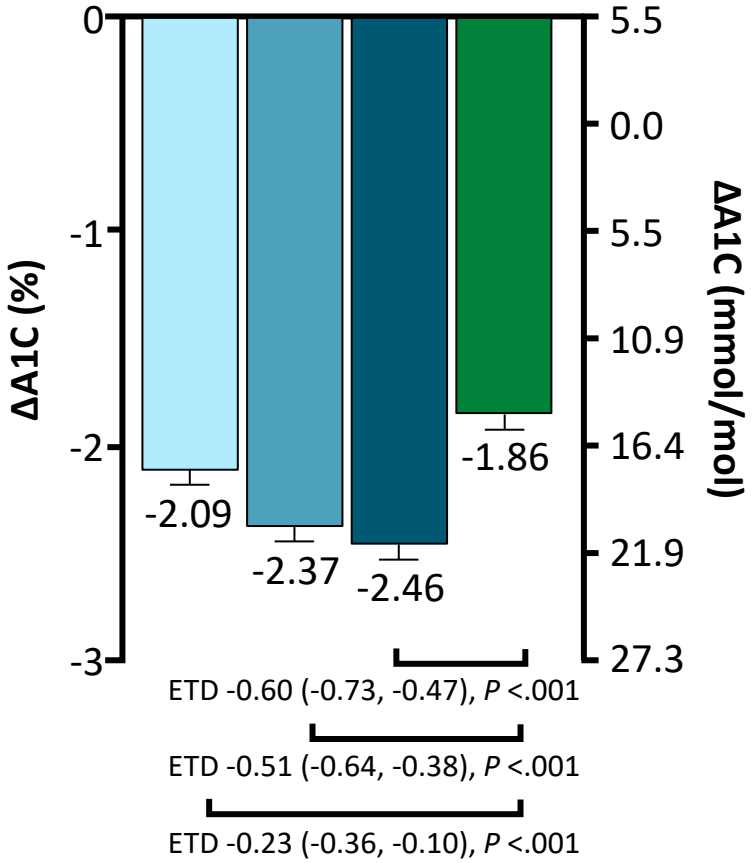
* Denotes statistical significance to comparator.

Slide credit: clinicaloptions.com

SURPASS-2: A1C Over Time and Change From Baseline at 40 Wk



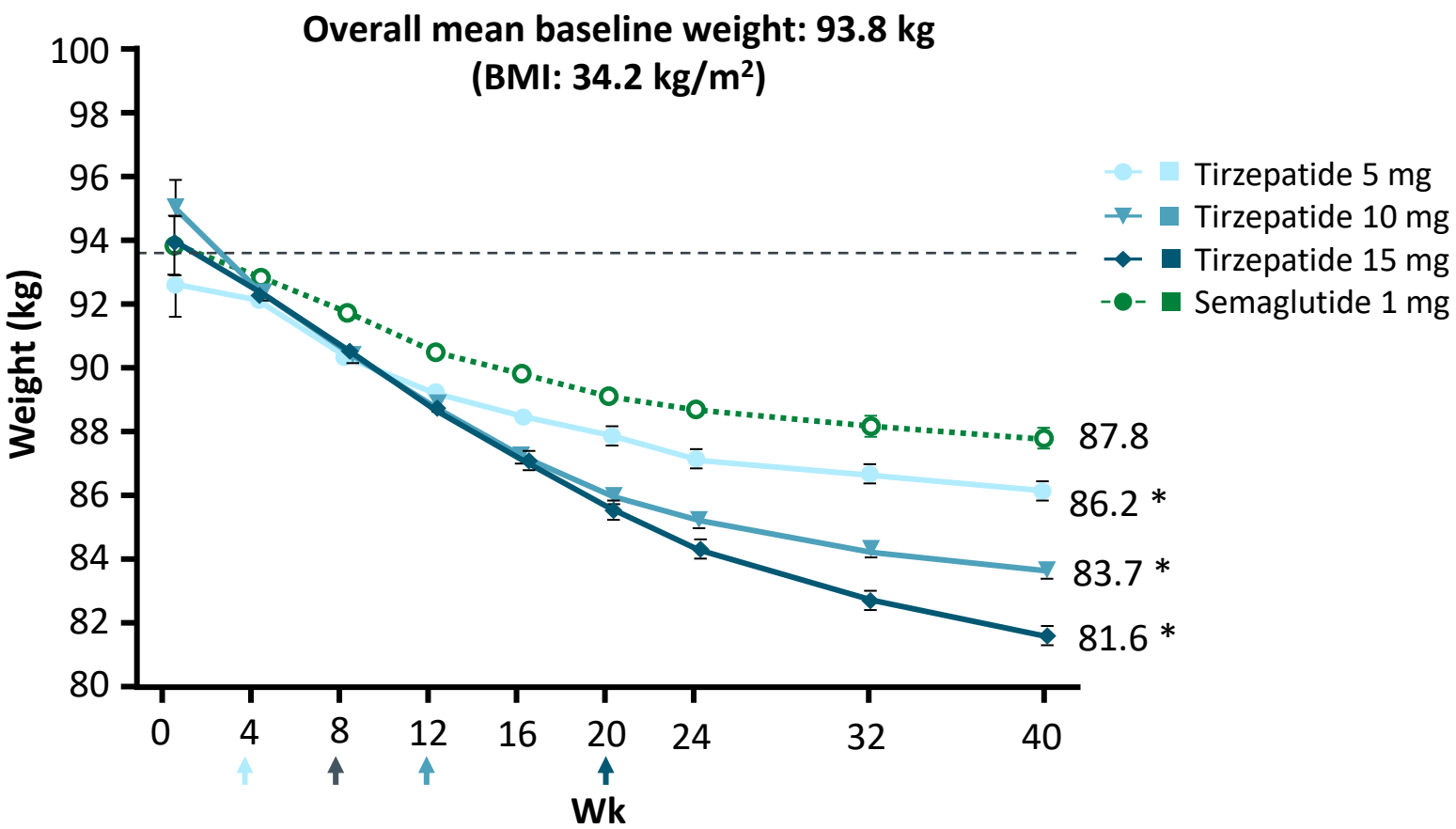
Arrows indicate when the maintenance dose of tirzepatide 5 mg, 10 mg, and 15 mg and semaglutide 1 mg is achieved. **P* <.001 vs semaglutide 1 mg.

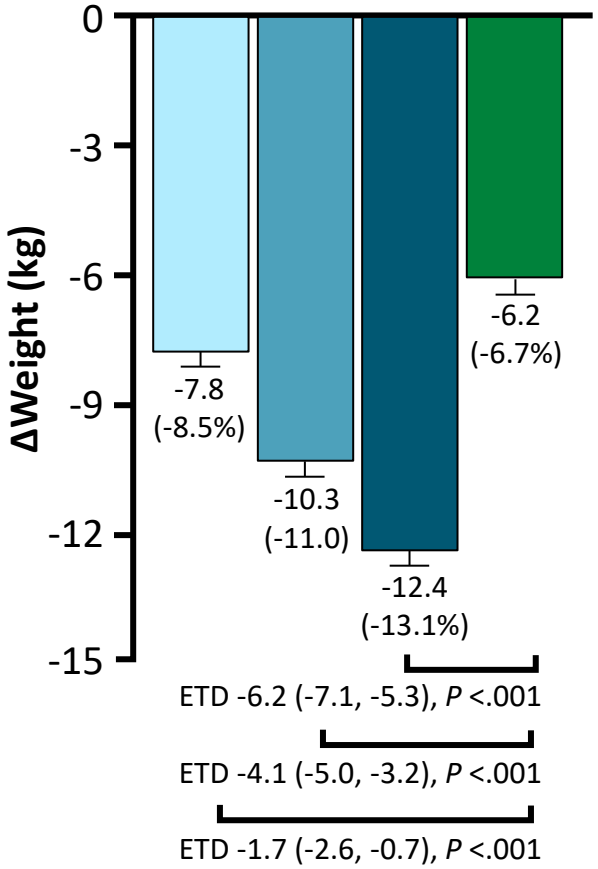


Frias. NEJM. 2021;385:503. Frias. ADA 2021. Abstr 84-LB.

Slide credit: clinicaloptions.com

SURPASS-2: Body Weight Over Time and Change From Baseline at 40 Wk





Arrows indicate when the maintenance dose of tirzepatide 5 mg, 10 mg, and 15 mg and semaglutide 1 mg is achieved. *P <.001 vs semaglutide 1 mg.

Frias. ADA 2021. Abstr 84-LB. Frias. NEJM. 2021;385:503.

Slide credit: clinicaloptions.com

SURPASS-2: Treatment Discontinuations

Parameter	TZP 5 mg (N = 470)	TZP 10 mg (N = 469)	TZP 15 mg (N = 470)	SEMA 1 mg (N = 469)	Overall *P* Value
Permanent discontinuation from study drug, n (%)	39 (8.3)	58 (12.4)	62 (13.2)	41 (8.7)	.027
Adverse event*	28 (6.0)	40 (8.5)	40 (8.5)	19 (4.1)	.012
Death	4 (0.9)	4 (0.9)	4 (0.9)	1 (0.2)	.567
Failure to meet randomization criteria	0	0	1 (0.2)	1 (0.2)	.624
Lost to follow-up	4 (0.8)	4 (0.9)	8 (1.7)	9 (1.9)	.318
Physician decision	0	3 (0.6)	0	2 (0.4)	.081
Protocol deviation	0	1 (0.2)	0	1 (0.2)	.374
Withdrawal by subject	6 (1.3)	7 (1.5)	7 (1.5)	7 (1.5)	.980
Pregnancy	1 (0.2)	0	1 (0.2)	1 (0.2)	1.000
Other	0	3 (0.6)	5 (1.1)	1 (0.2)	.060

Frias. ADA 2021. Abstr 84-LB. Frias. NEJM. 2021;385:503.

*Deaths also included as discontinuations due to AE.

Slide credit: clinicaloptions.com

SURPASS-2: Effects on Cardiovascular Risk Factors

Mean Change From Baseline	TZP 5 mg (N = 470)	TZP 10 mg (N = 469)	TZP 15 mg (N = 470)	SEMA 1 mg (N = 469)
A1C, %	-2.01	-2.24	-2.3	-1.86
Weight, kg	-7.6	-9.3	-11.2	-5.7
LDL, %	-7.7	-5.8	-5.2	-6.1
HDL, %	+6.8	+7.9	+7.1	+4.4
TG, %	-19.0	-24.1	-24.8	-11.5
SBP/DBP, mm Hg	-4.8/-1.9	-5.3/-2.5	-6.5/-2.9	-3.6/-1.0

- Both semaglutide and dulaglutide have FDA indication for reduction of 3-point MACE in people with T2D and CVD

Dulaglutide PI. Frias. NEJM. 2021;385:503. Semaglutide PI.

Slide credit: clinicaloptions.com

Summary

- In the phase III studies, treatment with tirzepatide demonstrates greater reduction in A1C vs semaglutide 1 mg, degludec, and glargine
- Similarly, treatment with tirzepatide is associated with greater reduction in body weight
- Compared with semaglutide 1 mg, treatment with tirzepatide is associated with greater reduction in cardiovascular risk factors of A1C, weight, BP, and greater improvements in TG and HDL-C
- Reductions in LDL-C were significant, but similar to semaglutide 1 mg
- Gastrointestinal side effects were similar to GLP-1 RA, but were numerically greater with tirzepatide compared with semaglutide 1 mg

What about weight loss in this patient

Not approved for weight loss

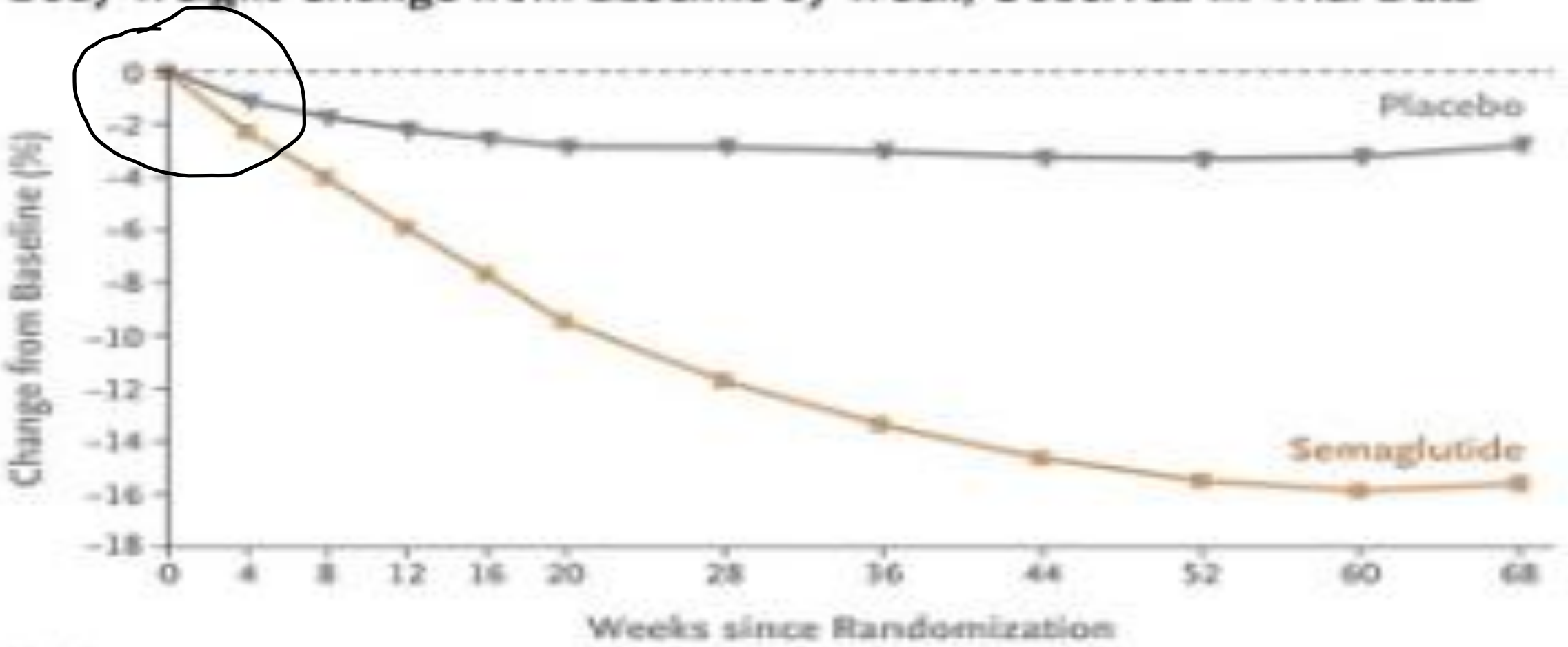
- Semaglutide (Ozempic) not approved for weight loss across all studies 15-18 % over study period
- Dulaglutide (Trulicity): not approved for weight loss across all studies 4.5 mg dose as much as 10 pounds over study period
- Oral semaglutide (Rybelsus) not approved for weight loss may lose 5-10 pounds over study period.
- Empagliflozin not approved for weight loss one study 2-3 percent body weight in 24 weeks.
- Dapagliflozin not approved for weight loss may lose 7 pounds in 24 weeks.

RESEARCH SUMMARY

Once-Weekly Semaglutide in Adults with Overweight or Obesity

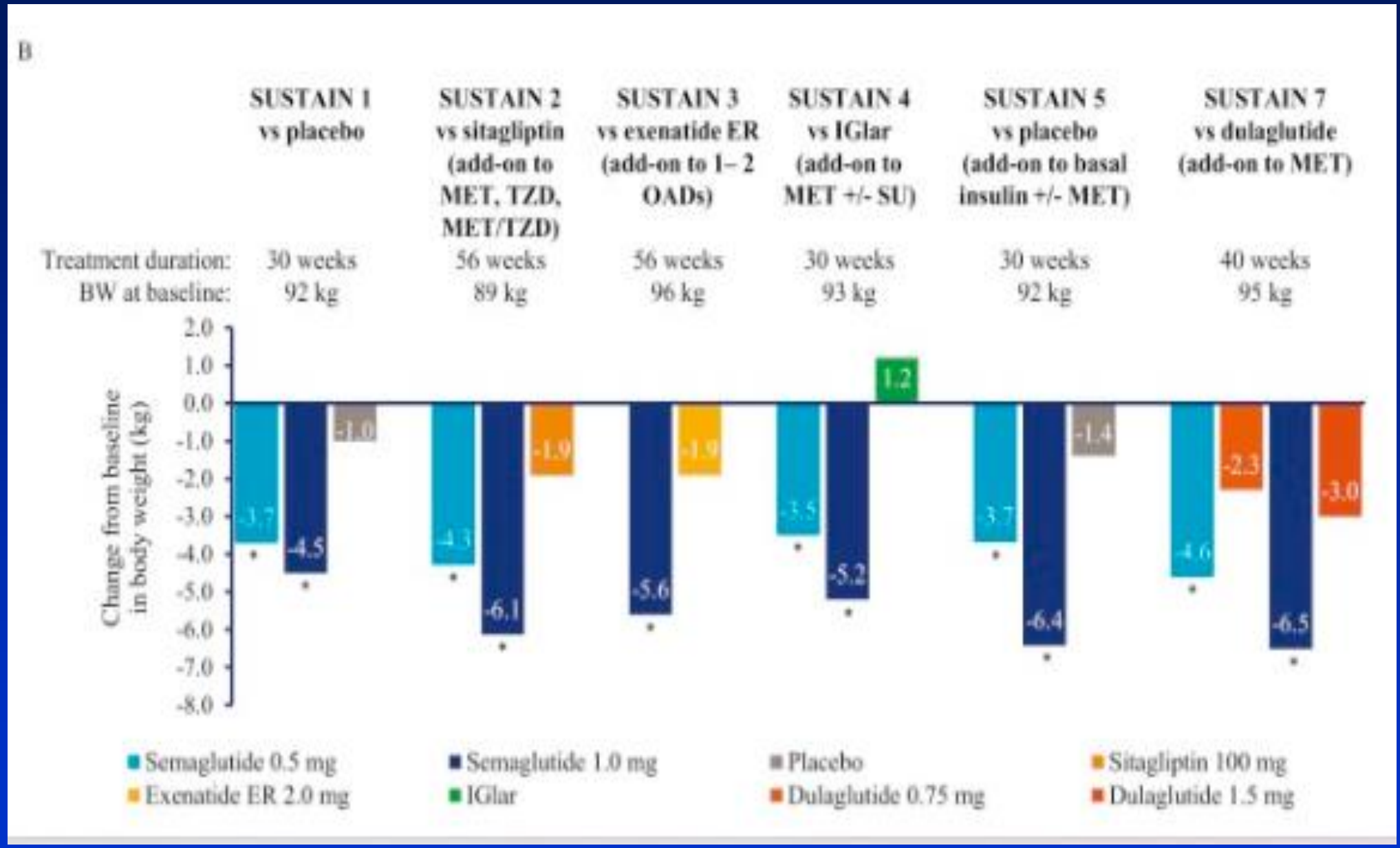
Wilding JPH. et al. DOI: 10.1056/NEJMoa2032183

Body Weight Change from Baseline by Week, Observed In-Trial Data



No. at Risk

Placebo	655	649	641	619	615	603	592	571	554	549	540	577
Semaglutide	1306	1290	1281	1262	1252	1248	1232	1228	1207	1203	1190	1212


B
SUSTAIN 1 vs placebo
SUSTAIN 2 vs sitagliptin (add-on to MET, TZD, MET/TZD)
SUSTAIN 3 vs exenatide ER (add-on to 1– 2 OADs)
SUSTAIN 4 vs IGlar (add-on to MET +/- SU)
SUSTAIN 5 vs placebo (add-on to basal insulin +/- MET)
SUSTAIN 7 vs dulaglutide (add-on to MET)
Treatment duration: 30 weeks 56 weeks 56 weeks 30 weeks 30 weeks 40 weeks
BW at baseline: 92 kg 89 kg 96 kg 93 kg 92 kg 95 kg
Change from baseline in body weight (kg)
2.0
1.0
0.0
-1.0
-2.0
-3.0
-4.0
-5.0
-6.0
-7.0
-8.0
-3.7
-4.5
-1.0
-4.3
-6.1
-1.9
-5.6
-1.9
1.2
-3.5
-5.2
-3.7
-6.4
-1.4
-4.6
-2.3
-6.5
-3.0
Semaglutide 0.5 mg
Semaglutide 1.0 mg
Placebo
Sitagliptin 100 mg
Exenatide ER 2.0 mg
IGlar
Dulaglutide 0.75 mg
Dulaglutide 1.5 mg

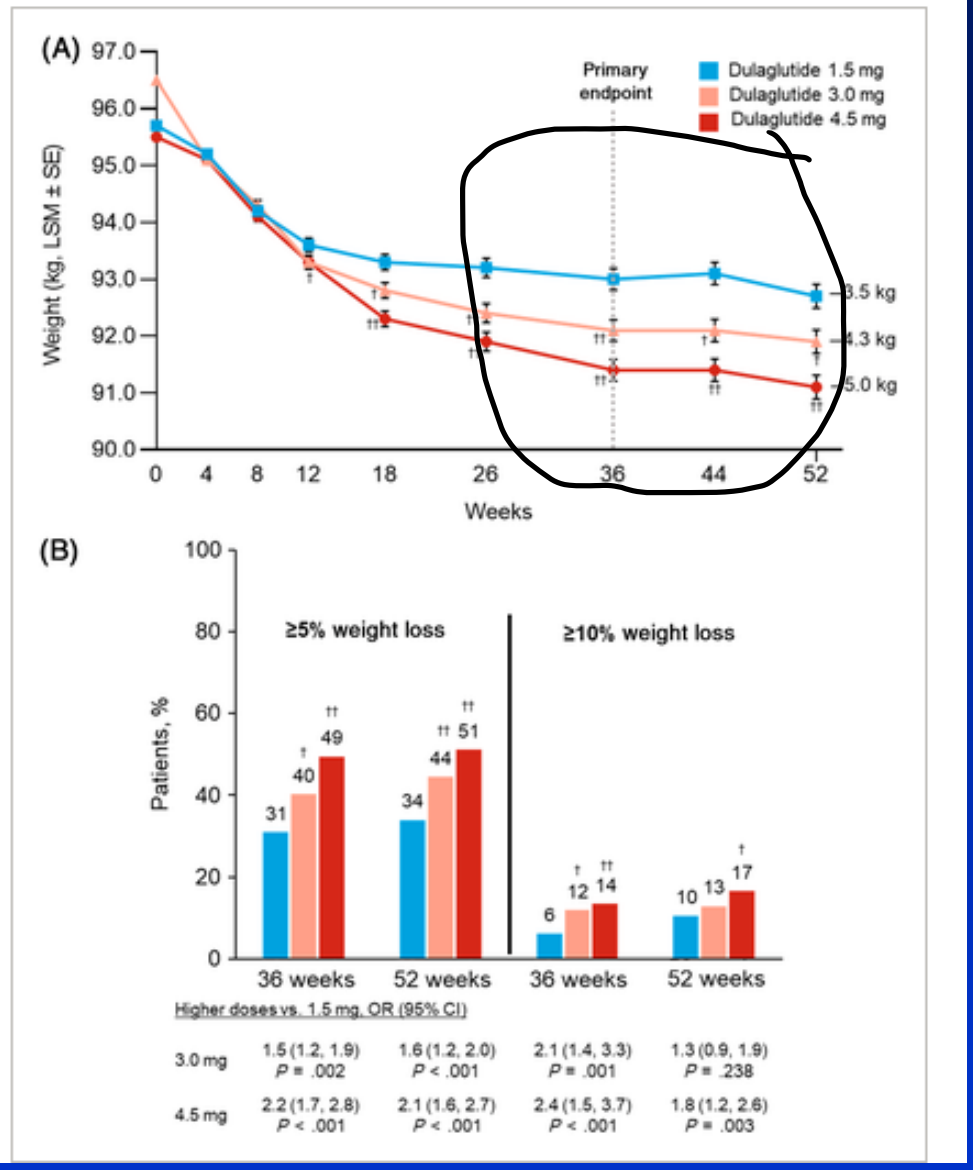
Sustain Forte

- Type 2 DM Met with/without SU
- 961 participants semiglutide 1.0 vs 2.0 mg
- A1C changd 2.2% vs 1.9% 2.0 vs 1.0 mg
- Wt loss 6.9 vs 6.0 kg

Effect of dulaglutide 3.0 and 4.5 mg on weight in patients with type 2 diabetes: Exploratory analyses of AWARD-11

Enzo Bonora MD, Juan P. Frias MD, Francisco J. Tinahones MD, Joanna Van DO, Raleigh E. Malik PhD, Zhuoxin Yu PhD, Reema Mody PhD, Angelyn Bethel MD, Anita Y. M. Kwan MSc, David A. Cox PhD

First published: 29 June 2021 | https://doi.org/10.1111/dom.14465 | Citations: 1



Phase III SURMOUNT Studies: Tirzepatide for Weight Loss

- SURMOUNT-1 and -2: persons with type 2 diabetes with obesity or BMI >27 kg/m^2, with comorbidities
- SURMOUNT-3 and -4: persons with obesity
- Anticipated completion in 2023

NCT04184622. NCT04657003. NCT04657016. NCT04660643.

ORIGINAL ARTICLE FREE PREVIEW

Tirzepatide Once Weekly for the Treatment of Obesity

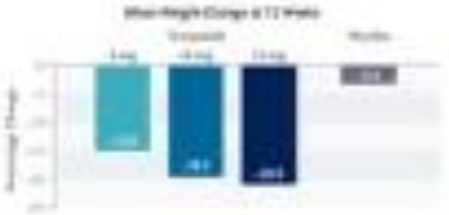
Ania M. Jastreboff, M.D., Ph.D., Louis J. Aronne, M.D., Nadia N. Ahmad, M.D., M.P.H., Sean Wharton, M.D., Pharm.D., Lisa Connery, M.D., Breno Alves, M.D., Arihiro Kiyosue, M.D., Ph.D., Shuyu Zhang, M.S., Bing Liu, Ph.D., Mathijs C. Bunck, M.D., Ph.D., and Adam Stefanski, M.D., Ph.D. for the SURMOUNT-1 Investigators*

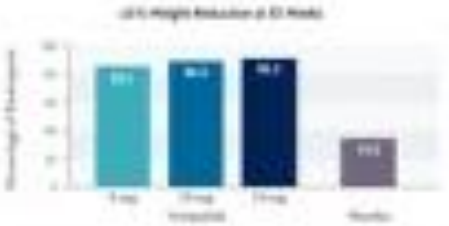
Press release

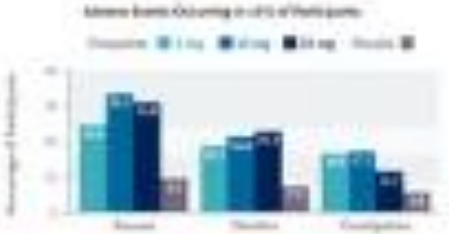
SURMOUNT-1 Study Finds Individuals with Obesity Lost up to 22.5% of their Body Weight when Taking Tirzepatide

June 04, 2022 | New Orleans, Louisiana

Tirzepatide Once Weekly for the Treatment of Obesity







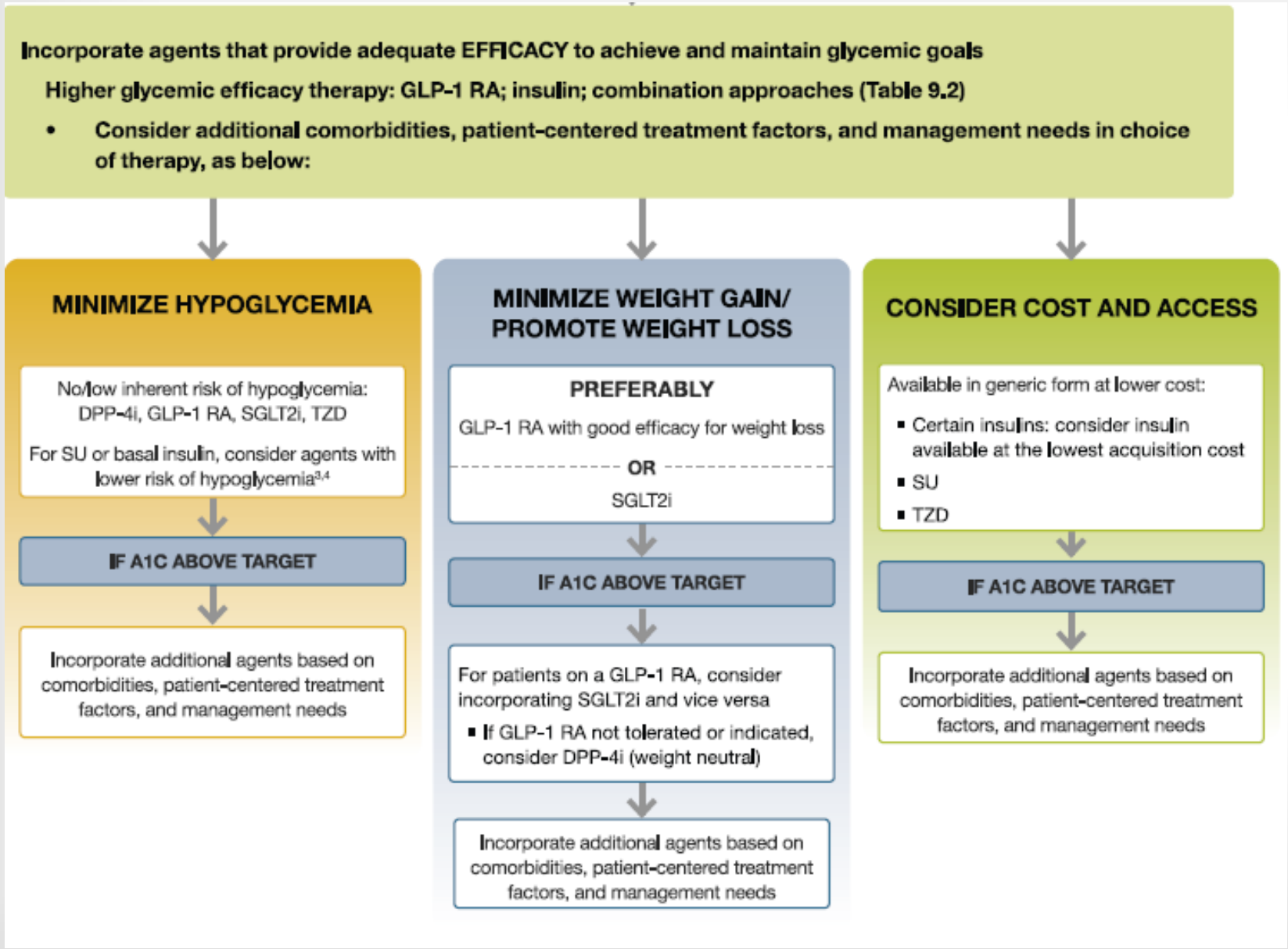
CONCLUSIONS

In these trials of once-weekly subcutaneous tirzepatide, [illegible] and sustained weight reduction occurred in obese adults who did not have diabetes.

Approved for Weight loss

- Phentermine 7.5% wt loss
- Bariatric surgery 25-30% body weight.
- Liraglutide (3.0 mg) 60% of individuals lost >5% BW 33% of individuals lost >10 % BW
- Semaglutide (Wegovy) 14.9% wt loss in 68 weeks

PHARMACOLOGIC APPROACHES TO GLYCEMIC TREATMENT



Glucose-lowering Medication in Type 2 Diabetes: 2021 ADA Professional Practice Committee (PPC) adaptation of Davies et al. and Buse et al.

Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2022*. *Diabetes Care* 2022;45(Suppl. 1):S125-S143

American Diabetes Association.
Connected for Life

Pitfall Case 2

- 45 y/o male scheduled for CABG. T2DM A1C 7.2 %
- Meds empagliflozin 25 mg daily, lisinopril 20 mg daily, atorvastatin 40 mg daily

- Cautions or concerns with SGLT-I and surgery?

Chacko B et al. Postoperative euglycaemic diabetic ketoacidosis associated with SGLT-2 i Anaesth Intensive Care. 2018;215-9.

- Discontinue Empa, Cana, Dapa 3 days prior to surgery. Steglatro 4 days prior. Overall perioperative management of SGLT-2i on a case by case basis

Case 3 CV T2DM

- 54 year old female evaluated for Type 2 DM control.
- DM x 12 years current treatment metformin 1500 mg per day and sitagliptin 50 mg per day
- Hx CAD, hypertension, mixed hyperlipidemia, CKD 3A, and obesity

- Other meds lisinopril 10 mg daily, rosuvastatin 10 mg daily, ASA 81 mg daily, and metoprolol 25 mg daily
- BMI 32 BP 132/78 exam normal
- **A1C 6.6 %** Lipids TG 138, LDLC 72, HDL C 38

Pitfall To stop here!

- Is it time to rest?
- Is there anything to do to reduce CV CKD risk ?
- Lots of choices!!

Cardiovascular Outcomes Trials for DPP-4 Inhibitors

				Primary Endpoint	Hazard Ratio
SAVOR-TIMI 53[1]	**CVD or CRFs** **A1c 6.5–12.0%** n=16,492	**Saxagliptin**	**Median follow-up** 2.1 years	CV death, nonfatal MI, or nonfatal stroke	1.00 (95% CI 0.89, 1.12) p=0.99
EXAMINE[2]	**ACS** **A1c 6.5–11.0%** n=5,380	**Alogliptin**	**Median follow-up** 1.5 years	CV death, nonfatal MI, or nonfatal stroke	0.96 (upper boundary of 1-sided repeated CI 1.16) p=0.315
TECOS[3]	**CVD** **A1c 6.5–8.0%** n=14,735	**Sitagliptin**	**Median follow-up** **3 years**	CV death, nonfatal MI, or nonfatal stroke, or UA requiring hospitalization	0.98 (95% CI 0.88, 1.09) p=0.645 (superiority)

FARXIGA is a sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated in adults for:

Type 2 Diabetes Mellitus:

- as an adjunct to diet and exercise to improve glycemic control. (1.1)
- to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors. (1.1)

Heart Failure:

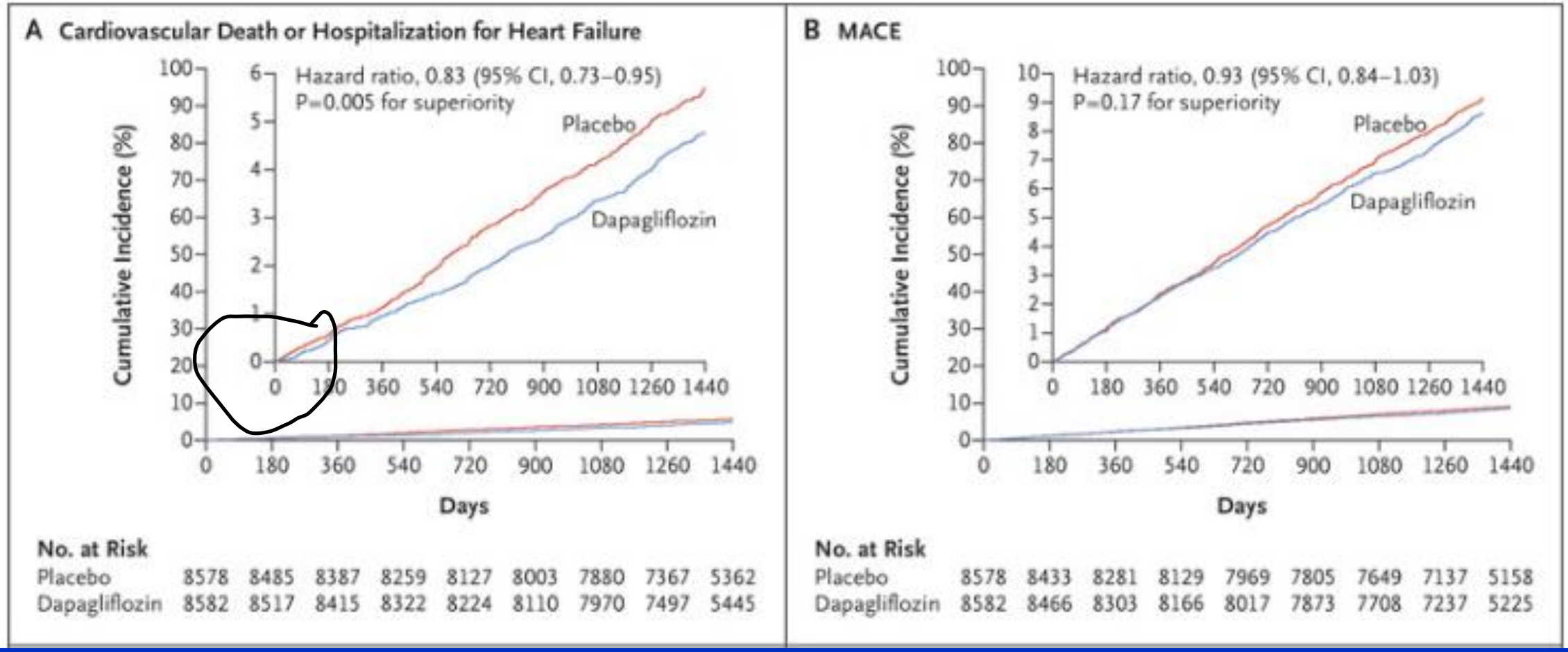
- to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA class II-IV). (1.2)

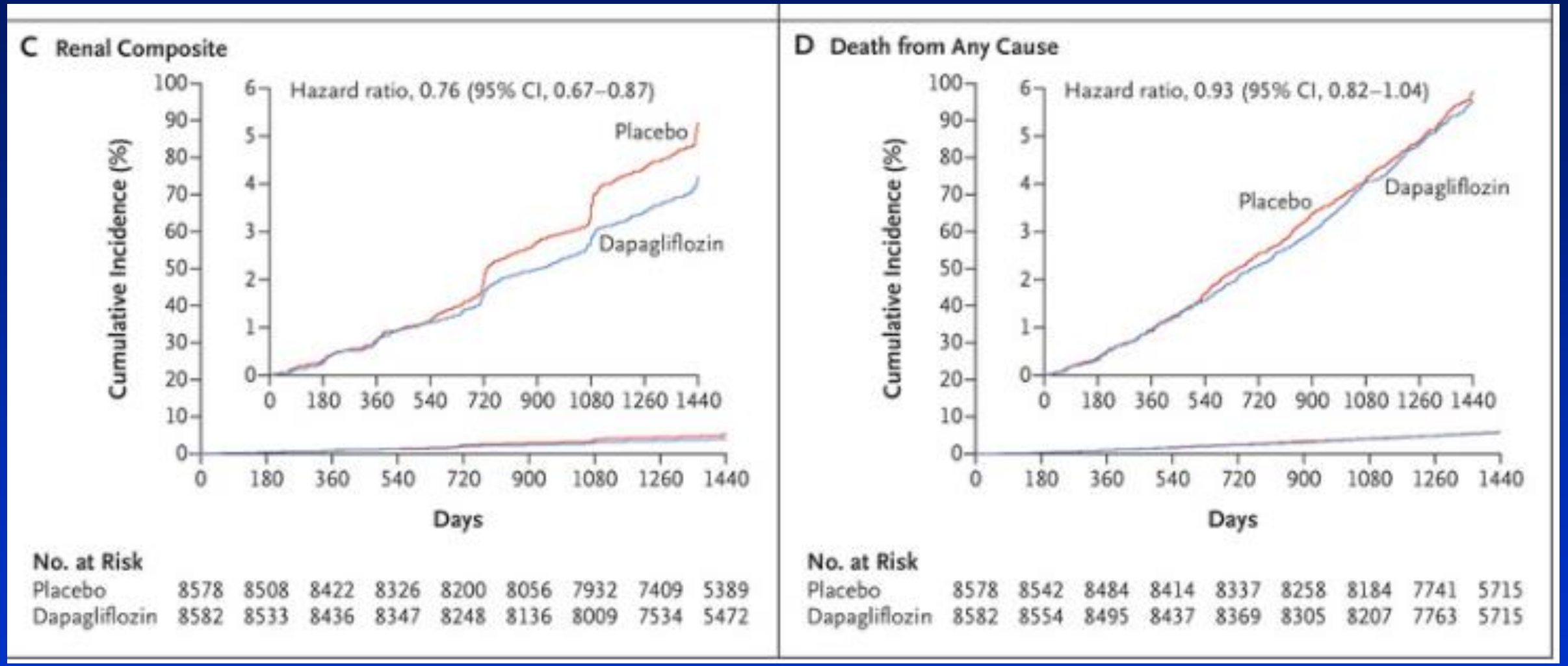
ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

Stephen D. Wiviott, M.D., Itamar Raz, M.D., Marc P. Bonaca, M.D., M.P.H., Ofri Mosenzon, M.D., Eri T. Kato, M.D., M.P.H., Ph.D., Avivit Cahn, M.D., Michael G. Silverman, M.D., M.P.H., Thomas A. Zelniker, M.D., Julia F. Kuder, M.A., Sabina A. Murphy, M.P.H., Deepak L. Bhatt, M.D., M.P.H., Lawrence A. Leiter, M.D., et al., for the DECLARE–TIMI 58 Investigators*

Figure 1. Major Cardiovascular and Renal Outcomes and Death from Any Cause.




C Renal Composite
Hazard ratio, 0.76 (95% CI, 0.67–0.87)
Placebo
Dapagliflozin
Cumulative Incidence (%)
Days
No. at Risk
Placebo 8578 8508 8422 8326 8200 8056 7932 7409 5389
Dapagliflozin 8582 8533 8436 8347 8248 8136 8009 7534 5472
D Death from Any Cause
Hazard ratio, 0.93 (95% CI, 0.82–1.04)
Placebo
Dapagliflozin
Cumulative Incidence (%)
Days
No. at Risk
Placebo 8578 8542 8484 8414 8337 8258 8184 7741 5715
Dapagliflozin 8582 8554 8495 8437 8369 8305 8207 7763 5715

Dapa-Preserved HF

- Improve CHF symptoms with HFpEF

Dapagliflozin And Prevention of Adverse-outcomes in CKD (DAPA-CKD)

Analysis of patients with and without cardiovascular disease at baseline

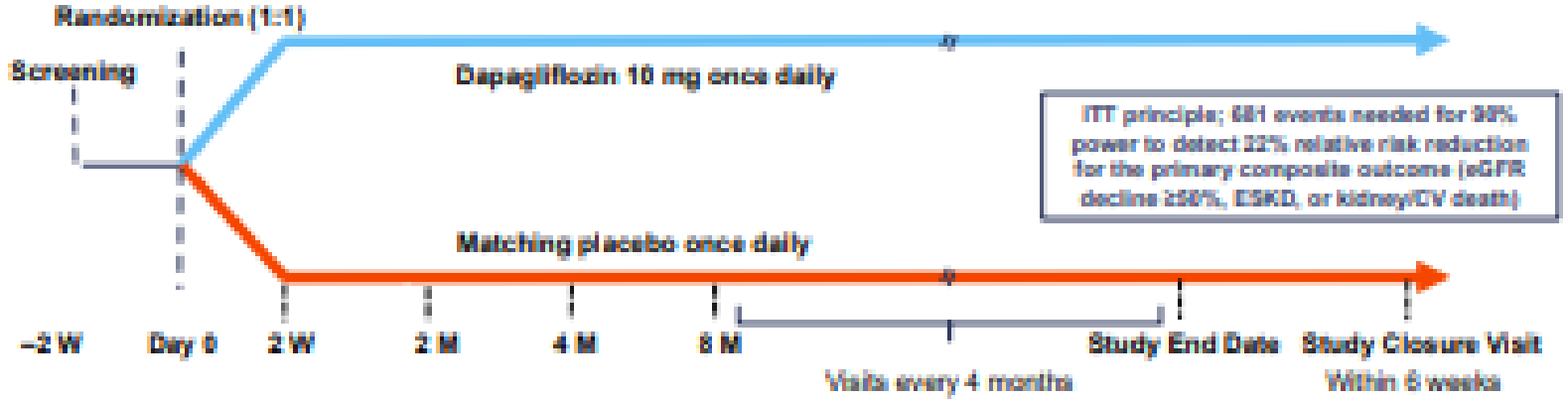
DAPA-CKD: Trial design

Conducted 2 Feb. 2017 to 12 June 2020*; 21 countries, 386 sites, 4304 participants; median follow-up 2.4 years.

**DMC recommended stopping early for efficacy 26 March 2020*

Key inclusion criteria:
- ≥18 years of age
- eGFR 25 to 75 mL/min/1.73m²
- UACR 200 to 5000 mg/g (22.6 to 565 mg/mmol)
- Stable maximum tolerated labelled dose of ACEi or ARB for ≥4 weeks (if not contraindicated)

Key exclusion criteria:
- Type 1 diabetes
- Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis
- Immunosuppressive therapy within 6 months prior to enrollment

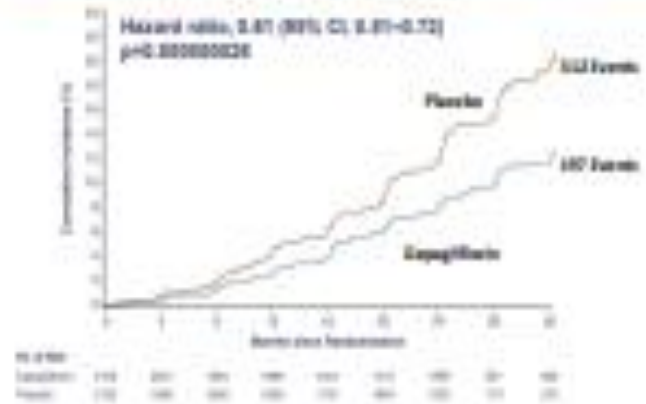


Outcome analyses based on Cox proportional hazard model stratified by type 2 diabetes and UACR and adjusted for eGFR

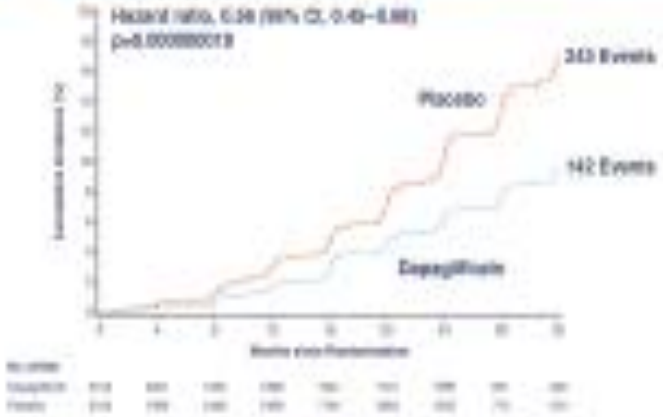
ANCA, anti-neutrophil cytoplasmic antibody; ITT, intention-to-treat; UACR, urinary albumin-to-creatinine ratio.

DAPA-CKD: Primary and secondary outcomes

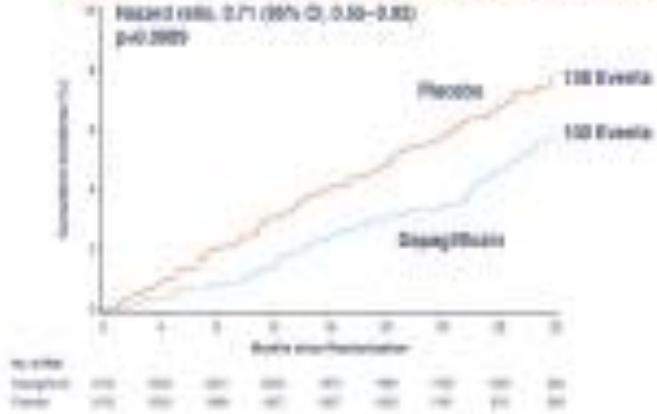
Primary outcome: eGFR decline ≥50%, ESKD, or kidney/CV death



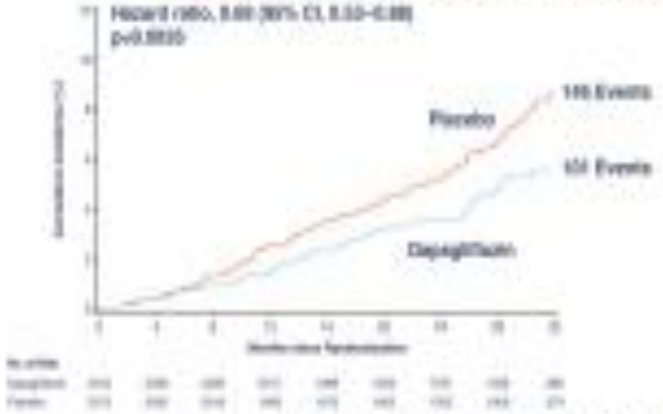
Secondary outcome: eGFR decline ≥50%, ESKD, or kidney death



Secondary outcome: CV death or HF hospitalization



Secondary outcome: All-cause mortality



Heerspink HJL, et al. N Engl J Med 2020;383:1436-1446

DAPA-CKD: Summary and conclusions

- In patients with CKD, with and without type 2 diabetes (T2D), dapagliflozin compared to placebo:
  - Reduced the risk of kidney failure
  - Reduced the risk of death from CV causes or hospitalization for HF
  - Prolonged survival
- **The benefits of dapagliflozin in CKD patients (with and without T2D) were consistent in those with and without cardiovascular disease**
- The results of DAPA-CKD are consistent with those of DAPA-HF
- In DAPA-CKD, dapagliflozin was well tolerated, in keeping with its established safety profile, with a similar picture to that observed in DAPA-HF

Expanded 4/30/21

- Reduce the risk of adverse kidney and CVD outcomes in patients with CKD who are at risk of progression

JARDIANCE is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)
- to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. (1)
- to reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure and reduced ejection fraction. (1)

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

This article was published on September 17, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1504720

2015.11.11

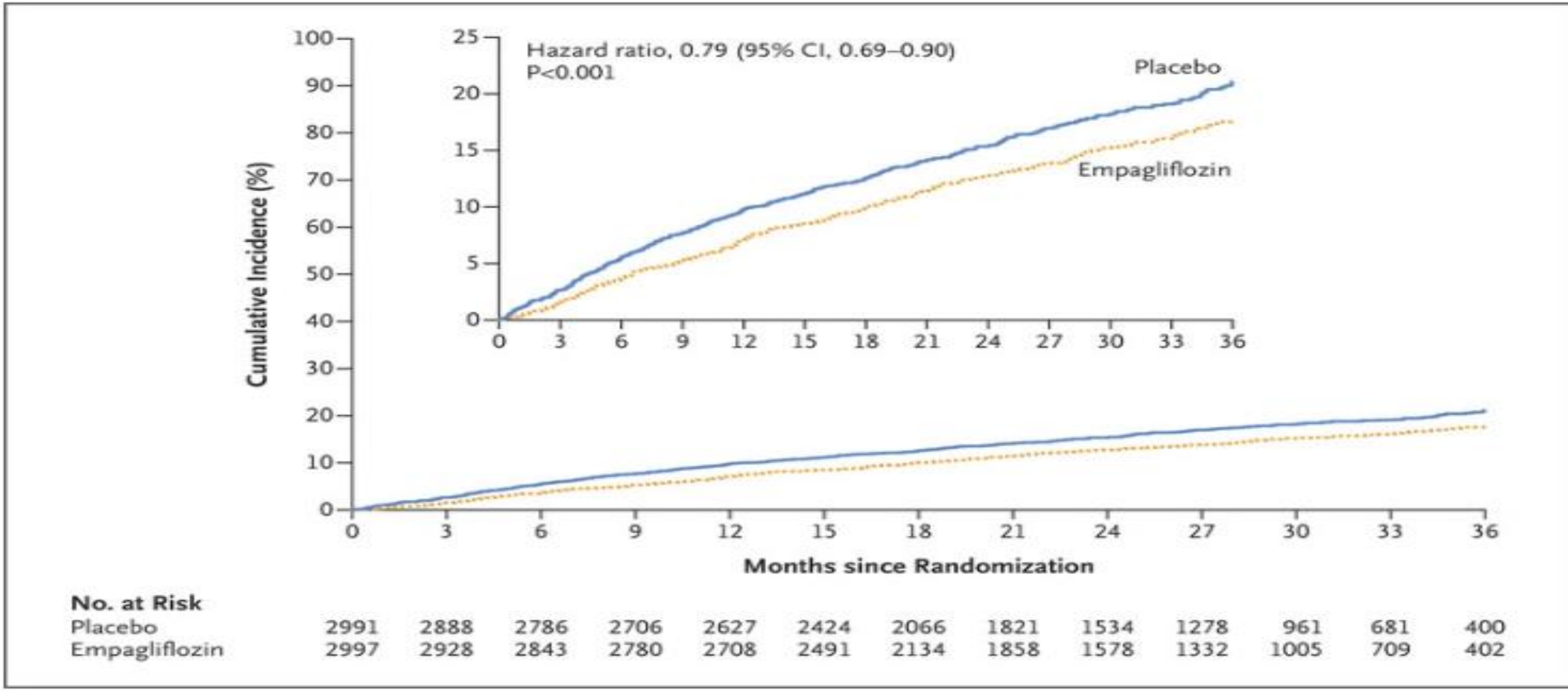
The primary outcome

- A composite of death from cardiovascular causes, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke.

The secondary outcome

- Primary outcome + Hospitalization for unstable angina.

Figure 1. Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.



The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis.

ADDITIONAL STUDIES

ORIGINAL ARTICLE FREE PREVIEW

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Stefan D. Anker, M.D., Ph.D., Javed Butler, M.D., Gerasimos Filippatos, M.D., Ph.D., João P. Ferreira, M.D., Edimar Bocchi, M.D., Michael Böhm, M.D., Ph.D., Hans-Peter Brunner–La Rocca, M.D., Dong-Ju Choi, M.D., Vijay Chopra, M.D., Eduardo Chuquiure-Valenzuela, M.D., Nadia Giannetti, M.D., Juan Esteban Gomez-Mesa, M.D., et al., for the EMPEROR-Preserved Trial Investigators*

US FDA approves Jardiance® (empagliflozin) to treat adults living with heart failure with reduced ejection fraction

- *New treatment options are critical, as approximately half of all people with heart failure die within five years of diagnosis*
- *Heart failure accounts for more than one million hospitalizations a year in the U.S.*

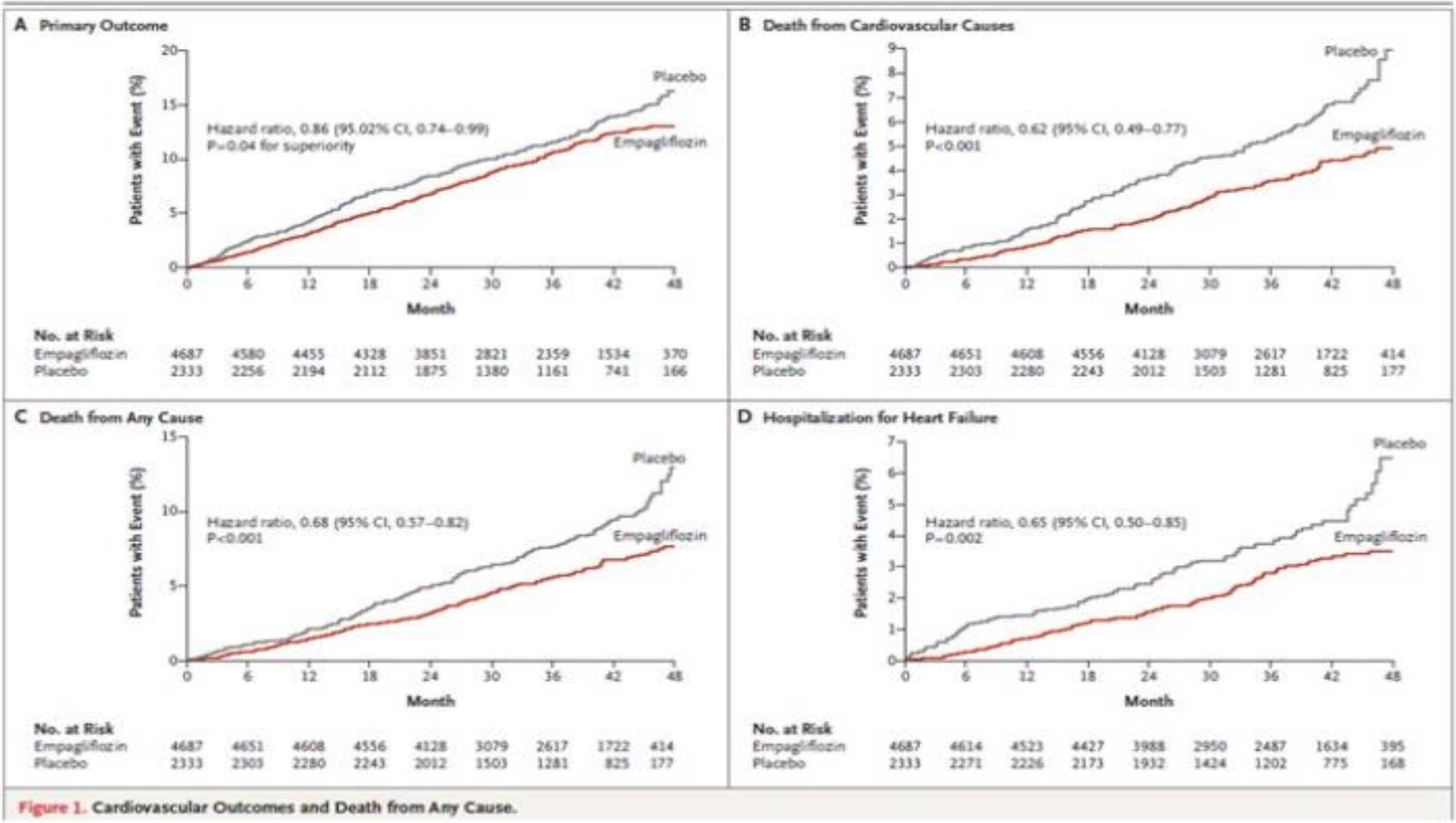
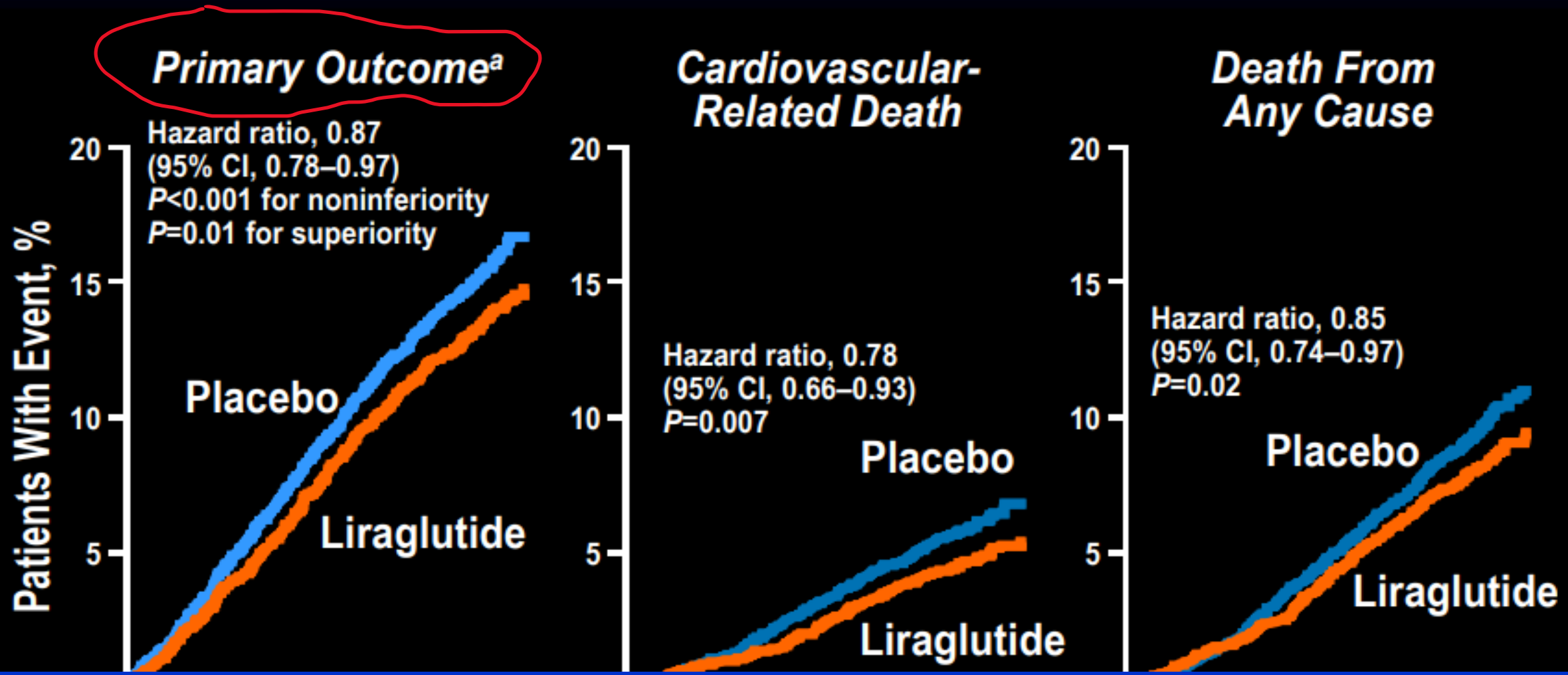


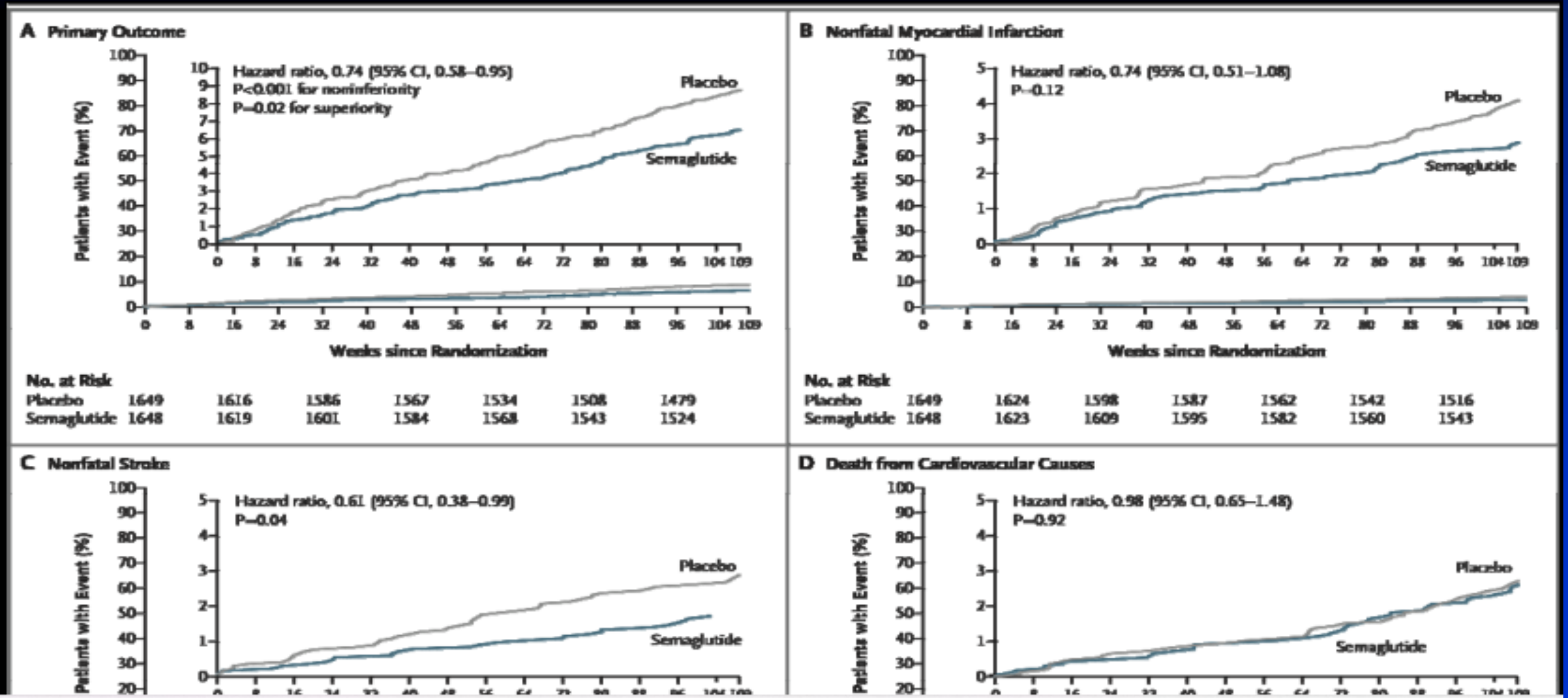
Figure 1. Cardiovascular Outcomes and Death from Any Cause.

- Expanded 2/24/22 to reduce the risk of cardiovascular death and hospitalization for heart failure in adults (Hfrf and Hfpf)

LEADER: Primary and Secondary Outcomes with Liraglutide



SUSTAIN 6: Primary and Secondary Outcomes With Semaglutide



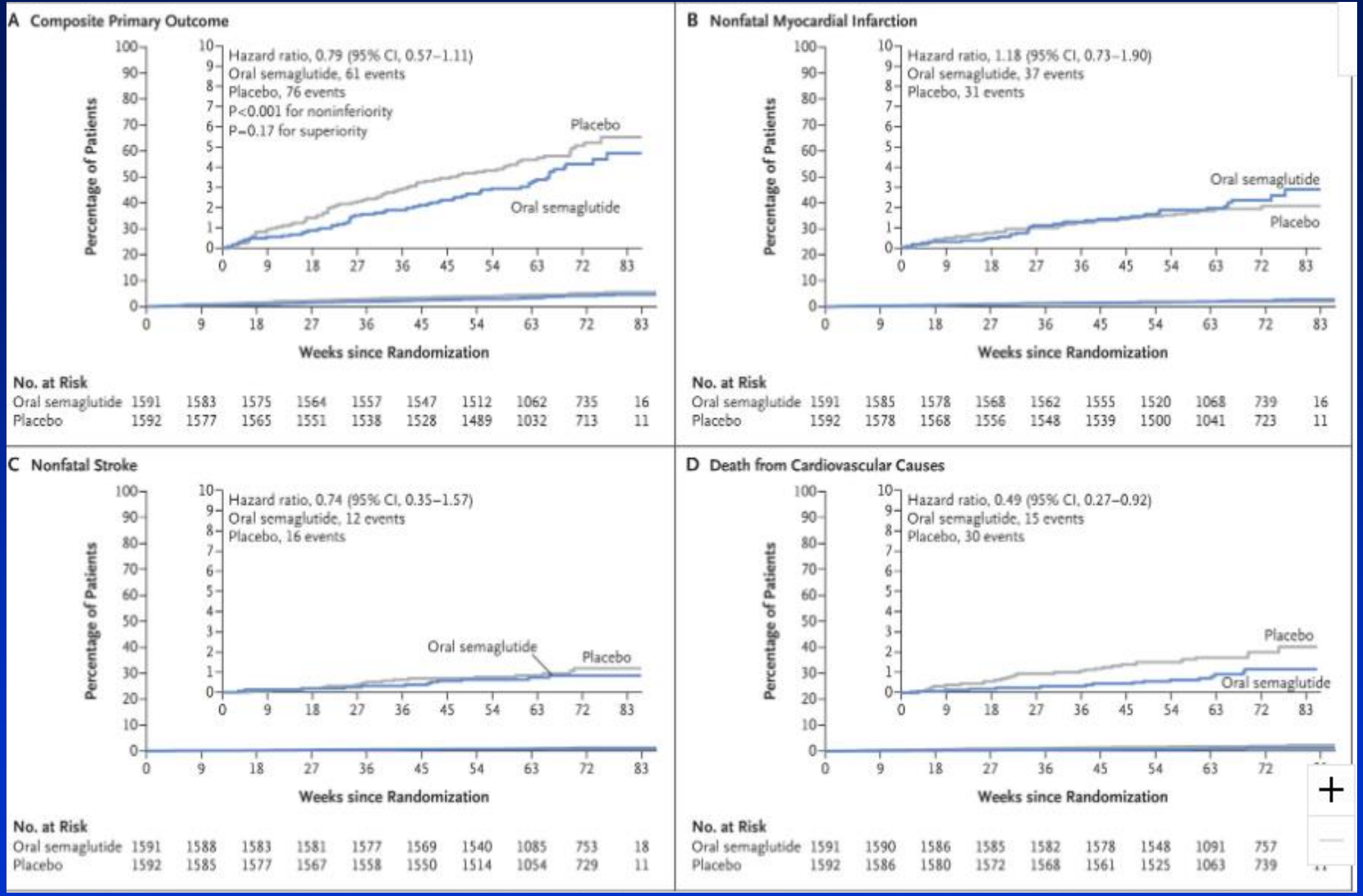
Pioneer 6 Rybelsus

- CVD outcome

RYBELSUS is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1).

Limitations of Use

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise (1, 5.1).
- Has not been studied in patients with a history of pancreatitis (1, 5.2).
- Not for treatment of type 1 diabetes mellitus (1).


A Composite Primary Outcome
Hazard ratio, 0.79 (95% CI, 0.57–1.11)
Oral semaglutide, 61 events
Placebo, 76 events
P<0.001 for noninferiority
P=0.17 for superiority
Placebo
Oral semaglutide
Percentage of Patients
Weeks since Randomization
No. at Risk
Oral semaglutide 1591 1583 1575 1564 1557 1547 1512 1062 735 16
Placebo 1592 1577 1565 1551 1538 1528 1489 1032 713 11
B Nonfatal Myocardial Infarction
Hazard ratio, 1.18 (95% CI, 0.73–1.90)
Oral semaglutide, 37 events
Placebo, 31 events
Oral semaglutide
Placebo
Percentage of Patients
Weeks since Randomization
No. at Risk
Oral semaglutide 1591 1585 1578 1568 1562 1555 1520 1068 739 16
Placebo 1592 1578 1568 1556 1548 1539 1500 1041 723 11
C Nonfatal Stroke
Hazard ratio, 0.74 (95% CI, 0.35–1.57)
Oral semaglutide, 12 events
Placebo, 16 events
Oral semaglutide
Placebo
Percentage of Patients
Weeks since Randomization
No. at Risk
Oral semaglutide 1591 1588 1583 1581 1577 1569 1540 1085 753 18
Placebo 1592 1585 1577 1567 1558 1550 1514 1054 729 11
D Death from Cardiovascular Causes
Hazard ratio, 0.49 (95% CI, 0.27–0.92)
Oral semaglutide, 15 events
Placebo, 30 events
Placebo
Oral semaglutide
Percentage of Patients
Weeks since Randomization
No. at Risk
Oral semaglutide 1591 1590 1586 1585 1582 1578 1548 1091 757
Placebo 1592 1586 1580 1572 1568 1561 1525 1063 739

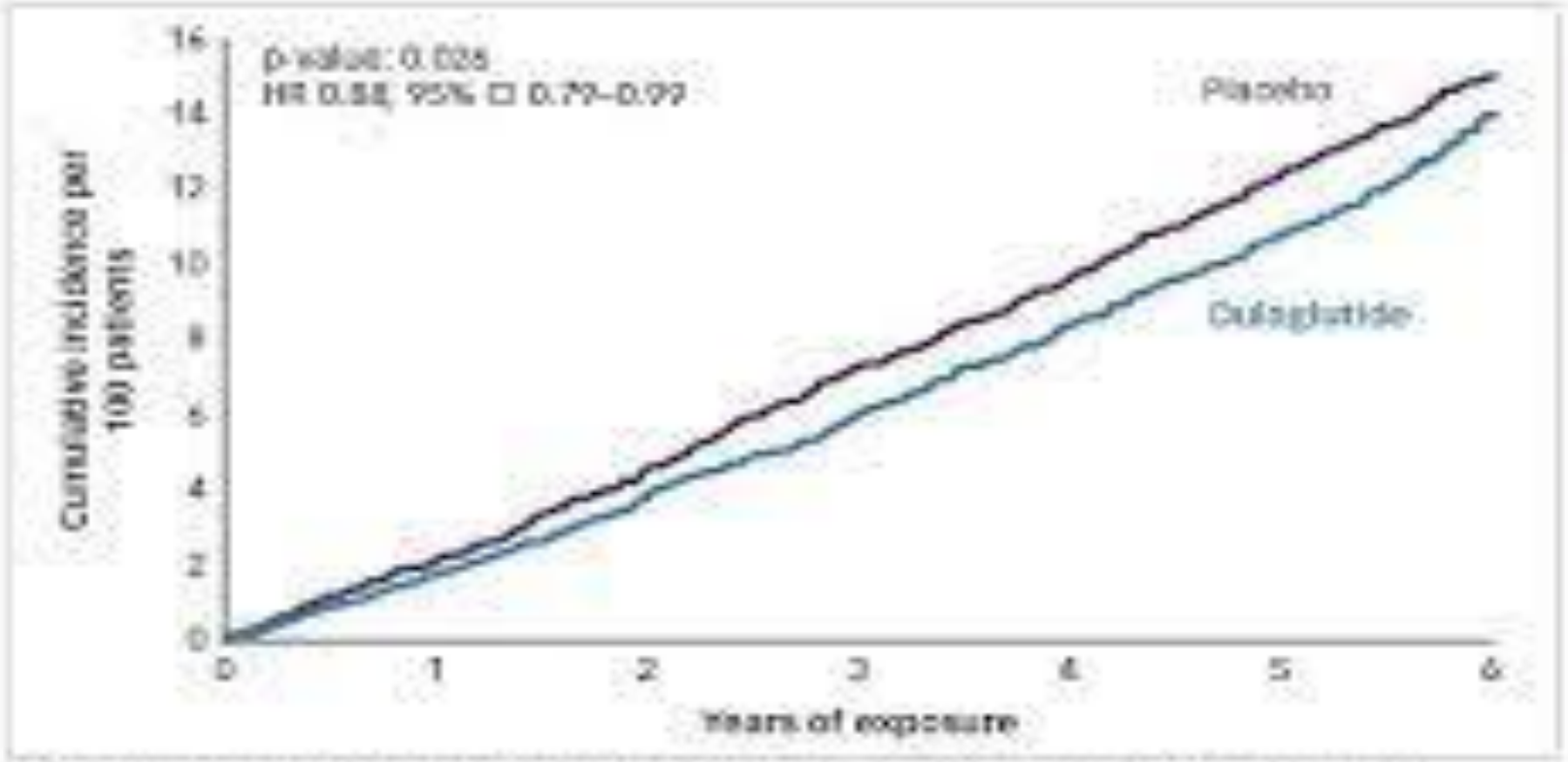
INDICATIONS AND USAGE

TRULICITY® is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus who have established cardiovascular disease or multiple cardiovascular risk factors


REWIND
Dulaglutide CV Outcomes Trial

Figure 1: REWIND trial—primary endpoint of major cardiovascular events



Major cardiovascular events included cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.
CI = confidence interval; HR = hazard ratio.
Reused with permission from The Lancet. Source: Gerstein et al. 2019.[8]

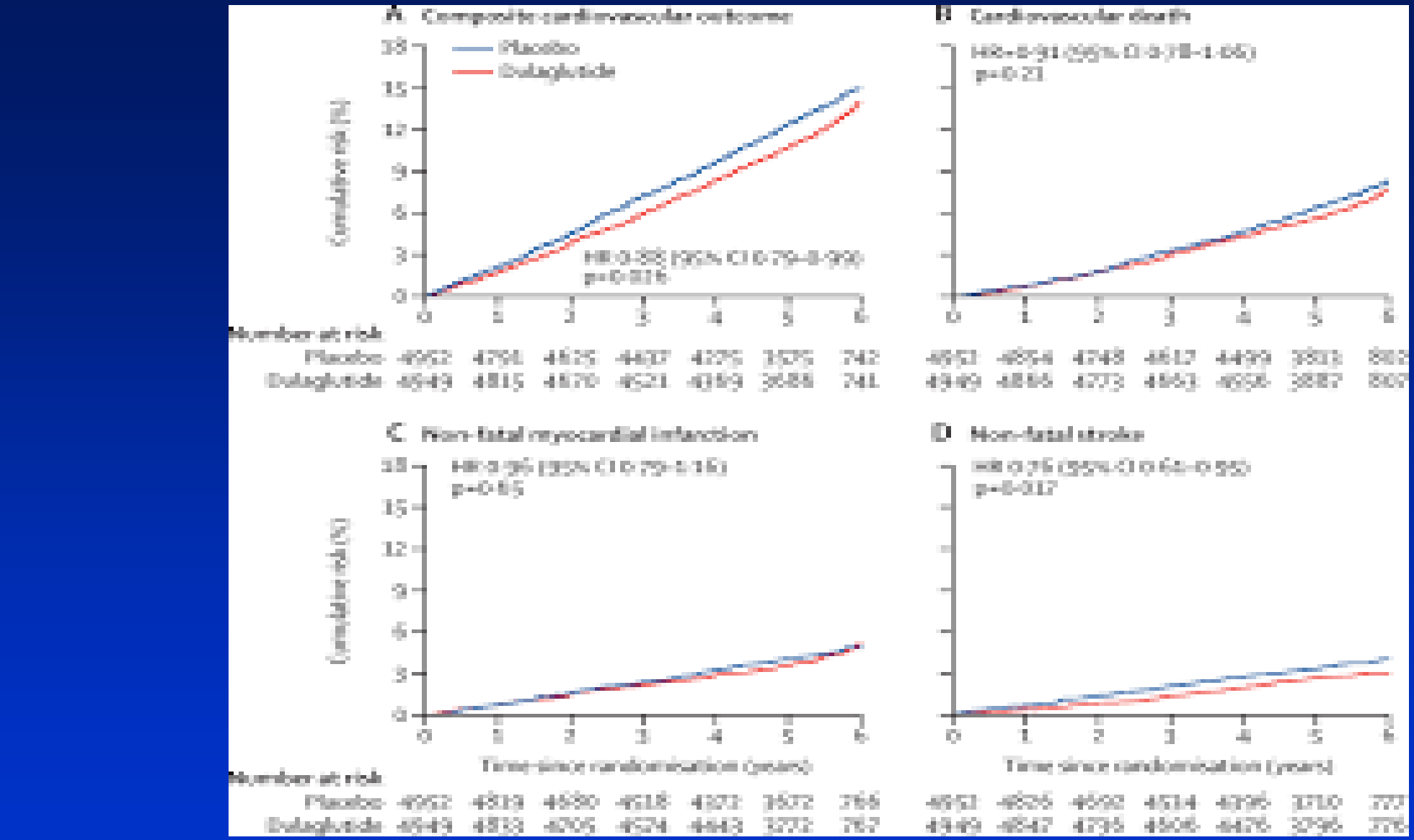
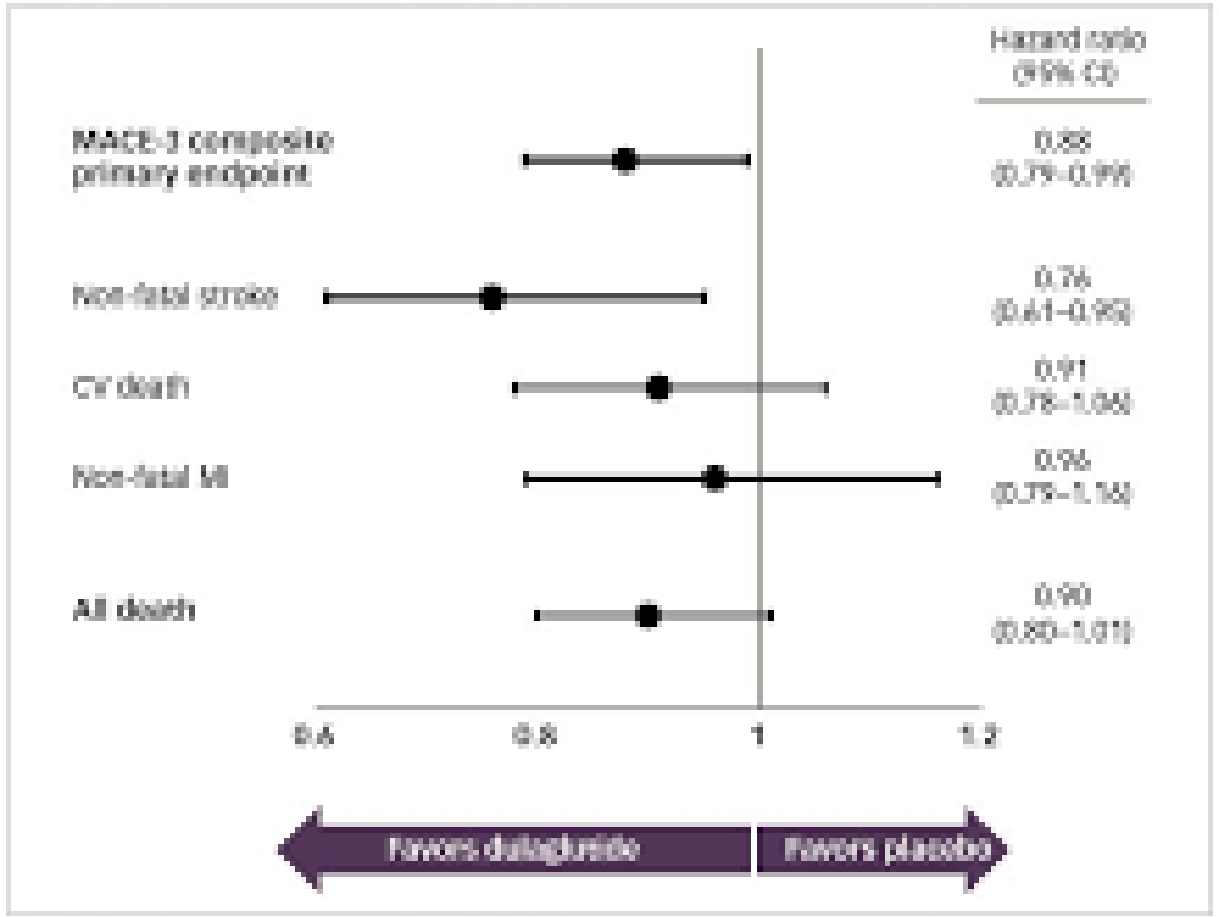

A
Placebo
Dulaglutide
HR 0·88 (95% CI 0·79–0·99)
p=0·026
B
HR=0·91 (95% CI 0·78–1·05)
p=0·21
C
HR 0·96 (95% CI 0·79–1·16)
p=0·65
D
HR 0·76 (95% CI 0·64–0·90)
p=0·017
Time since randomisation (years)
Number at risk
Placebo 9901 9701 9525 9337 9175 3575 742
Dulaglutide 9949 9815 9670 9521 9359 3688 741

Figure 2: Individual cardiovascular outcomes of the REWIND trial



CI = confidence interval; CV = cardiovascular; MACE = major cardiovascular events; MI = myocardial infarction.

Reused with permission from The Lancet. Source: Gerstein et al. 2019.[1]

Insulin

- ORIGIN

CONCLUSIONS: When used to target normal fasting plasma glucose levels for more than 6 years, insulin **glargine** had a neutral effect on cardiovascular outcomes and cancers. Although it reduced new-onset diabetes, insulin glargine also increased hypoglycemia and modestly increased weight. (Funded by Sanofi; ORIGIN ClinicalTrials.gov number, NCT00069784.).

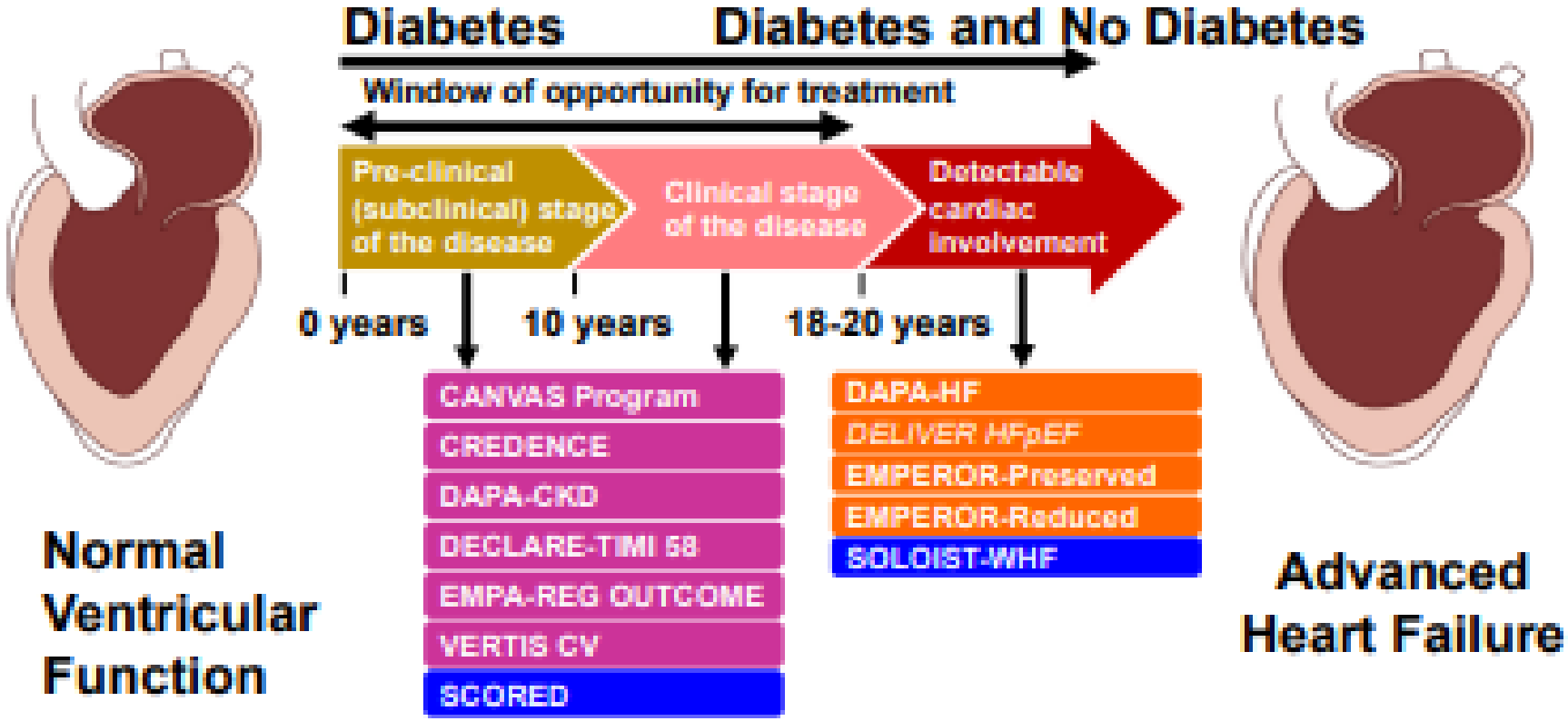
MAY NOT BE BEST CHOICE FOR CVD EVENT REDUCTION

Pitfall

- Not presenting the information to your patient !

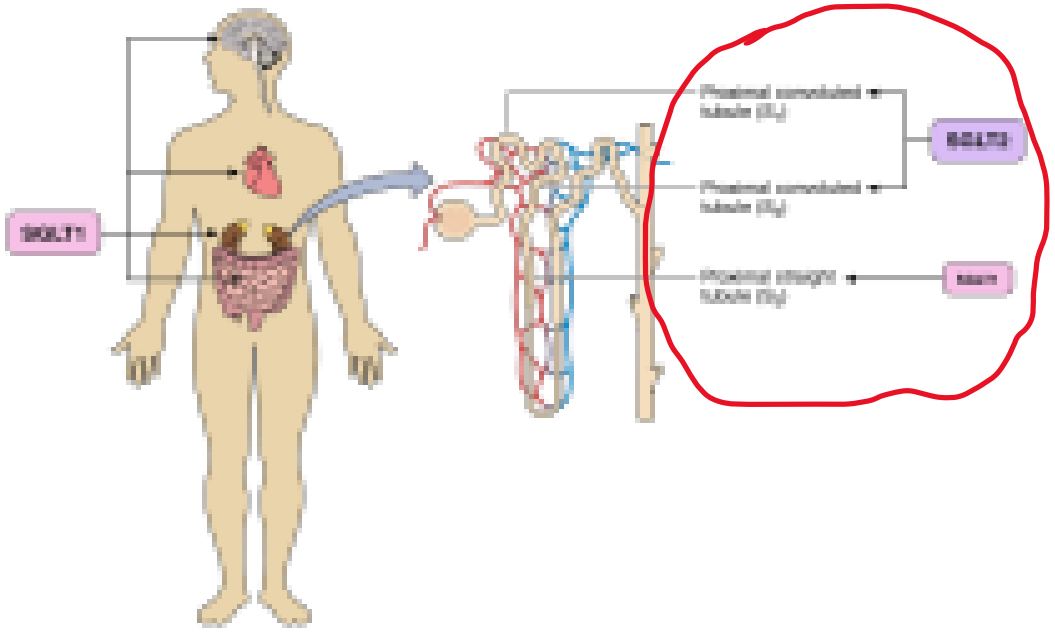
Whats on the horizon in the SGLT world?

The Evolution of SGLT2i in HF Management



Adapted from Bhatt DL, Verma S, Braunwald E. *Cell Metabolism*. 2019;30:847-849.

Sotagliflozin: Dual SGLT1 and SGLT2 Inhibitor



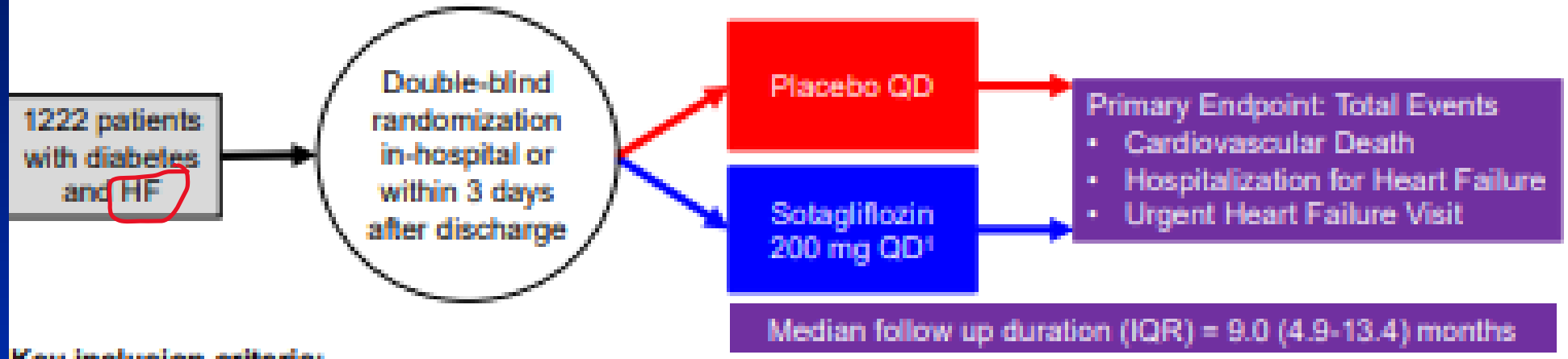
- SGLT1 is the primary transporter for absorption of glucose and galactose in the GI tract
- Pharmacologic inhibition by sotagliflozin is independent of insulin and does not depend on kidney function
- Potential effects on atherosclerotic risks

- SGLT2 is expressed in the kidney, where it reabsorbs 90% of filtered glucose
- Pharmacologic inhibition by sotagliflozin is independent of insulin but requires kidney function

B, Bhatt DL. *Circulation*. 2021.

SOLOIST-WHF Study Design

SOLOIST



Key inclusion criteria:

- Admission with signs and symptoms of HF
- Treatment with intravenous diuretics
- Stabilized, off oxygen, transitioning to oral diuretics
- BNP ≥150 pg/mL (≥450 pg/mL if afib) or NT-proBNP ≥600 pg/mL (≥1800 pg/mL if afib)
- Type 2 diabetes

Key exclusion criteria:

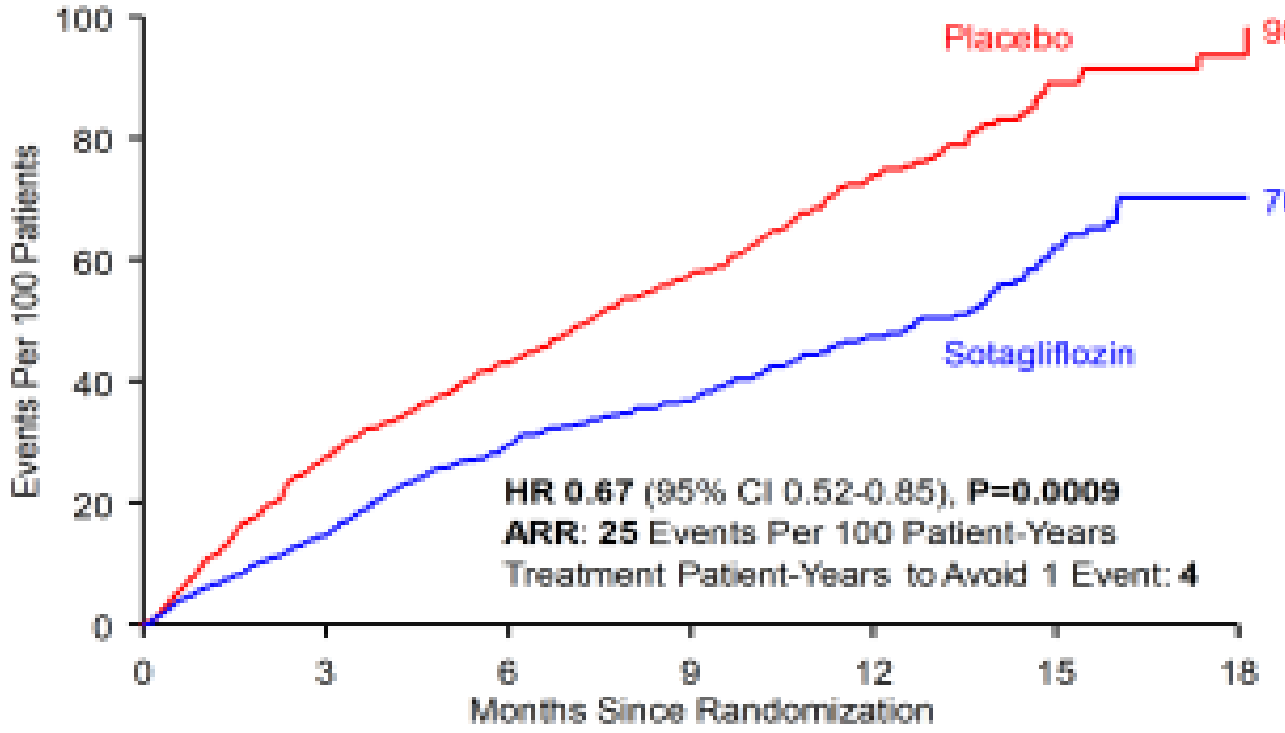
- End-stage HF
- Recent ACS, stroke, PCI, or CABG
- eGFR <30 mL/min/1.73m^2

[1]Goal of dose increase to 400 mg QD
[2]HF or reasons other than HF

hatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

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

SOLOIST



Bhatt DL, Szarek M, Steg PG, et al, and Pitt B. *N Engl J Med*. 2020. Bhatt DL. AHA 2020, virtual.

Efpeglenatide

Effect on HbA1c, Weight, BP, HR, eGFR & Adverse Events

Medication Changes at Final Visit

Increased Use of Glucose-Lowering Agents in Placebo Group

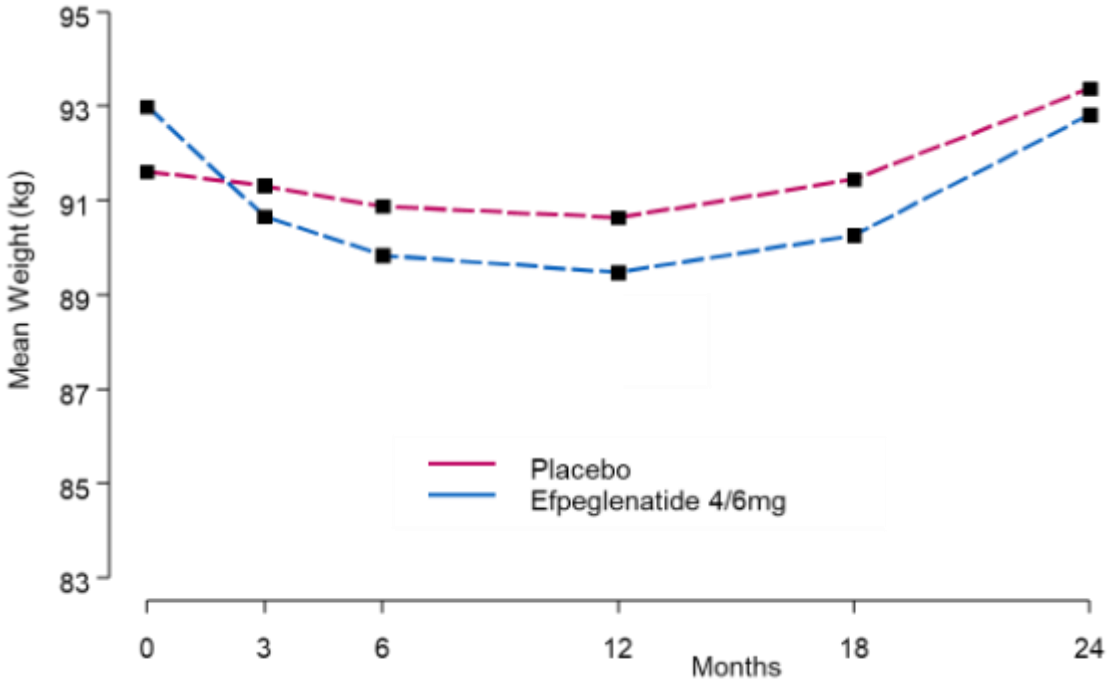
	Efpeglenatide	Placebo
Had a Final Visit	2715	1358
Metformin (%)	1975 (72.7)	991 (73.0)
Sulfonylureas (%)	652 (24.0)	354 (26.1)
Insulin (%)	1723 (63.5)	884 (65.1)
DPP4 inhibitor (%)	24 (0.9)	26 (1.9)
SGLT2 inhibitor (%)	475 (17.5)	288 (21.2)
ACE inhibitor or ARB (%)	2161 (79.6)	1085 (79.9)
Statin (%)	2222 (81.8)	1098 (80.9)
Aspirin (%)	1859 (68.5)	921 (67.8)
Beta blocker (%)	1842 (67.9)	896 (66.0)

Effect of Efpeglenatide on Clinical Measures

Body Weight and BMI Changes Over Time

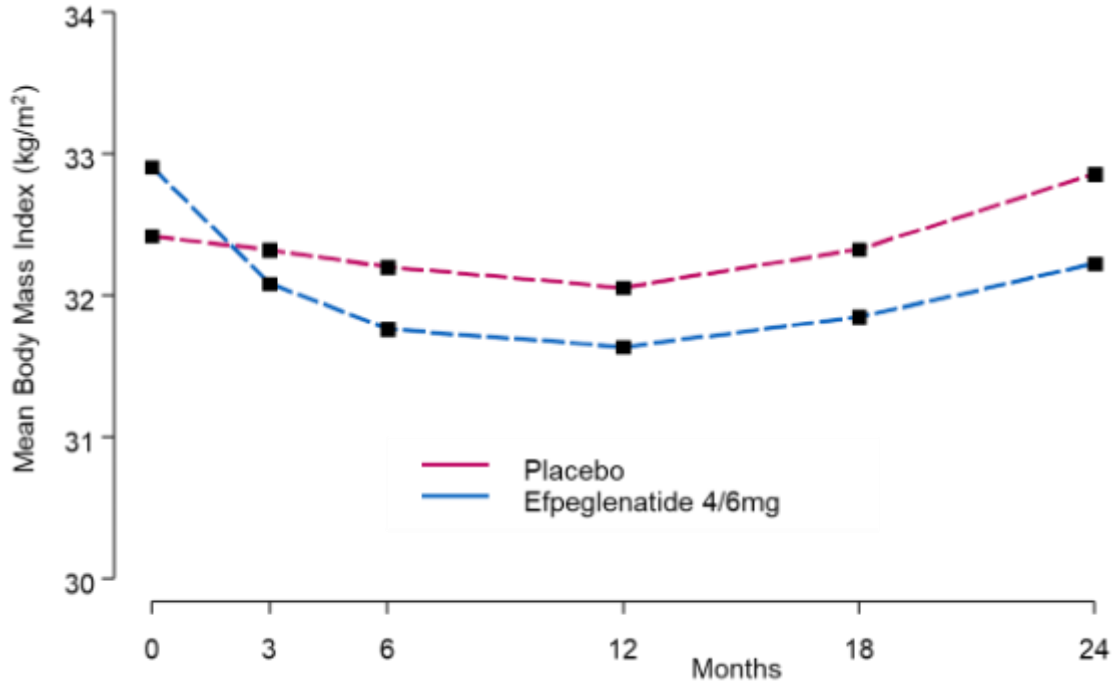
2.59 kg Lower
95% CI (2.29, 2.90)
P < 0.001

Body Weight



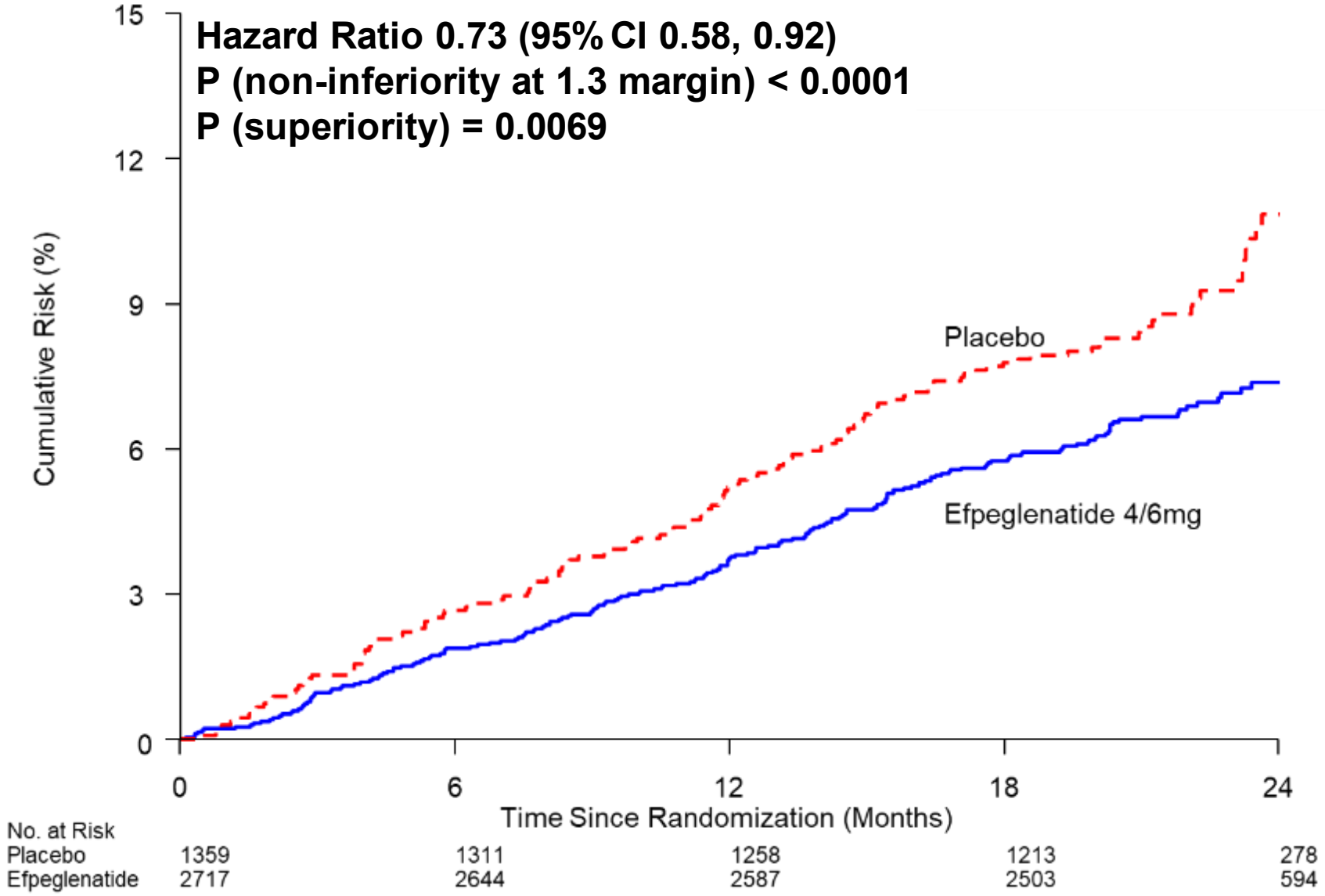
0.92 kg/m² Lower
95% CI (0.81, 1.03)
P < 0.001

Body Mass Index



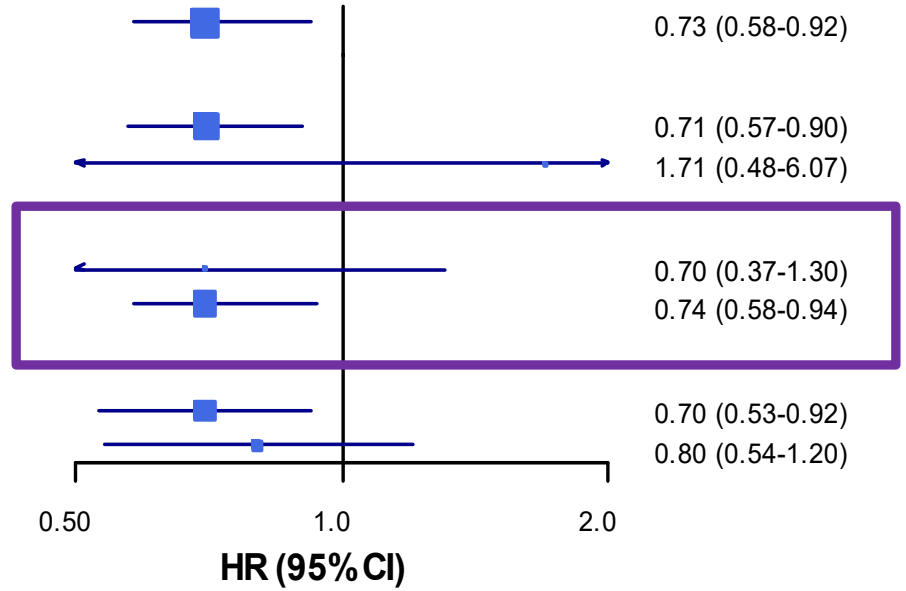
Efpeglenatide 4 or 6 mg *versus* Placebo

MACE



Effect on MACE Within Pre-specified Subgroups

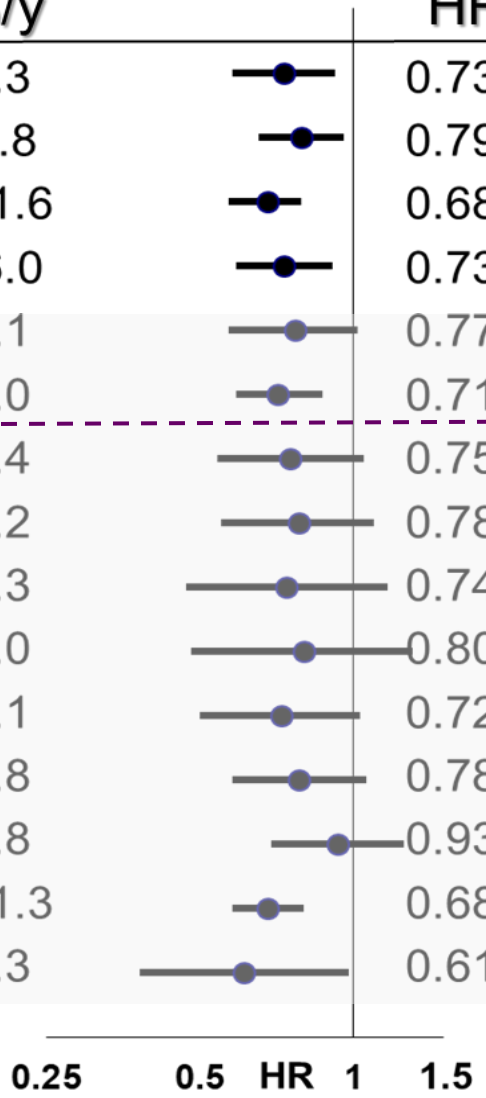
Subgroups	Efpeglenatide Events/Total (%)	Incidence per 100 py	Placebo Events/Total (%)	Incidence per 100 py	Hazard Ratio 95% CI*
Overall	189/2717 (7.0%)	3.9	125/1359 (9.2%)	5.3	0.73 (0.58-0.92)
CV Disease					
Prior CV Disease	177/2420 (7.3%)	4.1	122/1230 (9.9%)	5.7	0.71 (0.57-0.90)
No Prior CV Disease	12/297 (4.0%)	2.2	3/129 (2.3%)	1.3	1.71 (0.48-6.07)
SGLT2i Use					
Baseline SGLT2i Use	25/412 (6.1%)	3.4	17/206 (8.3%)	4.7	0.70 (0.37-1.30)
No Baseline SGLT2i Use	164/2305 (7.1%)	4	108/1153 (9.4%)	5.4	0.74 (0.58-0.94)
Metformin Use					
Baseline Metformin Use	127/1993 (6.4%)	3.6	87/992 (8.8%)	5	0.70 (0.53-0.92)
No Baseline Metformin Use	62/724 (8.6%)	4.9	38/367 (10%)	6	0.80 (0.54-1.20)



Baseline SGLT2i Use in = 618 (15.2%)

Summary of CV/Kidney Effects of Efpeglenatide

	Outcome	N (%)	%/y	N (%)	%/y	HR (95%CI)	
Significant	MACE	189 (7.0)	3.9	125 (9.2)	5.3	0.73 (0.58, 0.92)	Primary
	MACE/Cor Revasc/UA	257 (9.5)	5.4	158 (11.6)	6.8	0.79 (0.65, 0.96)	Secondary
	Renal Composite	353 (13.0)	7.7	250 (18.4)	11.6	0.68 (0.57, 0.79)	
	MACE or Death	216 (7.9)	4.5	143 (10.5)	6.0	0.73 (0.59, 0.91)	
Exploratory	Renal (no MA) or Death	121 (4.5)	2.5	76 (5.6)	3.1	0.77 (0.57, 1.02)	
	MACE, Death, HF, Renal	243 (8.9)	5.1	164 (12.1)	7.0	0.71 (0.59, 0.87)	
	Fatal or Nonfatal MI	91 (3.3)	1.9	58 (4.3)	2.4	0.75 (0.54, 1.05)	
	Nonfatal MI	85 (3.1)	1.7	53 (3.9)	2.2	0.78 (0.55, 1.10)	
	Fatal or Nonfatal Stroke	47 (1.7)	1.0	31 (2.3)	1.3	0.74 (0.47, 1.17)	
	Nonfatal Stroke	41 (1.5)	0.8	25 (1.8)	1.0	0.80 (0.48, 1.31)	
	CV Mortality	75 (2.8)	1.5	50 (3.7)	2.1	0.72 (0.50. 1.03)	
	Total Mortality	111 (4.1)	2.2	69 (5.1)	2.8	0.78 (0.58, 1.06)	
	Coronary Revascularization	126 (4.6)	2.6	66 (4.9)	2.8	0.93 (0.69. 1.26)	
	New Macroalbuminuria	348 (12.8)	7.6	244 (18.0)	11.3	0.68 (0.58, 0.80)	
	Heart Failure	40 (1.5)	0.8	31 (2.3)	1.3	0.61 (0.38, 0.98)	



Overall Conclusion

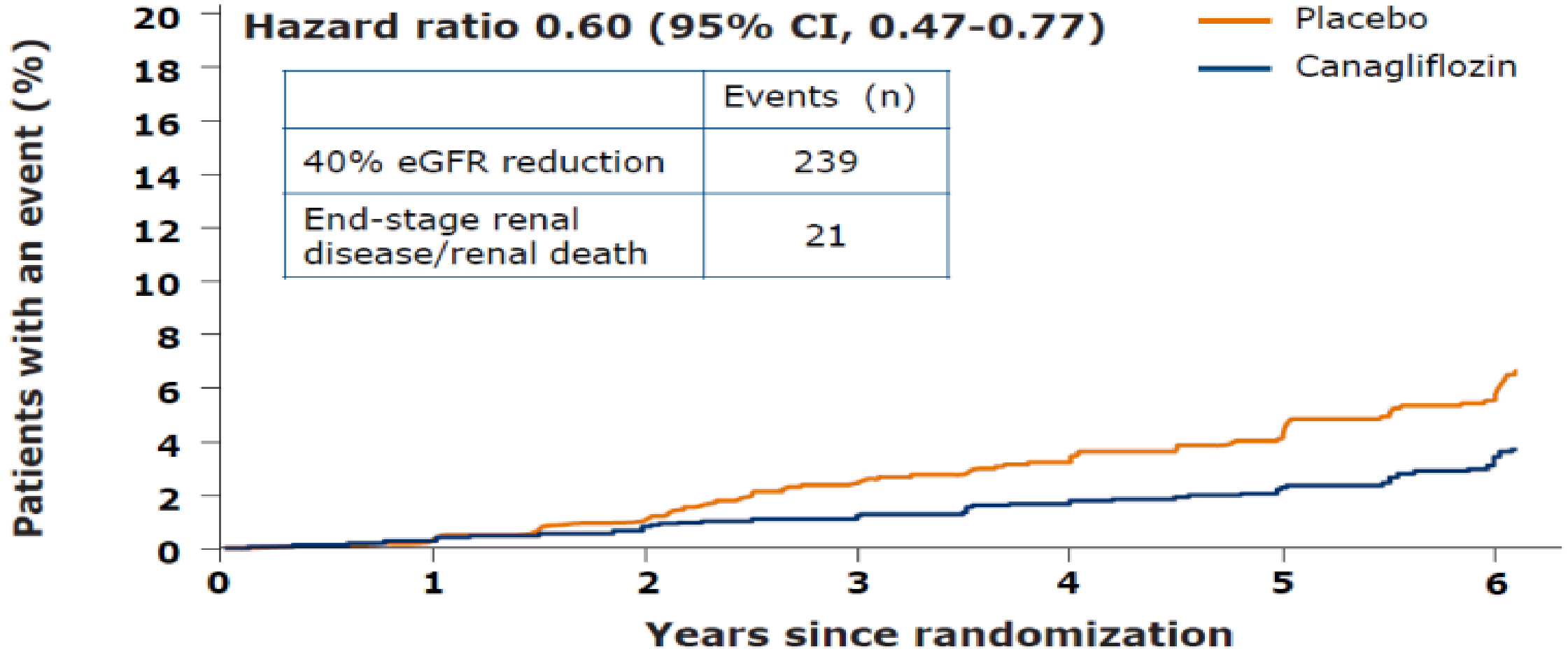
The AMPLITUDE O trial shows that the exendin-4 based GLP-1 RA drug efpeglenatide…

… safely reduces major cardiovascular and renal outcomes in high-risk people with type 2 diabetes while lowering glucose, blood pressure and weight

Summary: SGLT-2 CVOTs

Study Name & Drug	Study Description	Benefits	Adverse Concerns
CREDENCE Study, 2019, canagliflozin (Invokana)	T2DM patients received canagliflozin 100 mg or placebo once daily. Primary endpoint was composite of ESKD, doubling of serum creatinine, and renal or cardiovascular death.	30% decrease in Primary Endpoint • 22% (p=?) claimed decrease in CV death • Driven by 40% reduction in doubling of serum creatinine and 32% reduction in ESKD Secondary: 39% reduction in hospitalization for heart failure (HHF)	• No statistically significant decrease in ***atherosclerotic*** CV events • CV Death 22% (p=?) • Nonfatal Stroke 20% (NS) • Nonfatal MI 19% (NS) • No benefit (HR=1.00) in North America; benefit primarily driven in South America (HR= .58) • Potential increase in breast cancer • Slight increase (HR=1.11) in amputations, venous thromboembolisms (HR=1.28) • 4x Genital Infections
DAPA-HF Trial; 2019, dapagliflozin (Farxiga)	Patients, with or without T2DM, were an age of at least 18 years, an ejection fraction of 40% or less, & NYHA class II, III, or IV symptoms. Primary outcome was a composite of worsening HF or death from CV causes. Patients received dapagliflozin 10mg or placebo.	• 26% reduction in primary composite endpoint • Regardless of presence of T2DM • 30% reduction in HHF • 18% reduction in CV death (p=?) • Hoping to show weight loss • Unremarkable AE profile	• Unknown effect on ASCVD vs HF events • No statistical benefit in North America or Europe • Statistical benefit only in Asia and Central America • No statistical benefit in NYHA Classes III & IV • HF benefit only in Class II

Composite of 40% Reduction in eGFR, End-stage Renal Disease, or Renal Death

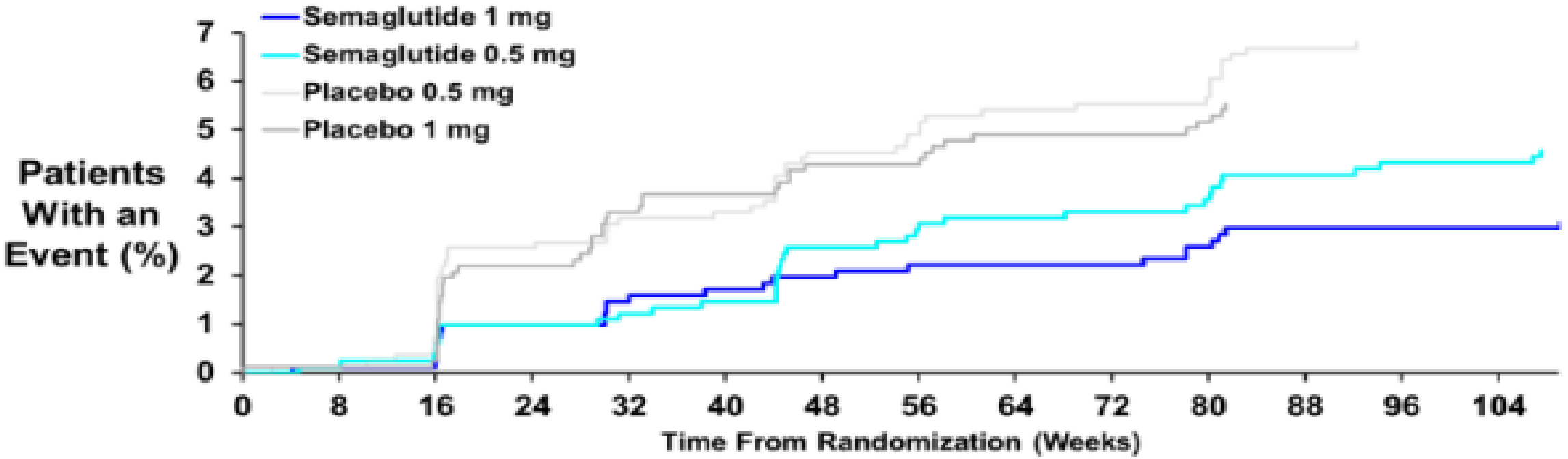


	Events (n)
40% eGFR reduction	239
End-stage renal disease/renal death	21

No. of patients

Placebo	4347	4227	3029	1274	1229	1173	819
Canagliflozin	5795	5664	4454	2654	2576	2495	1781

- Urinary albumin-to-creatinine ratio (UACR) values were below baseline with Ozempic® at end-of-treatment, while increasing over the entire trial period with placebo (estimated treatment ratio [ETR]: 0.78; 95% CI [0.68; 0.89] for Ozempic® 0.5 mg and ETR: 0.71; 95% CI [0.62; 0.81] for Ozempic® 1 mg).[3]



Patients at Risk

Sema 0.5 mg	826	815	807	790	778	767	758
Sema 1 mg	822	815	798	790	785	774	767
Placebo 0.5 mg	824	812	785	770	753	741	726
Placebo 1 mg	825	817	785	775	765	757	745

Figure 1. SUSTAIN 6 Kaplan Meier Plot of Time to First Occurrence of EAC-Confirmed New or Worsening Nephropathy[3]

Primary Analysis Component	Semaglutide N (%)	Placebo N (%)	HR (95% CI)
New or worsening nephropathy	62 (3.8)	100 (6.1)	0.64 (0.46; 0.88)
Macroalbuminuria	44 (2.7)	81 (4.9)	0.54 (0.37; 0.77)
Doubling of serum creatinine	18 (1.1)	14 (0.8)	1.28 (0.64; 2.58)
Need for continuous renal replacement therapy	11 (0.7)	12 (0.7)	0.91 (0.40; 2.07)
Renal death	0 (0.0)	0 (0.0)	-

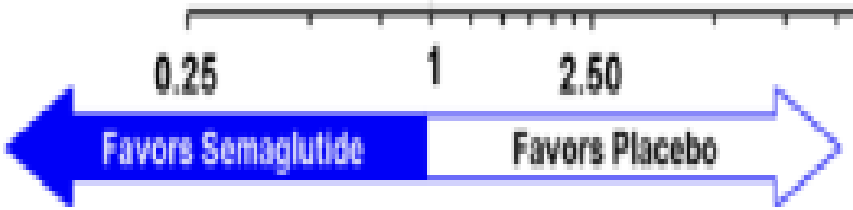
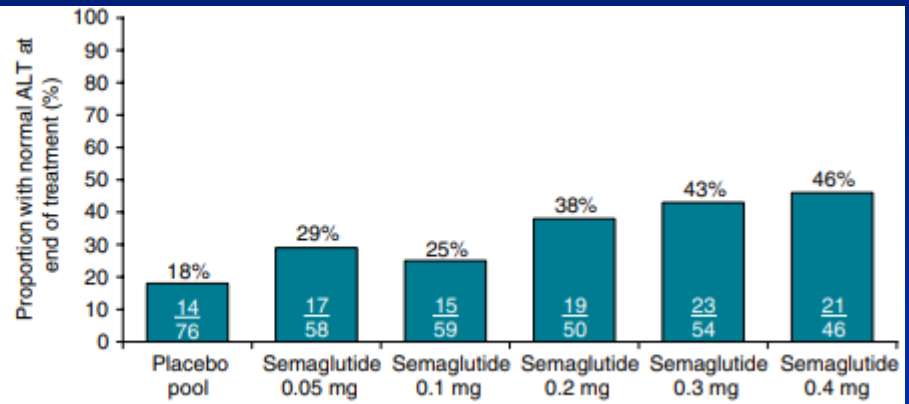


Figure 2. SUSTAIN 6 Forest Plot of Treatment Contrasts from Time to First EAC-confirmed Nephropathy Event[3]

FIGURE 4 Normalisation of ALT at week 52 among subjects with elevated baseline ALT in weight management trial NCT02453711. ALT, alanine aminotransferase



Glucose-lowering Medication in Type 2 Diabetes: 2021 ADA Professional Practice Committee (PPC) adaptation of Davies et al. and Buse et al.

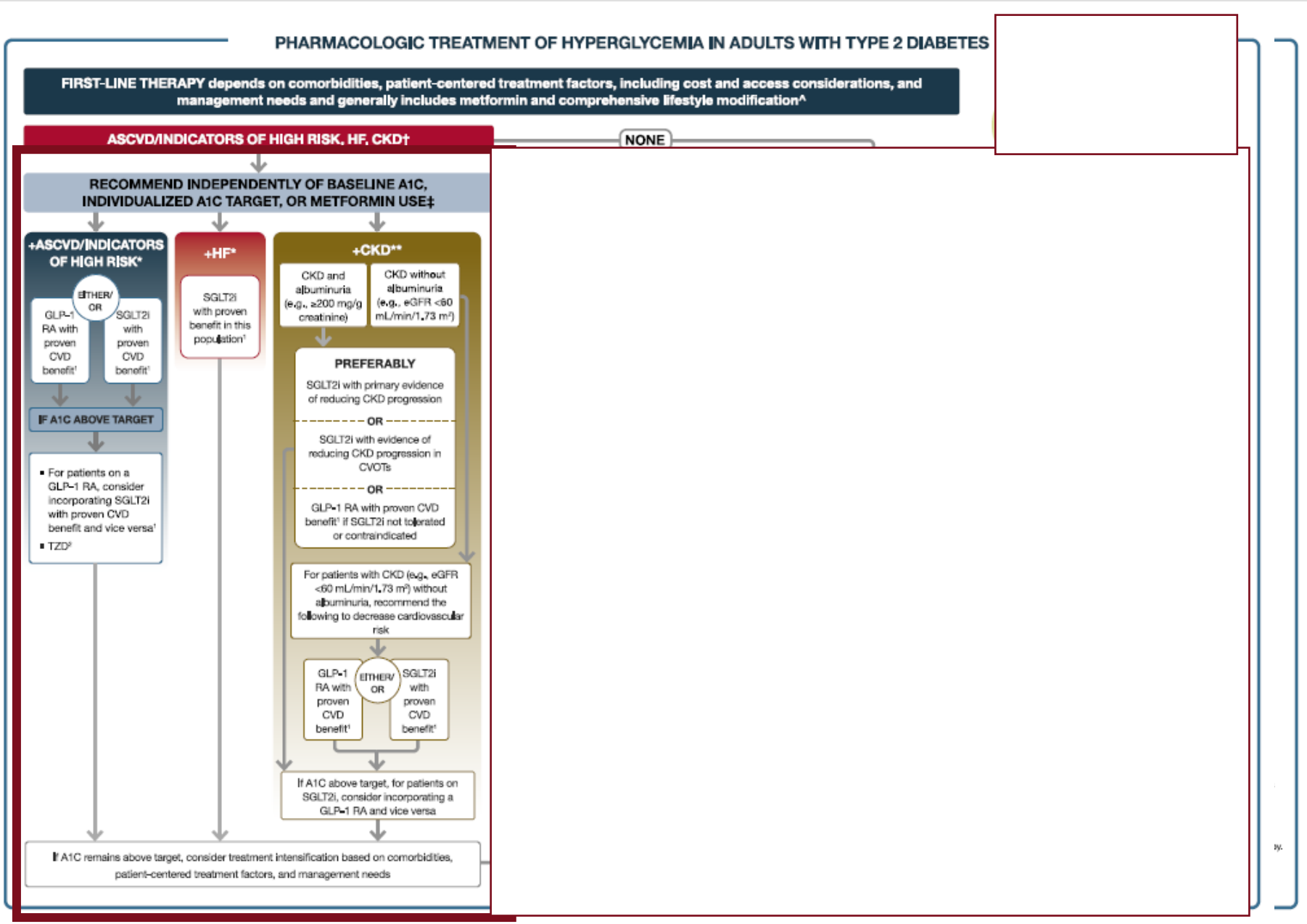


Figure 9.3—Pharmacologic treatment of hyperglycemia in adults with type 2 diabetes. 2022 ADA Professional Practice Committee (PPC) adaptation of Davies et al. (43) and Buse et al. (44). For appropriate context, see **Fig. 4.1**. The 2022 ADA PPC adaptation emphasizes incorporation of therapy rather than sequential add-on, which may require adjustment of current therapies. Therapeutic regimen should be tailored to comorbidities, patient-centered treatment factors, and management needs. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.

Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2022*. *Diabetes Care* 2022;45(Suppl. 1):S125-S143

American Diabetes Association.
Connected for Life

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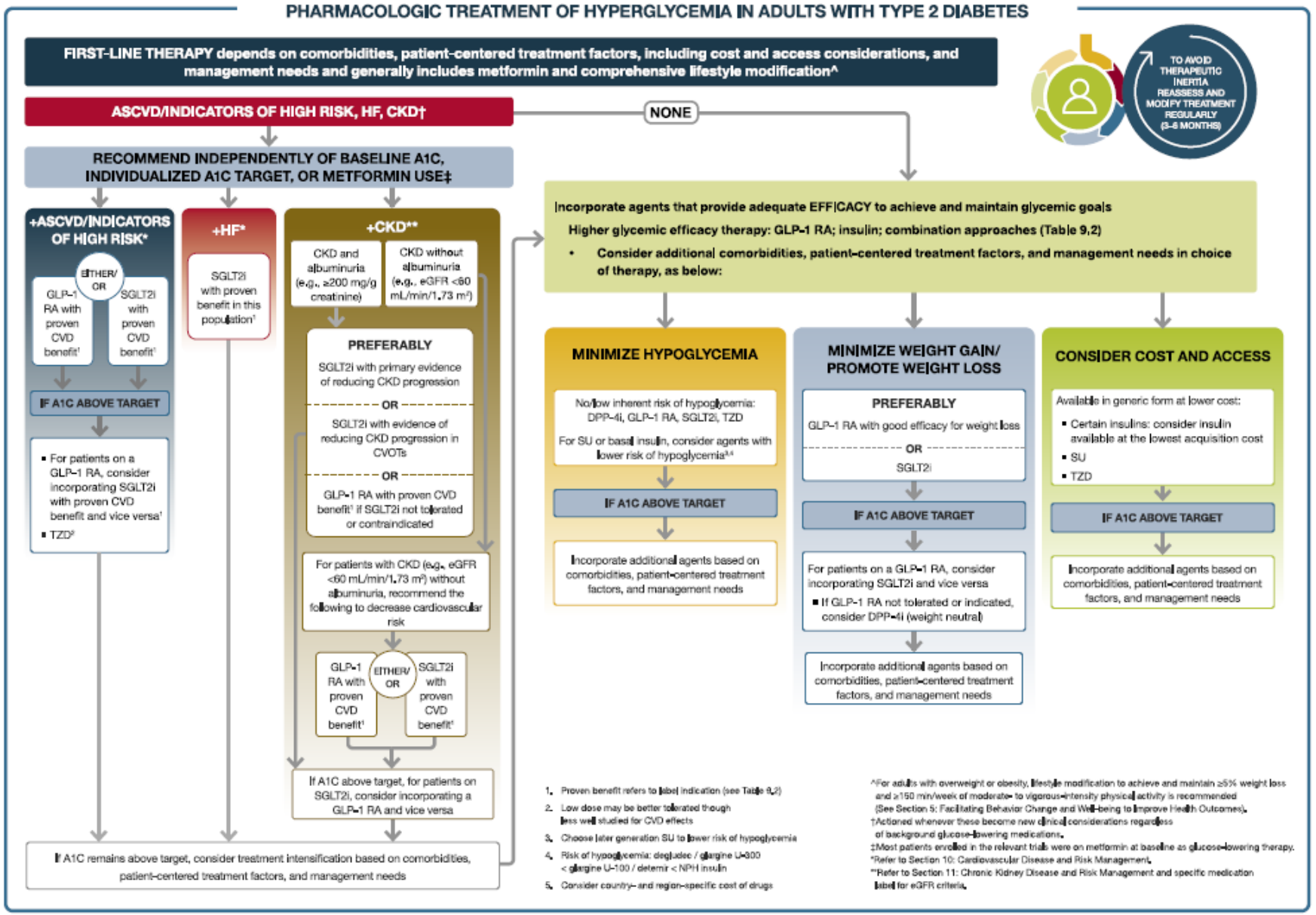

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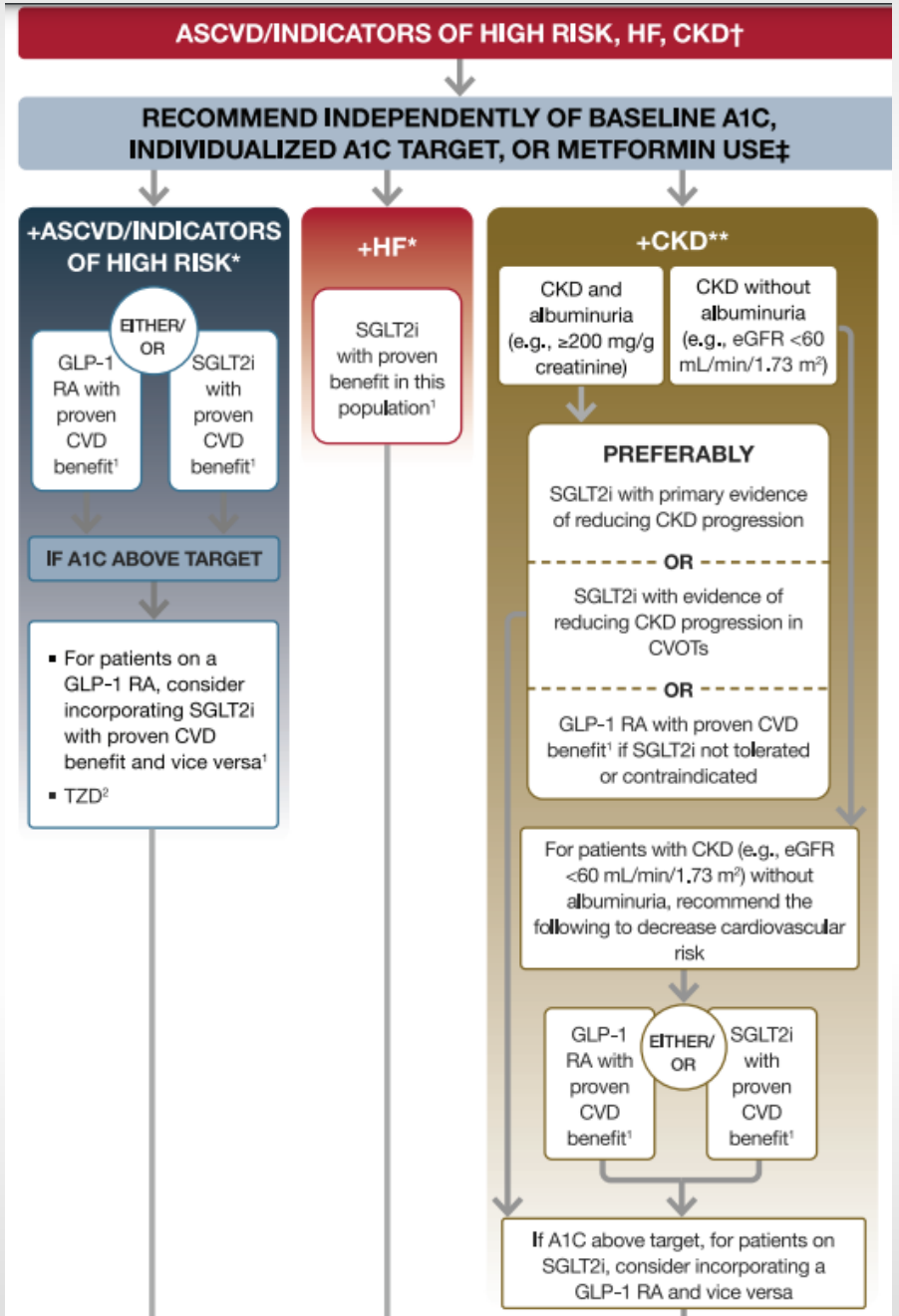

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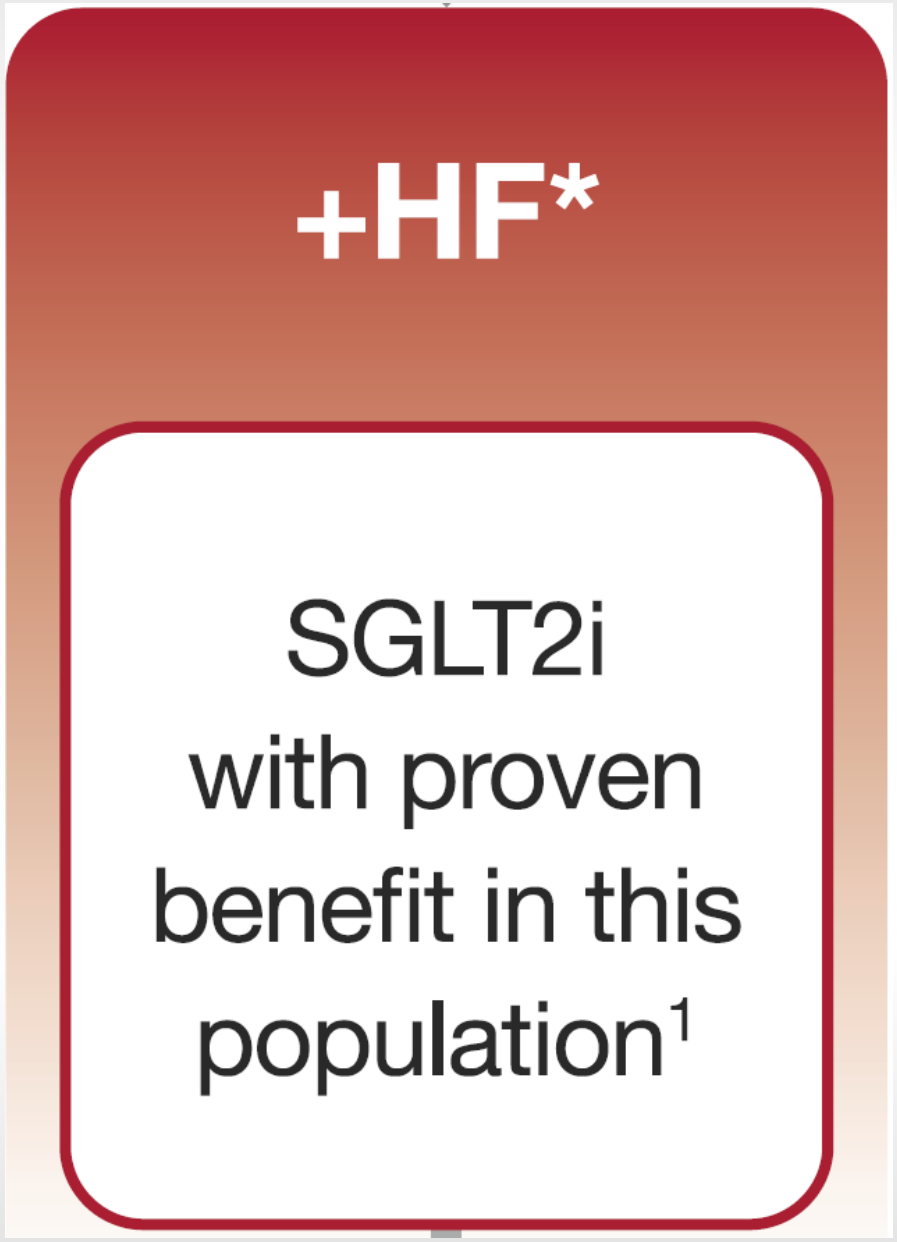

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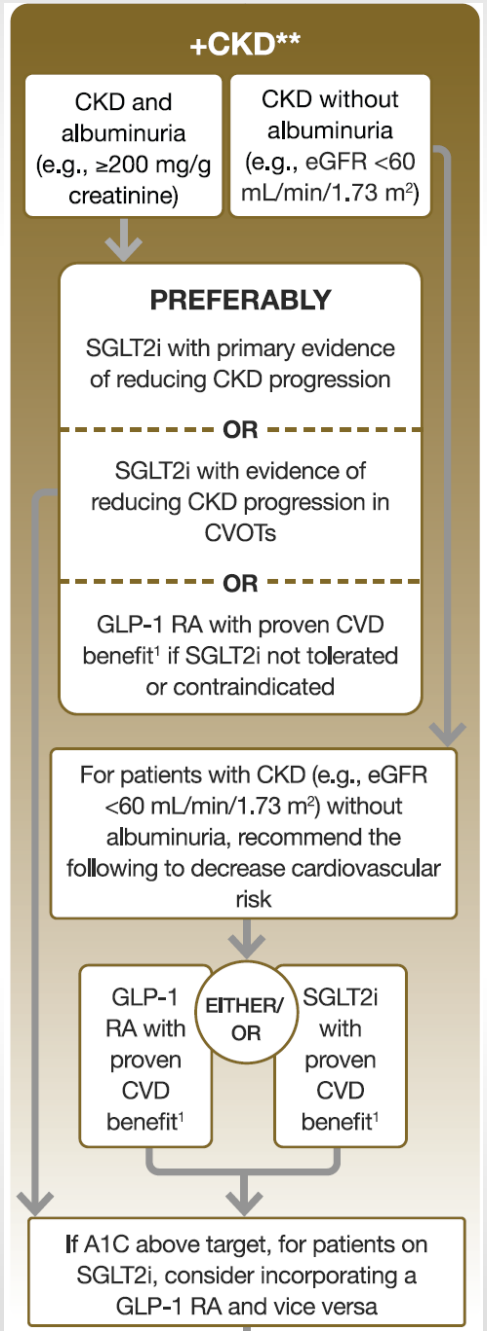

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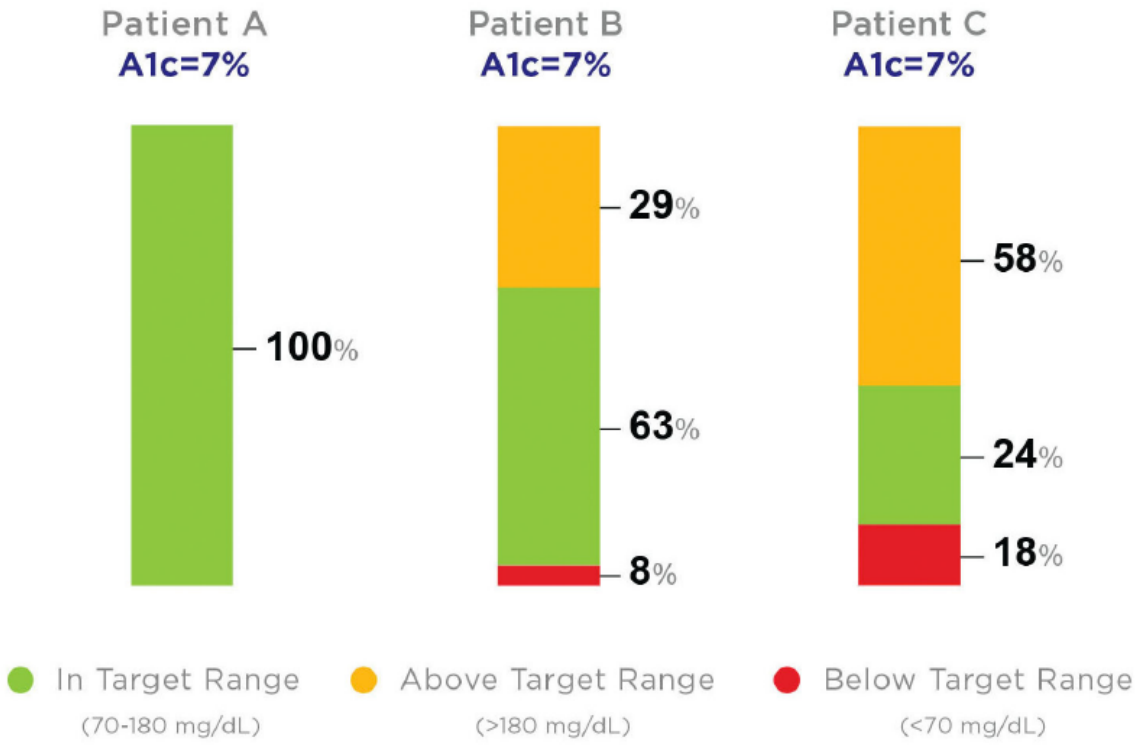
Case 4

- 63 y/o female T2DM
- Checks fingersticks pre breakfast and dinner and is proud of her efforts.
- Placed Libre
- What is your focused discussion now?

Not All A1cs Are Created Equal

HbA1c only provides a broad look at a patient's glucose history. Time in Range provides more actionable information than A1c alone and should complement A1c.[1]



Law of averages!!

Not actual patient data; for illustrative purposes only.

1. Battelino T, Danne T, Berganstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care.* 2019;42(8):1593-1603.

Estimated Average Glucose

Table 6.1—Estimated average glucose (eAG)

A1C (%)	mg/dL*	mmol/L
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)

Data in parentheses are 95% CI. A calculator for converting A1C results into eAG, in either mg/dL or mmol/L, is available at professional.diabetes.org/eAG. *These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, or no diabetes. The correlation between A1C and average glucose was 0.92 (6,7). Adapted from Nathan et al. (6).

Glycemic Targets:
Standards of Medical Care in Diabetes - 2021. *Diabetes Care* 2021;44(Suppl. 1):S73-S84

AGP Report

Name

MRN

GLUCOSE STATISTICS AND TARGETS

26 Feb 2019–10 Mar 2019	**13 days**
% Time CGM is Active	**99.9%**

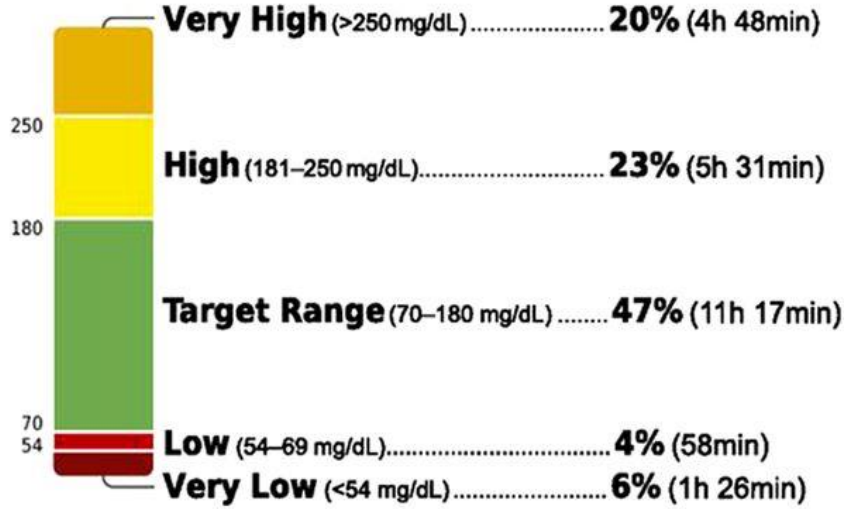
Glucose Ranges	**Targets** [% of Readings (Time/Day)]
Target Range 70–180 mg/dL	Greater than 70% (16h 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 180 mg/dL	Less than 25% (6h)
Above 250 mg/dL	Less than 5% (1h 12min)

Each 5% increase in time in range (70–180 mg/dL) is clinically beneficial.

Average Glucose	**173 mg/dL**
Glucose Management Indicator (GMI)	**7.6%**
Glucose Variability	**49.5%**

Defined as percent coefficient of variation (%CV); target ≤36%

TIME IN RANGES



Glycemic Targets:
Standards of Medical Care in Diabetes - 2020. *Diabetes Care* 2020;43(Suppl. 1):S66-S76

How CGM Can Help Reduce Diabetes Management Challenges

Moving beyond A1c

Using a combination of metrics allows for a more complete picture of glucose profile[1]

A1c + AGP (Ambulatory Glucose Profile)

Combining each patient's A1c with their ambulatory glucose profile (AGP) uncovers critical daily patterns

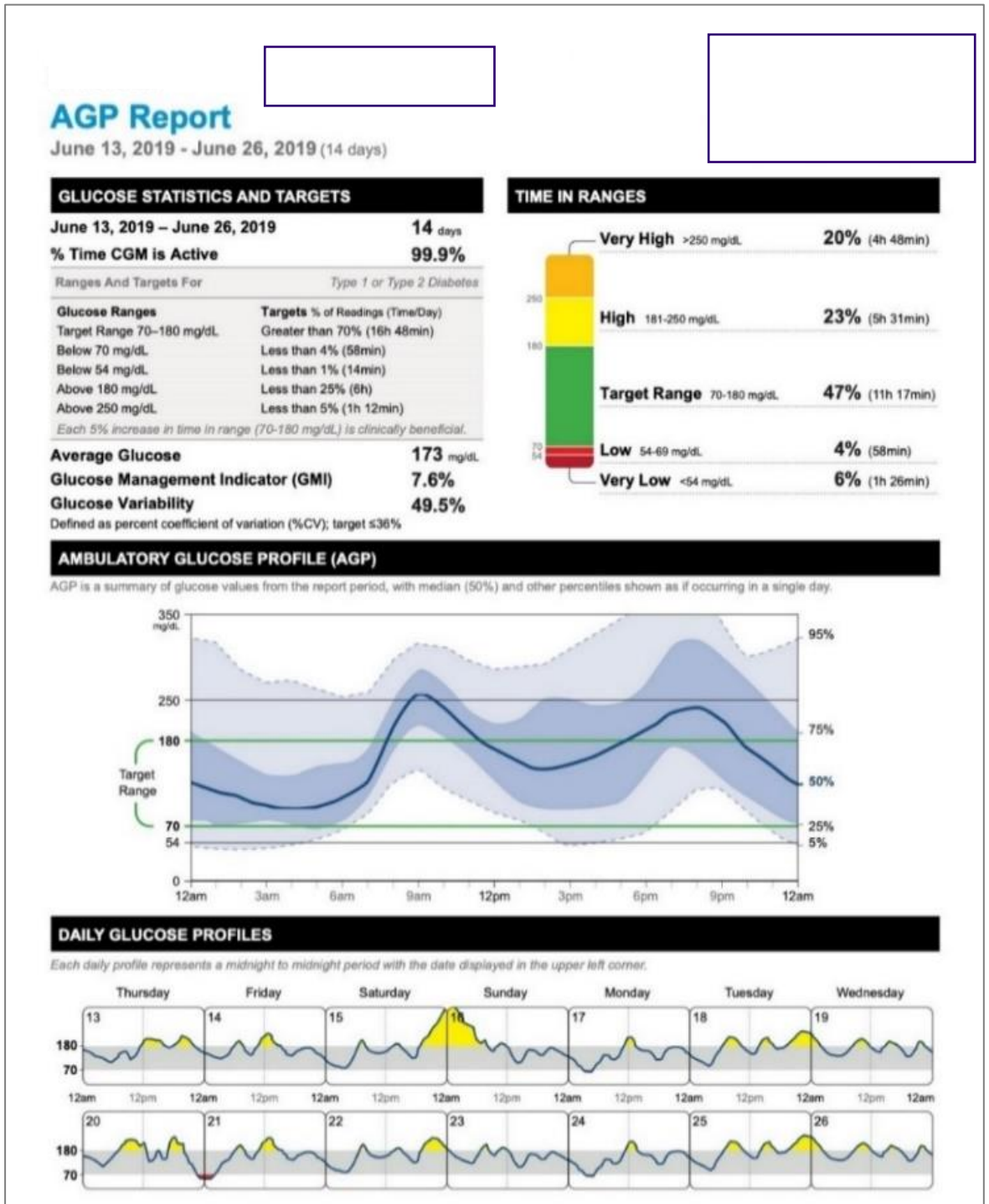
TIR (Time in Range) + TBR (Time below range)

Monitoring TIR and TBR glucose variability helps show how closely readings of an individual patient fall within target range, or below, in hypoglycemia

Glucose data

Additional access to acute, daily, and long-term (90 days) data allows for more informed treatment decisions

AGP provides a standardized visualization that condenses glucose data generated from GGM over several days or weeks into a single, 24-hour window.



1. Battelino T, Danne T, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019 Aug;42(8):1593-1603.

Antihyperglycemic Therapy

Prevent CVD/CKD Events Regardless of Glycemic Status
Manage Glycemia to Individualized, Established Goals

Lifestyle Therapy

Reduce ASCVD and Kidney Risks Based on Comorbidities

CAD	HFrEF HFpEF	CKD	Stroke/TIA
LA GLP1-RA	SGLT2i	SGLT2i	LA GLP1-RA
SGLT2i		LA GLP1-RA	Pio
Pio			

Recommended Hierarchy

Preferred
- GLP1-RA
- SGLT2i
- Metformin
- TZD
- DPP4i
- Insulin
- SU

Less used
- Glinide
- Colesevelam
- AGI
- Bromocriptine QR
- Pramlintide

Manage Hyperglycemia to Individualized Goal

Younger, healthier, at lower CV risk

A1C: 6.0% 6.5% 7.0% 7.5%

Most patients

Older, complex, more frail, at higher CV risk

- Use initial combination therapy for patients with A1C >1-2% above goal
- Assess glucose control with A1C (3 months), CGM or SMBG (daily, weekly, or monthly), glycated albumin or fructosamine (3 weeks)
- Add agents with complementary MOA to maintain glucose control at goal[a]
- Choose agents according to recommended hierarchy, based on patient's individualized risks and benefits, preferences, and access to therapies
- Insulin is necessary for patients with diabetes symptoms

Proven benefits in CVOTs

Hypoglycemia and/or HF risk

LA GLP1-RA = dulaglutide, liraglutide, or semaglutide.

[a] Do not combine GLP1-RA and DPP4i. Use caution when combining insulin + SU or insulin + TZD.

Summary

- Changes have occurred in the focus of diabetes management GLUCOSE MANAGEMENT>CVD RISK REDUCTION>CKD REDUCTION WT MANAGEMENT

CLINICIANS ARE RESPONSIBLE FOR PRESENTING THE OPTIONS TO OUR PATIENTS