Making the world a little less sweet, one patient at a time. An update in type 2 diabetes management

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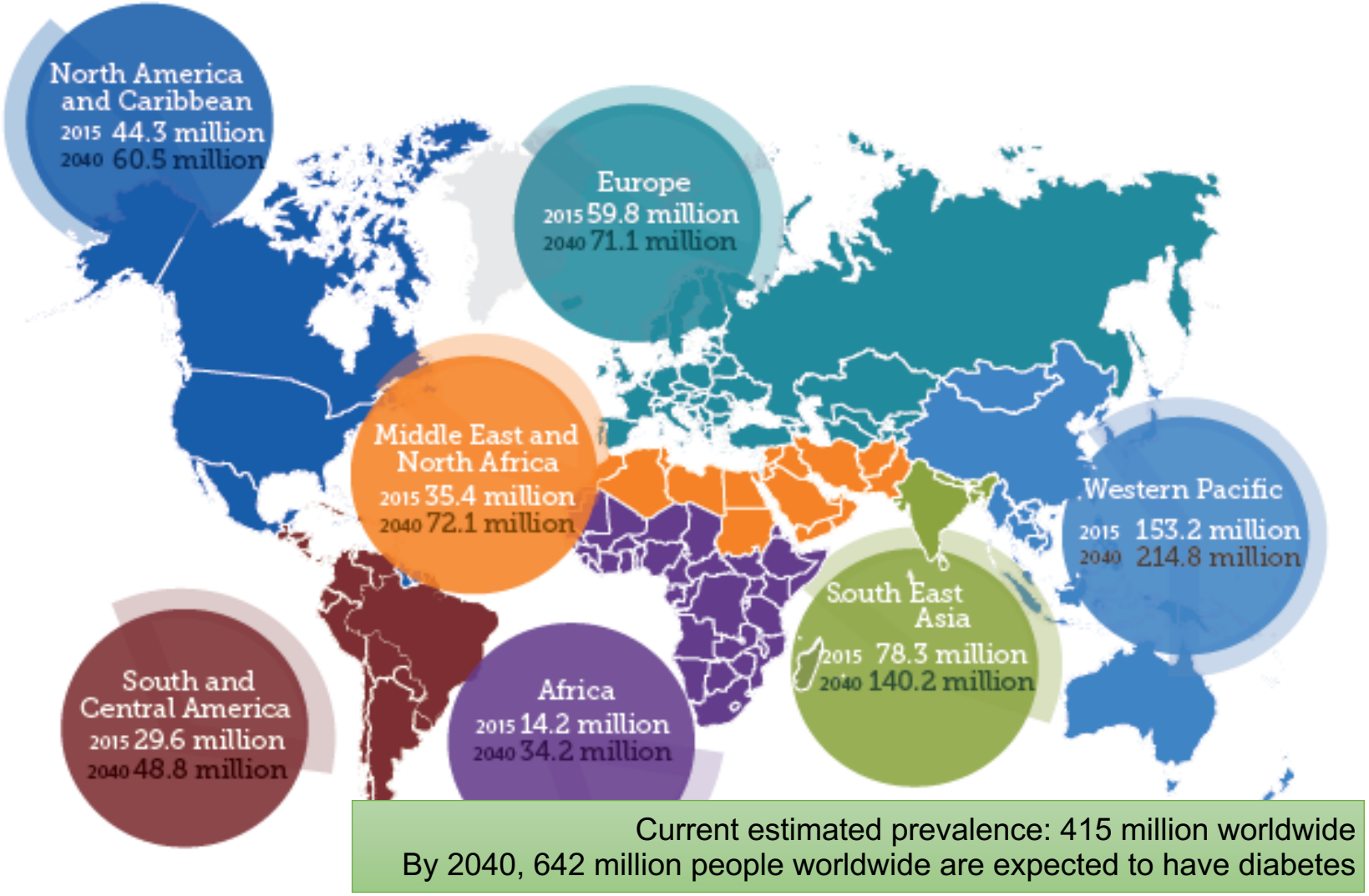
Diabetes continues to be a world wide epidemic

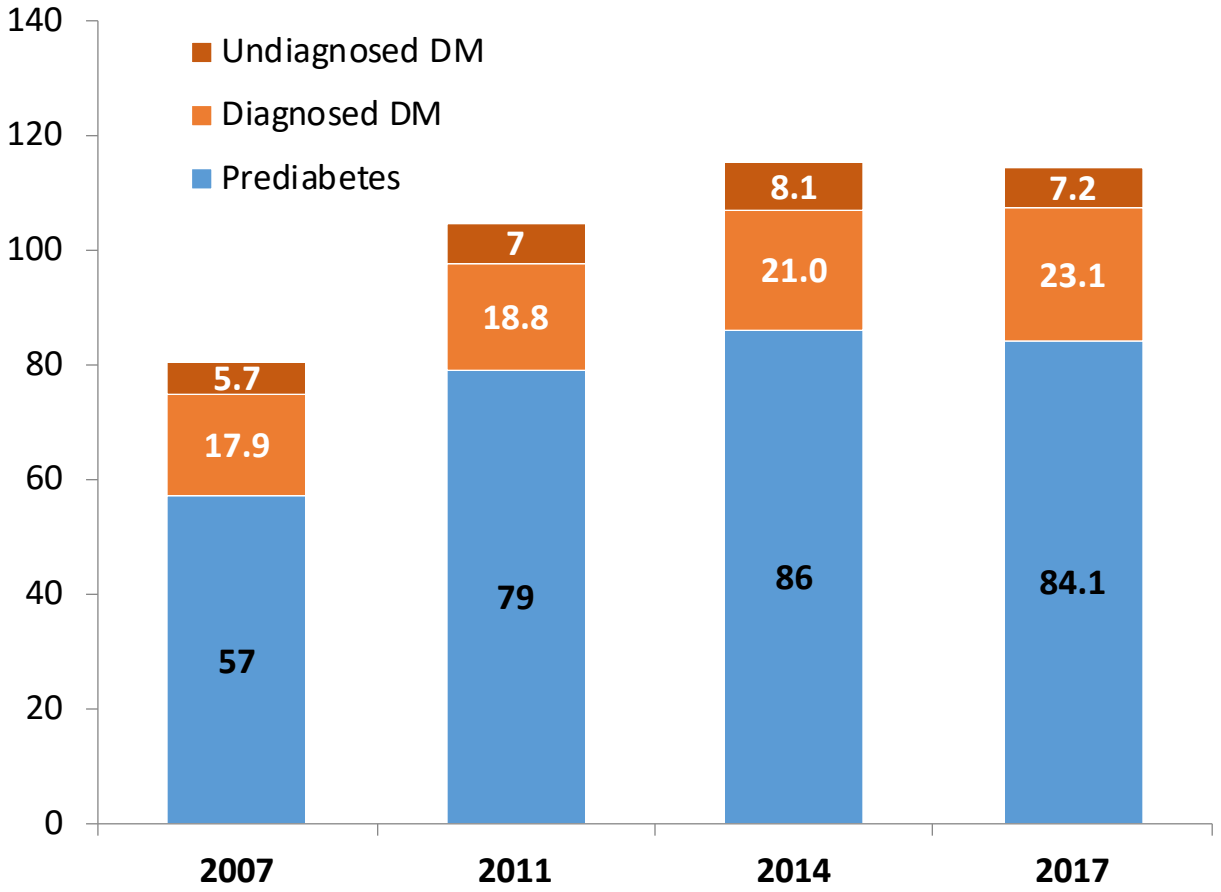
Worldwide Prevalence of Diabetes



Current estimated prevalence: 415 million worldwide
By 2040, 642 million people worldwide are expected to have diabetes

IDF. Diabetes Atlas Update 2015. Available at: http://www.idf.org/sites/default/files/Atlas7e-poster.pdf.

Prevalence of Diabetes and Prediabetes in the United States

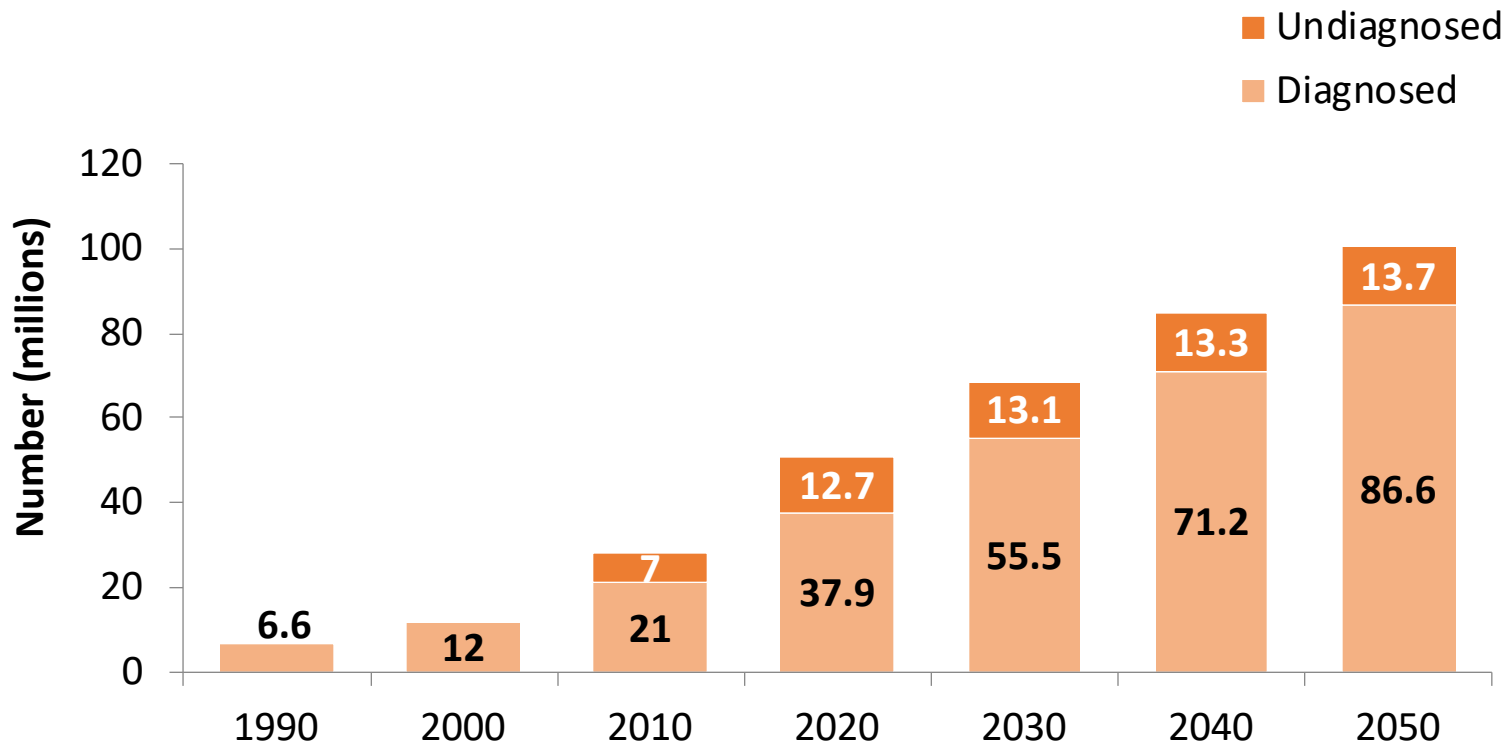


Diabetes
9.4% of US population

Prediabetes
34% of US population

CDC. National diabetes fact sheet, 2008. CDC. National diabetes fact sheet, 2011. CDC. National diabetes statistics report, 2014. CDC. National diabetes statistics report, 2017. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf.

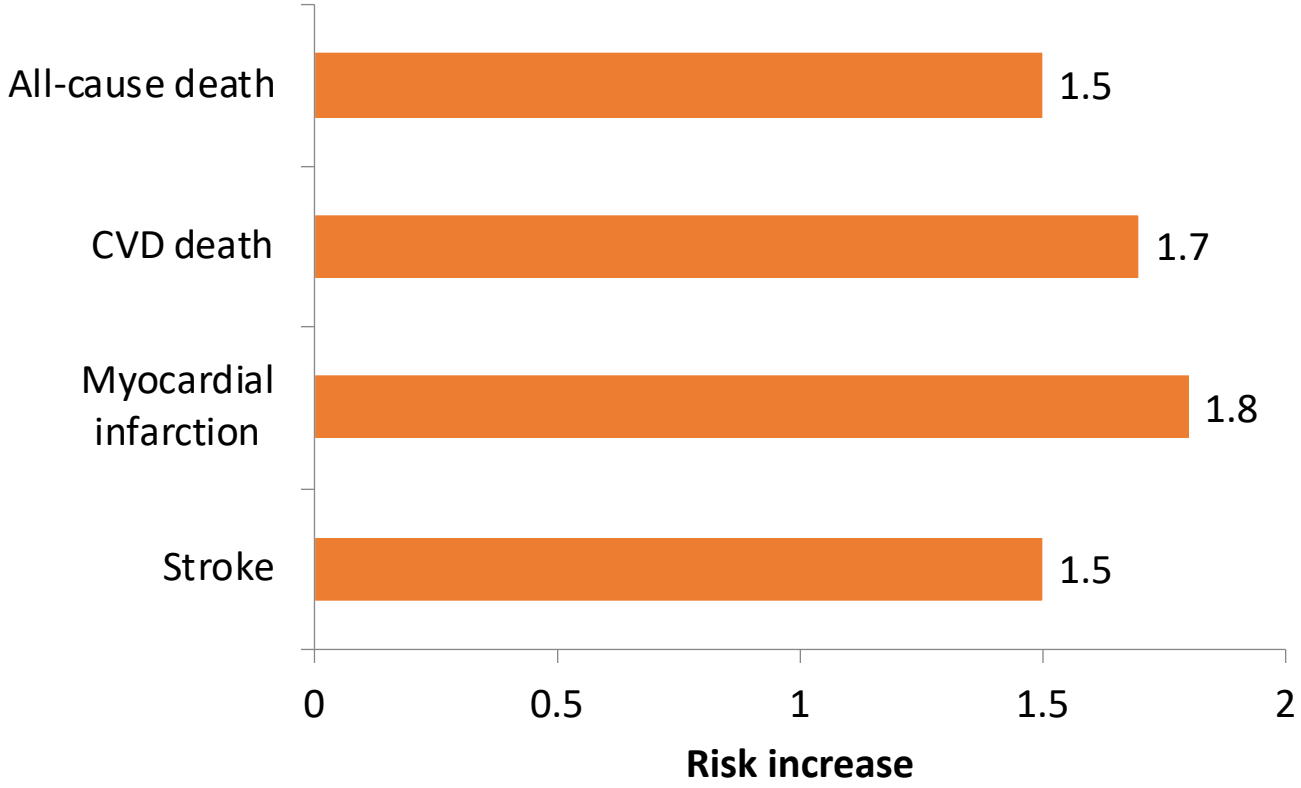
Projected Prevalence of Diabetes in the United States: 1990 to 2050



1. National Diabetes Surveillance System. http://www.cdc.gov/diabetes/statistics/prev/national/figpersons.htm. 2. CDC. National diabetes fact sheet, 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. 3. Boyle JP, et al. *Popul Health Metr*. 2010 Oct 22;8:29.

Diabetes continues to a major cause of Morbidity and Mortality

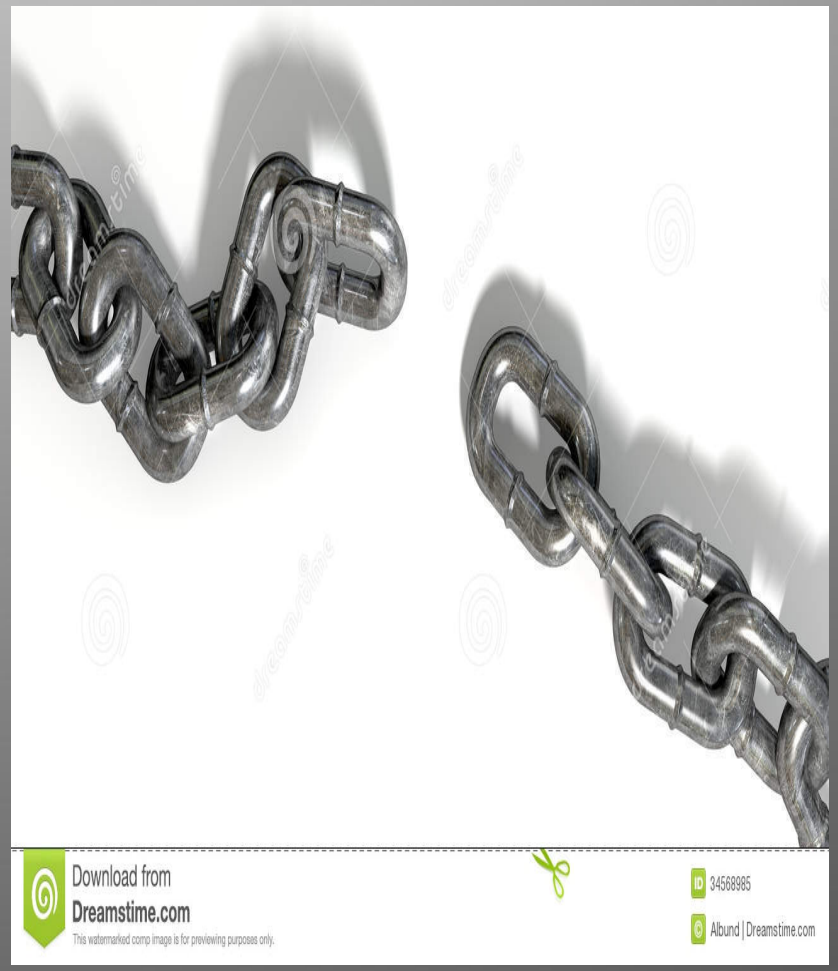
Diabetes and Morbidity and Mortality



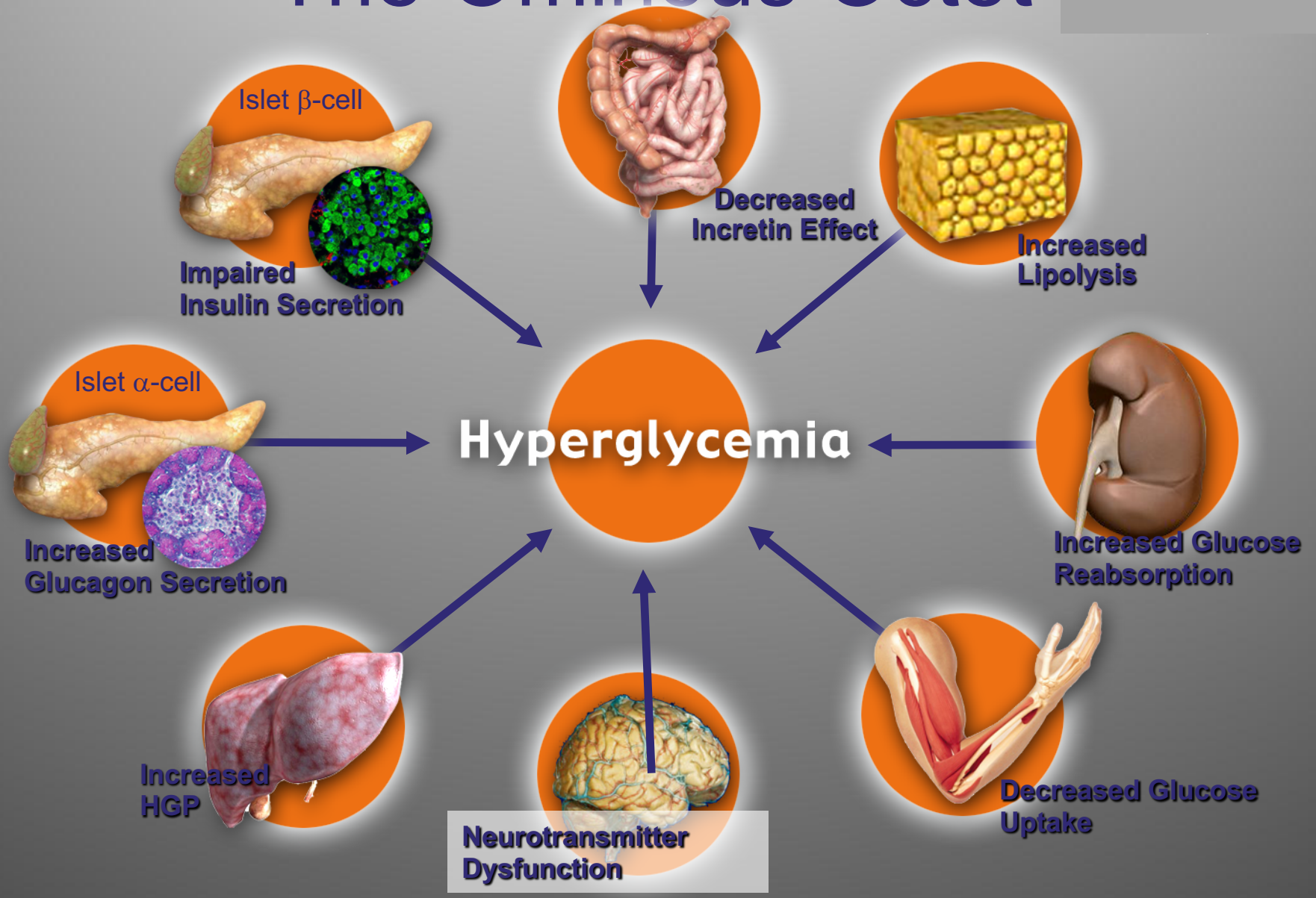
CDC. National diabetes statistics report, 2014. http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf

What were we missing?

- Are we treating symptoms or treating the problem?
- What else could be contributing to the process of type 2 diabetes?
- What about cardiovascular safety?



The Ominous Octet



Where are we today?

2019

- Its not enough anymore to just focus on A1c
- How we treat patients is now more important than ever

- Even more critical in those with CV disease or multiple risk factors
- Irrespective of A1c, our choices matter and may save lives

SGLT- 2 Therapy

Canagliflozin (Invokana)

Dapagliflozin (Farxiga)

Empagliflozin (Jardiance)

Ertugliflozin (Steglatro)

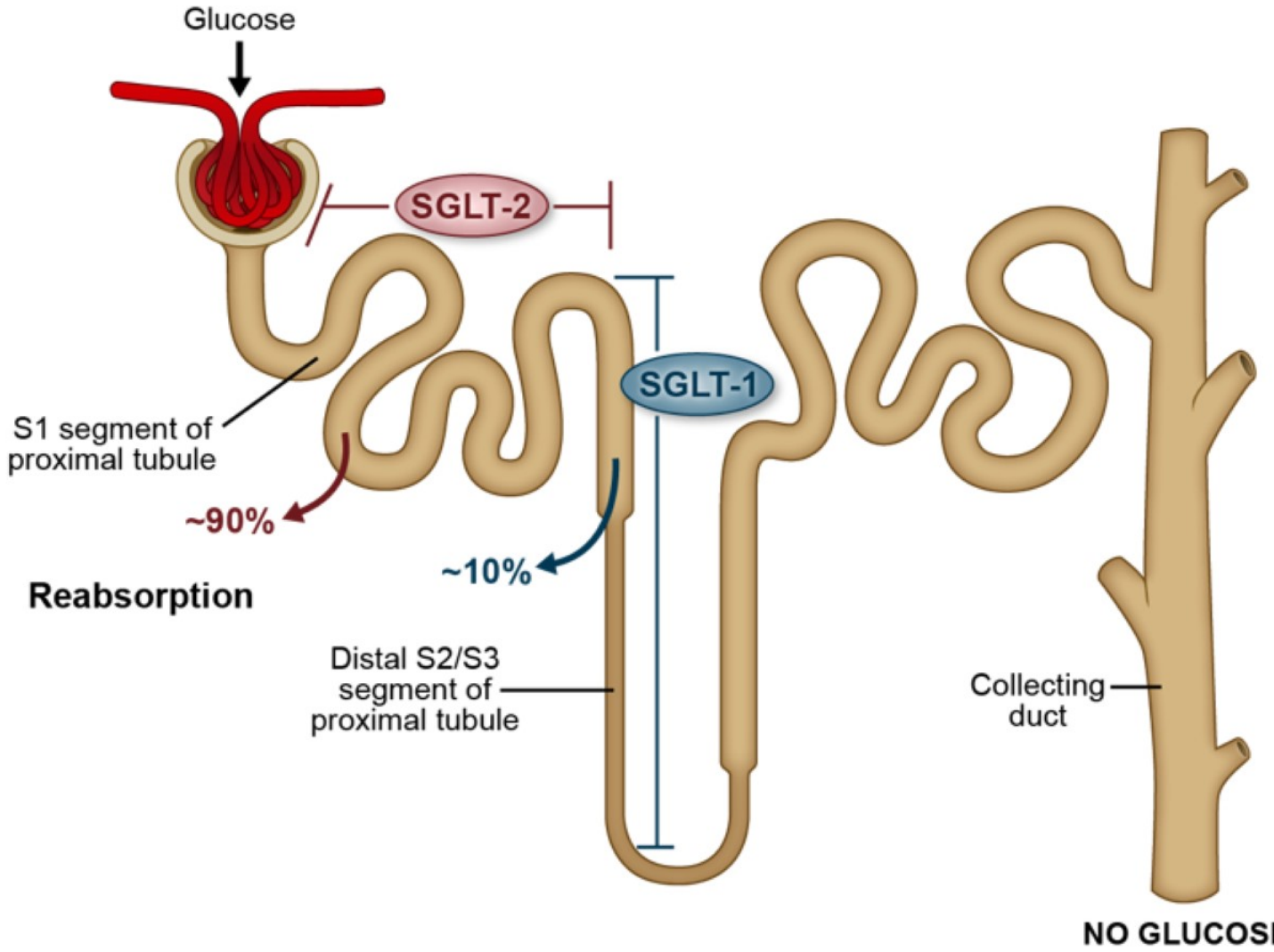
Kidneys Play an Important Role in Handling Glucose

Total glucose stored in body	~450 g
Glucose in Western diet	~180 g/d
Renal glucose filtration and reabsorption	~180 g/d
Urinary glucose	0 g

Virtually all glucose is reabsorbed in the proximal tubules and reenters the circulation in a healthy person; Virtually no glucose is excreted in urine

Wright EM, et al. *J Intern Med*. 2007;261:32-43.[2]

Renal Handling of Glucose



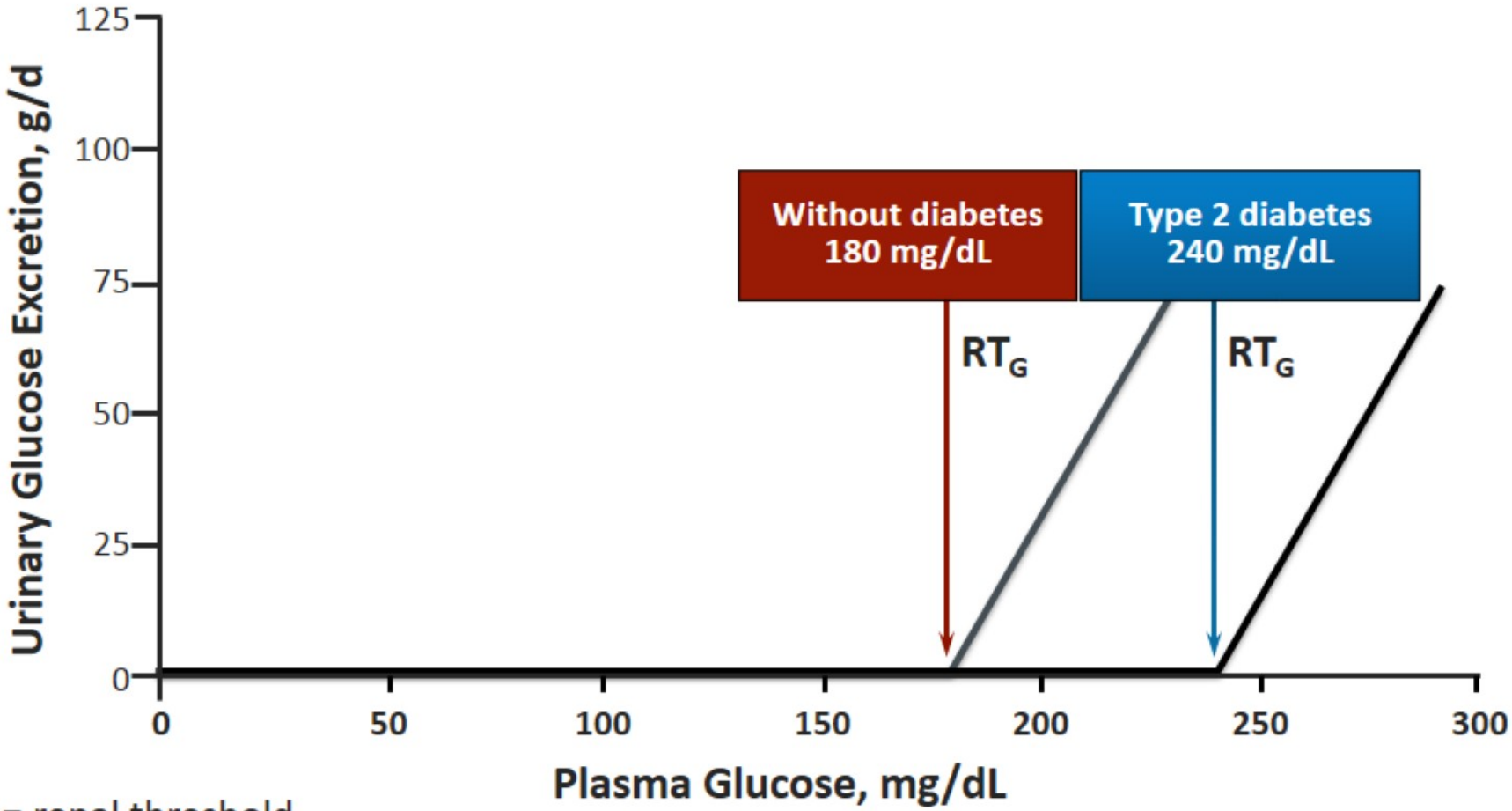
Wright EM, et al. *J Intern Med*. 2007;261:32-43[2]; Kanai Y, et al. *J Clin Invest*. 1994;93:397-404[3]; Wright EM. *Am J Physiol Renal Physiol*. 2001;280:F10-F18.[4]

Altered Renal Glucose Control in T2D

- Renal gluconeogenesis is increased in patients with T2D
  - Renal contribution to hyperglycemia
  - 3-fold increase relative to patients without T2D
- Glucose reabsorption is increased
  - Increased SGLT2 expression and activity in renal epithelial cells from patients with T2D vs normoglycemic individuals

a. Marsenic O. *Am J Kidney Dis*. 2009;53:875-83.[7]; b. Bakris GL, et al. *Kidney Int*. 2009;75:1272-77.[8]; c. Rahmoune H, et al. *Diabetes*. 2005;54:3427-34.[9]

Renal Threshold for Glucose Excretion

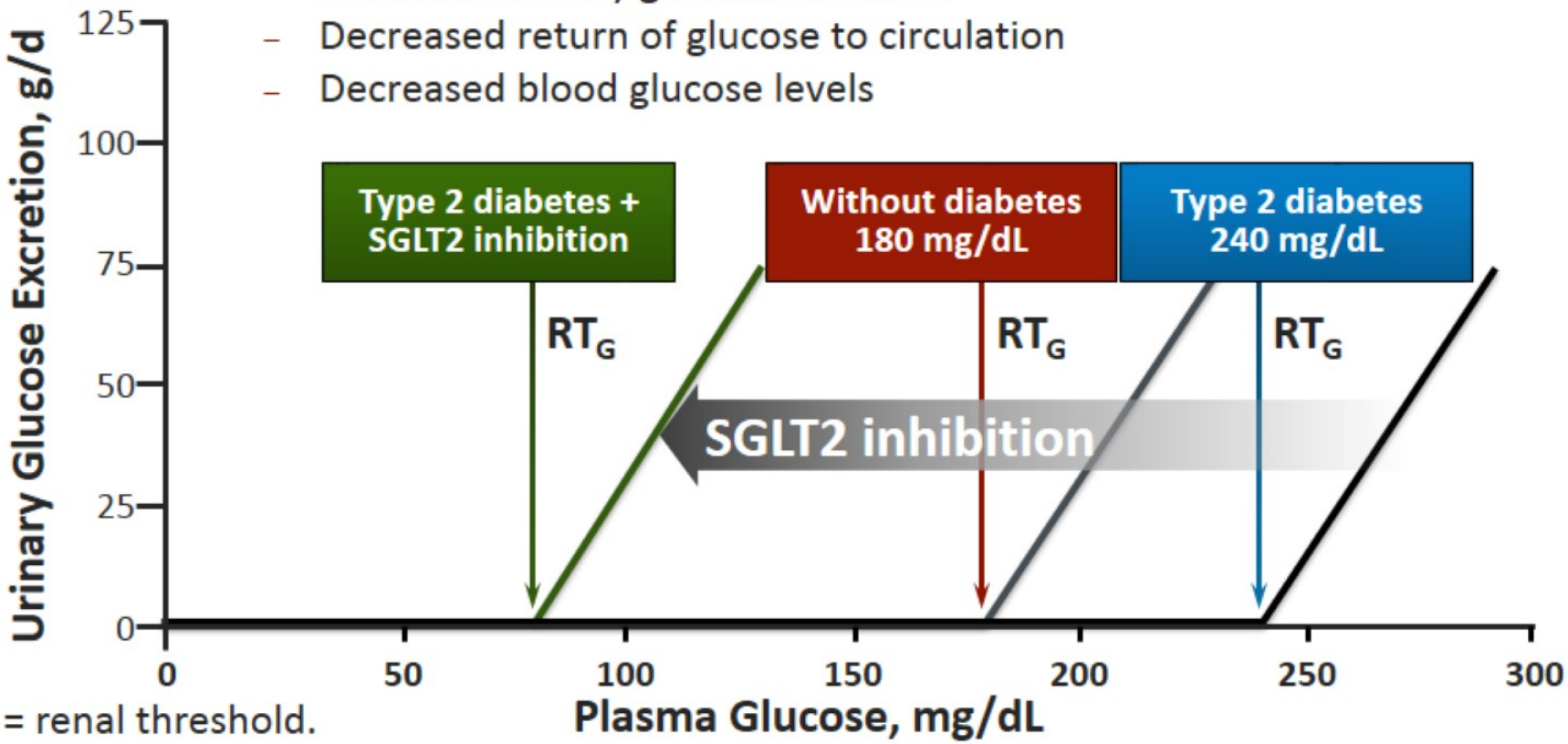


RT = renal threshold.

Nair S, Wilding JP. *J Clin Endocrinol Metab*. 2010;95:34-42[6]; Abdul-Ghani MA, DeFronzo RA. *Endocr Pract*. 2008;14:782-790.[10]

Inhibiting SGLT2 Promotes Urinary Glucose Excretion

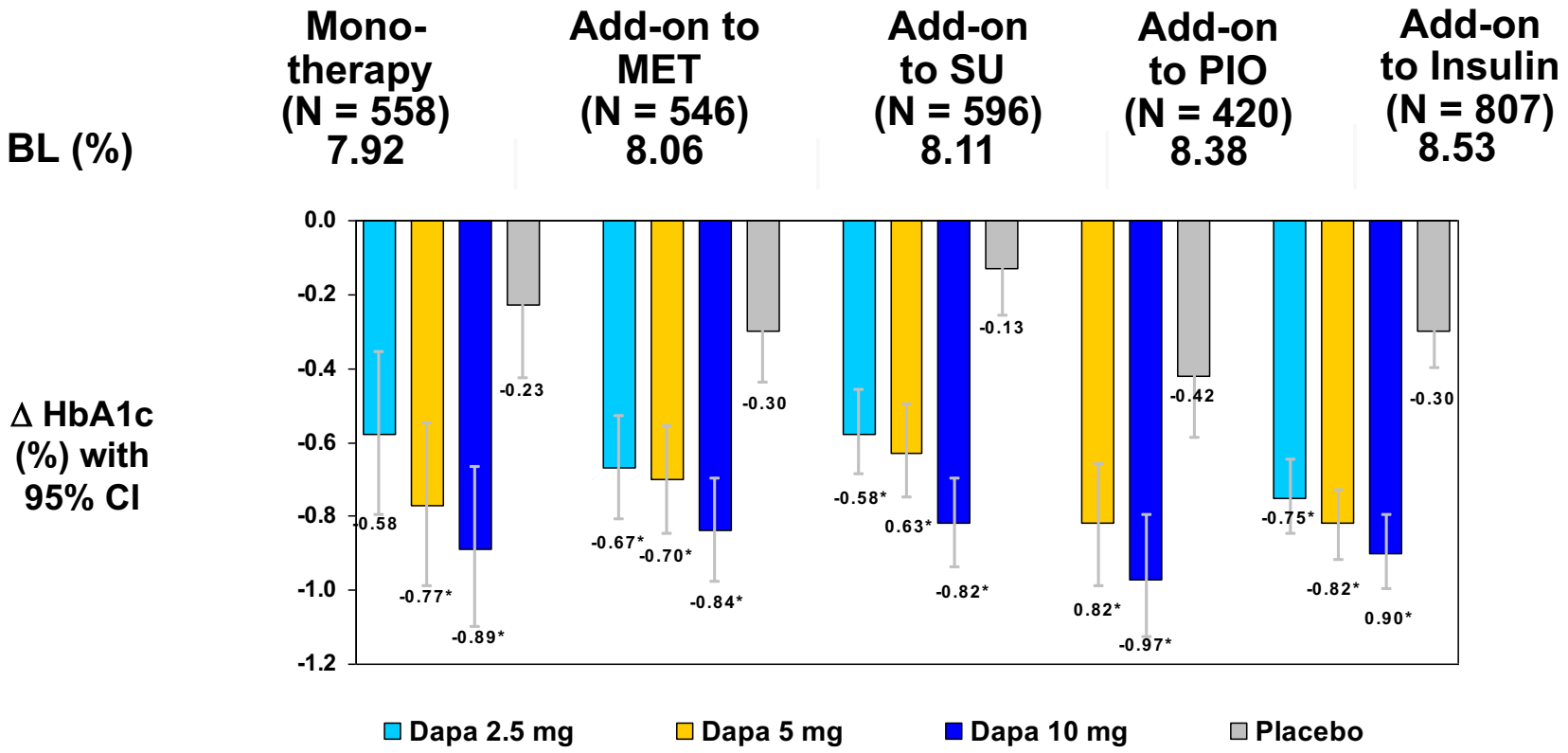
- SGLT2 inhibitors lower the threshold at which glucose is excreted, leading to
  - Increased urinary glucose excretion
  - Decreased return of glucose to circulation
  - Decreased blood glucose levels



RT = renal threshold.

Nair S, Wilding JP. *J Clin Endocrinol Metab*. 2010;95:34-42[6]; Abdul-Ghani MA, et al. *Endocr Pract*. 2008;14:782-790[10]; Chao EC, et al. *Nat Rev Drug Discov*. 2010;9:551-559.[11]

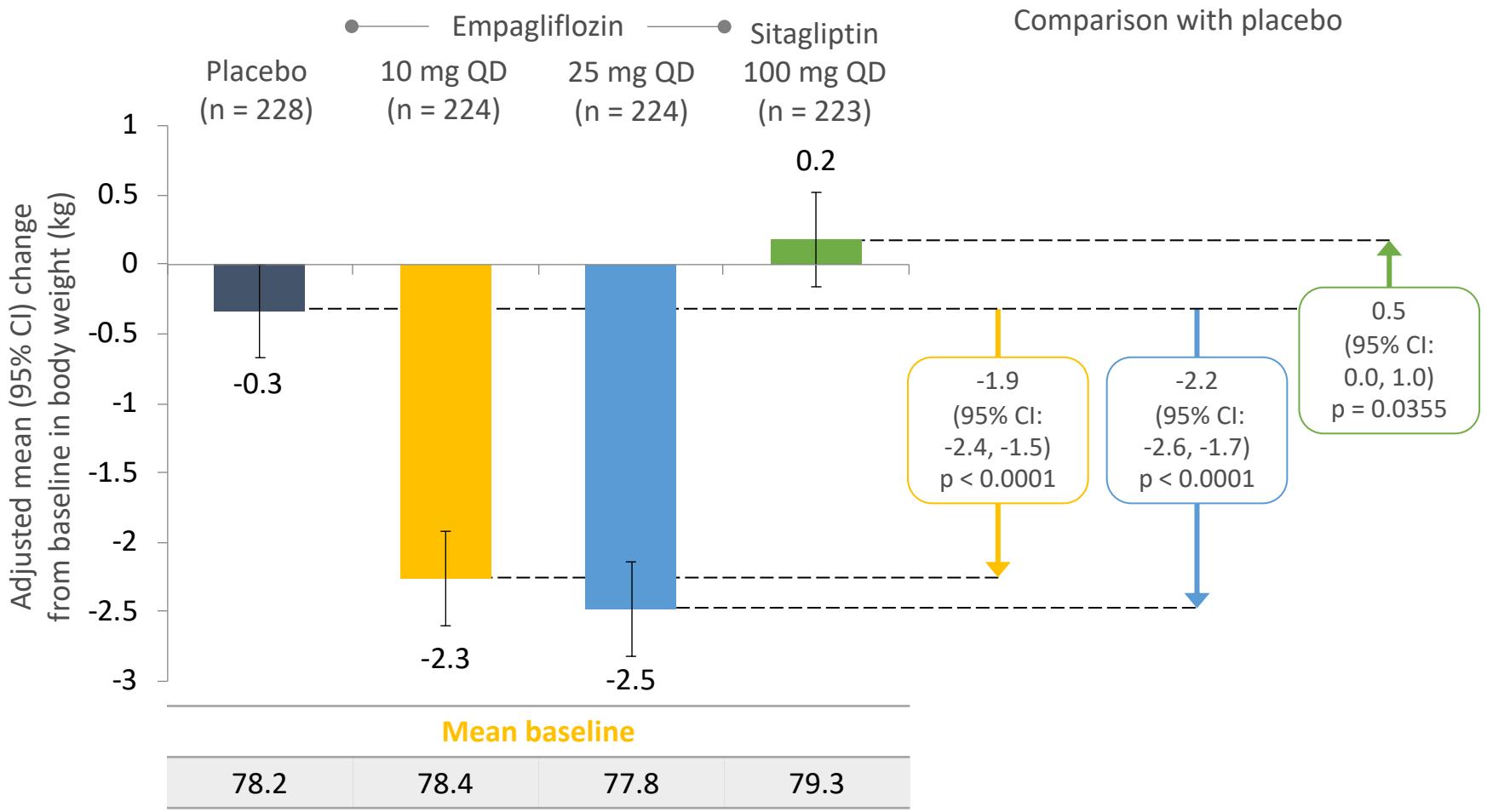
Change in HbA1c with Dapagliflozin Across 24-Week Studies



*P <.05 vs placebo.

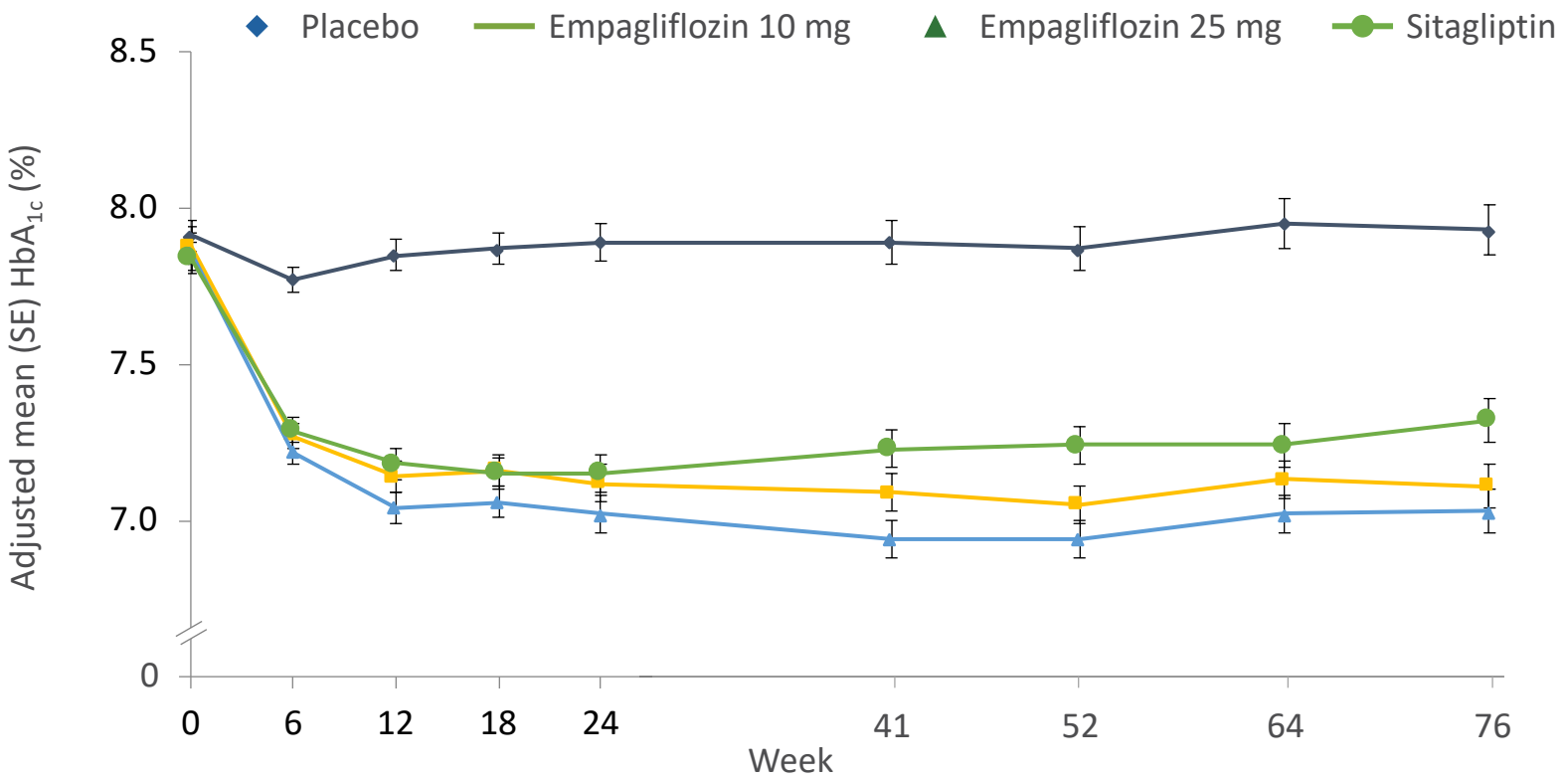
Abbreviations: BL, baseline; MET, metformin; PIO, pioglitazone; SU, sulfonylurea.
FDA Advisory Committee 19th July 2011: http://www.fda.gov.

24-week empagliflozin monotherapy versus placebo and sitagliptin
Change in body weight at Week 24



CI, confidence interval; QD, once daily.
ANCOVA, FAS (LOCF).
Roden M, et al. *Lancet Diabetes Endocrinol.* 2013;1:208–219.

52-week extension of empagliflozin monotherapy versus placebo and sitagliptin HbA_{1c} over time



Number of patients analysed									
Placebo	212	211	186	173	158	96	81	73	65
EMPA 10 mg	215	215	211	206	203	156	144	134	132
EMPA 25 mg	221	221	208	204	203	147	143	138	132
Sitagliptin	220	219	213	203	198	134	123	114	108

EMPA, empagliflozin; HbA_{1c}, glycosylated haemoglobin; SE, standard error.
MMRM in FAS (OC).
Roden M, et al. ADA 2014, Abstract 264-OR.

SGLT therapy Glycemic benefits

- 1. A1c reduction across the broad population of patients
- 2. Low risk of hypoglycemia
- 3. Well tolerated with mycotic infections and increased urination as the main side effect

SGLT2 Therapy- Non Glycemic Benefits

- 1. Weight loss
- 2. Blood pressure benefits
- **3. Cardiovascular**
- **4. Renal preservation**
- **5. CHF**

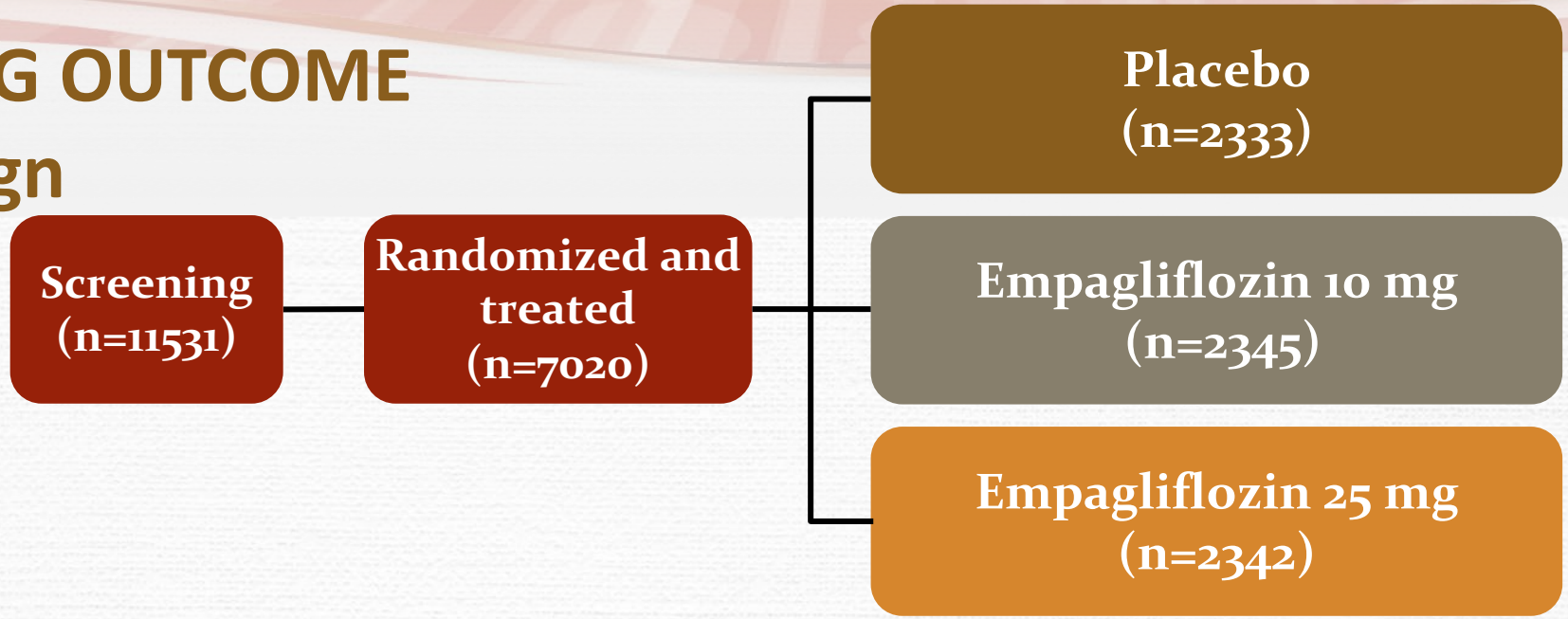
Cardiovascular Outcomes Trials: A Brief History

- 2008 FDA guidance mandating assessment of CV safety of all antihyperglycemic agents in RCTs
  - Designed as noninferiority studies to demonstrate study drug was not associated with more MACE than placebo
    - Some study designs tested for superiority if noninferiority criteria were met
  - Primary endpoint: composite of cardiovascular death, nonfatal MI, and nonfatal stroke
    - Some primary endpoints included additional components

MACE = major adverse cardiovascular events; RCTs, randomized controlled trials.

FDA. Guidance for industry: evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf.

EMPA-REG OUTCOME
Trial design



- **Study medication was given in addition to standard of care.**
- **The trial was to continue until ≥ 691 patients experienced an adjudicated primary outcome event.**
- **Key inclusion criteria:**
  - Adults with type 2 diabetes and established CVD
  - BMI ≤45 kg/m^2; HbA1c 7–10%; eGFR ≥30 mL/min/1.73m^2 (MDRD)

CV, cardiovascular; BMI, body mass index; eGFR, estimated glomerular filtration

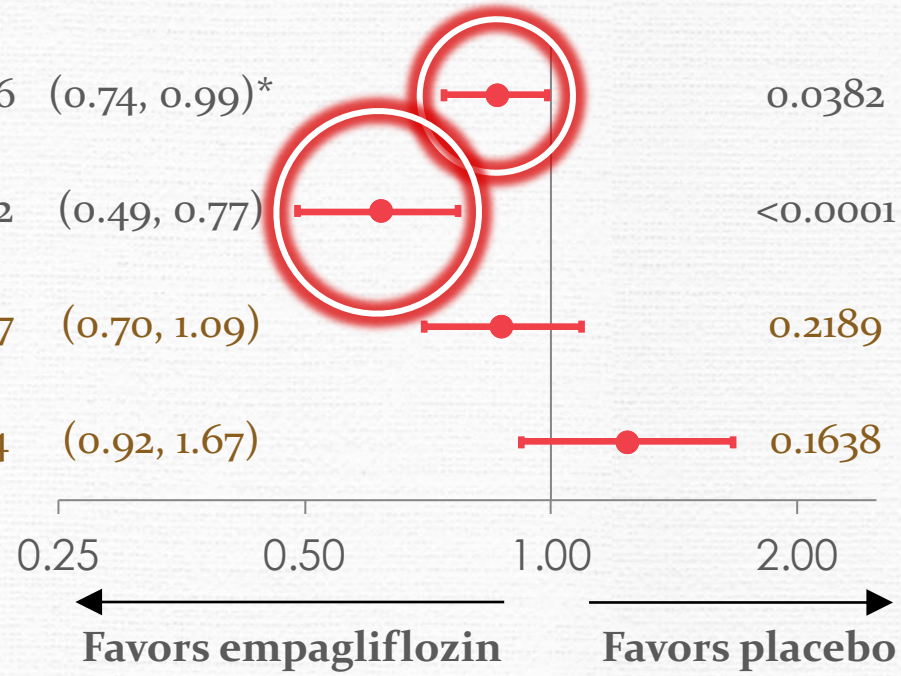
Planned outcomes and analyses

- **Primary outcome: 3-point MACE**
- **Further outcomes included: heart failure hospitalization or CV death, hospitalization for heart failure, all-cause mortality**
- **Analysis compared empagliflozin 10 mg and 25 mg (pooled) vs. placebo in patients treated with ≥1 dose of study drug (intent-to-treat population)**
- **Secondary analyses included comparisons of individual empagliflozin doses vs. placebo**
- **Subgroup analyses were based on baseline characteristics, including the presence/absence of investigator-reported heart failure**

3-point MACE: Time to first occurrence of CV death, non-fatal MI or non-fatal stroke.
MACE, Major Adverse Cardiovascular Event; CV, cardiovascular; MI, myocardial infarction.
Zinman B et al. N Engl J Med 2015 [Epub ahead of print].

Primary outcome

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



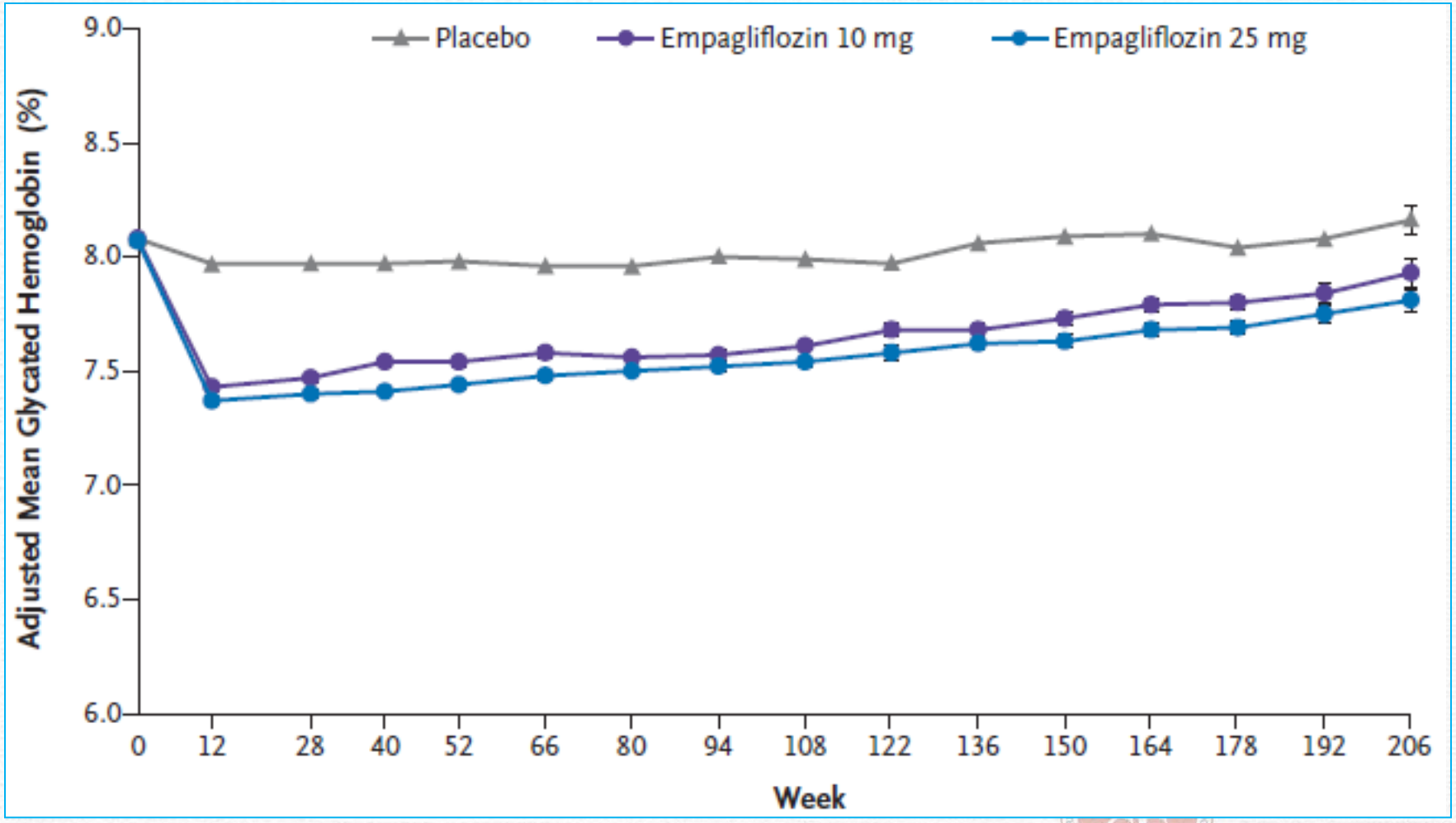
Cox regression analysis. 3-point MACE: Time to first occurrence of CV death, non-fatal MI or non-fatal stroke.

MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.

*95.02% CI

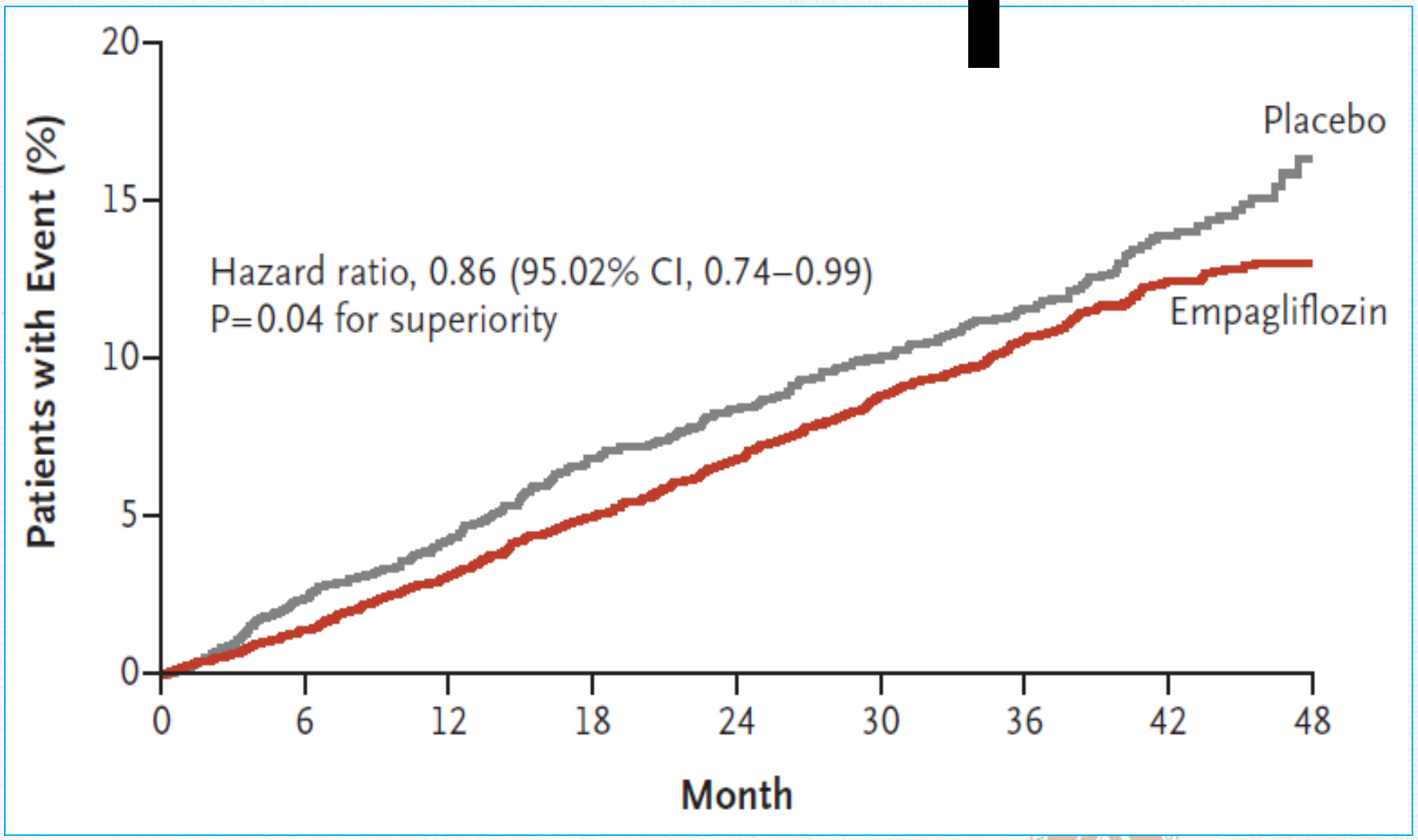
Zinman B et al. N Engl J Med 2015 [Epub ahead of print].

Modest A1c reduction with EMPA



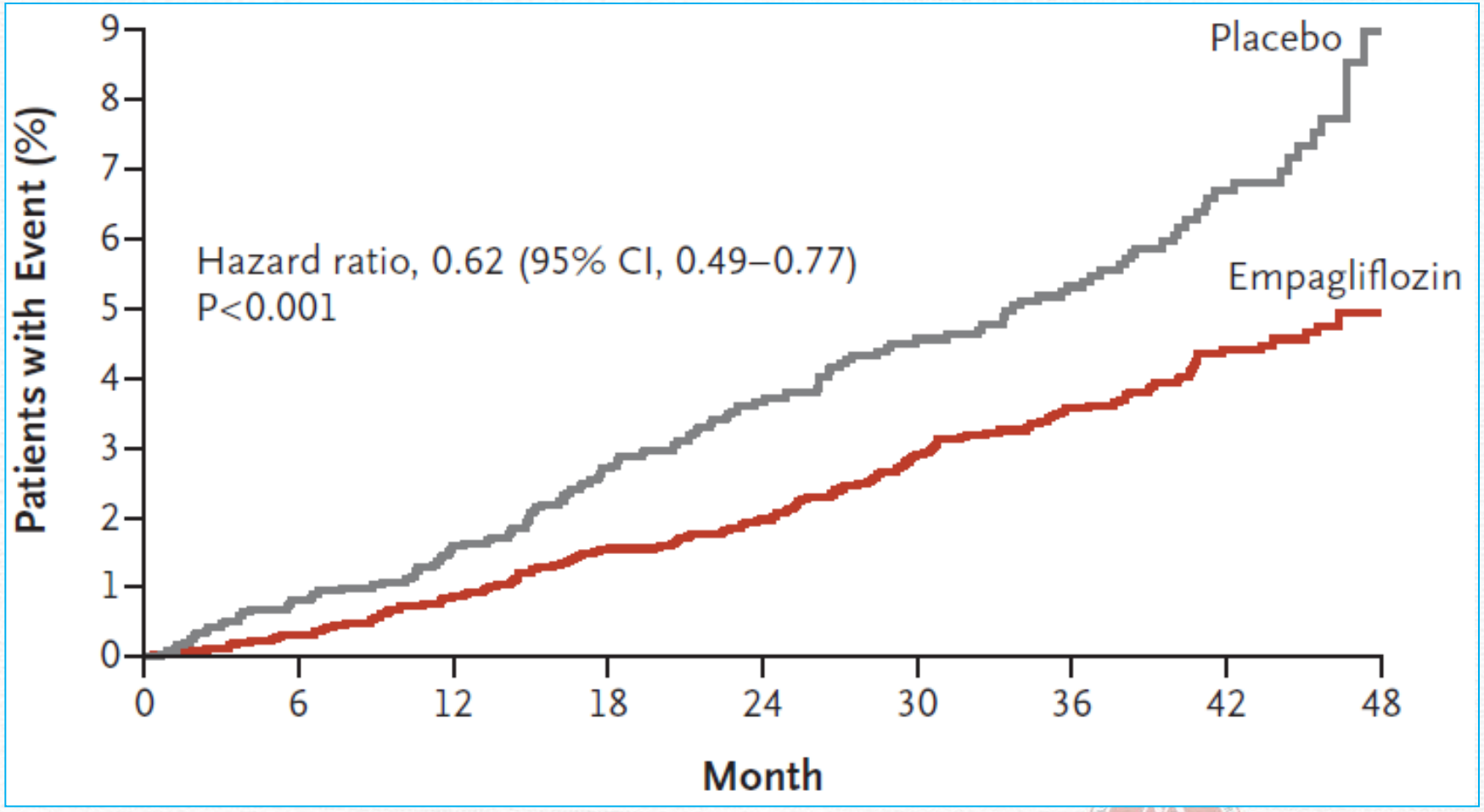
N Engl J Med 2015;373:2117-2128.

endpoint (MACE)



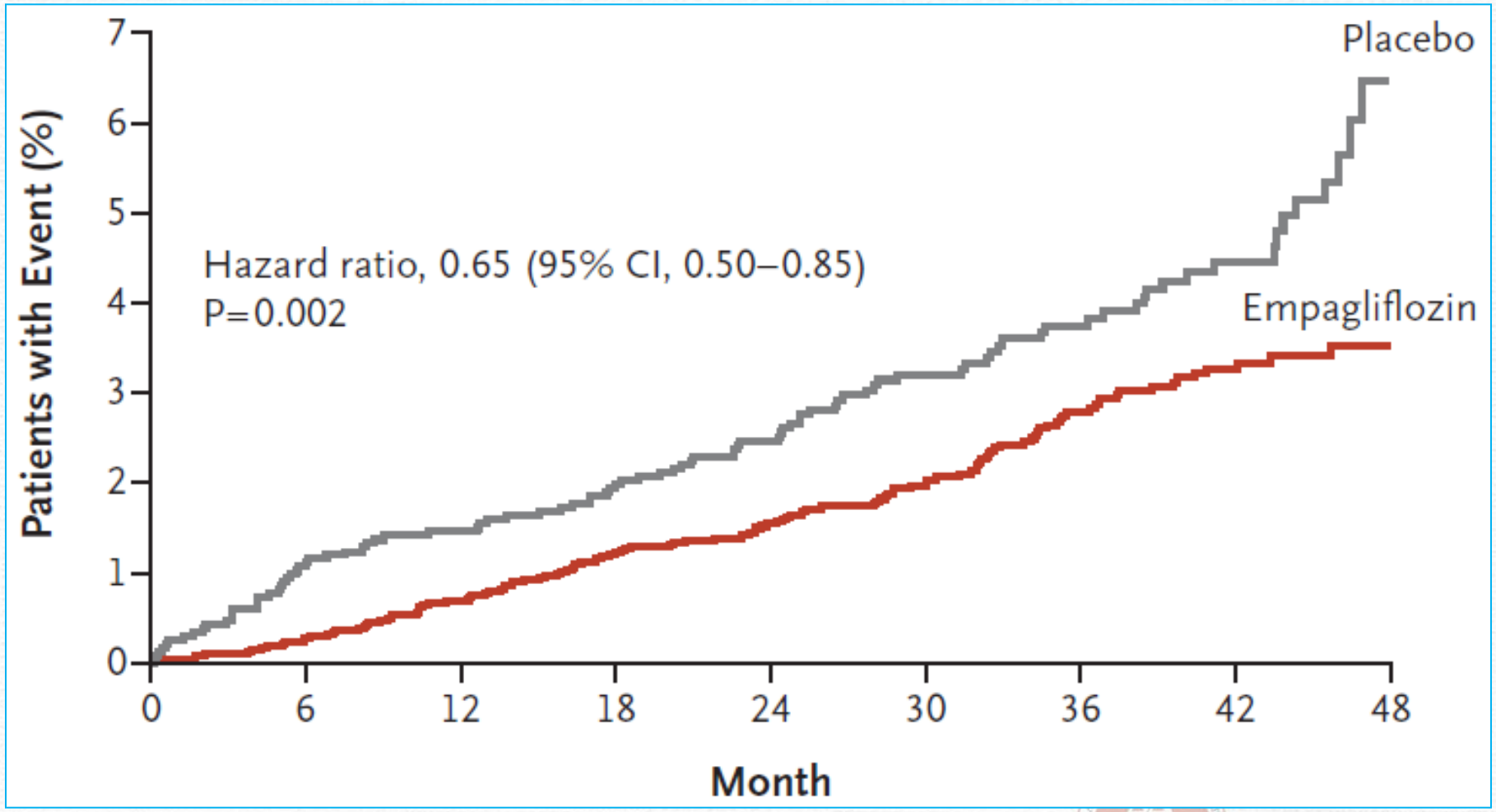
N Engl J Med 2015;373:2117-2128.

CV Death reduced by 38%



N Engl J Med 2015;373:2117-2128.

HF Hospitalization reduced by 35%



N Engl J Med 2015;373:2117-2128.

What is the explanation for the reduction in CV death?

No difference in rates of MI or CVA

Only 10% with HF at baseline

Diuretics (excepting aldosterone antagonists) have not been shown to reduce mortality

What is the explanation for the reduction in CV death?

Related to modest BP reduction (~4 mmHg)?

Related to modest weight loss (~2 kg)?

Unidentified mechanism?

EMPA-REG OUTCOME and CANVAS
Results

EMPA-REG OUTCOME (secondary prevention cohort)[a]

- Empagliflozin decreased MACE by 14% (HR = 0.86 [95% CI: 0.74, 0.99]; *P* = .04 for superiority)
  - 38% reduction in CV death (significant)
  - 32% reduction in all-cause mortality (significant)
  - 35% reduction in HF-related hospitalization

CANVAS, CANVAS-R (primary prevention cohort)[b]

- Canagliflozin decreased MACE by 14% (HR = 0.86 [95% CI: 0.75, 0.97]), composite of CV death, nonfatal MI, and nonfatal stroke
  - 13% reduction in CV death
  - 22% reduction in CV death or HF-related hospitalization
  - 13% reduction in all-cause mortality (nonsignificant)

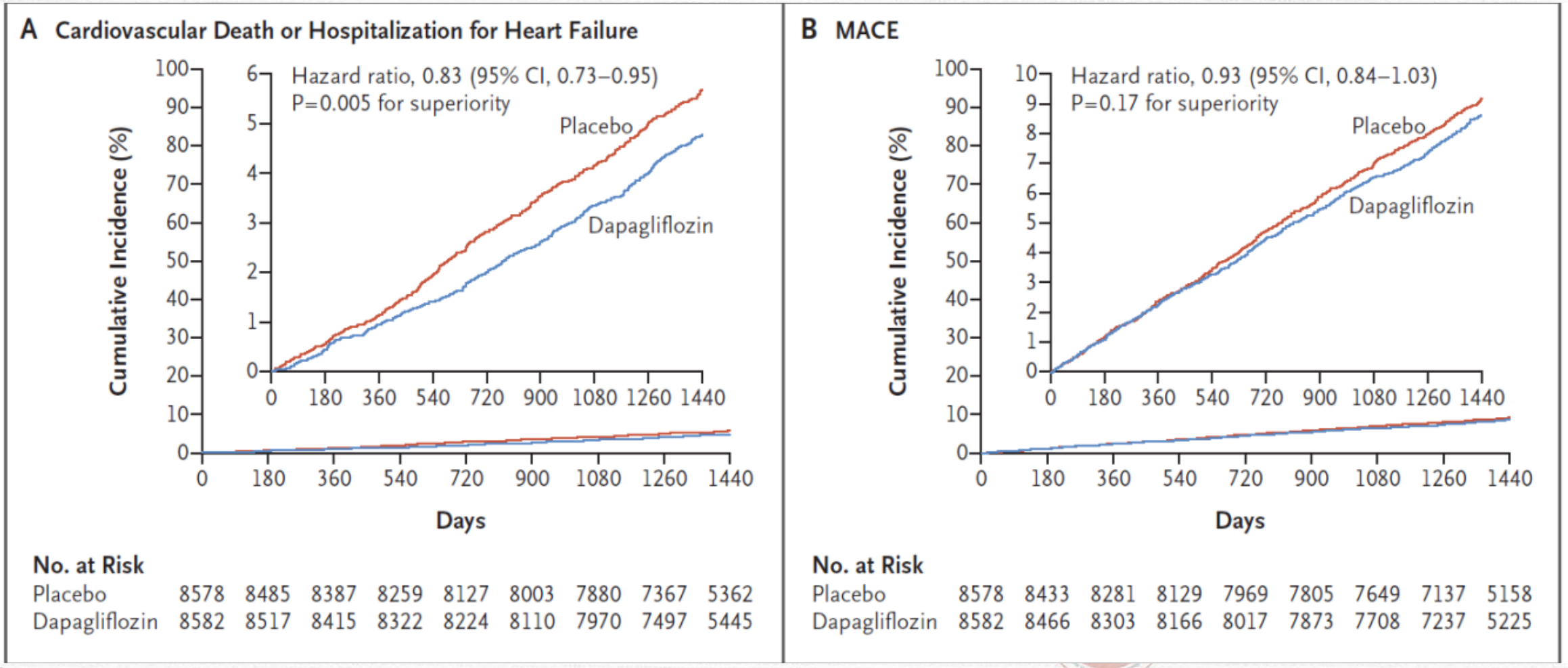
a. Zinman B, et al. *N Engl J Med.* 2015;373:2117-2128; b. Neal B, et al. *N Engl J Med.* 2017;377:644-657.

DECLARE-TIMI58 and VERTIS-CV
Outcome Measures

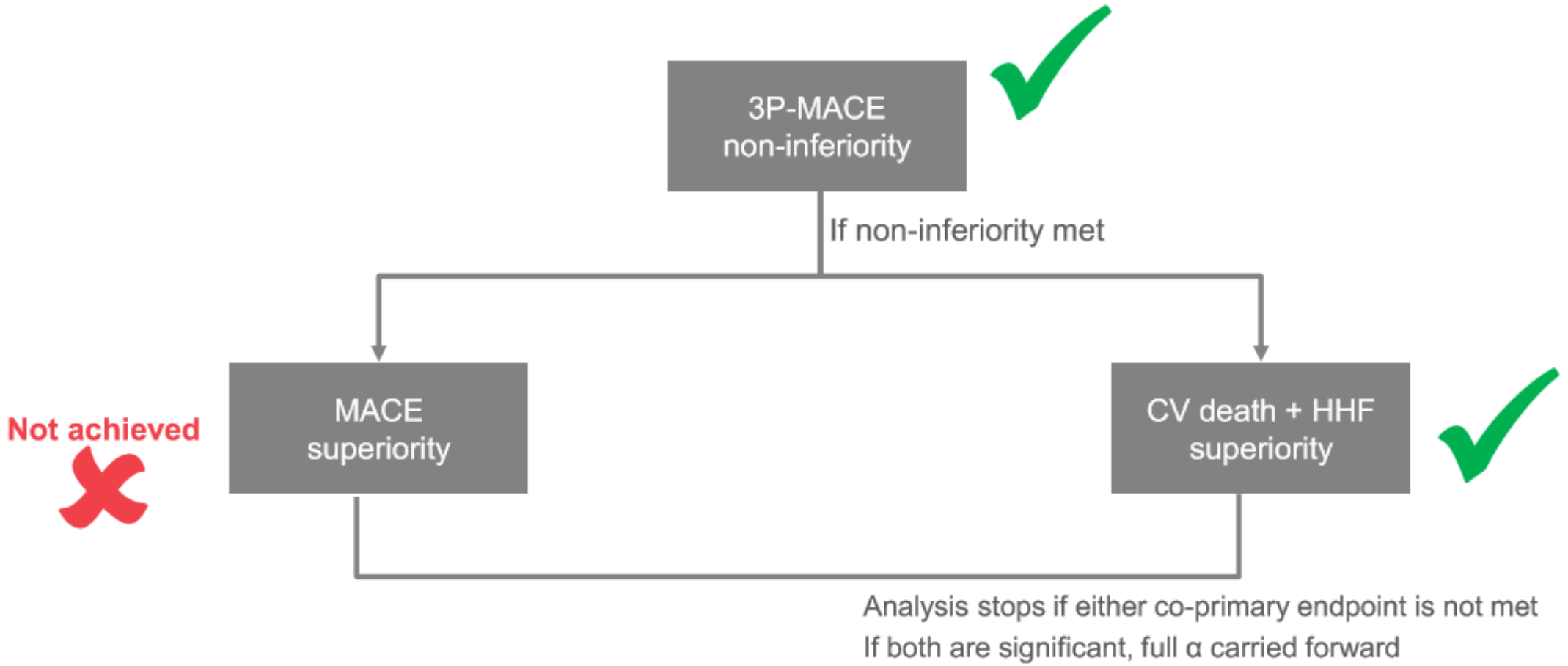
DECLARE TIMI58 (dapagliflozin)[a,b]	Primary outcomes: • Time to first event included in the composite endpoint of CV death, MI, or ischemic stroke • Time to first event included in the composite endpoint of CV death or hospitalization because of HF Secondary outcomes: • Time to first event of renal composite endpoint • Time to all-cause mortality
VERTIS-CV (ertugliflozin)[c]	Primary outcome: • Time to the first event of CV death, nonfatal MI, or nonfatal stroke Secondary outcomes: • The composite endpoint of CV death or hospitalization for HF • CV death • The composite endpoint of renal death, dialysis/transplant, or doubling of serum creatinine from baseline

a. ClinicalTrials.gov. NCT01730534.; b. Raz I, et al. *Diabetes Obes Metab*. 2018;20:1102-1110; c. Cannon CP, et al. ACC 2018. Poster 1212-406.

DAPAGLIFLOZIN:DECLARE-TIMI 58



DECLARE-TIMI 58: analysis plan



CV Outcomes Trials With SGLT-2 Inhibitors in T2DM

CV safety in post-marketing prospective trials compared with placebo

Trial →	DECLARE[a]	EMPA-REG[b]	CANVAS[b]
	Dapagliflozin HR, 95% CI	Empagliflozin HR, 95% CI	Canagliflozin HR, 95% CI
3-point MACE	**0.93** 0.84, 1.03	**0.86*** 0.74, 0.99	**0.86*** 0.75, 0.97
CV death	**0.98** 0.82, 1.17	**0.62*** 0.49, 0.77	**0.87** 0.72, 1.06
Non-fatal MI	**0.89** 0.77, 1.01	**0.87** 0.70, 1.09	**0.85** 0.69, 1.05
Non-fatal stroke	**1.01** 0.84, 1.21	**1.24** 0.92, 1.67	**0.90** 0.71, 1.15
Hospitalised HF	**0.73*** 0.61, 0.88	**0.65*** 0.50, 0.85	**0.67** 0.52, 0.87
All cause death	**0.93** 0.82, 1.04	**0.68*** 0.57, 0.82	**0.87** 0.74, 1.01
Prior CVD(%)	41	99	65
Types of prior CVD	CVD or ≥ 1 CV risk factor	MI, CHD, CVD, PVD	MI, CHD, CVD, PVD

*Statistically significant or nominally statistically significant.

a. Wiviott SD, et al. *N Engl J Med.* 2019; 380:347-357; b. Bailey CJ, Marx N. *Diabetes Obes Metab*. 2019;21:3-14.

SGLT2 Heart Failure Data

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687/7020	2333/7020	463	19·7	30·1	30·9		0·66 (0·55–0·79)
CANVAS Program	3756/6656	2900/6656	524	21·0	27·4	32·8		0·77 (0·65–0·92)
DECLARE-TIMI 58	3474/6974	3500/6974	597	19·9	23·9	36·4		0·83 (0·71–0·98
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)								**0·76 (0·69–0·84)**
Patients with multiple risk factors								
CANVAS Program	2039/3486	1447/3486	128	8·9	9·8	30·2		0·83 (0·58–1·19)
DECLARE-TIMI 58	5108/10 186	5078/10 186	316	7·0	8·4	69·8		0·84 (0·67–1·04)
Fixed effects model for multiple risk factors (p=0·0634)								**0·84 (0·69–1·01)**

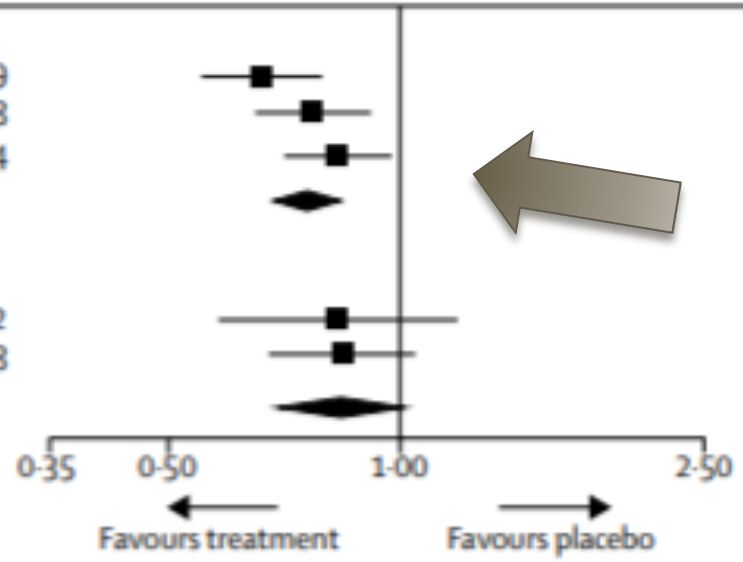
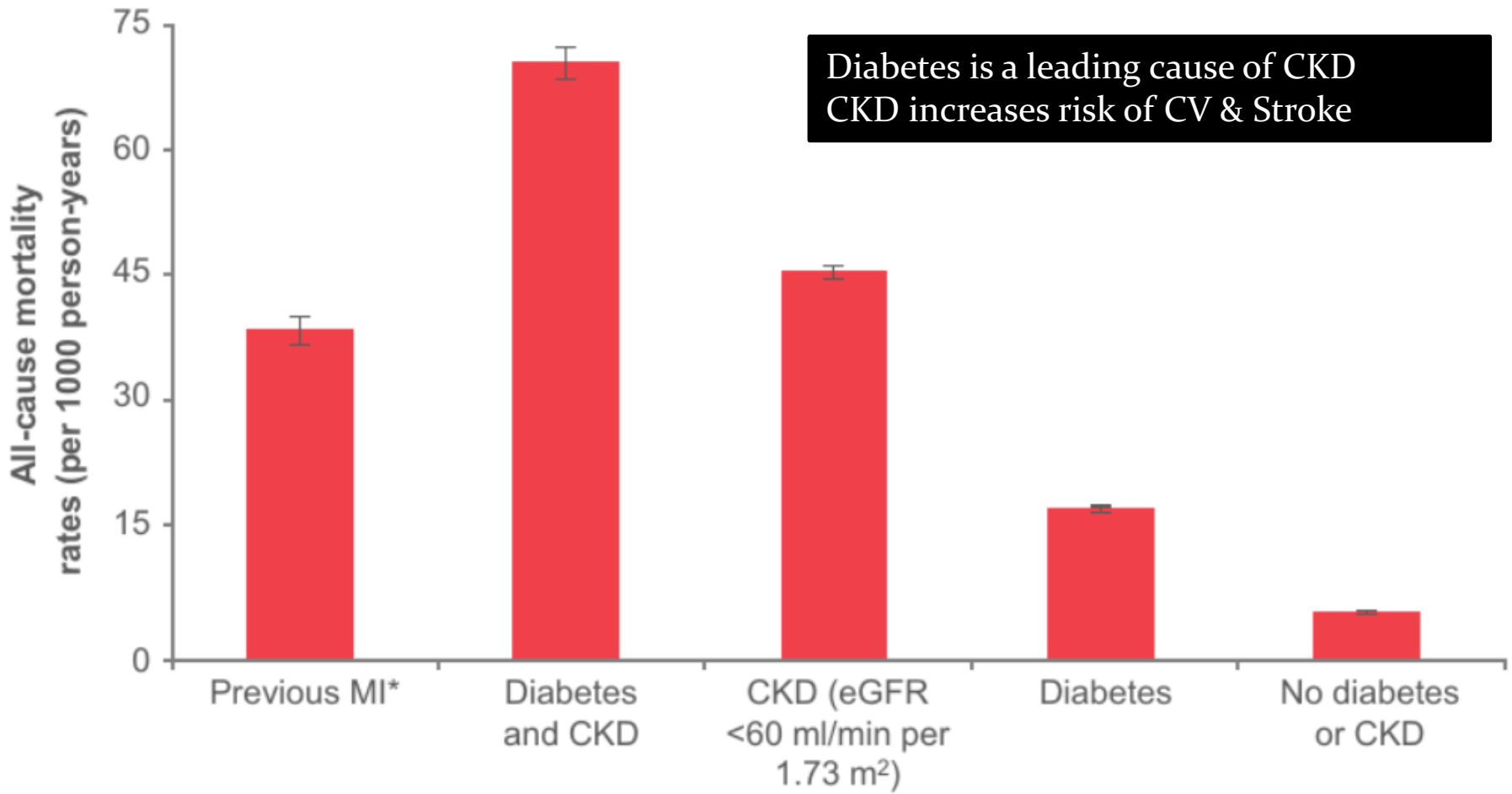


Figure 2: **Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by the presence of established atherosclerotic cardiovascular disease**

Kidney disease is associated with increased all-cause mortality

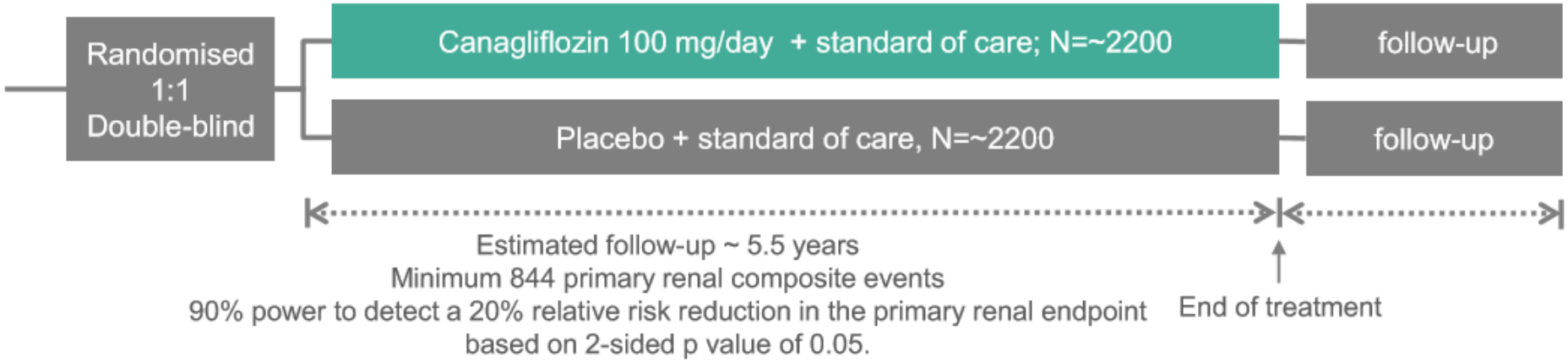


Diabetes is a leading cause of CKD
CKD increases risk of CV & Stroke

*Includes participants with or without diabetes and chronic kidney disease
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction
Tonelli M *et al. Lancet* 2012;380:807

CREDENCE: study design

Aim: Evaluate whether canagliflozin reduces the risk of kidney failure and CV events in patients with T2DM and markers of established kidney disease compared to placebo when used in addition to standard of care



Main inclusion criteria

- HbA1c ≥6.5% and ≤12.0%
- eGFR ≥30 and <90 mL/min/1.73 m^2
- UACR >300 and ≤5,000 mg/g
- Maximum tolerated labeled daily dose of an ACE inhibitor or ARB for ≥4 weeks prior to randomization

Main exclusion criteria

- Non diabetic kidney disease who have a history of treatment of kidney disease with immunosuppression, or a history of treatment with dialysis or kidney transplantation
- Combination use of an ACEi and ARB or use of a DRI
- Hx of CV events within the previous 12 weeks or a history of NYHA class IV heart failure

Primary endpoint: time to first occurrence of renal composite endpoint:

- **ESRD**
- **Doubling of serum creatinine**
- **CV or renal death**

Key secondary endpoints: time to first occurrence of :

- **CV death or Hospitalized congestive heart failure**
- **CV death/ nonfatal MI/ nonfatal stroke**
- **Composite of ESRD/doubling of serum creatinine/renal death**

Jardine M et al. Am J Nephrol 2017:46:462-472.

CREDENCE: Study design

Aim **Compound-specific**

To determine whether canagliflozin has a renal/vascular protective effect vs placebo

Main inclusion criteria

1. Stage 2 or 3 CKD and macroalbuminuria
2. On ACE inhibitor or ARB
3. Age ≥ 30 years

+ Usual care for T2D

Canagliflozin (100 mg) vs Placebo

N = 3700; expected duration of follow-up ~4 years

Primary endpoint: time to first occurrence of:

- End-stage kidney disease
- Serum creatinine doubling
- Renal or CV death

Other endpoints:

Composite CV safety endpoint*

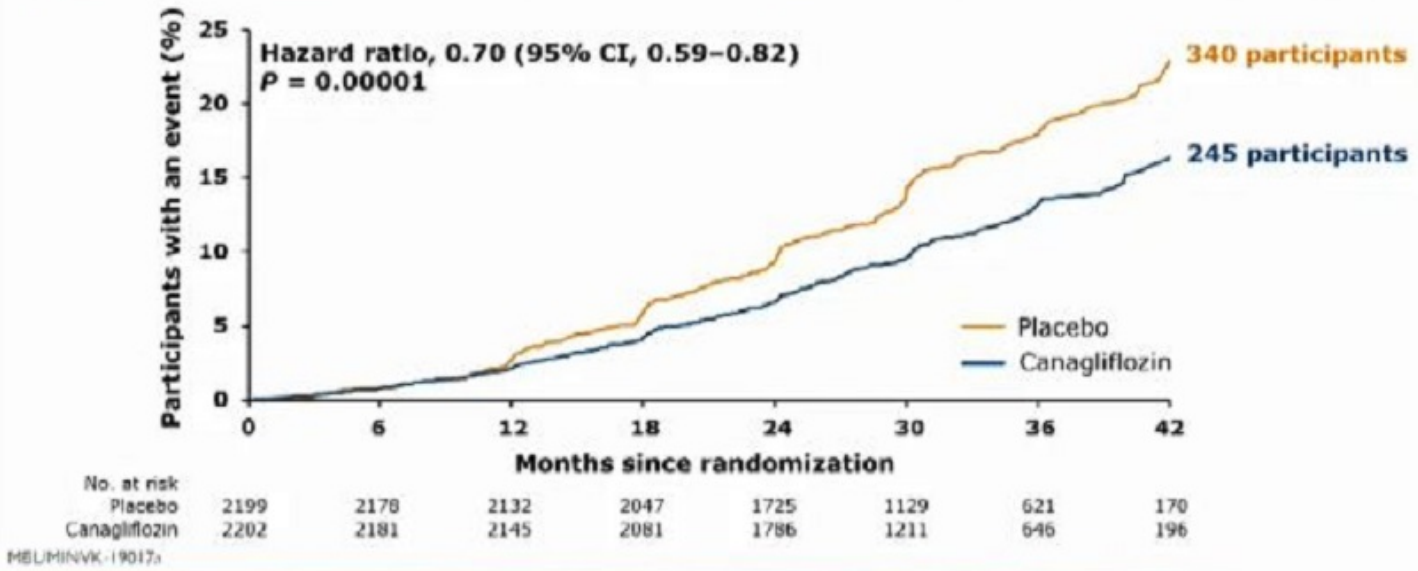
Although primarily a renal study, CREDENCE will prospectively collect adjudicated CV outcomes, as required by the FDA mandate

*CV death, non-fatal MI, non-fatal stroke, hospitalised congestive heart failure and hospitalised unstable angina.

NCT02065791.

Back

Primary Outcome:
ESKD, Doubling of Serum Creatinine, or Renal or CV Death



Summary

Primary	Hazard ratio (95% CI)	*P* value	
1. ESKD, doubling of serum creatinine, or renal or CV death	0.70 (0.59–0.82)	0.00001	✔
Secondary			
2. CV death or hospitalization for heart failure	0.69 (0.57–0.83)	<0.001	✔
3. CV death, MI, or stroke	0.80 (0.67–0.95)	0.01	✔
4. Hospitalization for heart failure	0.61 (0.47–0.80)	<0.001	✔
5. ESKD, doubling of serum creatinine, or renal death	0.66 (0.53–0.81)	<0.001	✔
6. CV death	0.78 (0.61–1.00)	0.0502	Not significant
7. All-cause mortality	0.83 (0.68–1.02)	–	Not formally tested
8. CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina	0.74 (0.63–0.86)	–	Not formally tested

- 1st drug since ACE/ARB that is in studies has shown promise for pts with renal complication from diabetes.
- Study was stopped at 2.6 yrs due to + results

Now indicated to reduce the risk of end stage renal disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in those with type diabetes, diabetic nephropathy and albuminuria >300 mg/day

CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)

Use principles in Figure 1

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Use metformin unless contraindicated or not tolerated

If not at HbA_{1c} target:

- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add SGLT2i or GLP–1 RA with proven cardiovascular benefit[1] (See below)

If at HbA_{1c} target:

- If already on dual therapy, or multiple glucose–lowering therapies and not on an SGLT2i or GLP–1 RA, consider switching to one of these agents with proven cardiovascular benefit[1] (See below)

OR reconsider/lower individualised target and introduce SGLT2i or GLP–1 RA

OR reassess HbA_{1c} at 3 month intervals and add SGLT2i or GLP–1 RA if HbA_{1c} goes above target

ASCVD predominates

GLP–1 RA with proven CVD benefit[1]

EITHER/ OR

SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

If HbA_{1c} above target

If further intensification is required or patient is unable to tolerate GLP–1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP–1 RA or SGLT2i) with proven CVD benefit[1]
- DPP–4i if not on GLP–1 RA
- Basal insulin[5]
- TZD[6]
- SU[7]

HF or CKD predominates

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP–1 RA with proven CVD benefit[1,4]

If HbA_{1c} above target

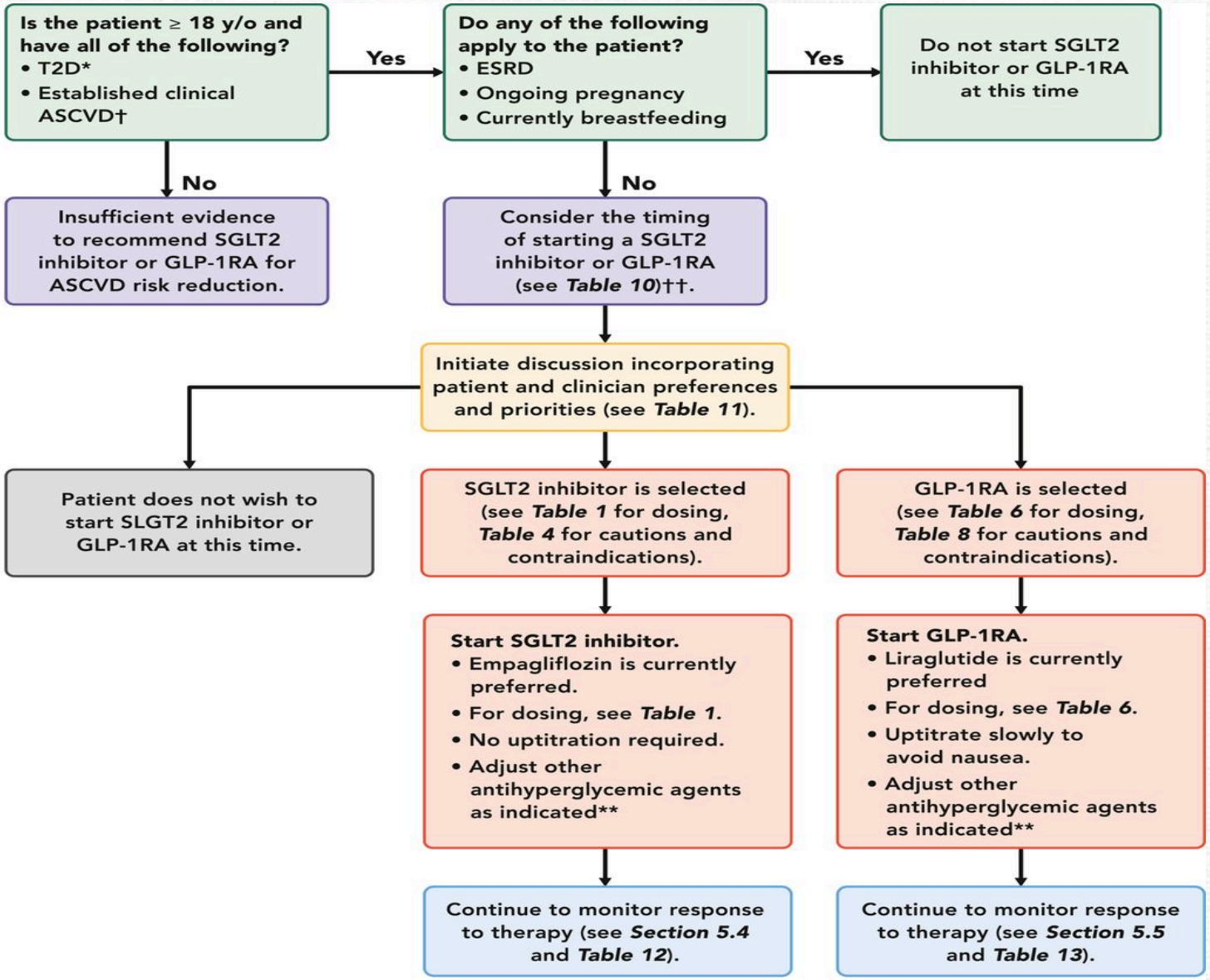
- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit[1]
- DPP–4i (not saxagliptin) in the setting of HF (if not on GLP–1 RA)
- Basal insulin[5]
- SU[7]

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP–1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs
4. Caution with GLP–1 RA in ESRD
5. Degludec or U100 glargine have demonstrated CVD safety
6. Low dose may be better tolerated though less well studied for CVD effects

2018 ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction With Type 2 Diabetes and Atherosclerotic Cardiovascular Disease



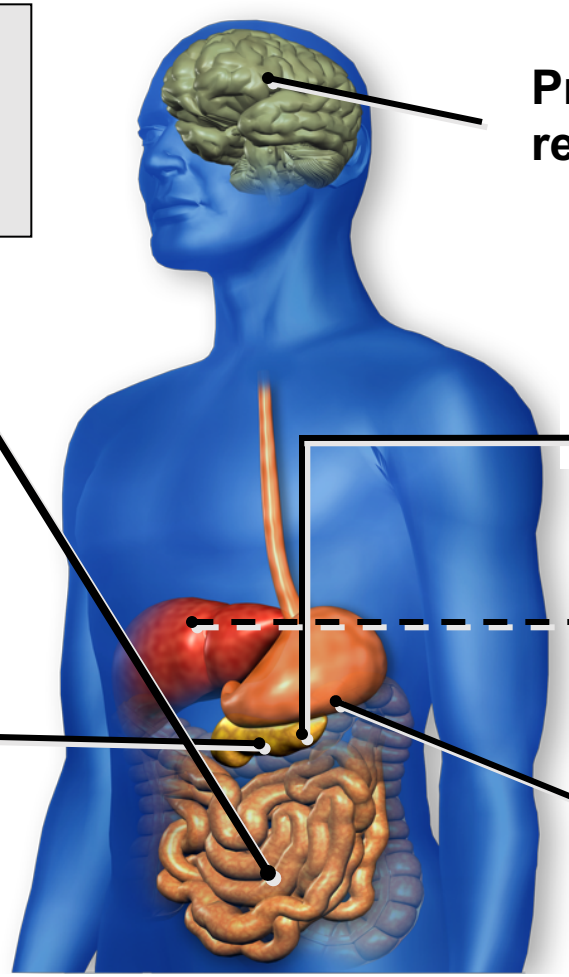
*SGLT2 inhibitors and GLP-1RA have not been studied in and do not have an FDA -approved indication for patients with type 1 diabetes.

GLP-1

- 14 years on the market
- Provide A1c reduction across a broad population of patients
- Low risk of hypoglycemia
- Added benefit of weight reduction
- Cardiovascular benefits
- Main side effects are GI with nausea and vomiting the most common and less common, pancreatitis

GLP-1 Modulates Numerous Functions

GLP-1: Secreted upon the ingestion of food



Promotes satiety and reduces appetite

Alpha cells:
↓ Postprandial glucagon secretion

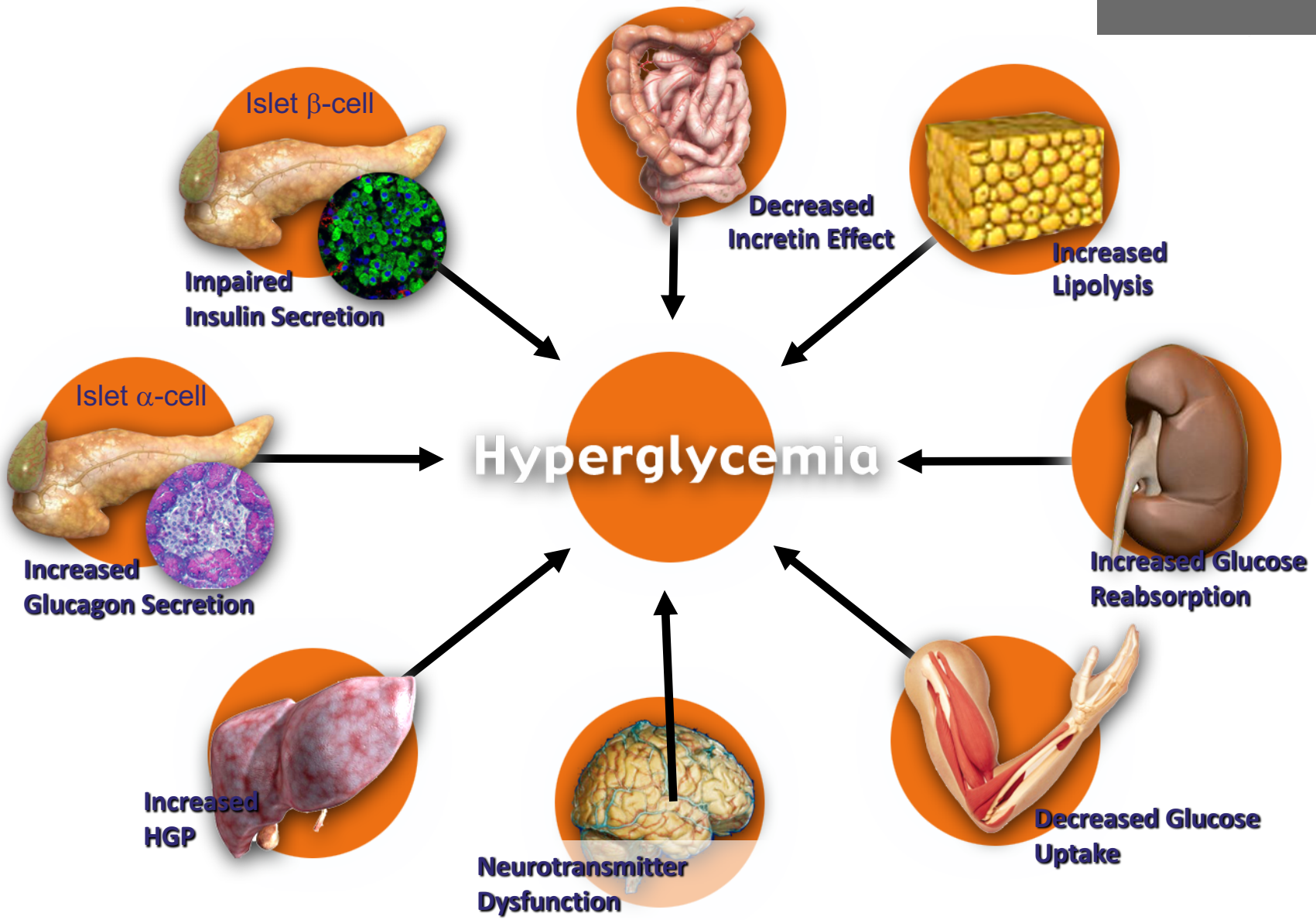
Beta cells:
Enhances glucose-dependent insulin secretion

Liver:
↓ Glucagon reduces hepatic glucose output

Stomach:
Helps regulate gastric emptying

Data from Flint A, et al. J Clin Invest. 1998;101:515-520; Data from Larsson H, et al. Acta Physiol Scand. 1997;160:413-422
Data from Nauck MA, et al. Diabetologia. 1996;39:1546-1553; Data from Drucker DJ. Diabetes. 1998;47:159-169

The Ominous Octet



GLP-1 agonists

- Exenatide
- Liraglutide
- Dulaglutide
- Lixisenatide
- Semiglutide

GLP-1-Not all created equally

Weekly

-Exenatide LAR (BCISE, Bydureon)

-Dulaglutide (Trulicity)

-Semiglutide (Ozempic)

Daily

-Liraglutide (Victoza)

-Lixisenatide (Adlyxin)

GLP-1-Not all created equally

A1c reduction

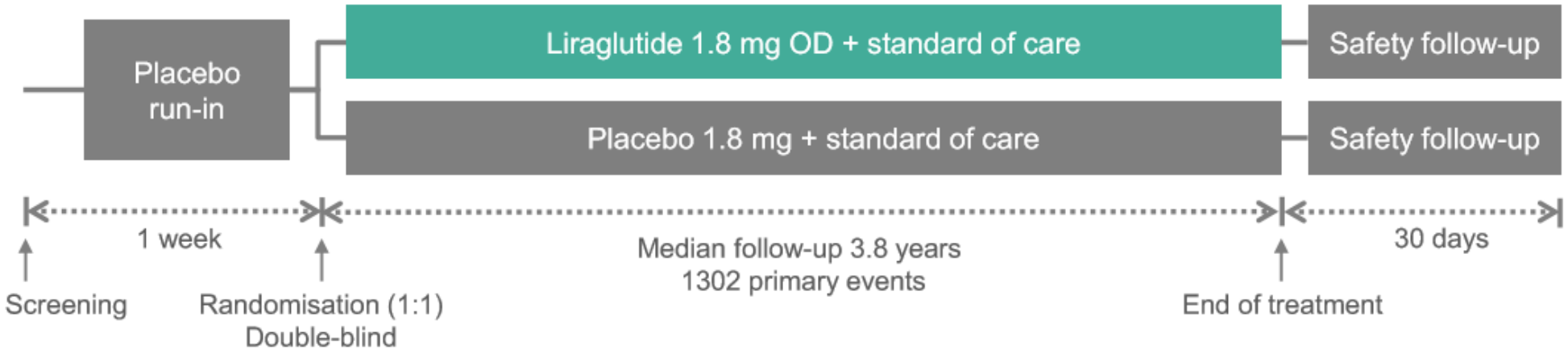
1. Semiglutide
2. Dulaglutide/Liraglutide
3. Exenatide LAR
4. Adlyxin

Tolerability (less GI symptoms)

1. Exenatide LAR/Adlyxin
2. Semiglutide/Dulaglutide/Liraglutide

LEADER: study design

Aim: to assess the CV safety of liraglutide relative to placebo, on top of standard of care (non-inferiority margin upper bound of 95% CI <1.3, superiority if 95% CI <1.0)



Main inclusion criteria

- Type 2 diabetes, HbA1c ≥7.0%
- Glucose-lowering drug naïve; glucose-lowering agents and/or basal/premix insulin
- **Age ≥50 years and established CV disease or chronic renal failure, or**
- **Age ≥60 years and risk factors for CV disease**

Main exclusion criteria

- Type 1 diabetes
- Acute coronary event or cerebrovascular event within 14 days before screening and randomisation
- Use of GLP-1 RAs, DPP-4 inhibitors, pramlintide or rapid-acting insulin
- Familial or personal history of MEN-2 or MTC

Primary endpoint: time to first occurrence of major adverse cardiovascular events:

- **CV-related death**
- **Non-fatal MI**
- **Non-fatal stroke**

CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; LEADER, liraglutide effect and action in diabetes: evaluation of cardiovascular outcomes results; MEN-2, multiple endocrine neoplasia type 2; MI, myocardial infarction; MTC, medullary thyroid cancer

Marso SP *et al. N Engl J Med* 2016;375:311

LEADER: baseline characteristics

	Liraglutide (n=4668)	Placebo (n=4672)
Age, years (mean ± SD)	64.2±7.2	64.4±7.2
Male, n (%)	3011 (64.5)	2992 (64.0)
Diabetes duration, years	12.8±8.0	12.9±8.1
Geographic region, n (%)		
Europe	1639 (35.1)	1657 (35.5)
North America	1401 (30.0)	1446 (31.0)
Asia	360 (7.7)	351 (7.5)
Rest of the world	1268 (27.2)	1218 (26.1)
BMI, kg/m^2 (mean ± SD)	32.5±6.3	32.5±6.3
HbA1c, %, (mean ± SD)	8.7±1.6	8.7±1.5
Established CVD + age ≥50 years, n (%)	3831 (82.1)	3767 (80.6)
≥1 CVD risk factor + age ≥60 years, n (%)	837 (17.9)	905 (19.4)
Heart failure NYHA I–III, n (%)	835 (17.9)	832 (17.8)
Systolic blood pressure, mmHg (mean ± SD)	135.9±17.8	135.9±17.7
Diastolic blood pressure, mmHg (mean ± SD)	77.2±10.3	77.0±10.1

Marso SP *et al. N Engl J Med* 2016;375:311; supplementary appendix

LEADER
Once-Daily Liraglutide

- Liraglutide significantly reduced CV death, as well as nonfatal MI or nonfatal stroke, compared with placebo
- N = 9340 for median of 3.8 years

	Hazard Ratio (95% CI)	*P*-Value
Primary composite endpoint*	0.87 (0.78, 0.97)	.01
CV death	0.78 (0.66, 0.93)	.007
Death from any cause	0.85 (0.74, 0.97)	.02
Fatal or nonfatal MI	0.86 (0.73, 1.00)	.046

*First occurrence of death from CV causes, nonfatal (including silent) MI, or nonfatal stroke.
Marso SP, et al. *N Engl J Med*. 2016;375:311-322.

SUSTAIN 6
Once-Weekly Semaglutide Results

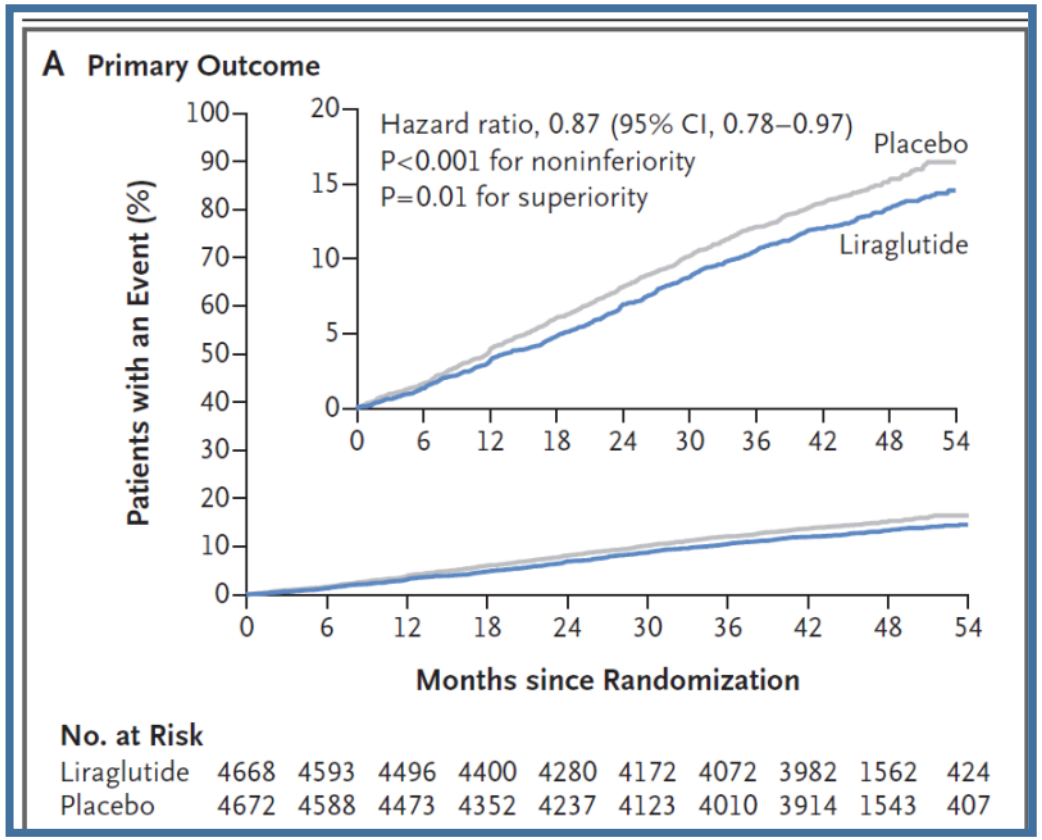
- Designed to access the noninferiority of semaglutide in terms of CV safety; N = 3297
- Semaglutide demonstrated CV benefit compared with placebo

	Hazard Ratio (95% CI)	*P*-Value
Primary outcome*	0.74 (0.58, 0.95)	<.001 noninferiority .02 superiority
Nonfatal Stroke	0.61 (0.38, 0.99)	.04
Nonfatal MI	0.74 (0.51, 1.08)	.12
Death from CV causes	0.98 (0.65, 1.48)	.92

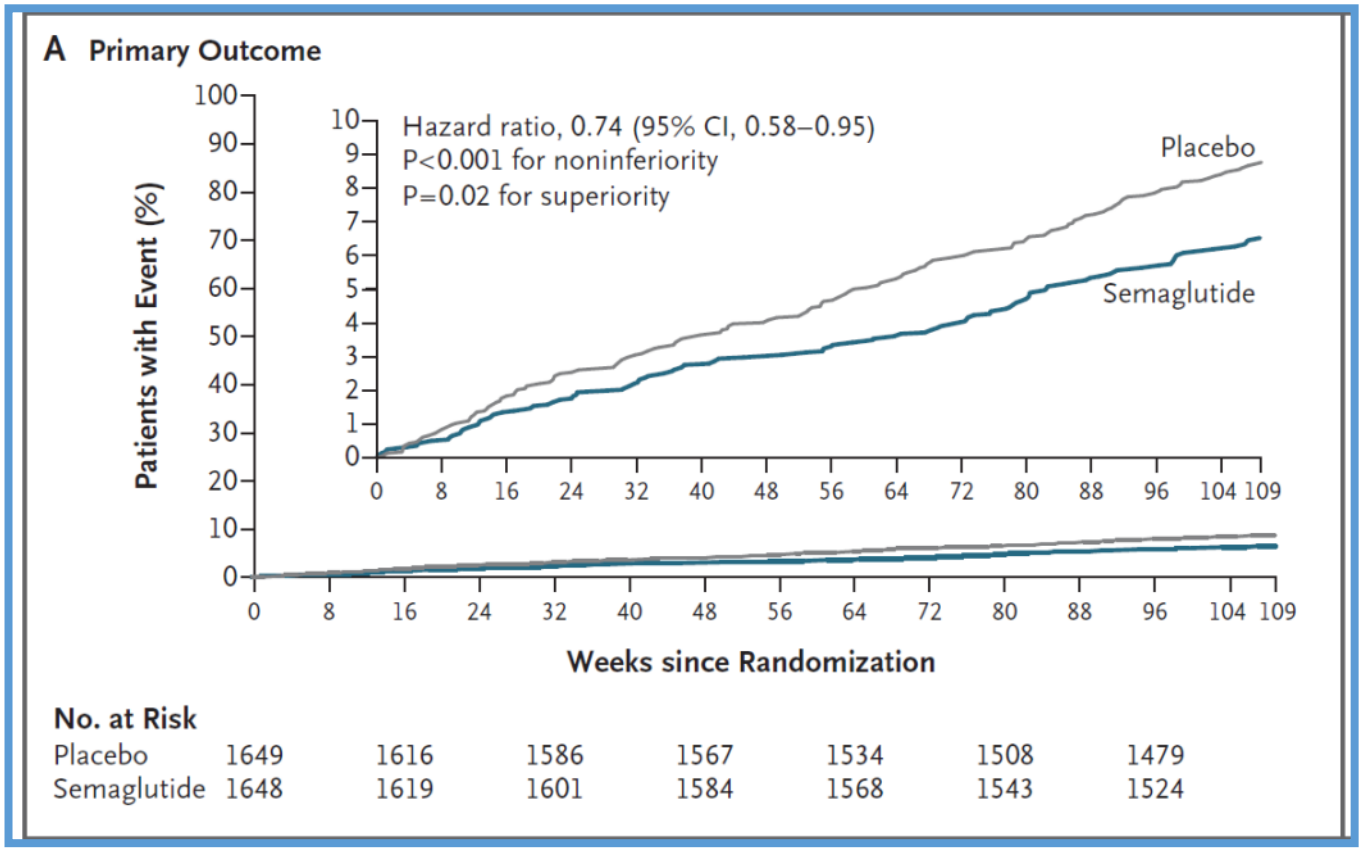
*First occurrence of death from CV causes, nonfatal MI (including silent), or nonfatal stroke.

Marso SP, et al. *N Engl J Med*. 2016;375:1834-1844.

Liraglutide



Semaglutide



Benefit apparent at 1 year

EXSCEL CVOT
Exenatide Once-Weekly

- Largest and most inclusive patient population of any CVOT of the GLP-1 RA class conducted to date
- N = 14,752 patients at 687 trial sites across 35 countries
- Primary prevention: enrolled predominately patients with established CV disease as well as population that did not have CV disease
- Other key inclusion criteria:
  - People as young as age 18
  - Use of DPP-4 inhibitors
    - Not common in clinical practice to add a GLP-1 receptor agonist in these scenarios
    - Done in EXSCEL to promote glycemic equipoise and to promote attainment of HbA_{1c} targets

Holman RR, et al. *N Engl J Med*. 2017;377:1228-1139.

EXSCEL
Once-Weekly Exenatide Results

- Once-weekly exenatide did not increase the incidence of major adverse CV events compared with placebo
- Fewer CV events (11.4% vs 12.2%)

	Hazard Ratio (95% CI)	*P*-Value
Primary CV outcome	0.91 (0.83, 1.00)	<.001 noninferiority .06 superiority
Death from CV causes	0.88 (0.76, 1.02)	
All-cause mortality	0.86 (0.77, 0.97)	

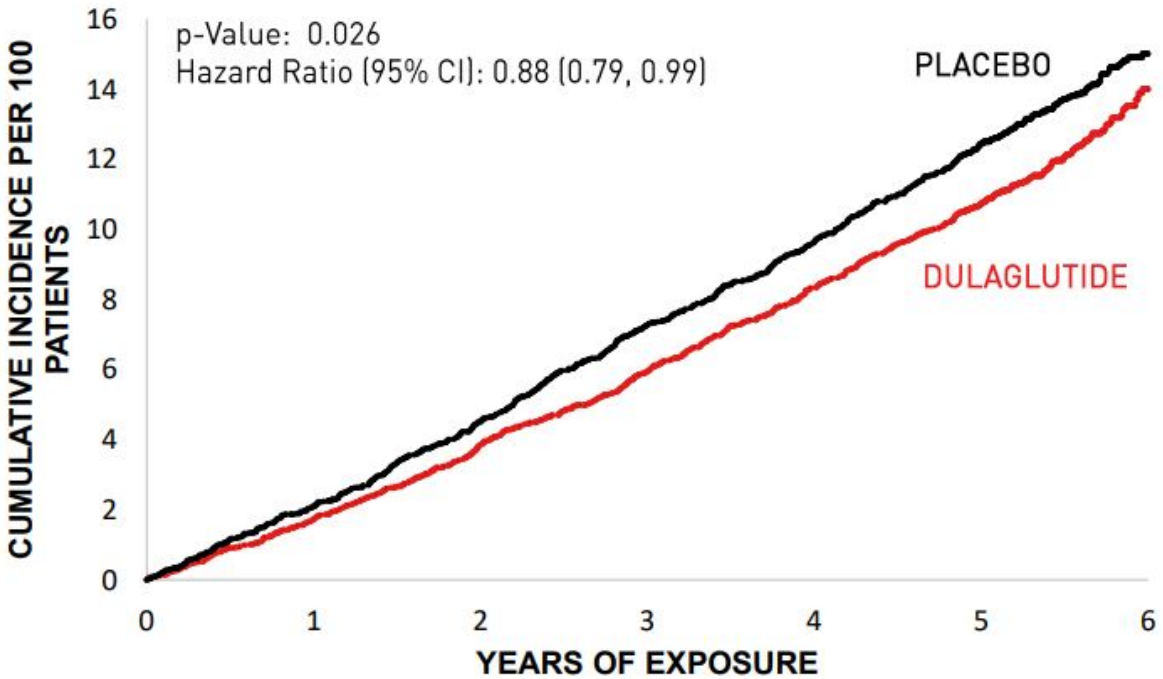
*First occurrence of any component of the composite outcome of death from CV causes, nonfatal MI, or nonfatal stroke.

Holman RR, et al. *N Engl J Med*. 2017;377:1228-1139.

TRULICITY CV OUTCOME TRIAL

PRIMARY MACE 3 RESULT

Dulaglutide significantly reduced the risk of Major Adverse Cardiovascular Events (MACE 3: CV death, non-fatal MI or non-fatal stroke) **by 12% vs. placebo**

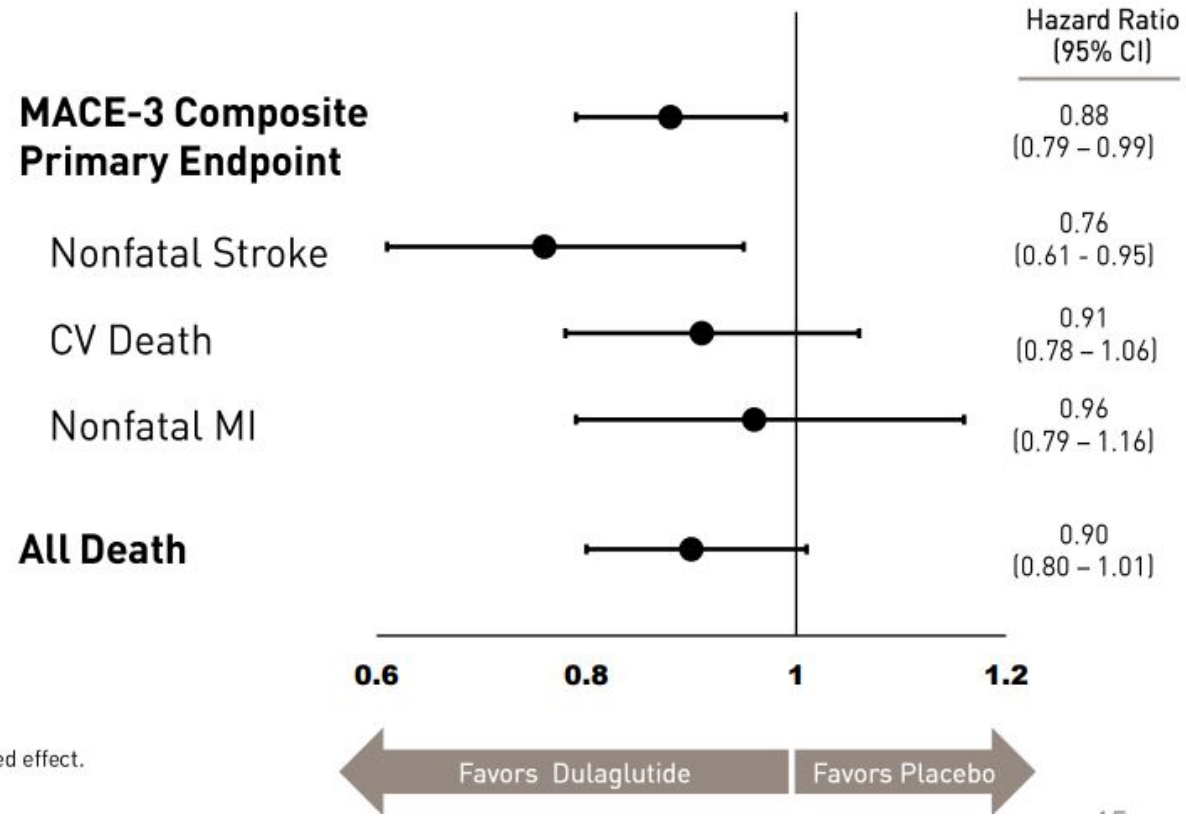


Note: Hazard Ratio and its CI and p-value obtained from Cox Proportional Hazards Regression Model with treatment as a fixed effect.

Gerstein et al. Lancet 2019.

CV OUTCOMES

Consistent effect across three components of MACE, greatest difference observed in Nonfatal Stroke



GLP1 Agonists

Generic	Trade Name	Trial	Result
Lixisenatide	AdlyxinTM	ELIXA	NEUTRAL
Liraglutide	Victoza	LEADER	POSITIVE
Semaglutide	Ozempic	SUSTAIN-6	POSITIVE
Exenatide	Bydureon/Byetta	EXSCEL	NEUTRAL (POS for ACM)
Dulaglutide	Trulicity	REWIND	positive
Albiglutide	Tanzeum	HARMONY	(Q2 2019)
Semaglutide PO		PIONEER 6	(Q3 2018)

Duke Clinical Research Institute

SUGGESTS PTS WITH INCREASED RISK SHOW MORE BENEFIT

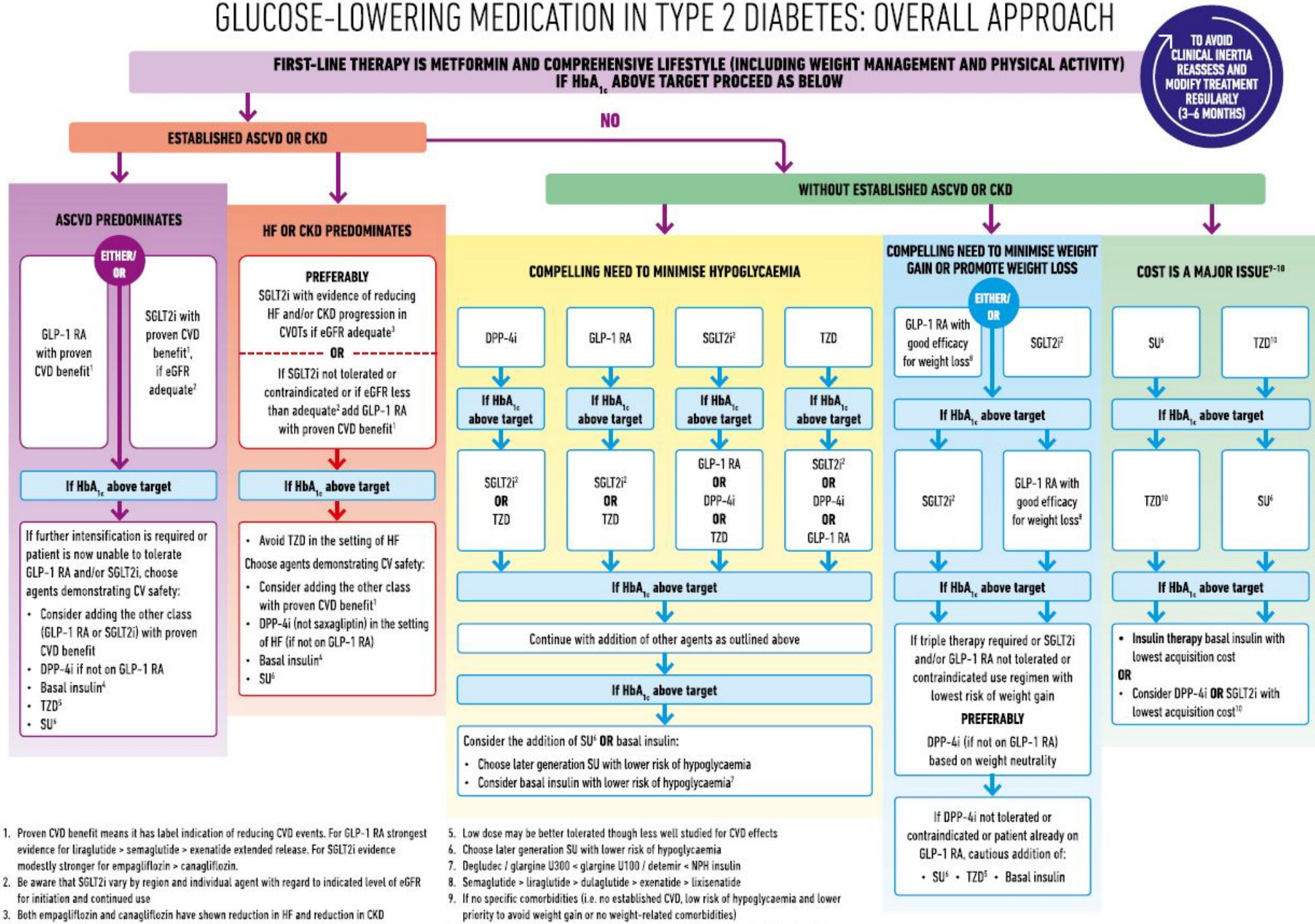
GLP-1 and SGLT2 therapy

- A1c remains important, but perhaps how we get there may be more impactful, particularly for those who have CV disease or those at high risk

- These agents offer A1c reduction across a broad patient population, limited risk of hypoglycemia and aid in weight loss

- CVOT data compelling for risk reduction with NNT similar to statin and and ACE –I

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper