DIABETES UPDATE

Saleem Malik
Medical Director CCDC

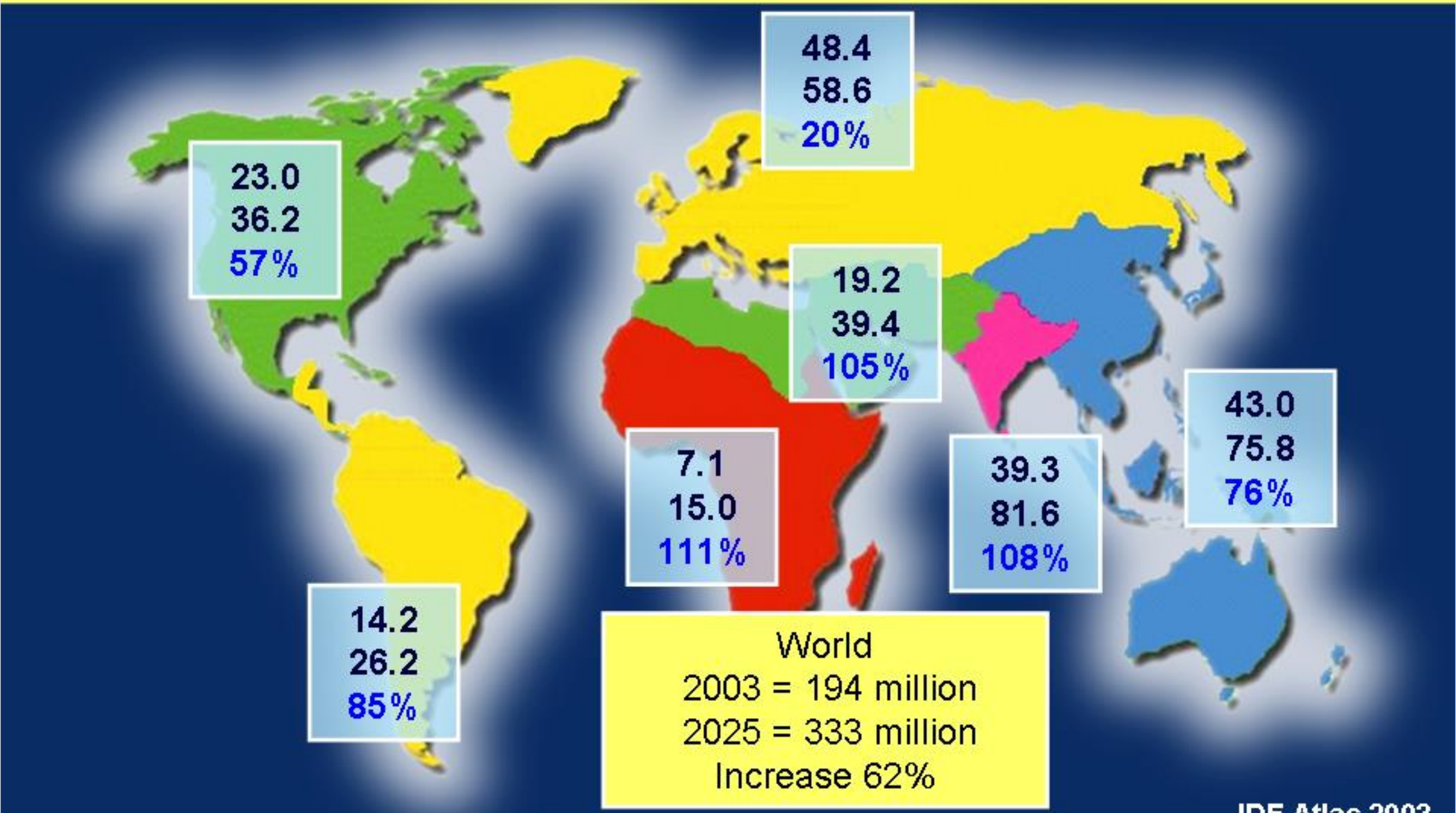
Disclosure Slide
Slide 1

- **Speaker:**
- **SALEEM MALIK**
- **Relationships with commercial interests:**
  - **Grants/Research Support:** none
  - **Speakers Bureau/Honoraria:** none
  - **Consulting Fees:** none
  - **Other:** none

Goals of presentation

- 1) SGLT-2 inhibitors and cardiorenal disease
- 2) GLP analogues
- 3) Heterogeneity of diabetes
- 4) Practical considerations in diabetes management

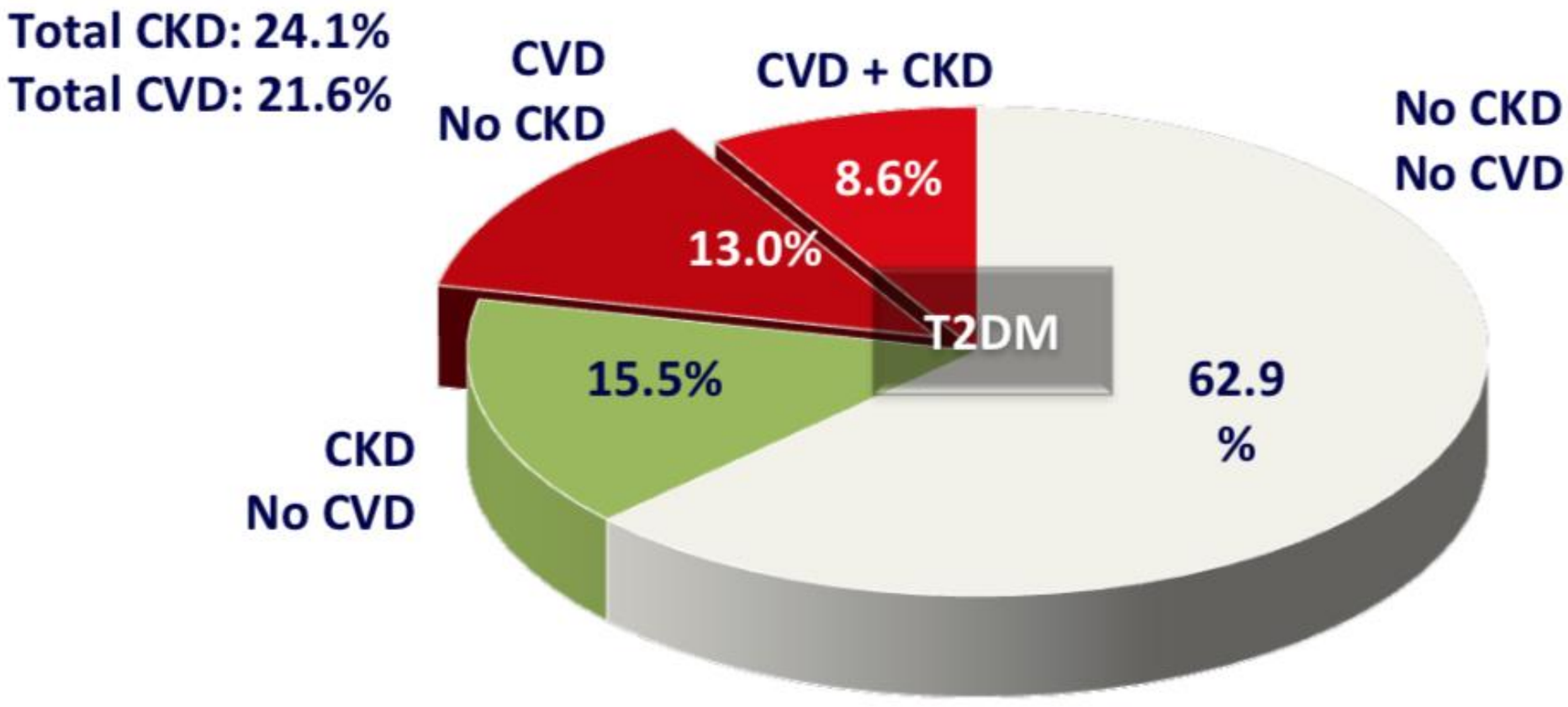
Global Projections for the Diabetes Epidemic: 2003-2025 (millions)



IDF Atlas 2003

Cardiac and renal disease in diabetes

Prevalence and Co-prevalence of Comorbidities in T2DM (Q-EMR) (N=1.39 million)



Patients with CVD represent only 21.6% of all patients with DM

CKD was defined based on the presence of an ICD-9-CM diagnosis code or, if a code was not present, an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 using the most recent measurement prior to the index date. If not already estimated in the database, eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) study equation.

Iglay K et al. Curr Med Res Opin. 2016;32:1243-52.

Type 2 diabetes is associated with an increased incidence of CVD

In a cohort of nearly 2 million people, there was a:

62% increase in **Stable angina**

53% increase in **Unstable angina**

54% increase in **Nonfatal MI**

43% increase in **Unheralded coronary death**

56% increase in **Heart failure**

72% increase in **Ischemic stroke**

in people with type 2 diabetes compared to the general population

nheralded coronary death=coronary death that was not previously expected/recognized.
nah AD. *Lancet Diabetes Endocrinol*. 2015;3:105–113.

Prevalence of diabetes in recent HFrEF trials

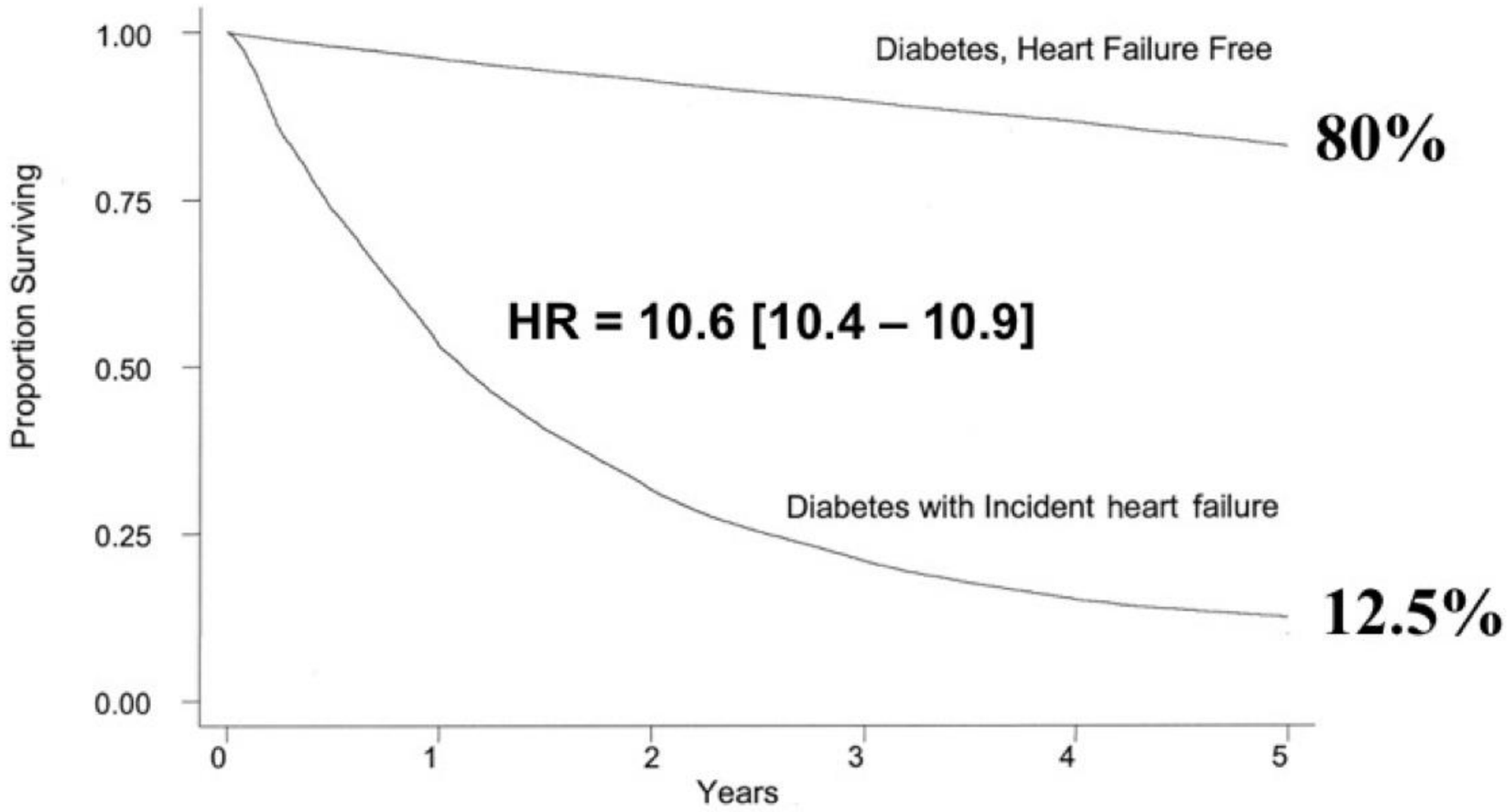
- **SHIFT** (2010) 31%
- **EMPHASIS** (2010) 34%
- **PARADIGM HF** (2014) 35 %

Prevalence of Diabetes Mellitus in HF With Preserved Ejection Fraction

	DIG	CHARM	PEP-CHF	I-Preserve
n	988	3025	850	4128
Age	66±10	67±11	76±5	72
Women	41%	40%	55%	60%
Diabetics	28%	28.5%	20.5%	30%
Ischemic	55%	56.5%	35%	56%
HT	60%	22.5%	79%	63%

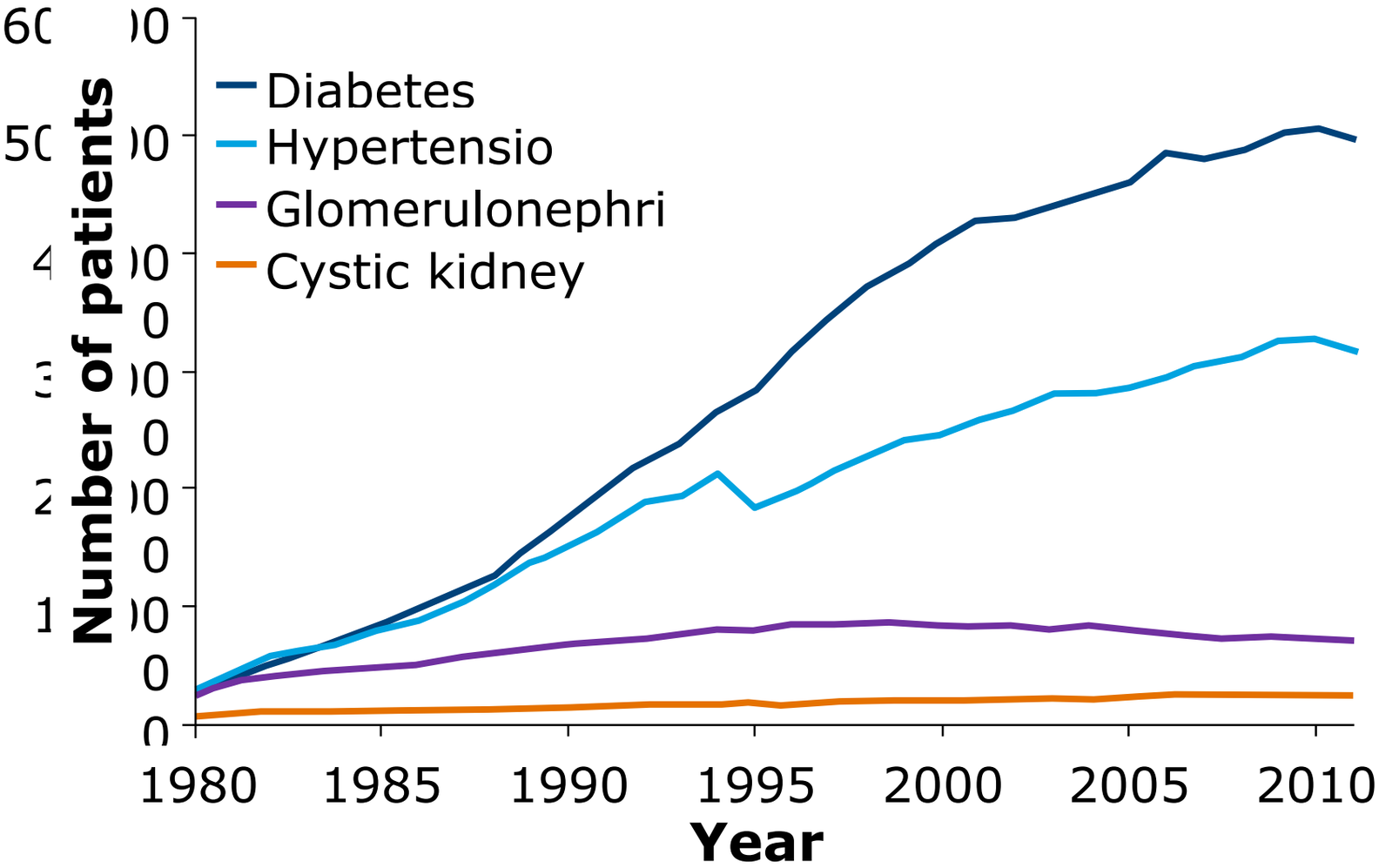
MEDICARE

* 151738 diabetic patients 65 years
* F/U 1994 - 1999



Bertoni: Diabetes Care 2004;27:699

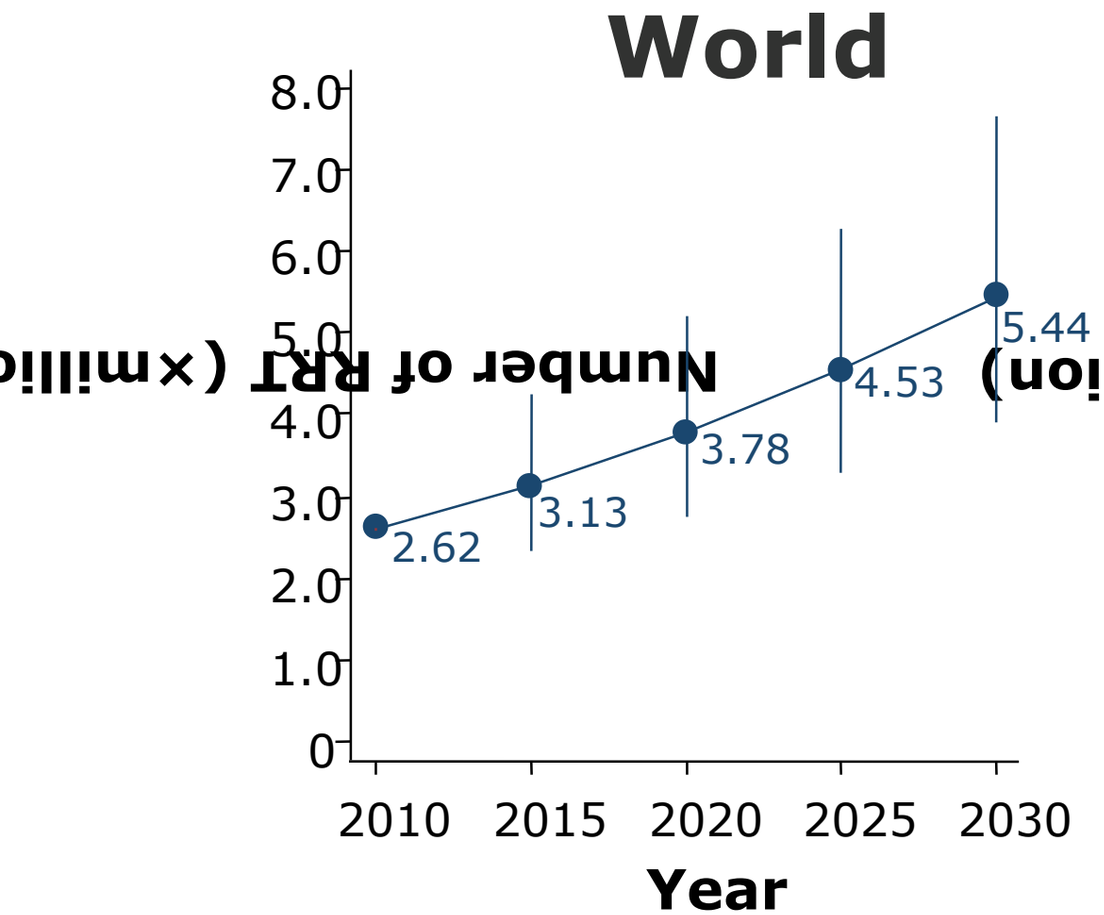
Diabetes Is the Leading Cause of Kidney Failure: US Data

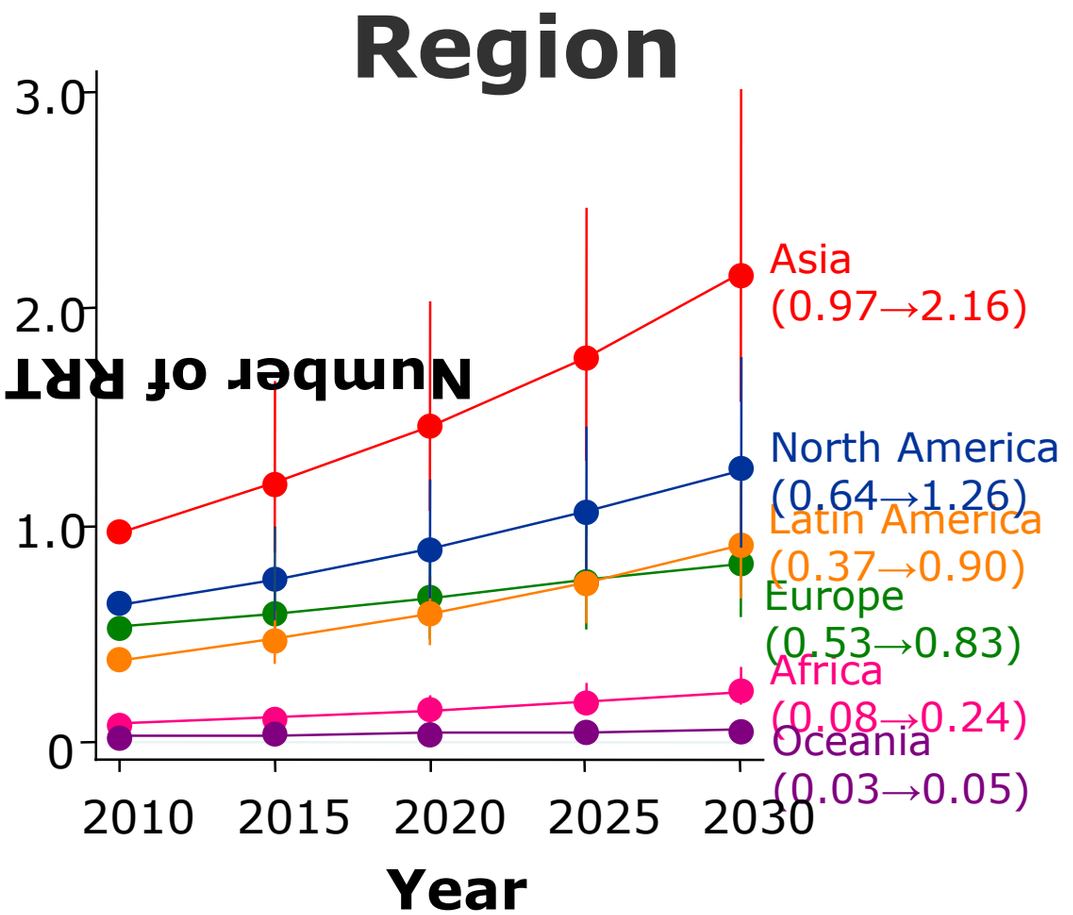


United States Renal Data System (USRDS). USRDS Annual Report, Chapter 1. https://www.usrds.org/2012/pdf/v2_ch1_12.pdf. Accessed March 15, 2019.

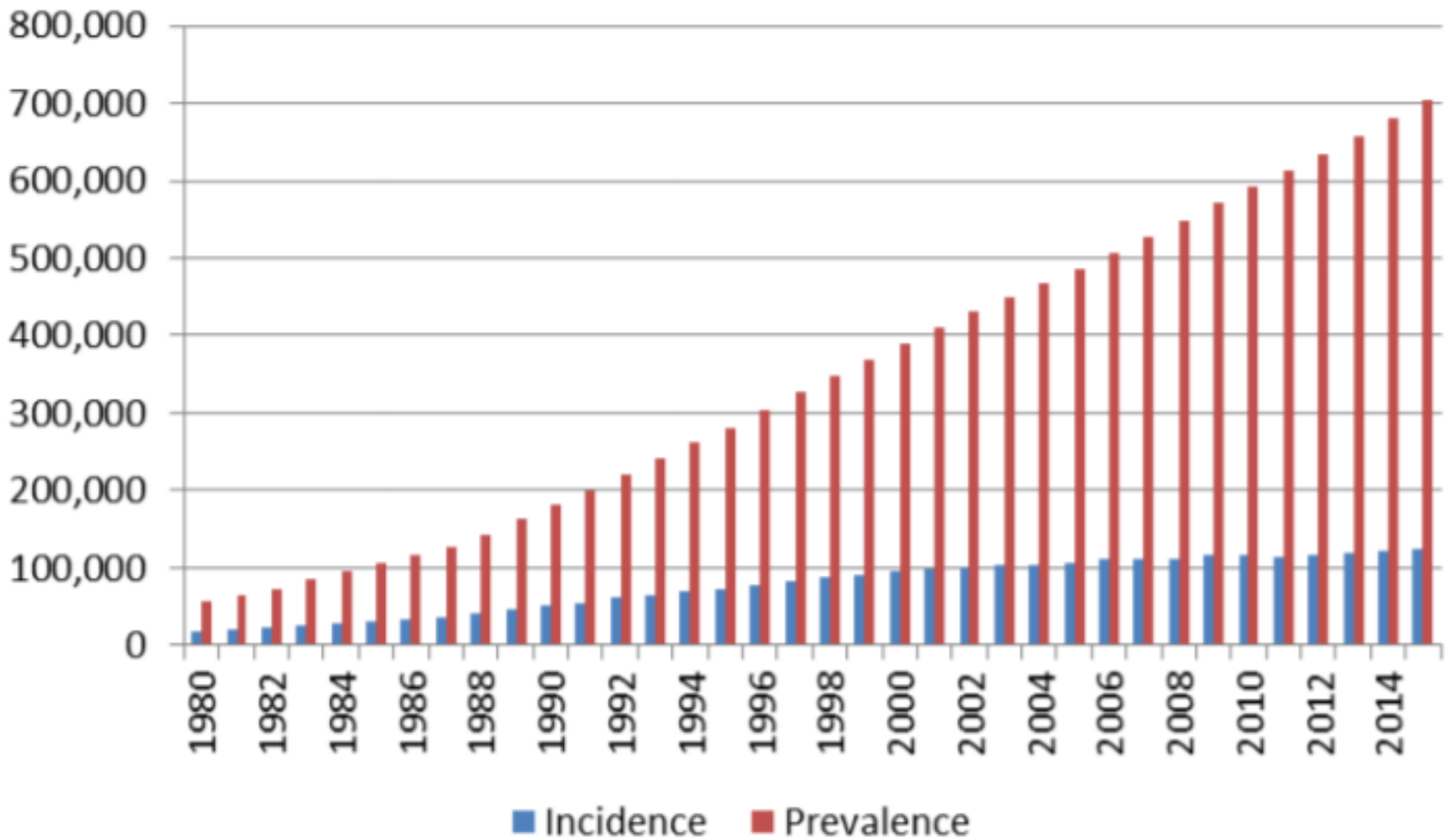
CREDENCE

Number of People Receiving Renal Replacement Therapy Is Projected to Double





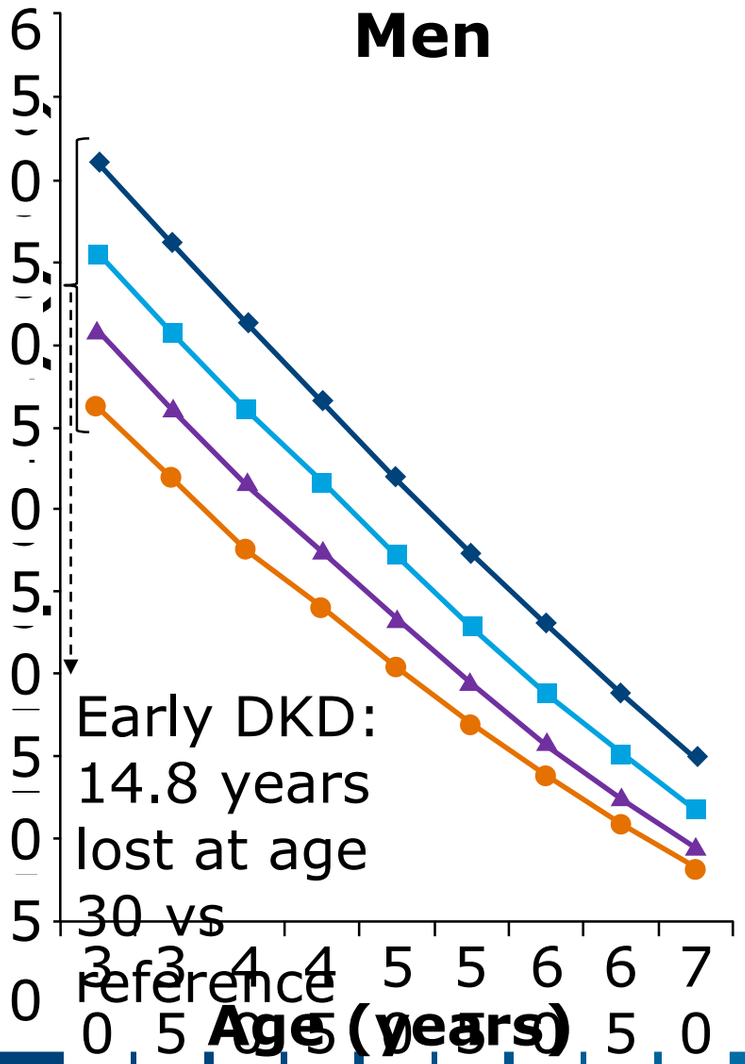
Increasing Incidence and Prevalence of ESKD: US Data

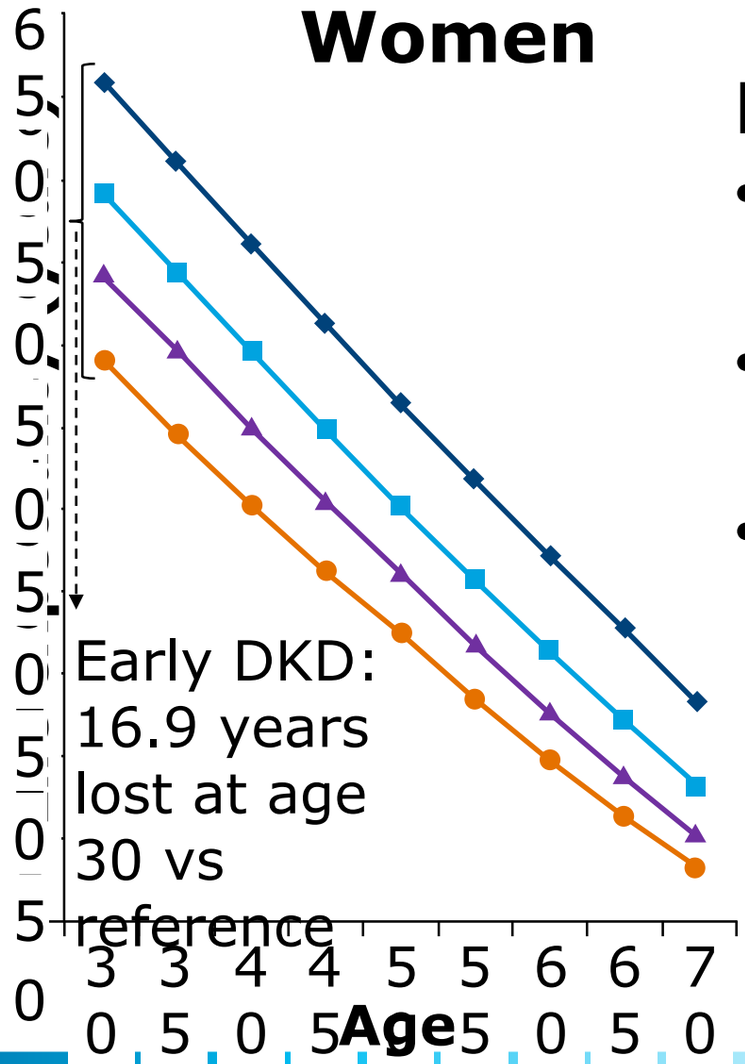


Kirchhoff S. Medicare coverage of end-stage renal disease (ESRD). https://fas.org/sgp/crs/misc/R45290.pdf. Accessed February 13, 2019.

CREDENCE

Diabetic Kidney Disease Shortens Life Span by 16 Years





Life span loss with:

- Early CKD: 6 years
- Diabetes: 10 years
- Early DKD: 16 years

Reference
Early CKD
Diabetes
Early DKD

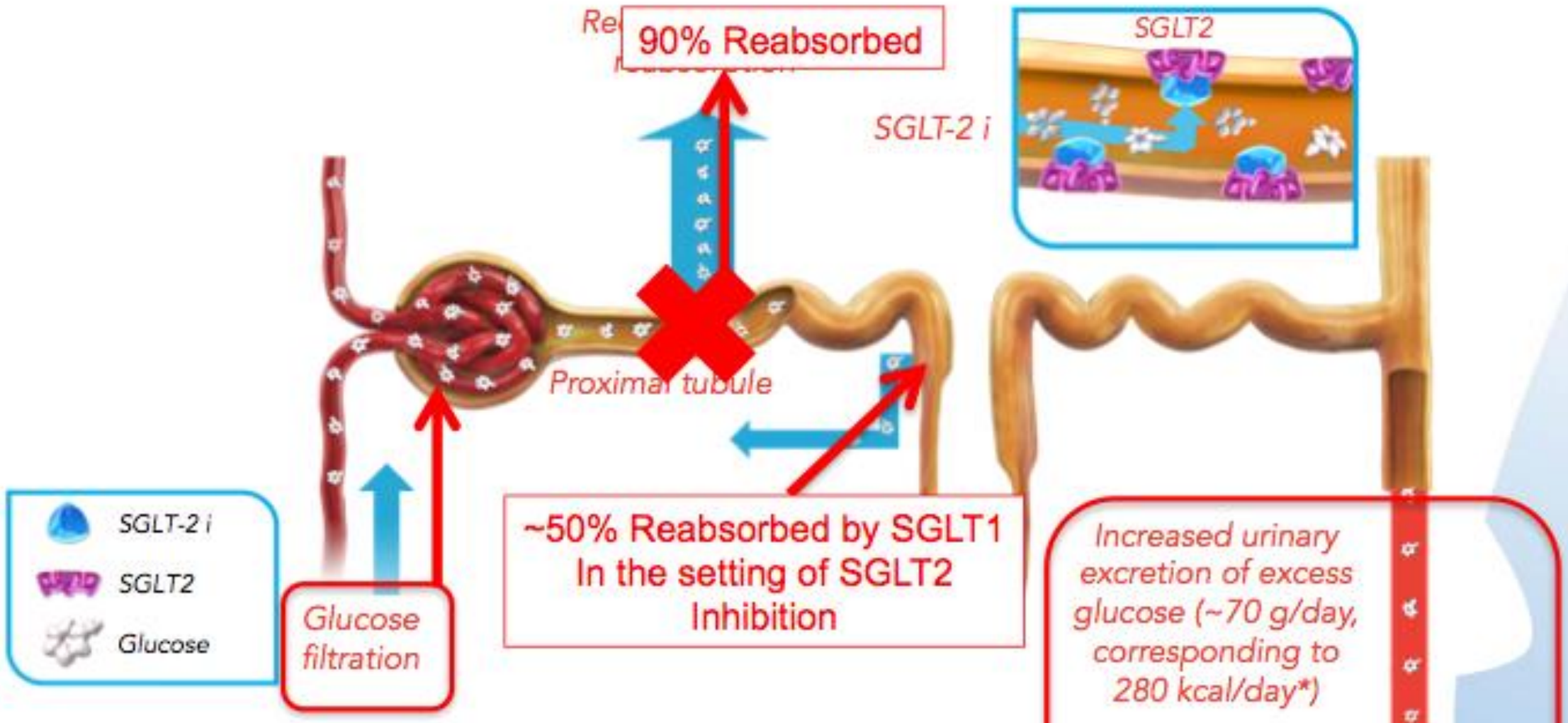
Wen CP, et al. *Kidney Int.* 2017;92(2):388-396.

CREDENCE

SGLT 2 inhibitors

Canagliflozin - Invokana
Empagliflozin - Jardiance
Dapagliflozin -Forxiga

SGLT-2 Inhibition: A novel insulin-independent approach to remove excess glucose



Selectively inhibit SGLT2 in the renal proximal tubule

*Increases urinary volume by only ~1 additional void/day (~375 mL/day) in a 12-week study of healthy subjects and patients with Type 2 diabetes.[4]

1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18; 2. Lee YJ, *et al. Kidney Int Suppl* 2007;**106**:S27–35; 3. Hummel CS, *et al. Am J Physiol Cell Physiol* 2011;**300**:C14–21; 4. Dapa®. Summary of product characteristics. Bristol-Myers Squibb/AstraZeneca EEIG, 2013.

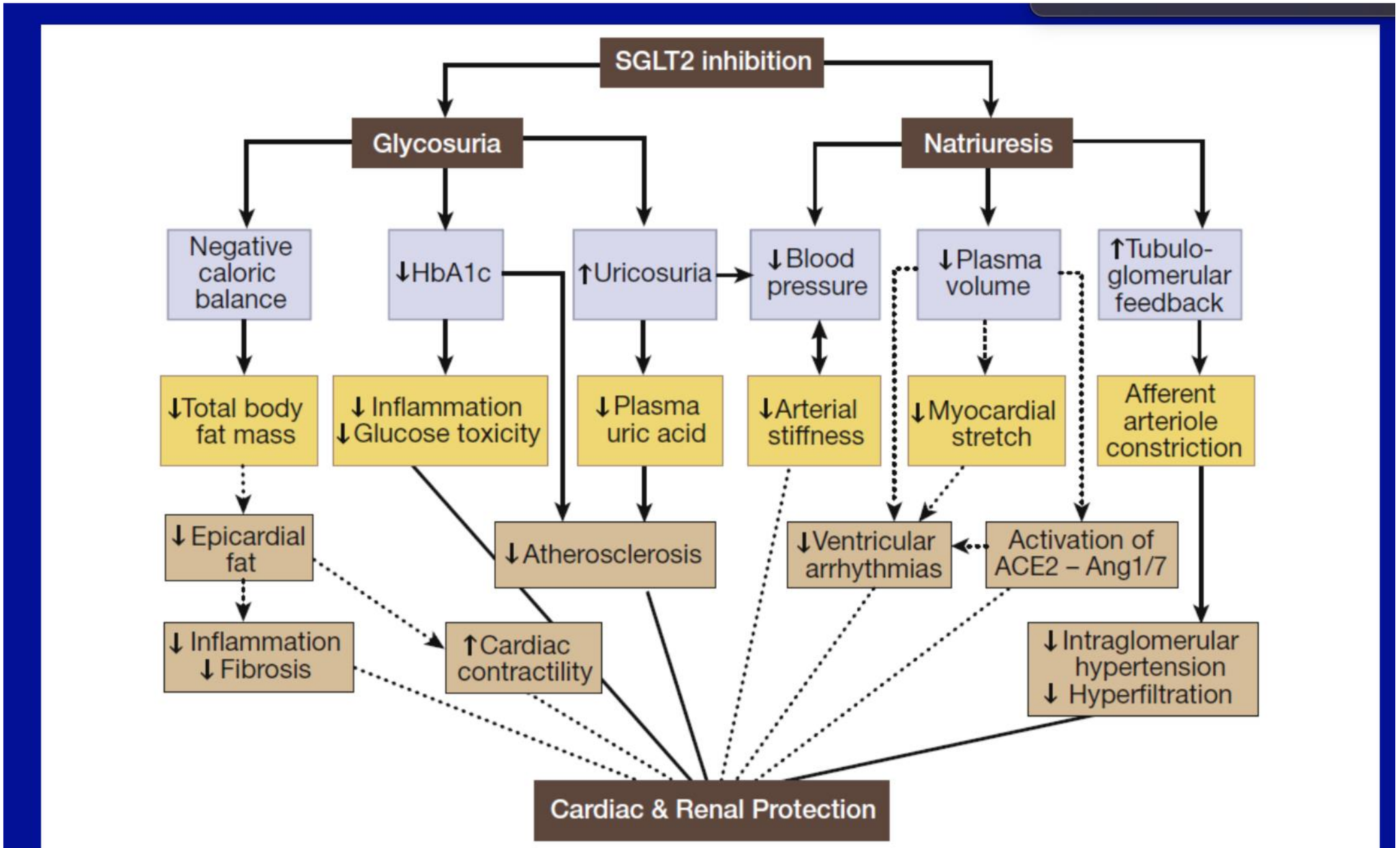


Figure 1 | Possible mechanisms responsible for cardiovascular and renal protection with sodium–glucose cotransporter 2 (SGLT2) inhibition. Solid lines represent pathways supported by existing data; dashed lines represent possible areas for future research. ACE2, angiotensin-converting enzyme-2; Ang1/7, angiotensin 1/7; HbA1c, hemoglobin A1c.

SGLT2 inhibitors and cardiac disease

Canagliflozin - Invokana
Empagliflozin - Jardiance
Dapagliflozin -Forxiga

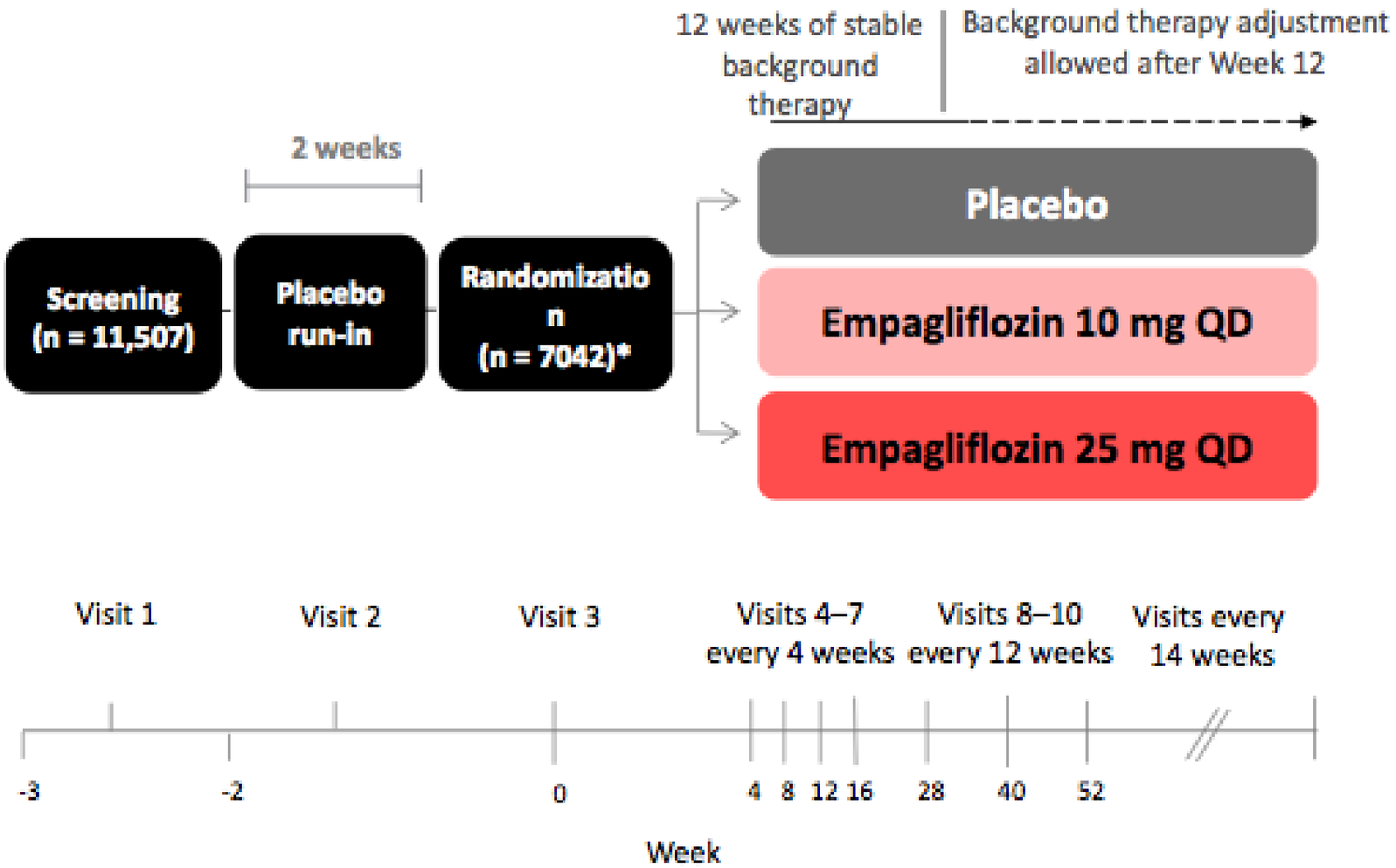
EMPA-REG OUTCOME
Study Design

Inclusion Criteria

- Age ≥ 18 years
- A1C ≥ 7% and ≤ 10% or ≥ 7% and ≤ 9% (drug-naïve)
- BMI ≤ 45 kg/m2

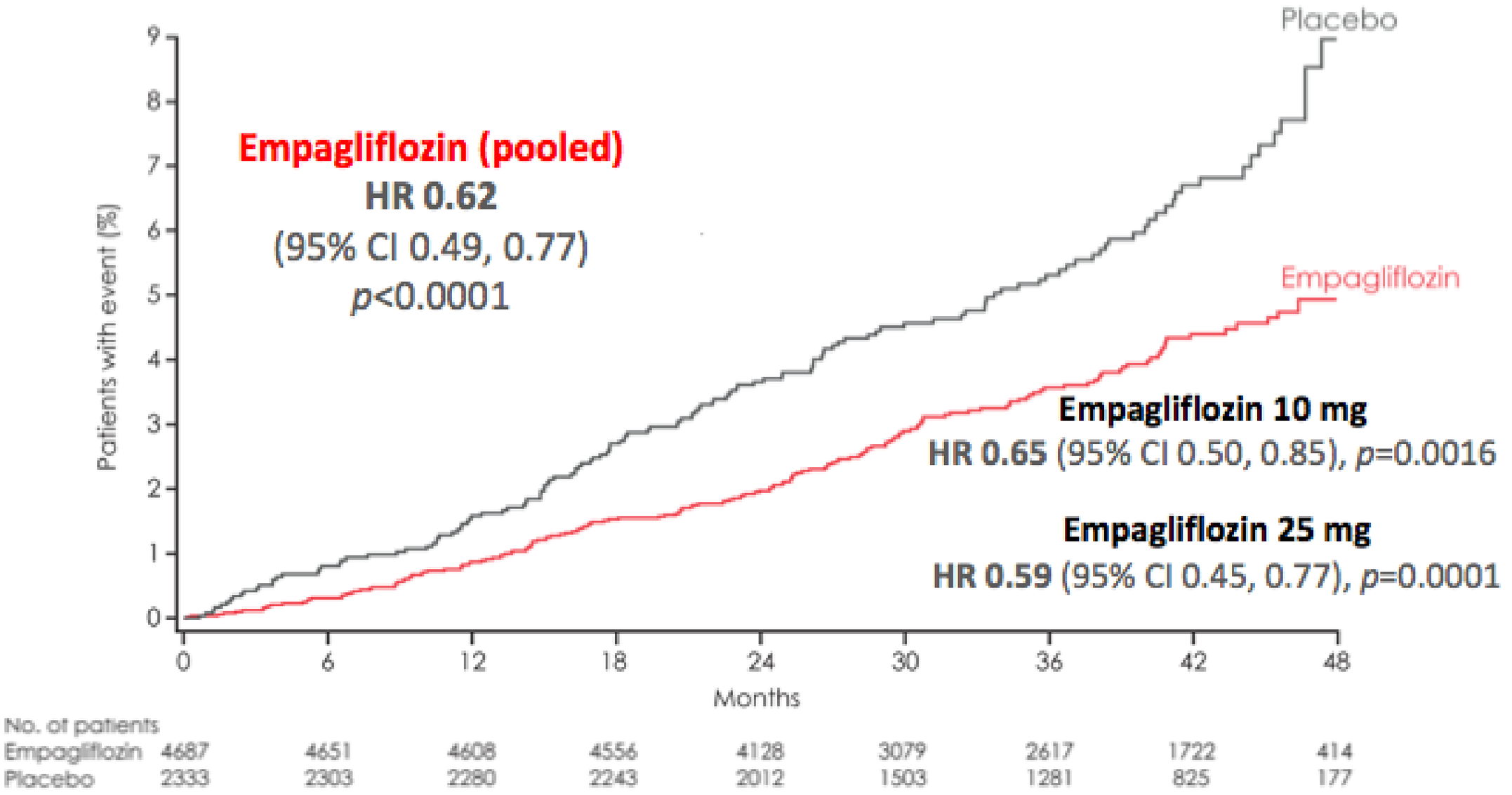
And to have ≥ 1 of the following criteria:

- History of MI (> 2 months prior to enrolment)
- Evidence of CAD in ≥ 2 major vessels or left main coronary artery
- Evidence of single-vessel CAD with no scheduled revascularisation/previously unsuccessful revascularisation and:
  - Positive non-invasive, functional stress test for ischaemia (ECG, echo or nuclear), or
  - Hospital discharge due to unstable angina pectoris ≤ 12 months before enrolment



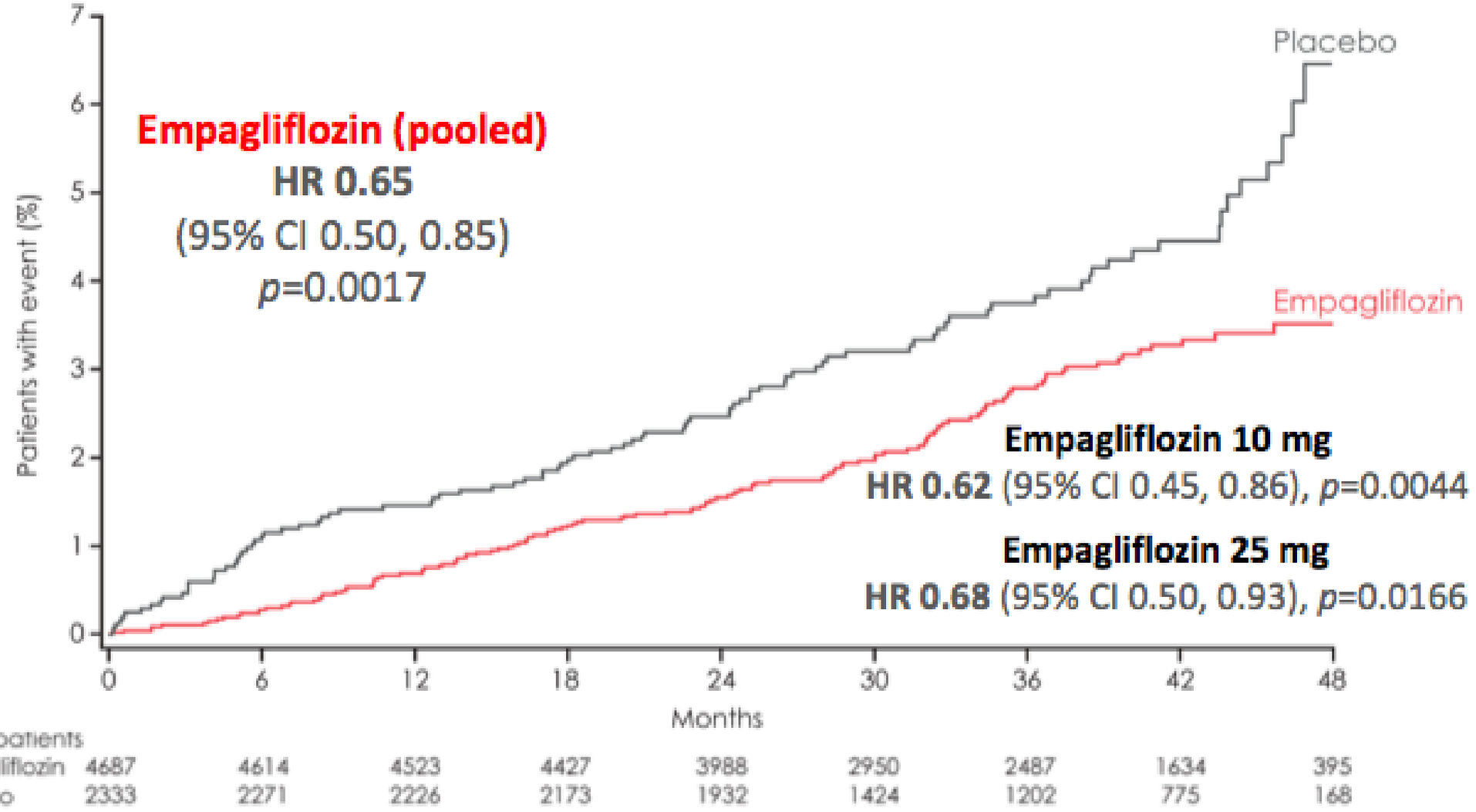
QD, once daily.
*7042 patients were randomized, 7034 of whom comprised the treated set.
Zinman B, et al. Cardiovasc Diabetol. 2014;13:102.

EMPA-REG Outcome
Cardiovascular Death



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

EMPA-REG Outcome
Hospitalization for Heart Failure



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

MACE: Cardiovascular outcomes of interest

In 2008, the US Food and Drug Administration (FDA) issued guidance requiring **robust assessment of cardiovascular safety** (CV) for **all antihyperglycemic therapies** to be licensed in the future

Major Adverse Cardiovascular Events (MACE)

MACE is the primary endpoint for the **majority of studies** and is a composite of all major CV events:

- CV death
- Non-fatal myocardial infarction
- Non-fatal stroke

MACE-plus

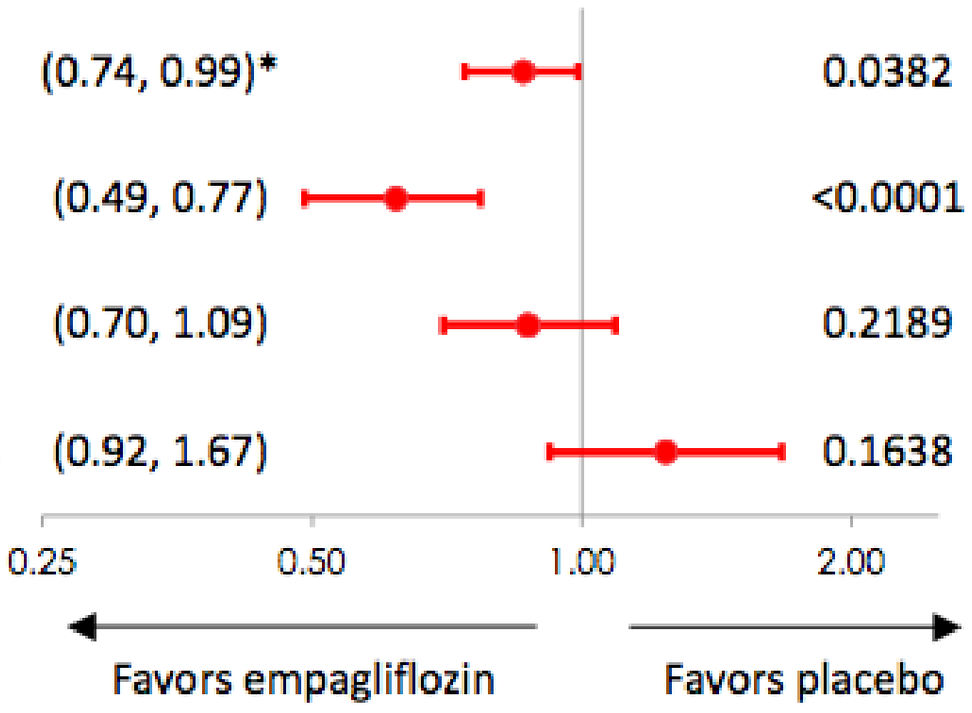
In some instances, additional CV outcomes could be included, such as:

- Hospitalization for cardiovascular causes (e.g., unstable angina, need for revascularization, acute heart failure or worsening of existent heart failure transient ischemic attack, and sudden death)

FDA Guidance for Industry: Diabetes Mellitus – Evaluating CV risk in new antidiabetic therapies to treat type 2 diabetes. www.fda.gov.

EMPA-REG Outcome
3-point MACE

	Patients with 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;373:2117-28.

SGLT2i CVOT summary

	Hazard ratio (95% CI)	*p* value
Empagliflozin (EMPA-REG, 3P)	0.86 (0.74; 0.99)	0.04
Canagliflozin (CANVAS, 3P)	0.86 (0.75; 0.97)	0.02

Significant secondary outcomes

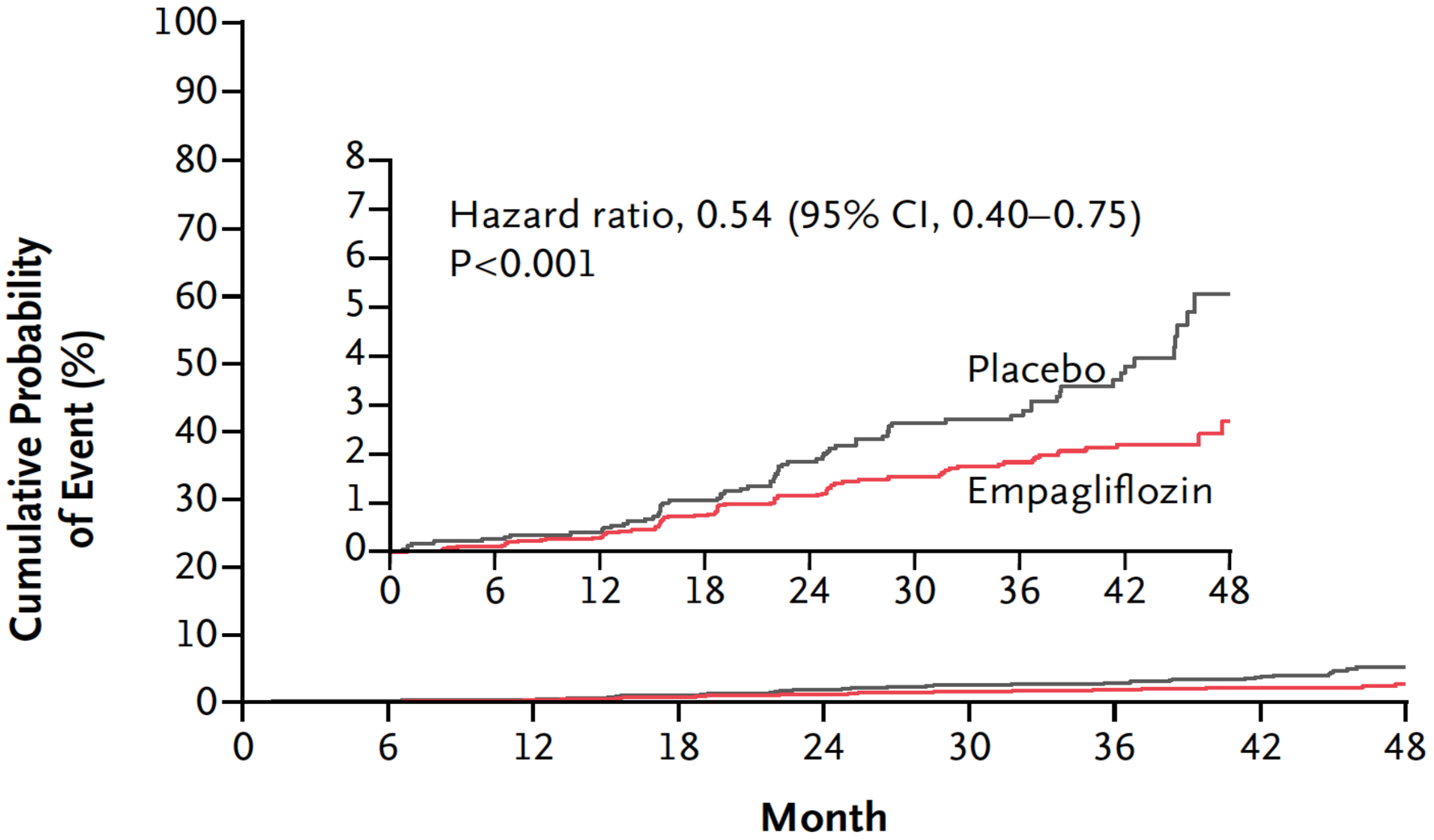
EMPA-REG OUTCOME

- ⬇ CV death (*p*<0.001)
- ⬇ All-cause death (*p*<0.001)
- ⬇ Hospitalizations for HF (*p*=0.002)
- ⬆ Genital infections

CANVAS

- ⬆ Lower limb amputations (*p*=<0.001)
- ⬇ HF (HR=0.67 [0.52–0.87])
- ⬆ Genital infections and fractures

Empagliflozin reduced doubling of serum creatinine*, initiation of renal replacement therapy, or death due to renal disease



No. at Risk

Empagliflozin	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2323	2229	2146	2047	1771	1289	1079	680	144

Hazard ratios are based on Cox regression analyses. *Accompanied by eGFR [MDRD] ≤45 ml/min/1.73m^2.
HR, hazard ratio; CI, confidence interval. *Post-hoc* analyses.

Wanner et al. N Engl J Med 2016; 75:323-334

SGLT2 inhibitors and diabetic renal disease

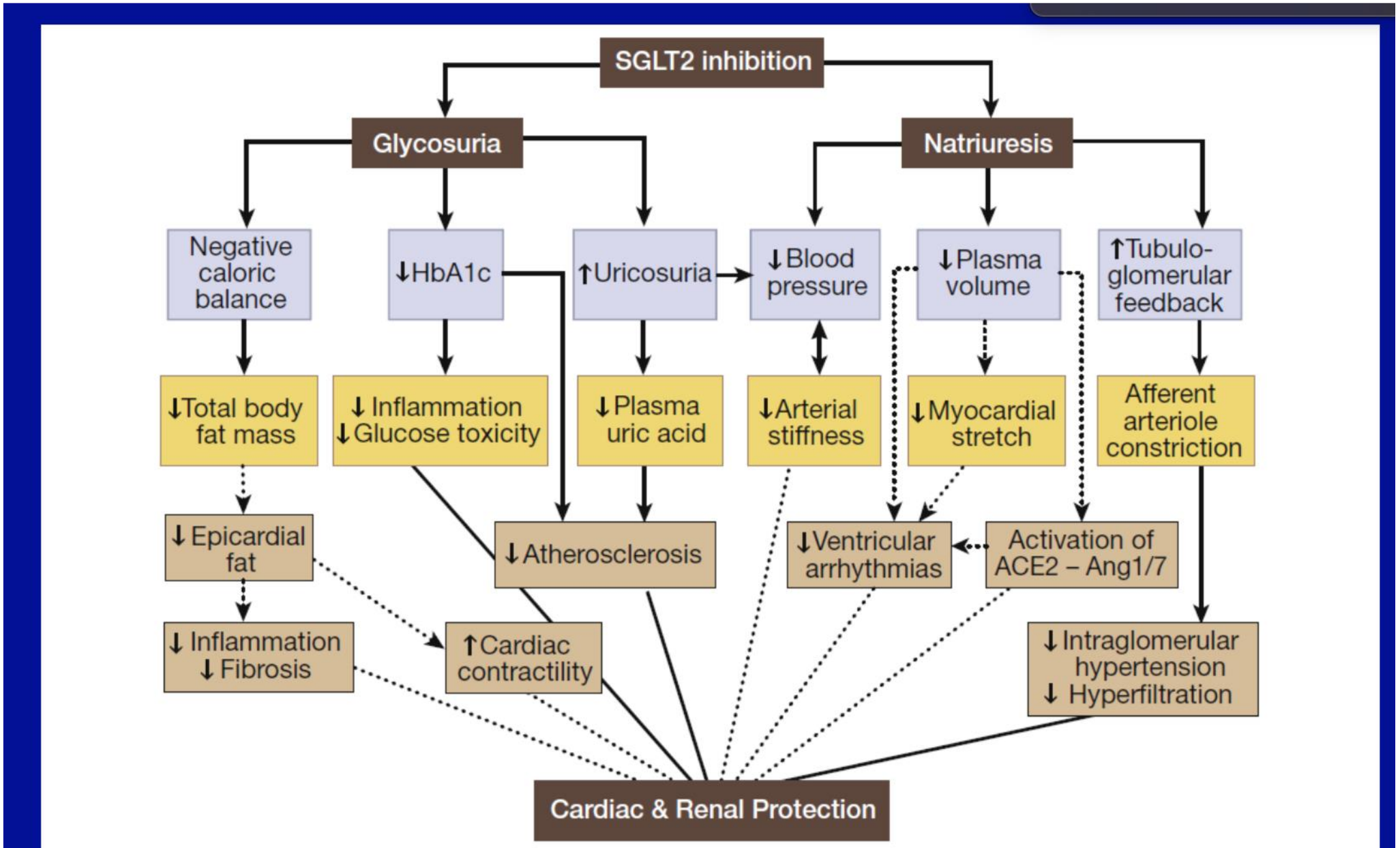


Figure 1 | Possible mechanisms responsible for cardiovascular and renal protection with sodium–glucose cotransporter 2 (SGLT2) inhibition. Solid lines represent pathways supported by existing data; dashed lines represent possible areas for future research. ACE2, angiotensin-converting enzyme-2; Ang1/7, angiotensin 1/7; HbA1c, hemoglobin A1c.

CREDENCE

Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation

34 Countries, 690 Sites, 4401 Participants

Europe (n = 1368)

- Bulgaria
- Czech Republic
- France
- Germany
- Hungary
- Italy
- Lithuania
- Poland

Central/South America (n = 941)

- Argentina
- Brazil
- Chile
- Colombia
- Guatemala

Asia Pacific* (n = 848)

- Australia (38)
- China (129)
- India (144)
- Japan (110)
- Korea (122)
- Malaysia (135)
- Ne
- Ph
- Ta
- Ur

*Analyzed as part of rest of world (n = 1414) in prespecified subgroup analyses.

CREDENCE

Study Design

Key inclusion criteria

- ≥30 years of age
- T2DM and HbA1c 6.5% to 12.0%
- eGFR 30 to 90 mL/min/1.73 m^2
- UACR 300 to 5000 mg/g
- Stable max tolerated labelled dose of ACEi or ARB for ≥4 weeks

Key exclusion criteria

- Other kidney diseases, dialysis, or kidney transplant
- Dual ACEi and ARB; direct renin inhibitor; MRA
- Serum K^+ >5.5 mmol/L
- CV events within 12 weeks of screening
- NYHA class IV heart failure
- Diabetic ketoacidosis or T1DM

2-week placebo run-in

Double-blind randomization (1:1)

Follow-up at Weeks 3, 13, and 26 (F2F) then every 13 weeks (alternating phone/F2F)

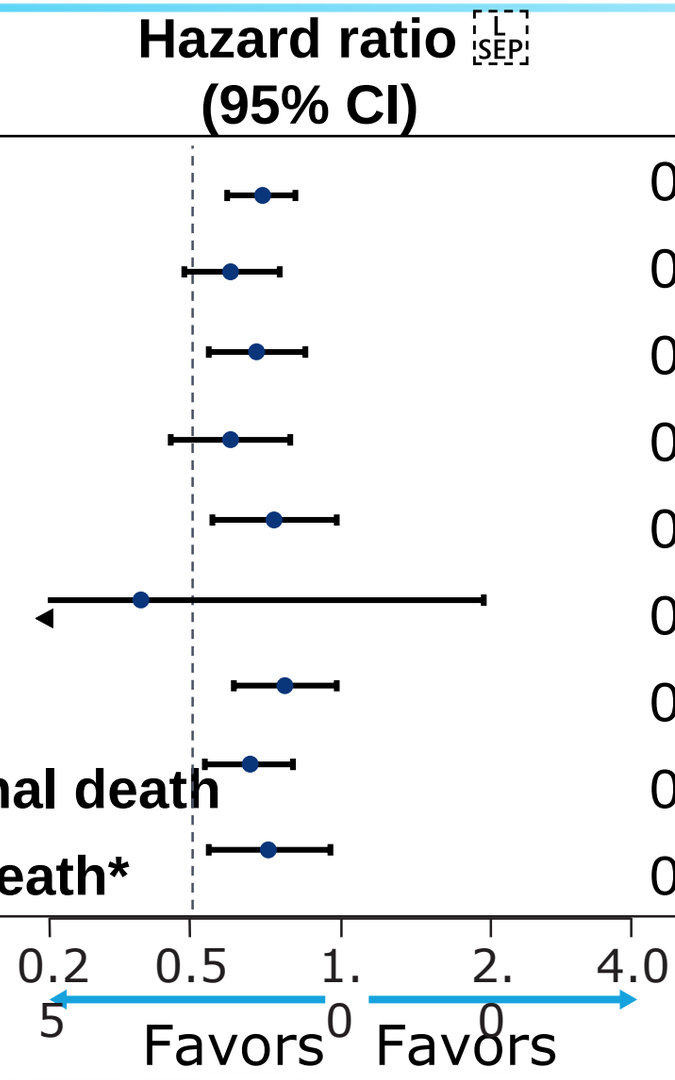
Participants continued treatment if eGFR was <30 mL/min/1.73 m^2 until chronic dialysis was initiated or kidney transplant occurred.

Primary Endpoint Definitions

- **ESKD**
  - Chronic dialysis for ≥30 days
  - Kidney transplantation
  - eGFR <15 mL/min/1.73 m^2 sustained for ≥30 days by central laboratory assessment
- **Doubling of serum creatinine**
  - Doubling from the baseline average sustained for ≥30 days by central laboratory assessment
- **Renal death**
  - Deaths in patients who have reached ESKD who die prior to initiating renal replacement therapy and no other cause of death is adjudicated
- **CV death**
  - Death due to MI, stroke, heart failure, sudden death, death during a CV procedure or as a result of procedure-related complications, presumed sudden CV death, death of unknown cause, or death resulting from a documented CV cause other than those listed

Summary Forest Plot

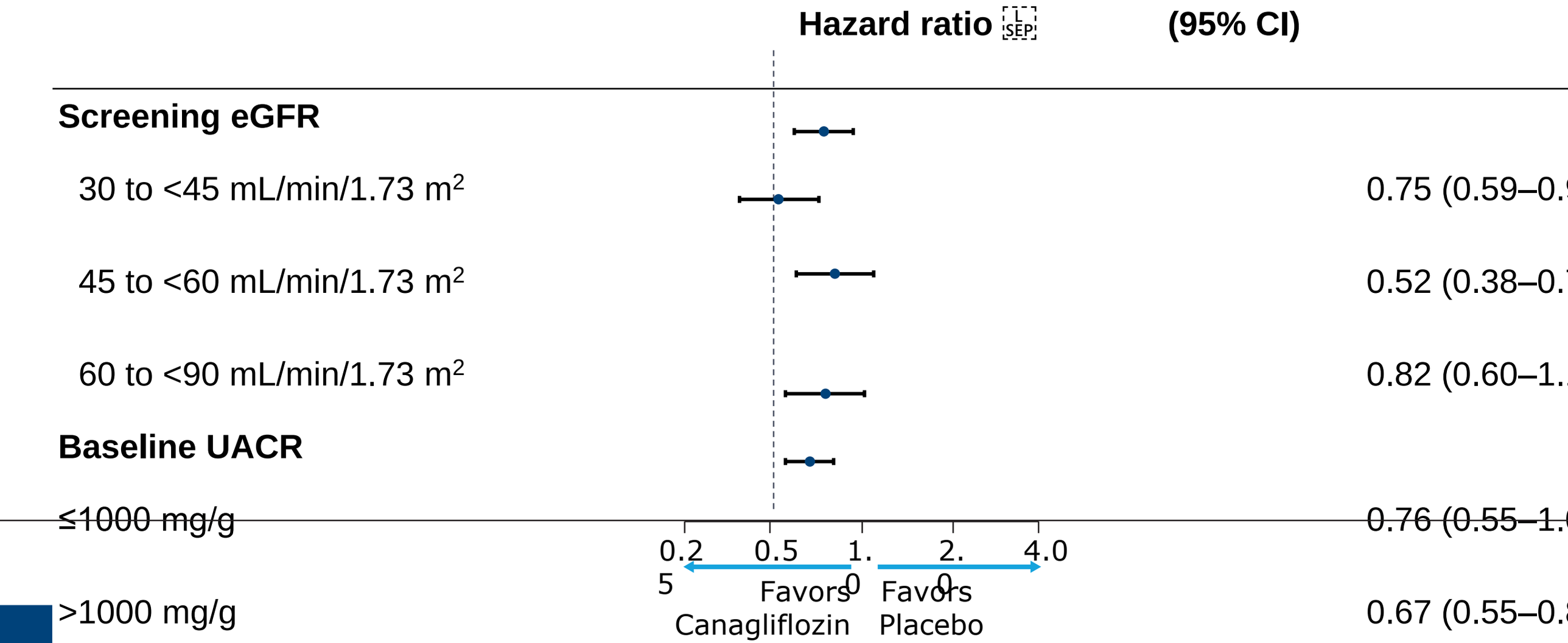
	Hazard ratio (95% CI)	*P* value
Primary composite outcome	0.70 (0.59–0.82)	0.00001
Doubling of serum creatinine	0.60 (0.48–0.76)	<0.001
ESKD	0.68 (0.54–0.86)	0.002
eGFR <15 mL/min/1.73 m^2	0.60 (0.45–0.80)	–
Dialysis initiated or kidney transplantation	0.74 (0.55–1.00)	–
Renal death	0.39 (0.08–2.03)	–
CV death	0.78 (0.61–1.00)	0.0502
ESKD, doubling of serum creatinine, or renal death	0.66 (0.53–0.81)	<0.001
Dialysis, kidney transplantation, or renal death*	0.72 (0.54–0.97)	–



*Post hoc analysis.

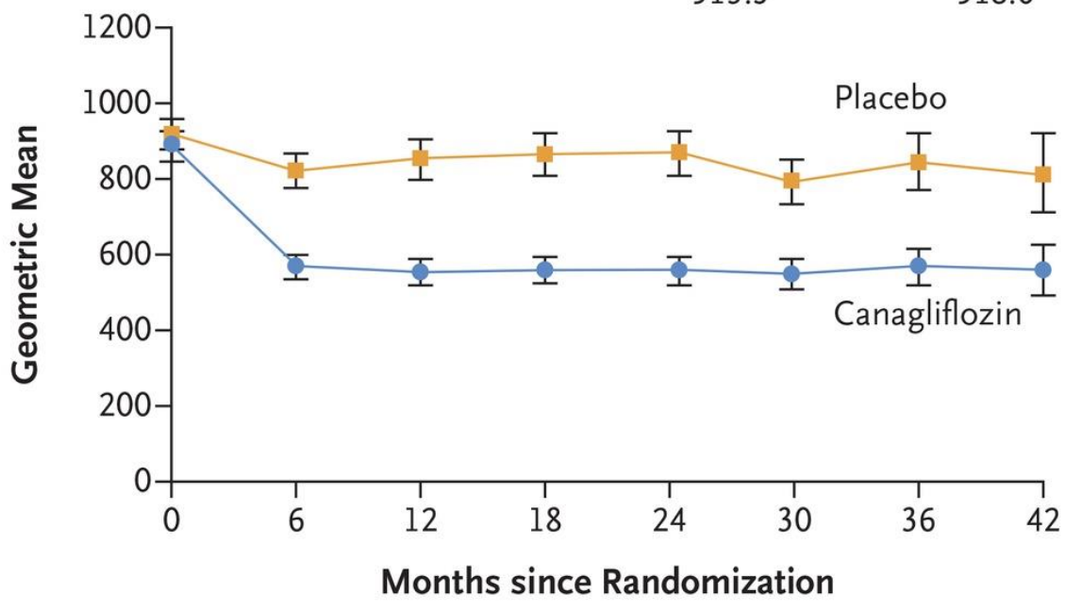
CREDENCE

Primary Outcome by Screening eGFR and Albuminuria



A Urinary Albumin-to-Creatinine Ratio

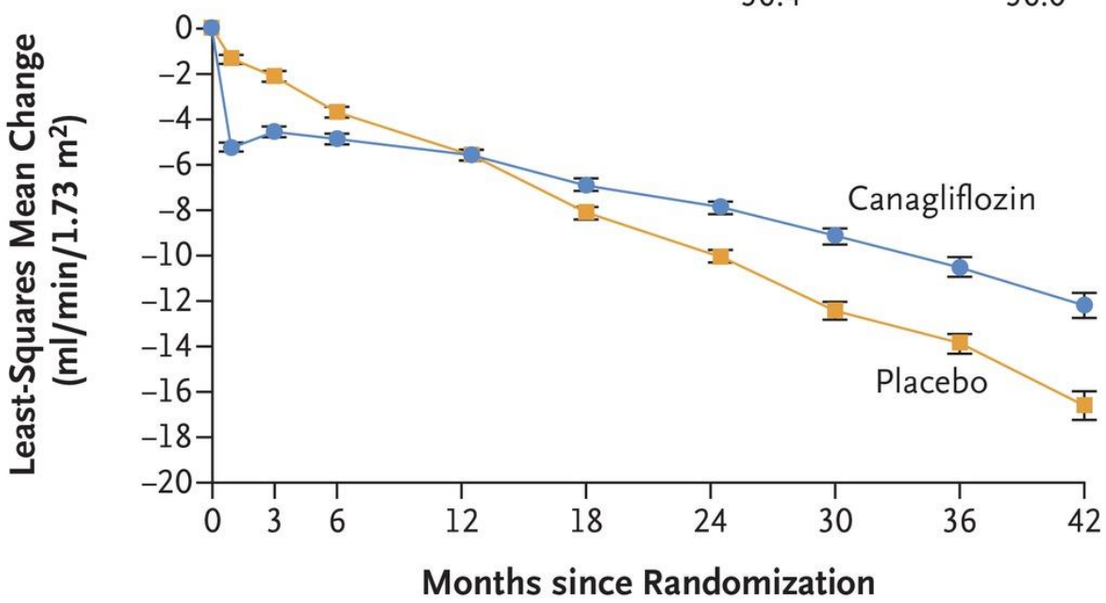
Median Baseline	
Canagliflozin	Placebo
913.5	918.0



No. of Patients								
Placebo	2113	2061	1986	1865	1714	1158	685	251
Canagliflozin	2114	2070	1919	1917	1819	1245	730	271

B Change from Baseline in Estimated GFR

Baseline (ml/min/1.73 m²)	
Canagliflozin	Placebo
56.4	56.0



No. of Patients								
Placebo	2178	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2005	1919	1782	1648	1116	652	241

The NEW ENGLAND JOURNAL of MEDICINE

Summary

- Canagliflozin **reduced the risk of the primary outcome** of ESKD, doubling of serum creatinine, or renal or CV death **by 30%** (*P* = 0.00001)
  - The results were consistent across a broad range of prespecified subgroups
- Canagliflozin also **reduced the risk of the secondary outcome** of ESKD, doubling of serum creatinine, or renal death **by 34%** (*P* <0.001)
- Similar risk reductions were seen for exploratory outcomes assessing components of the primary outcome
  - **ESKD: 32% lower** (95% CI, 14–46)
  - **Dialysis, transplantation, or renal death: 28% lower** (95% CI, 3–46)
- Canagliflozin **attenuated the slope of chronic eGFR decline** by 2.7 mL/min/1.73 m^2/year (1.9 vs 4.6)

CREDENCE

Summary

Primary	Hazard ratio (95% C
1. ESKD, doubling of serum creatinine, or renal or CV death	0.70 (0.59–0.82)
Secondary	
2. CV death or hospitalization for heart failure	0.69 (0.57–0.83)
3. CV death, MI, or stroke	0.80 (0.67–0.95)
4. Hospitalization for heart failure	0.61 (0.47–0.80)
5. ESKD, doubling of serum creatinine, or renal death	0.66 (0.53–0.81)
6. CV death	0.78 (0.61–1.00)
7. All-cause mortality	0.83 (0.68–1.02)
8. CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina	0.74 (0.63–0.86)

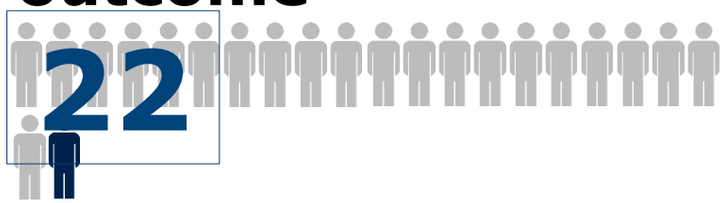
Not significant

Not formally tested

Not formally tested

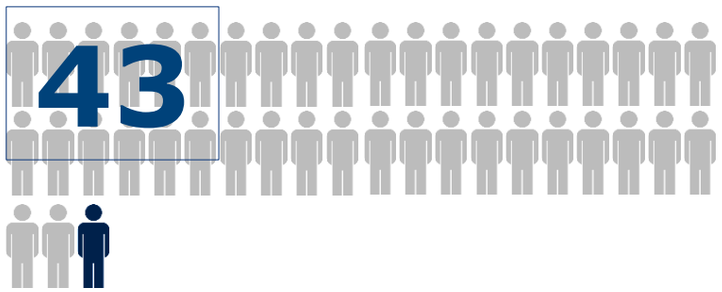
NNT for Renal and CV Outcomes Over 2.5 Years

Primary composite outcome

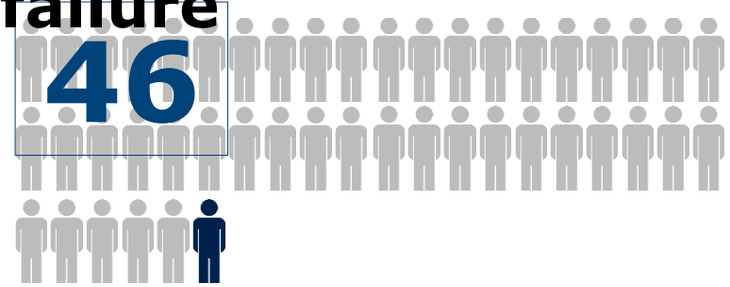


ESKD, doubling of serum creatinine, or renal death

ESKD



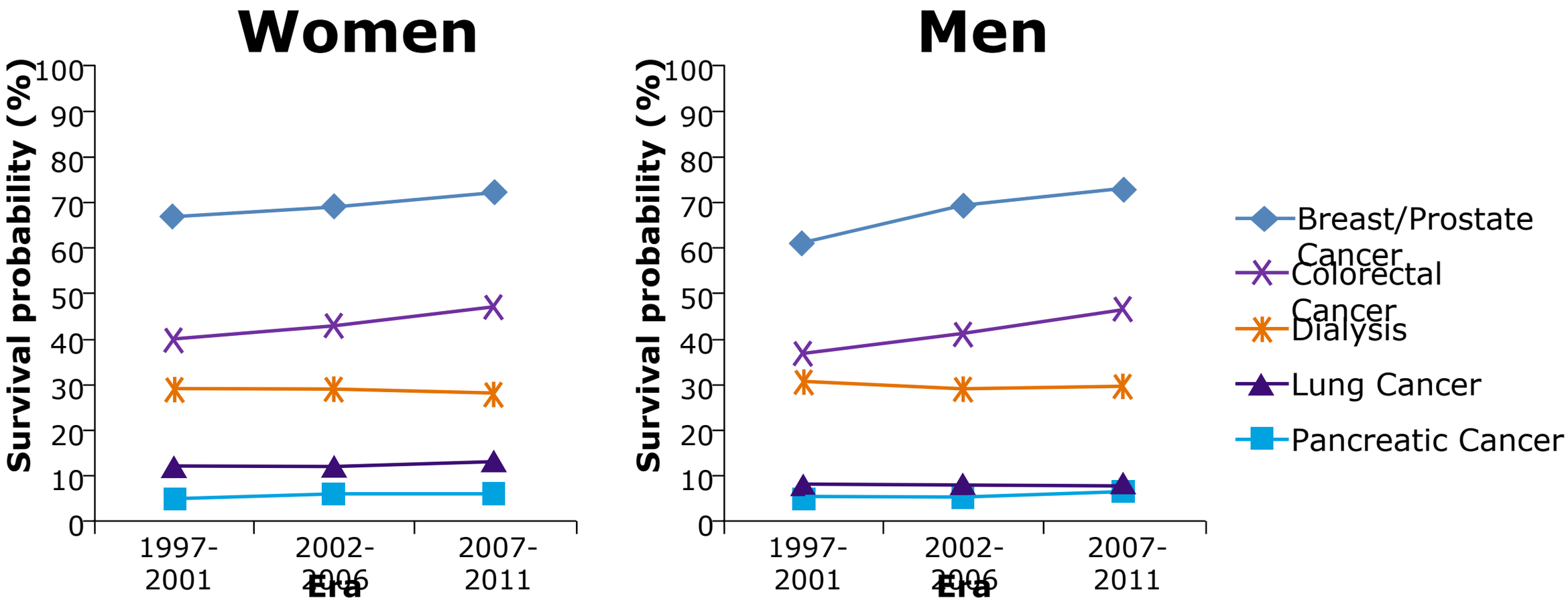
Hospitalization for heart failure



CV death, MI, or stroke

CREDENCE

Dialysis Survival Compared to Common Cancers



Unadjusted 10-year survival for all-cause mortality in Canada

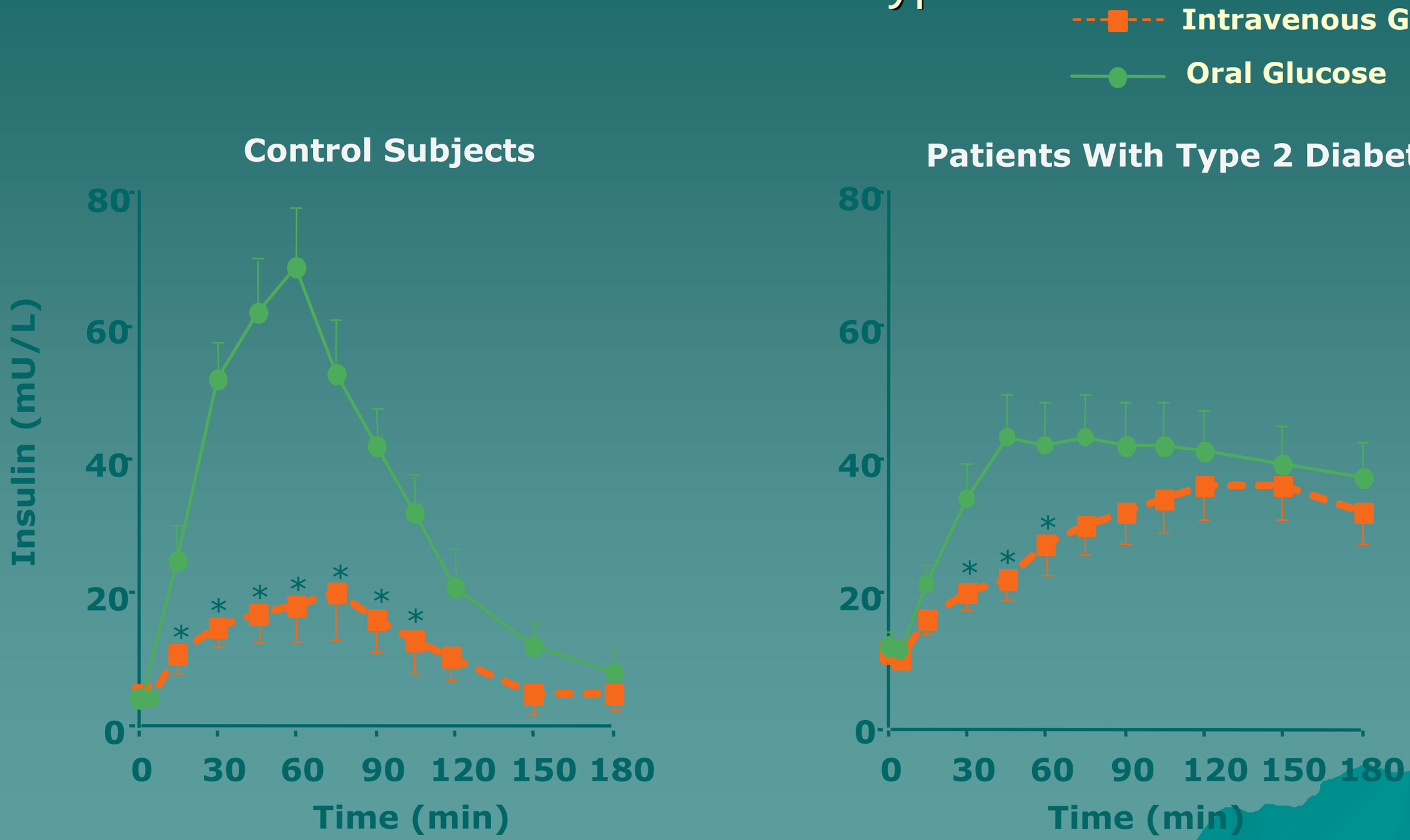
N = 33,500 incident maintenance dialysis patients; 532,452 incident cancer patients

Naylor KL, et al. *Am J Kidney Dis.* 2019. Epub ahead of print. doi:10.1053/j.ajkd.2018.12.011.

CREDENCE

Glucagon like peptides and DPP IV inhibitors

The Incretin Effect Is Reduced in Patients With Type 2 Diabetes



*$P \leq .05$ compared with respective value after oral load.

Nauck MA, et al. *Diabetologia*. 1986;29:46-52.

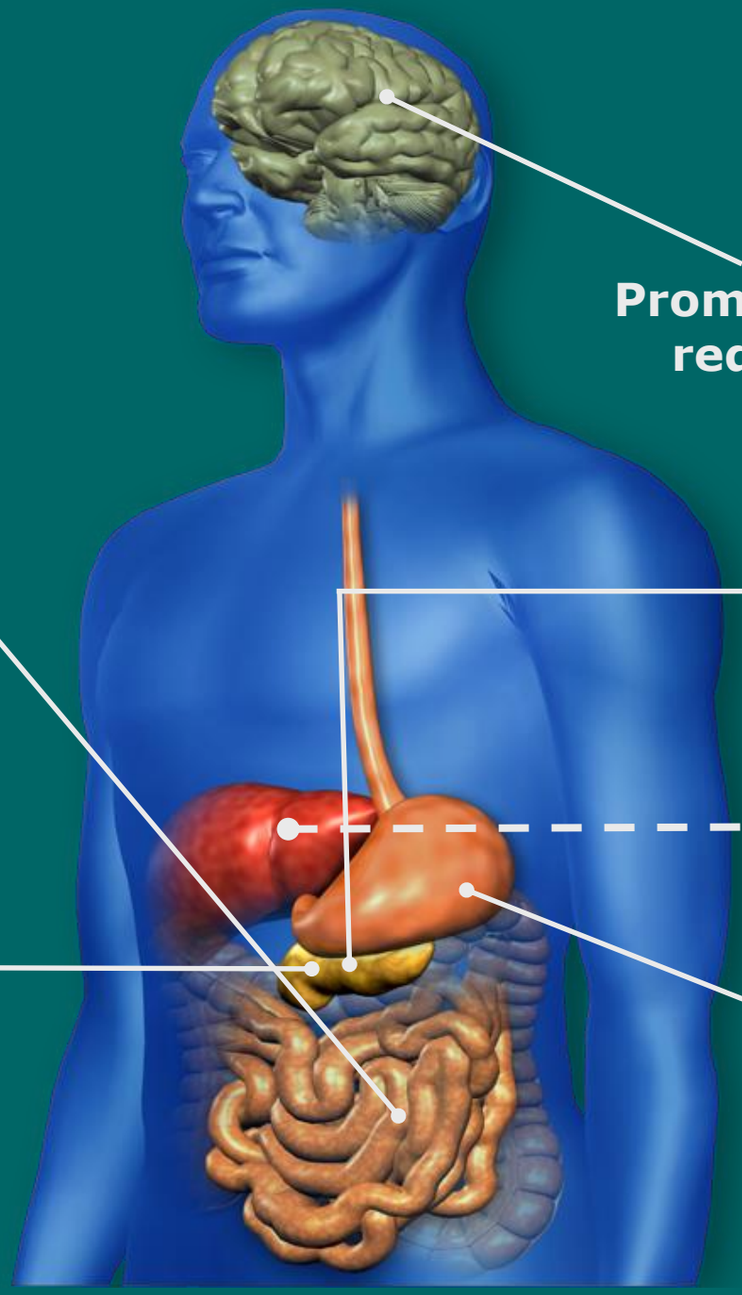
GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins

GLP-1 secreted upon the ingestion of food

↑ Beta-cell response

↓ Beta-cell workload

Promotes satiety and reduces appetite



Alpha cells:
↓ Postprandial glucagon secretion

Liver:
↓ Glucagon reduces hepatic glucose output

Beta cells:
Enhances glucose-dependent insulin secretion

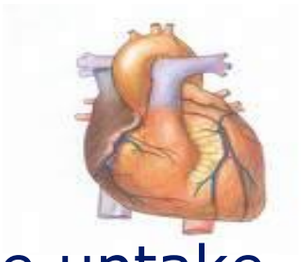
Stomach:
Helps regulate gastric emptying

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

Postulated effects of GLP-1 in the cardiovascular system

Kidney

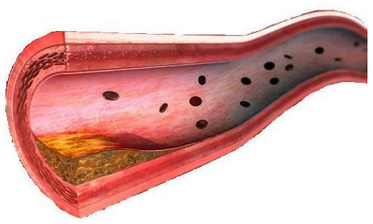
Increases diuresis and sodium excretion in response to sodium overload and volume expansion[1,2]



Heart

- Increases glucose uptake (non-insulin mechanisms)[6]
  - nitric oxide synthesis
  - p38 MAP kinase activity
  - GLUT-1 translocation
- Activates anti-apoptotic kinases[7]

GLP-



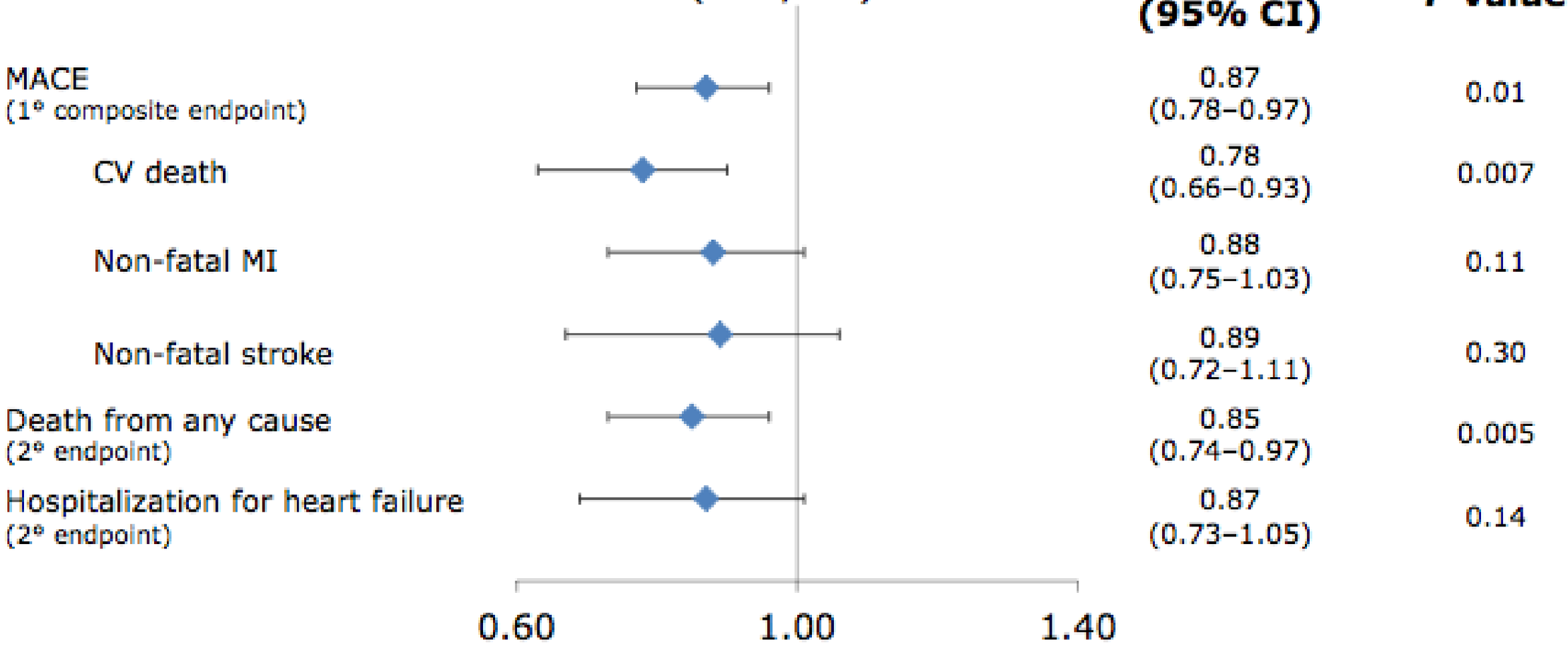
Vascular system

- Nitric oxide-dependent vasorelaxation[3]
- Reduces TNFα-mediated secretion of PAI-1 by cultured endothelial cells[4,5]

1. Gutzwiller *et al*. *Endocrinol Metab* 2004;89:3055–61; 2. Gutzwiller *et al. Digestion* 2006;73:142–50; 3. Golpon *et al. Regul Pept* 2001;102:81–6;
4. Liu *et al. J Endocrinol* 2008;196:57–65; 5. Liu *et al. J Endocrinol* 2009;201:59–66; 6. Zhao *et al. J Pharmacol Exp Ther* 2006;317:1106–13;
7. Bose *et al. Diabetes* 2005;54:146–51

LEADER: Cardiovascular outcomes for liraglutide vs. placebo

Key LEADER endpoints
(N=9,340)



	Hazard ratio (95% CI)	*P* value
MACE (1° composite endpoint)	0.87 (0.78–0.97)	0.01
CV death	0.78 (0.66–0.93)	0.007
Non-fatal MI	0.88 (0.75–1.03)	0.11
Non-fatal stroke	0.89 (0.72–1.11)	0.30
Death from any cause (2° endpoint)	0.85 (0.74–0.97)	0.005
Hospitalization for heart failure (2° endpoint)	0.87 (0.73–1.05)	0.14

Liraglutide-treated patients had **lower rates of CV events and all-cause death**. Decreases in microvascular events were also demonstrated.

Hazard ratios and p-values were estimated with the use of a Cox proportional-hazards model with treatment as a covariate.
CI, confidence interval; CV, cardiovascular; MI, myocardial infarction. Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Semaglutide: a human GLP-1 analog

Amino acid substitution at position 8
(Alanine to alpha-aminoisobutyric acid) protects against DPP-4 degradation[1]

Spacer and C-18 fatty di-acid chain attached to lysine in position 26 provide strong binding to albumin[1]

94% homology to human GLP-1[1]

$t_{½}$ of approximately 1 week[2–4]

Amino acid substitution at position 34
(lysine to arginine) prevents C-18 fatty acid binding at wrong site[1]

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; $t_{½}$, half-life.

1. Lau J et al. *J Med Chem* 2015;58:7370-80; 2. Kapitza C et al. *J Clin Pharmacol* 2015;55:497-504;
3. Marbury TC et al. *Diabetologia* 2014;57:S358;
4. Connor et al. Poster 1195–P. ADA 77th Scientific Sessions. June 9–13, 2017.

GLP-1RAs molecular size and struc

Key Outcomes of LEADER, SUSTAIN-6 and EMPA-REG OUTCOME

	LEADER[1] (N=9340)		SUSTAIN-6[2] (N=3297)		EMPA-REG OUTCOME*[3] (N=7020)	
	HR (95 % CI)	*p*-value	HR (95 % CI)	*p*-value	HR (95 % CI)	*p*-value
3P-MACE	0.87 (0.78, 0.97)	0.01*	0.74 (0.58, 0.95)	0.02*	0.86 (0.74, 0.99)	0.04*
CV death	0.78 (0.66, 0.93)	0.007	0.98 (0.65, 1.48)	0.92	0.62 (0.49, 0.77)	<0.001
Non-fatal MI	0.88 (0.75, 1.03)	0.11	0.74 (0.51, 1.08)	0.12	0.87 (0.70, 1.09)	0.22
Non-fatal stroke	0.89 (0.72, 1.11)	0.30	0.61 (0.38, 0.99)	0.04	1.24 (0.92, 1.67)	0.16
All-cause mortality	0.85 (0.74, 0.97)	0.02	1.05 (0.74, 1.50)	0.79	0.68 (0.57, 0.82)	<0.001
HHF	0.87 (0.73, 1.05)	0.14	1.11 (0.77, 1.61)	0.57	0.65 (0.50, 0.85)	0.002
NNT to prevent 1 death	98 for 3 years		N/A†		39 for 3 years	

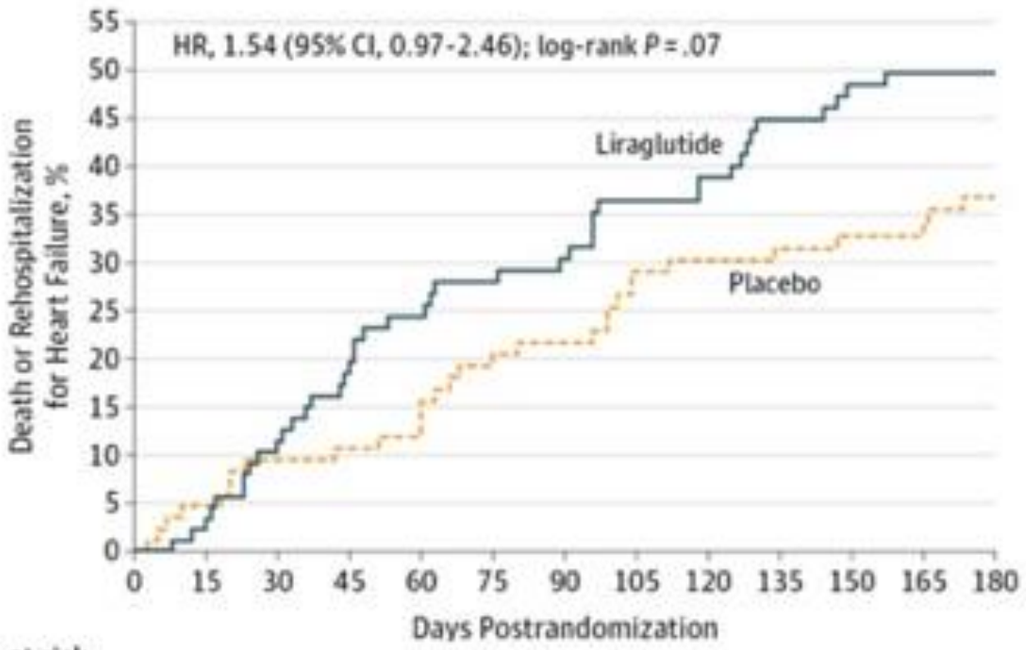
NOT HEAD-TO-HEAD TRIALS

*p-value for superiority; †NNT cannot be calculated as no effect on all-cause mortality.

1. Marso SP et al. N Engl J Med. 2016;375:311-22; 2. Marso SP et al. N Engl J Med. 2016;375:1834-1844; 3. Zinman B et al. N Engl J Med. 2015;373:2117-28.

Liraglutide in patients with acutely decompensated heart failure

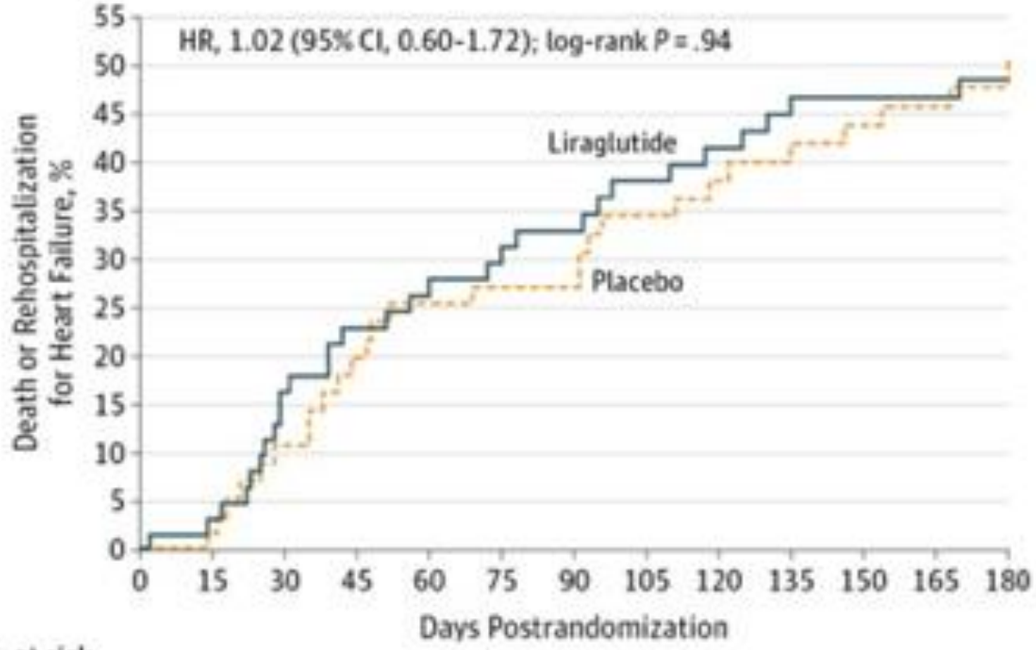
Patients with diabetes



No. at risk

Liraglutide	91	86	77	69	63	60	58	53	51	46	43	41	24
Placebo	87	80	75	73	72	66	64	58	57	56	52	50	31

Patients without diabetes



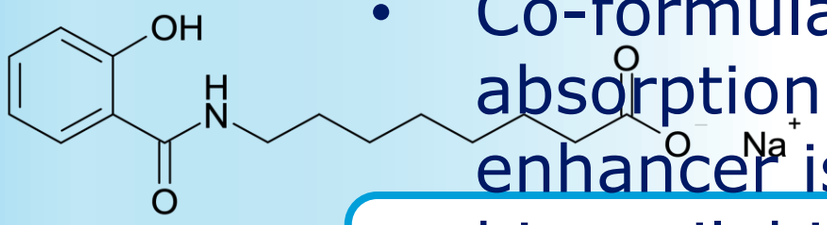
No. at risk

Liraglutide	63	60	51	46	44	42	40	36	34	32	31	29	16
Placebo	59	55	49	44	41	40	40	36	33	31	29	28	16

Margulies, KB, JAMA. 2016;316(5):500-508. doi:10.1001/jama.2016.10260

Oral semaglutide | Tablet co-formulation with SNAC

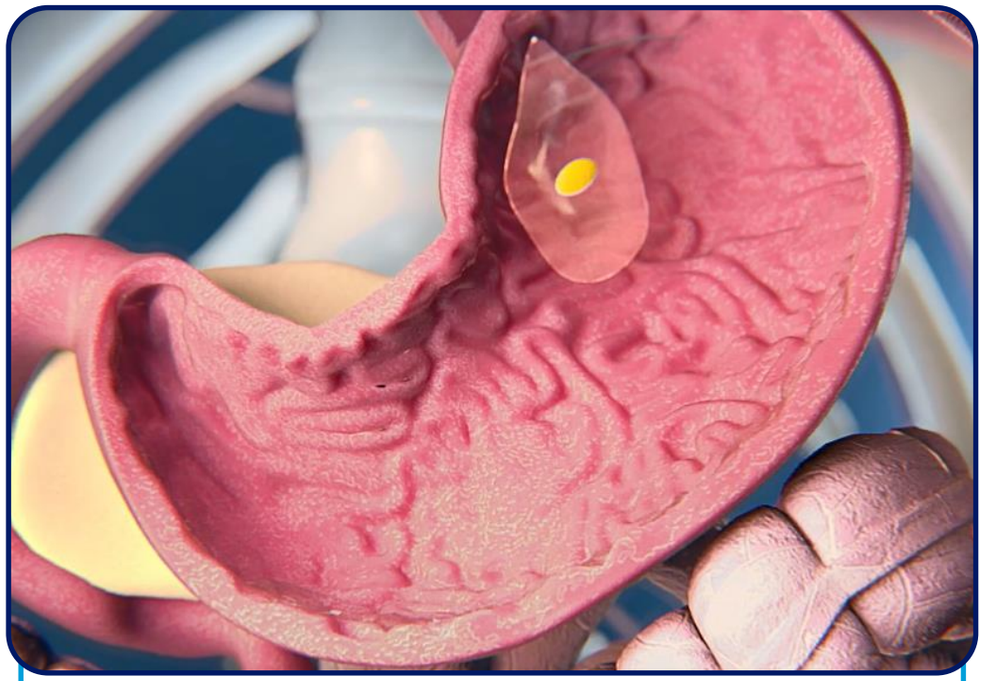
ium **N**-(8-(2-hydroxybenzoyl) **A**mino) **C**aprylate (SNAC)



- Co-formulation of semaglutide with an absorption enhancer is necessary to achieve adequate bioavailability of oral administration
- The **absorption enhancer**, SNAC, is a small fatty acid derivative that promotes absorption across the gastric epithelium
- Oral semaglutide is co-formulated with 300 mg SNAC

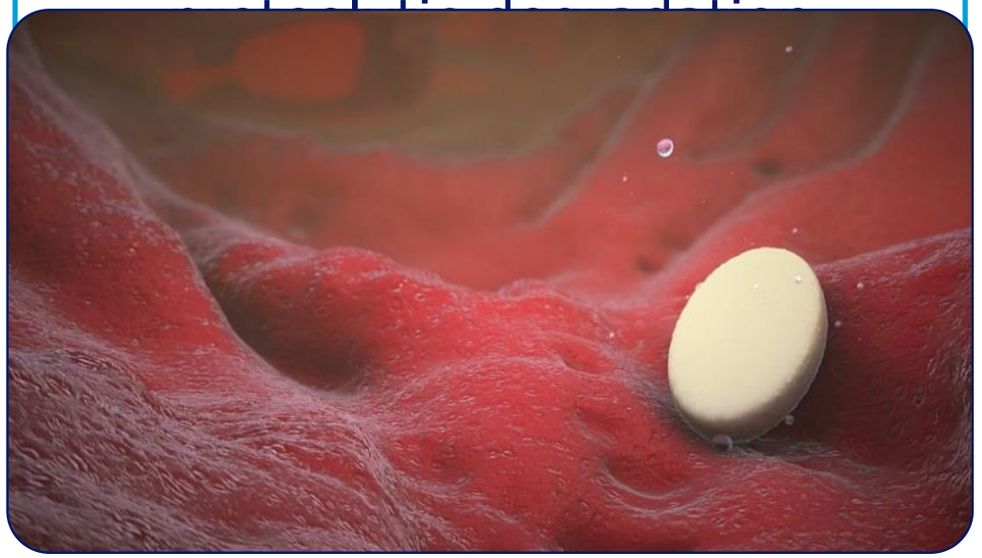
SNAC, Sodium N-(8-(2-hydroxybenzoyl) amino) caprylate.
Buckley ST, et al. *Sci Transl Med*. 2018;10.

Absorption of oral semaglutide *occurs in the stomach*



Absorption of semaglutide requires co-formulation with SNAC

SNAC causes a **local increase of pH** leading to higher solubility and protection from



SNAC: Sodium N-(8-(2-hydroxybenzoyl) amino) caprylate.
Buckley ST, et al. *Sci Transl Med*. 2018;10.

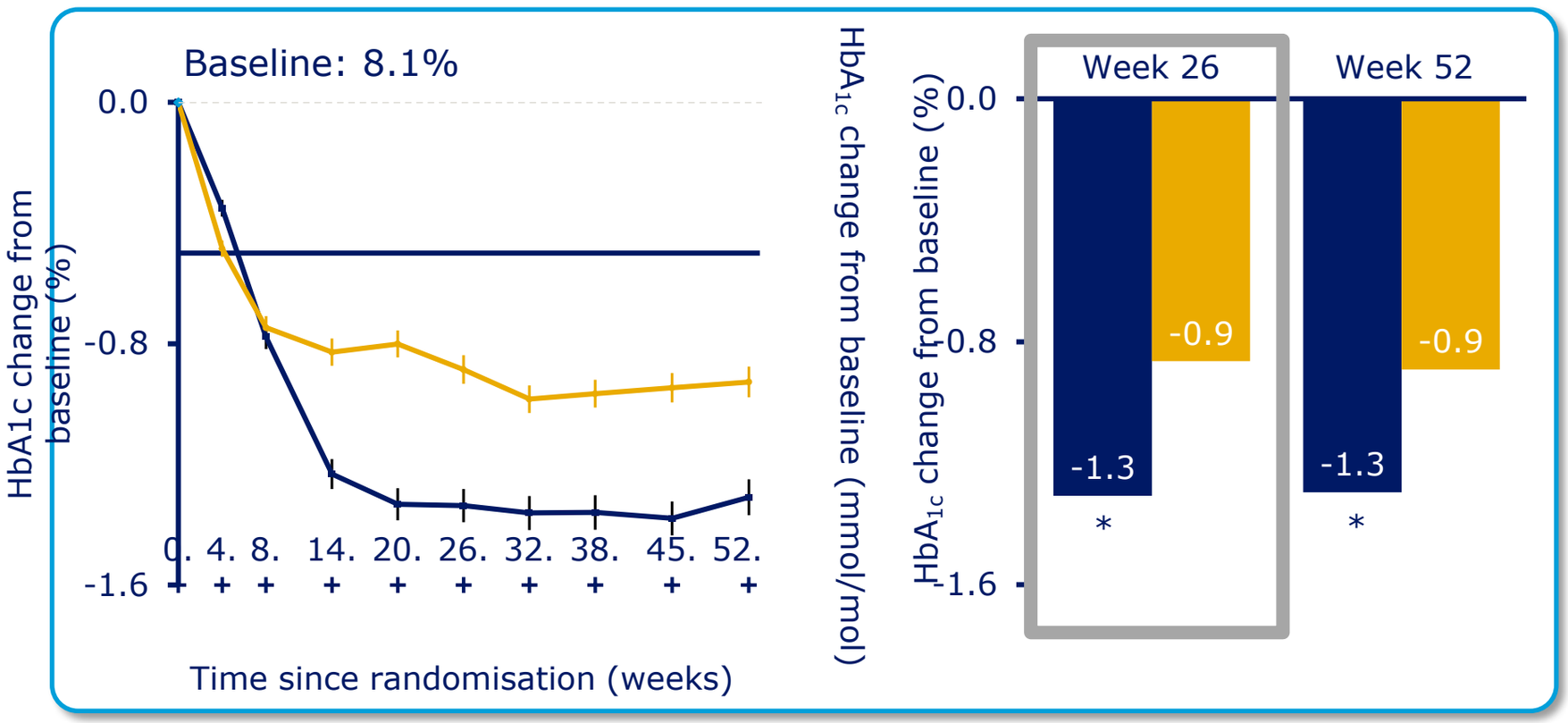
PIONEER 2: HbA_{1c}

CHANGE FROM BASELINE TO WEEKS 26 AND 52

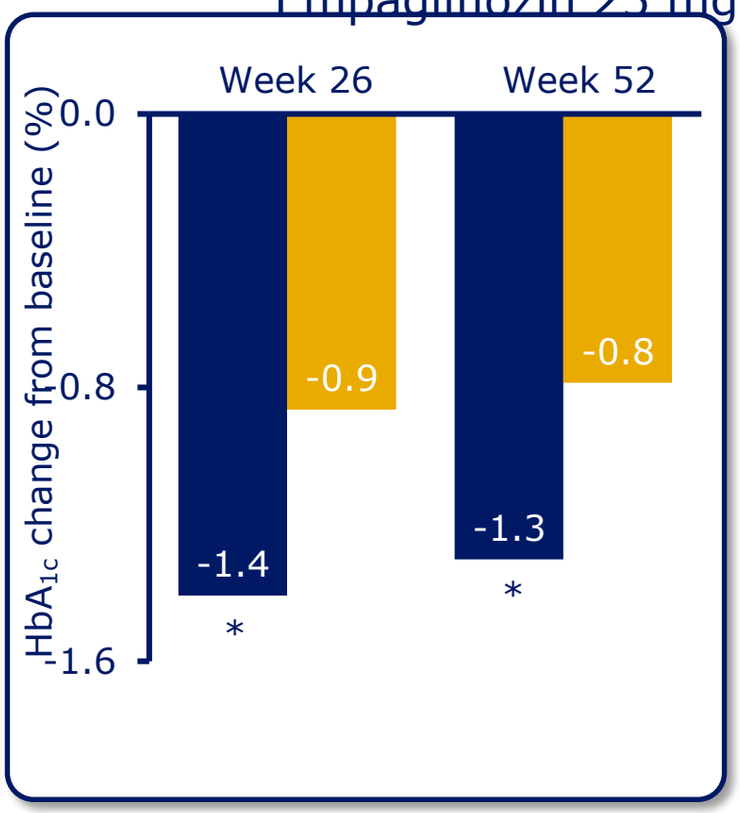
Oral semaglutide 14 mg

Empagliflozin 25 mg

Treatment policy estimand

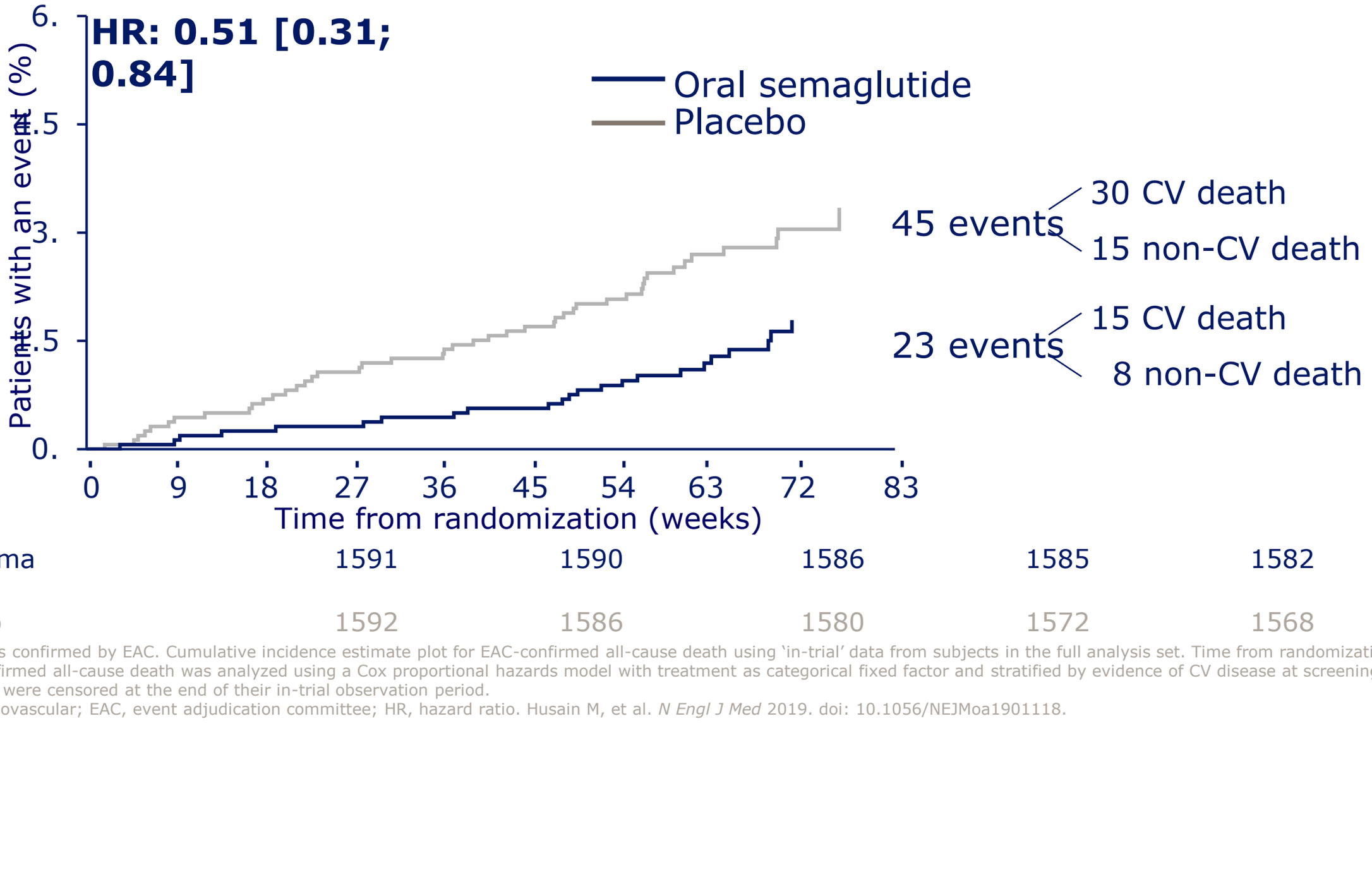


Trial product estimand



Line graph: values are observed means ± standard error of the mean. Bar graphs: estimated mean changes from baseline to week 26 and 52.
*Statistically significant in favour of oral semaglutide compared with empagliflozin at a 5% significance level.
Montanya E, et al. Oral presentation 54-OR. ADA 79th Annual Scientific Sessions. June 08, 2019.

PIONEER 6: All-cause death



All events confirmed by EAC. Cumulative incidence estimate plot for EAC-confirmed all-cause death using 'in-trial' data from subjects in the full analysis set. Time from randomization to EAC-confirmed all-cause death was analyzed using a Cox proportional hazards model with treatment as categorical fixed factor and stratified by evidence of CV disease at screening. Subjects were censored at the end of their in-trial observation period.

CV, cardiovascular; EAC, event adjudication committee; HR, hazard ratio. Husain M, et al. *N Engl J Med* 2019. doi: 10.1056/NEJMoa1901118.

SIDE EFFECTS SGLT-2 INHIBITORS

- GENITAL MYCOTIC INFECTIONS
- HYPOVOLEMIA
- FREQUENCY MICTUIRITION
- ? BONE FRACTURES
- ? EXACERBATION OF PERIPHERAL VASCULAR DISEASE
- DIABETIC KETOACIDOSIS

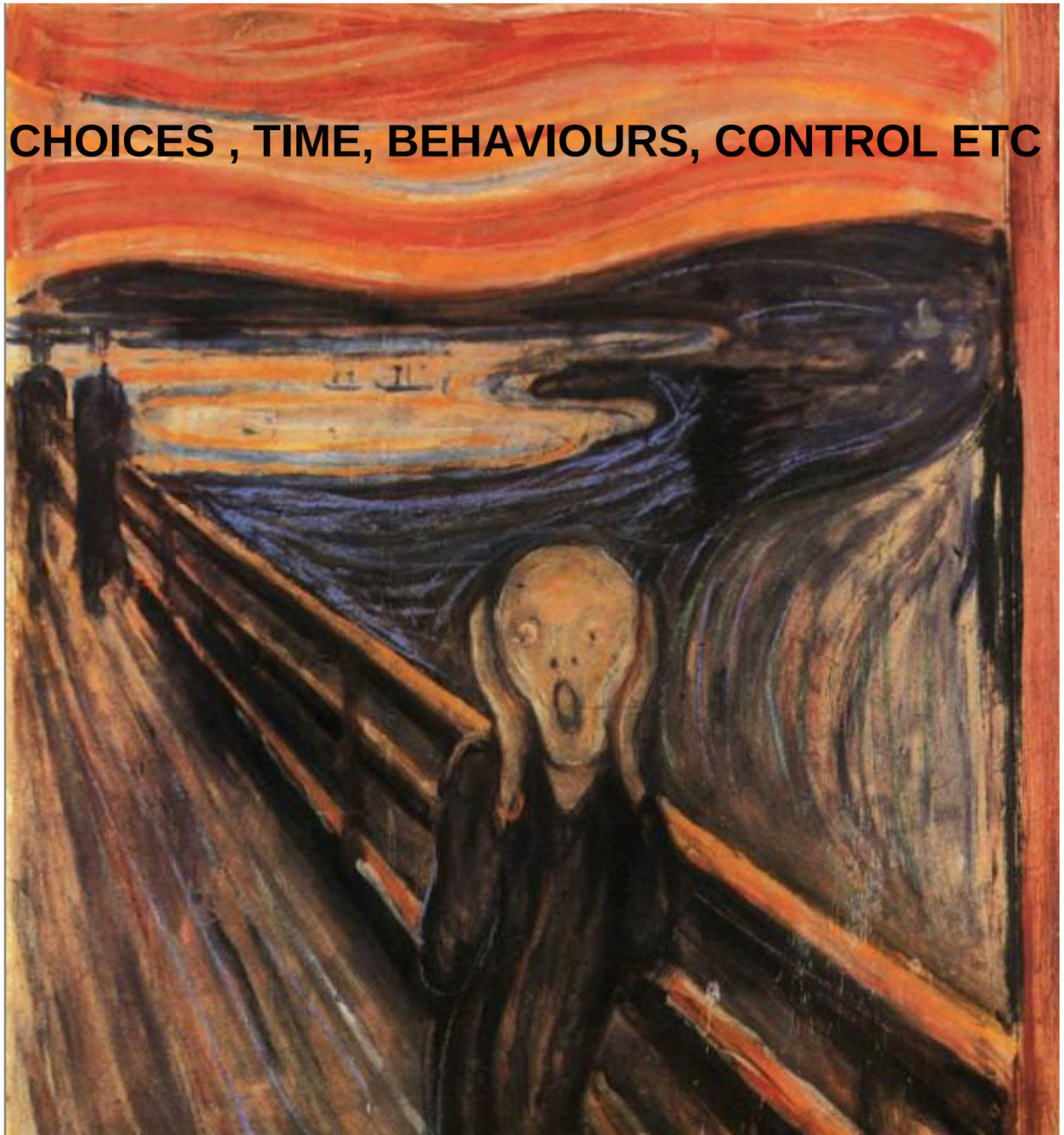
DKA AND SGLT-2 INHIBITORS

- COMMONER IN INSULINOPENIC STATES
- KETO DIETS
- STARVATION
- SEVERE EXCERCISE
- ALCOHOLIC EXCESS
- EUGLYCEMIC KETOACIDOSIS

SIDE EFFECTS GLP-1 ANALOGUES

- NAUSEA AND VOMITING
- HEART FAILURE EXACERBATION
- WORSENING OF RETINOPATHY

SOME PRACTICAL CONSIDERATIONS



Initial treatment- type 2 diabetes

- Metformin plus ???
    - Sulphonylurea
    - DPP-IV inhibitor
    - SGLT-2
    - Insulin (intensive therapy?)
    - GLP analogue

RE- EVALUATION OF TREATMENT

- 1)HISTORY AND SPP LIFESTYLE EVALUATION
- 2)ARE THEY PRODUCING INSULIN?- CLINICAL FEATURES AND C-PEPTIDE EVALUATION
- 3)BASAL INSULIN PLUS GLP
- 4) NO KNOWN ALGORITHM

FACTORS TO CONSIDER

- CLASSIFICATION - TYPE ?
- SOCIOECONOMIC FACTORS
- COMORBIDITIES (heart disease, renal failure, obesity
- AGE
- OTHER

case 1

- 68 year old woman BMI 23
- diagnosed with type 2 diabetes August 2017 (hyperglycaemia on routine blood work)
- treated with 4 oral hypoglycemics and basal insulin to try and control BG
- assessed in CCDC April 2018
- What’s unusual ??

Tests

- C- PEPTIDE - **225**(N 370 -1470)
- ANTI GAD TITRES - >**250** (N<5)

- DIAGNOSIS
- -
- **LATENT AUTOIMMUNE DIABETES OF ADULTS**

case 2

- 44 year old MAN BMI 28
- diagnosed with type 2 diabetes AGE 22
- treated with insulin within a year of diagnosis
- assessed in CCDC May 2016
- A1c 9, BMI 44
- Meds: lever 70u bedtime, 25 U homolog c meals , trajenta
- Whats unusual ??
- Management ?

Tests

- C- PEPTIDE <5 (N 370 -1470)
- ANTI GAD TITRES - >100 (N<5)

- DIAGNOSIS ?
- type 1 diabetes (hence not candidate for SGLT2 inhibitors etc)

Clinical and laboratory features of latent autoimmune diabetes of adulthood6,30,33.

Clinical considerations	Laboratory features
Age > 30 yr	GAD and ICA antibodies present
Patients may be overweight, but typically leaner than those with type 2 diabetes	Insulin antibodies often absent
Patients may have mild to moderate insulin resistance[27]	Autoimmune markers may show subtle differences from those of childhood type 1 diabetes, but are more similar to antibodies seen in adult-onset type 1 diabetes[29]
Occurs in people of various ethnicities	
Progression to insulin therapy slower than for patients with type 1 diabetes, but quicker than for those with type 2 diabetes	
Avoid β-cell stressors such as secretagogues[32]	
May be treated initially with oral antihyperglycemic agents, but insulin should be introduced early if glycemic control cannot be maintained	

Note: GAD = glutamic acid decarboxylase, ICA = islet cell antibodies.

Devin W. Steenkamp et al. CMAJ 2014;186:678-684

CMAJ·JAMC

Evolving weight & cardio-metabolic profile

Since 1980 doubling the prevalence of overweight & obesity

Used to be ——————— to ——————— current

Lean T1D

Overweight
Obese

- Insulin resistance
- Dyslipidemia
- Hypertension
- Inflammation

T2D familly history

Double diabetes

Conway B. et al., Diabet Med., 2010
Purnell JQ. et al., JAMA, 1998
Leroux C et al Can J Diab 2014

2018

ABCDES³ of Diabetes Care

✓**A** • A1C – optimal glycemic control (usually ≤7%)

✓**B** • BP – optimal blood pressure control (<130/80)

✓**C** • Cholesterol – LDL <2.0 mmol/L or >50% reduction

✓**D** • Drugs to protect the heart

A – ACEi or ARB | S – Statin | A – ASA if indicated | SGLT2i/GLP-1 RA with demonstrated CV benefit if type 2 DM with CVD and A1C not at target

✓**E** • Exercise / Healthy Eating

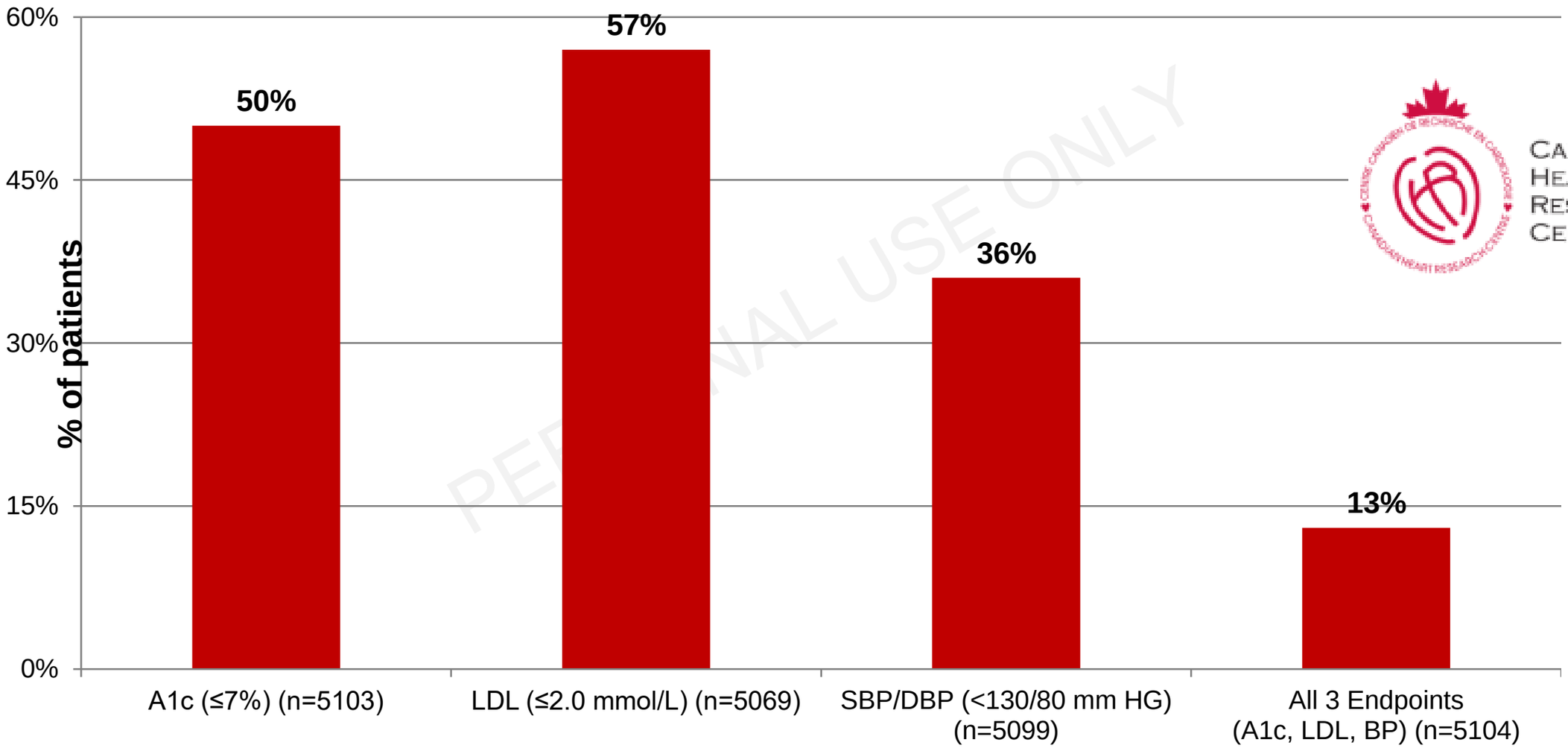
✓**S** • Screening for complications

✓**S** • Smoking cessation

✓**S** • Self-management, stress and other barriers

Guideline Targets Achieved

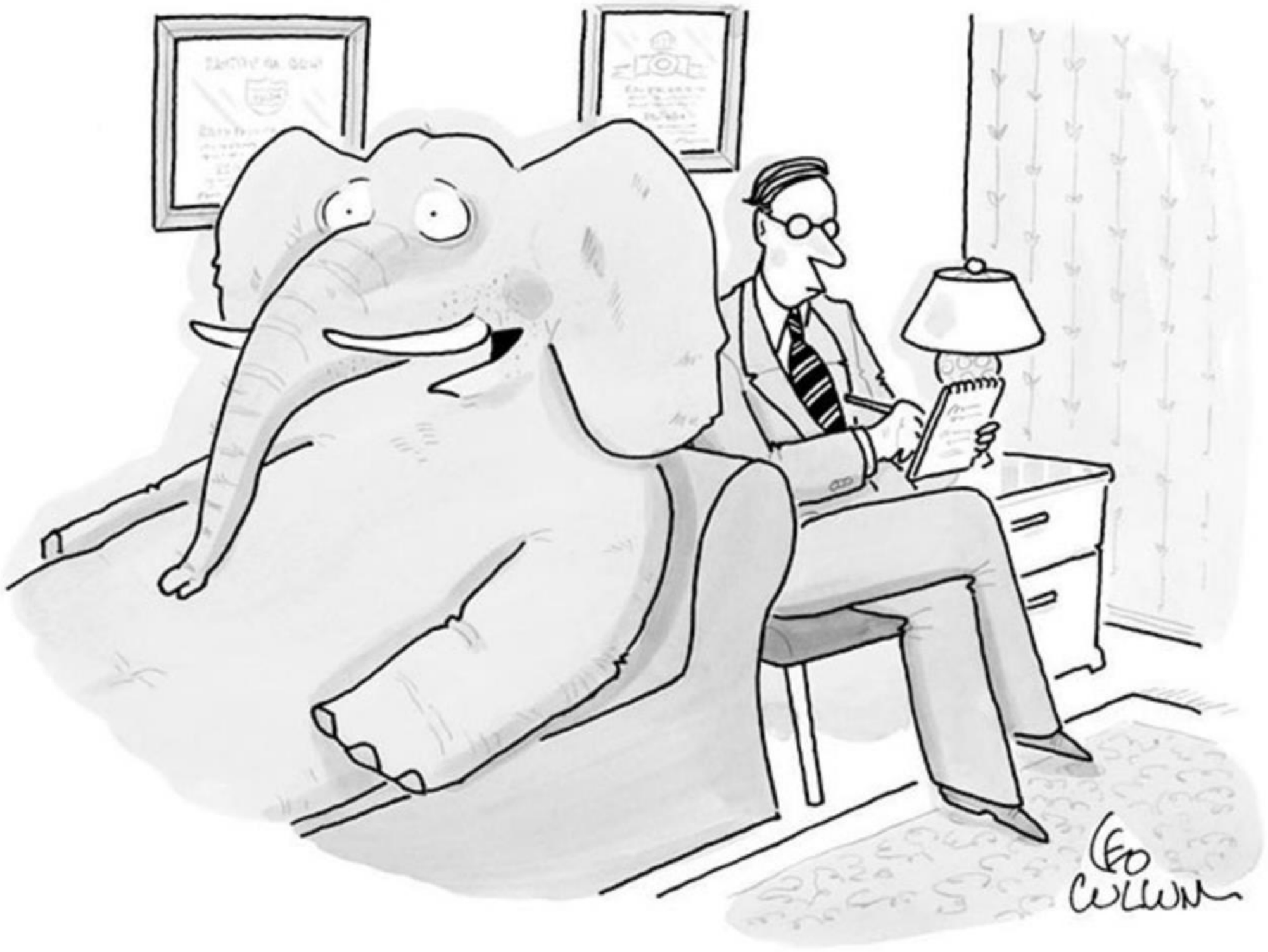
DM SCAN
Diabetes Mellitus Status in CANada
Le Diabète Mellitus Statut au CANada



CANADIAN HEART RESEARCH CENTRE

Leiter LA et al. Can J Diabetes 2013;37:82-89.

DIABETES CANADA



"I'm right there in the room, and no one even acknowledges me."


Feeling of life being controled by DM
Fear, angst or despair about living with DM
Feeling not being supported by Helathcare Providers
Fear of failing at keeping up with Diabetic Care
Social isolation or feeling lack of social support
Burden of living with chronic disease
Diabetes Distress
Other Quality of Life issues

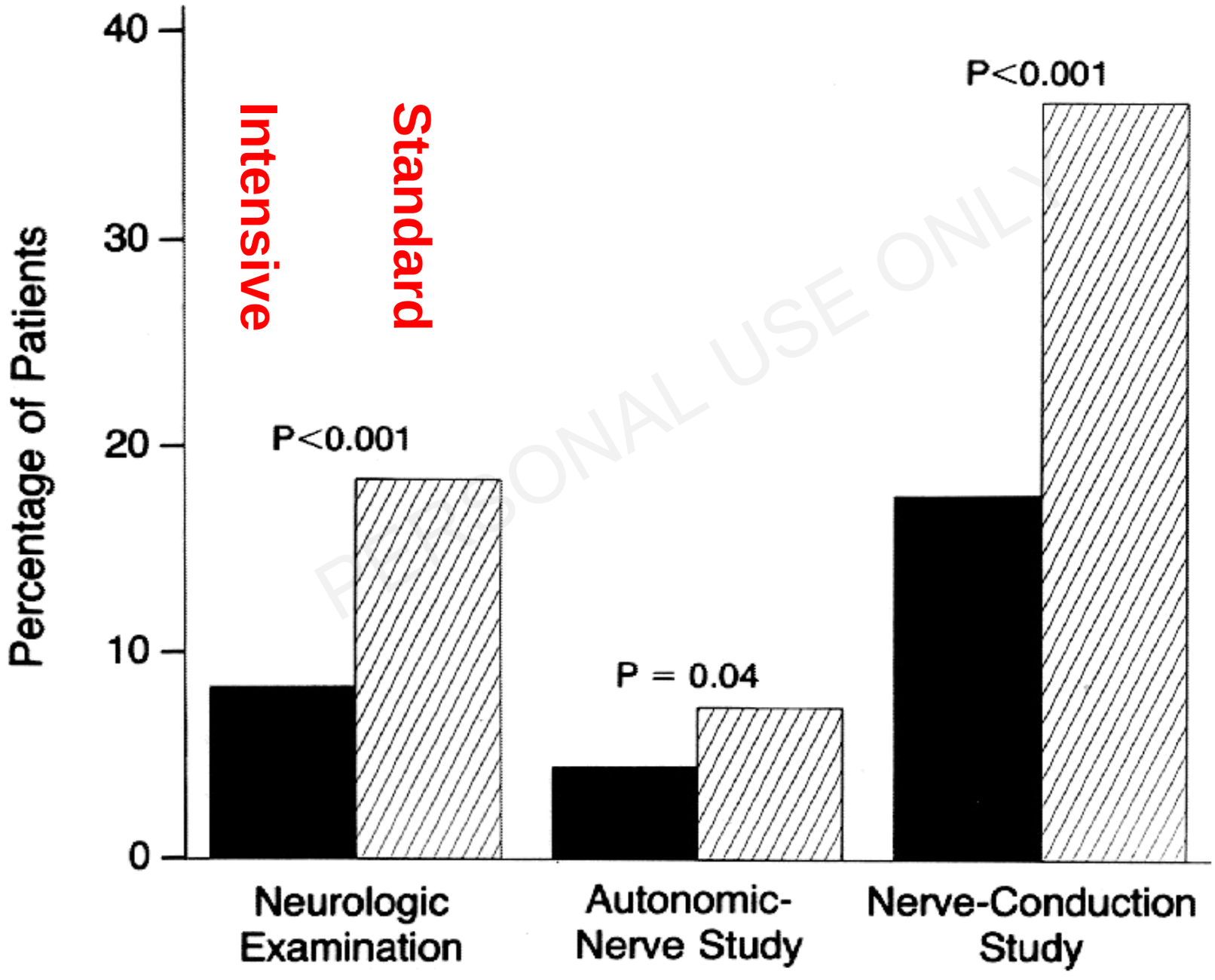
DIABETIC DISTRESS

"Of course you feel great. These things are loaded with antidepressants."

HEALTH CARE SYTEM RIGIDITY

"Never, ever, think outside the box."

Reduction in Neuropathy with Intensive Glycemic Control

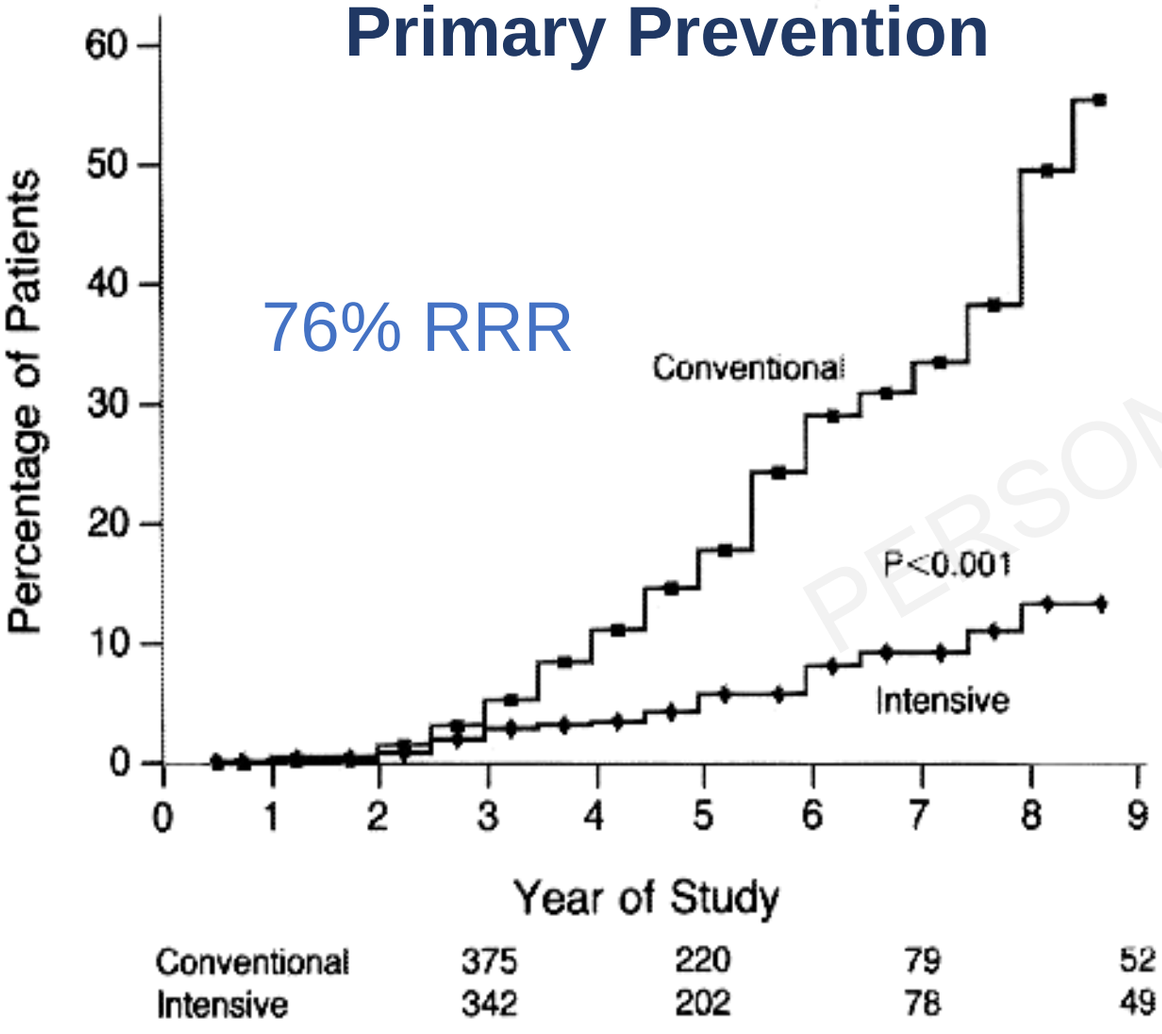


The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329:977-986.

DCCT: Reduction in Retinopathy with Intensive Glycemic Control

Primary Prevention

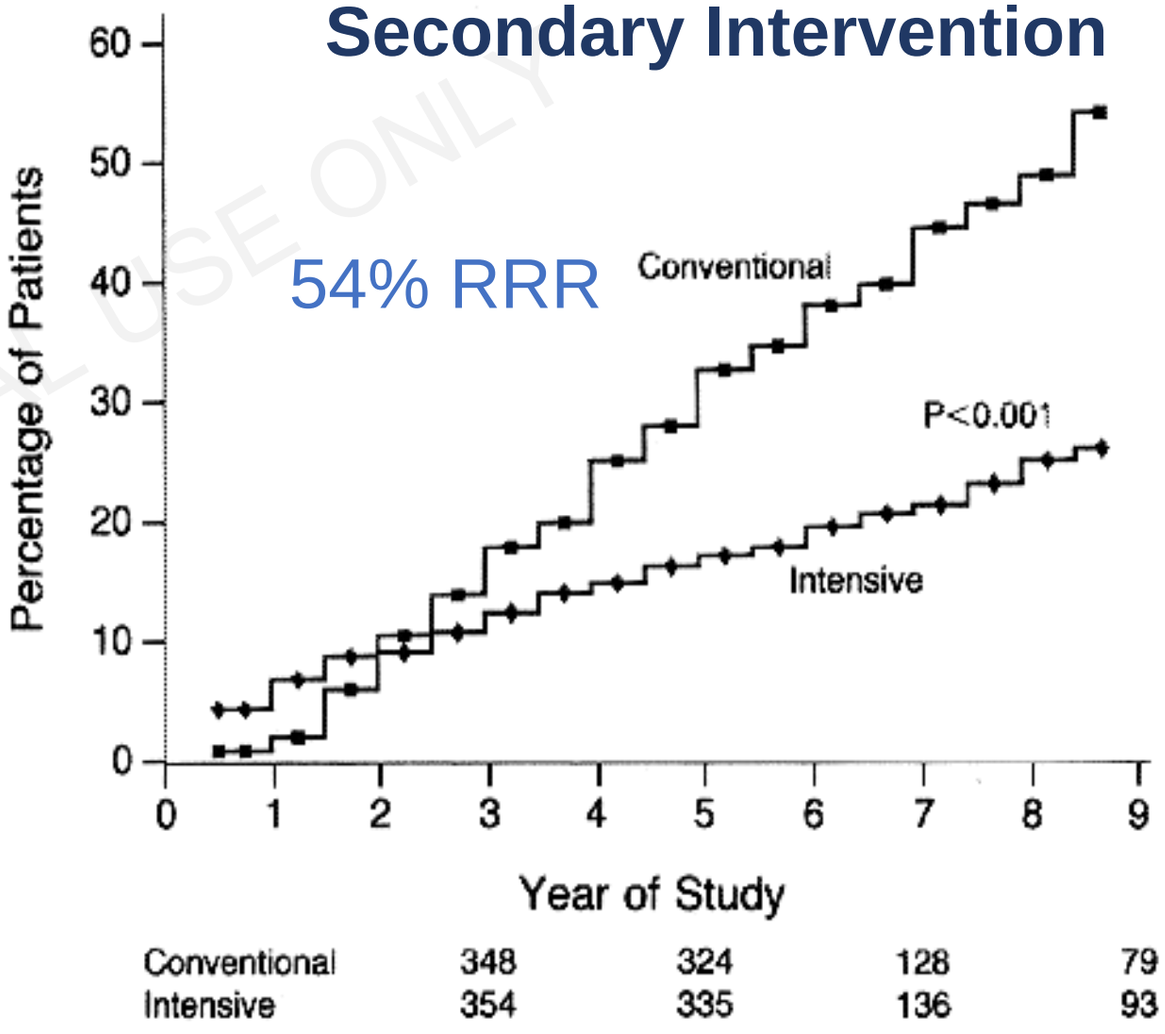
76% RRR



A

Secondary Intervention

54% RRR



B

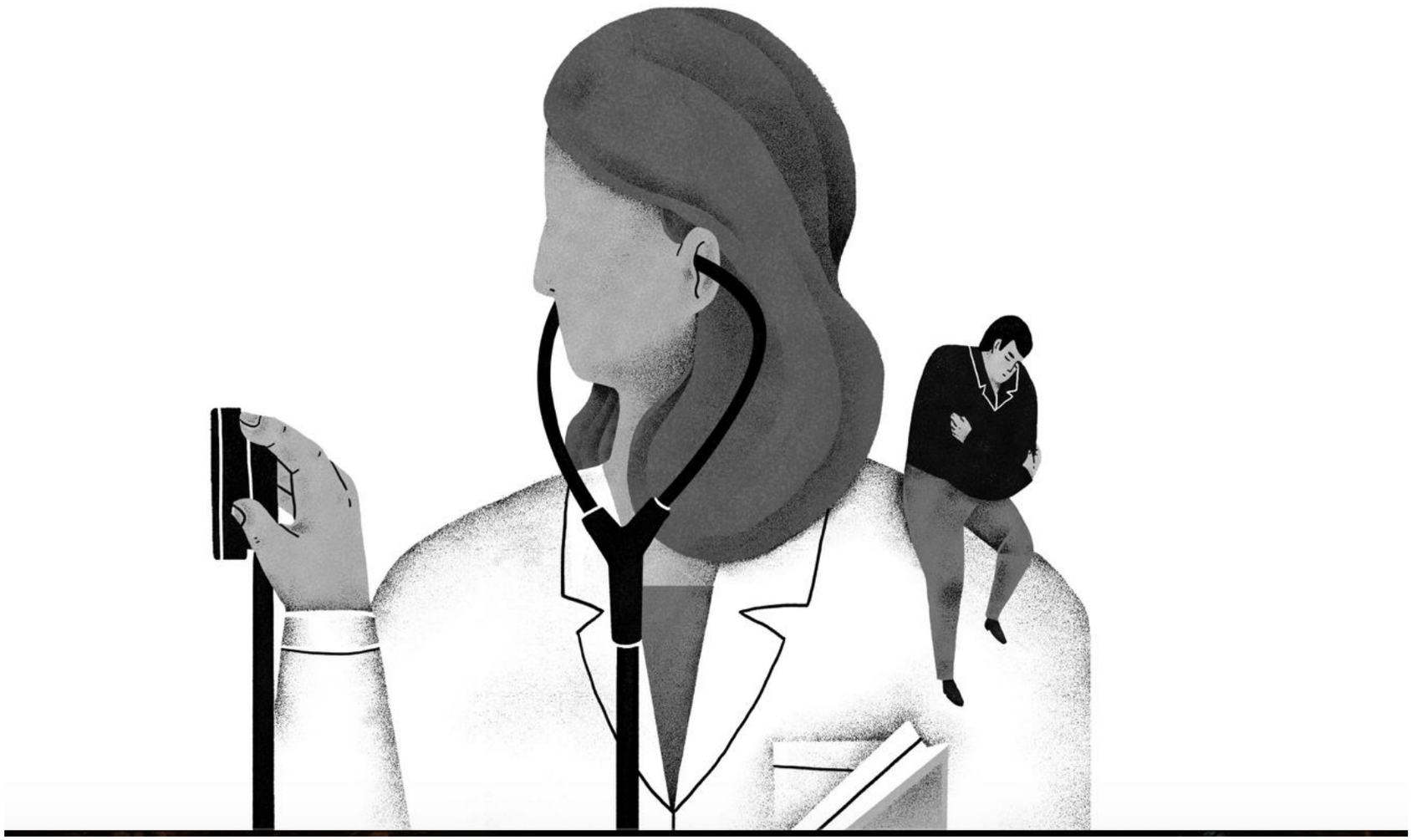
The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329:977-986.

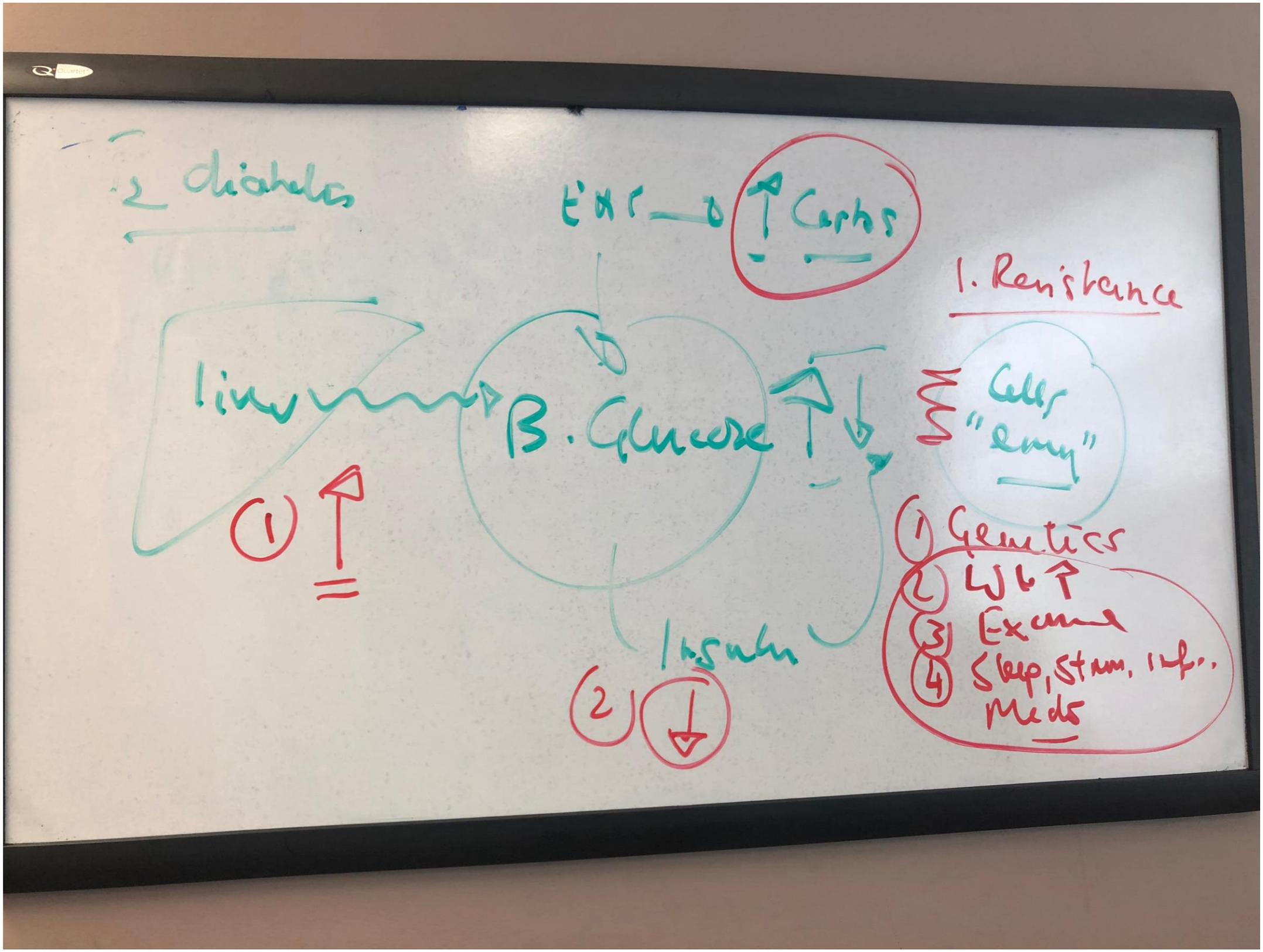
OP-ED CONTRIBUTOR

Doctor, Shut Up and Listen

By Nirmal Joshi

Jan. 4, 2015





Type to enter a caption.

Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

Emma Ahlqvist, PhD, Petter Storm, PhD, Annemari Käräjämäki, MD†, Mats Martinell, MD†, Mozhgan Dorkhan, PhD, Annelie Carlsson, PhD, Petter Vikman, PhD, Rashmi B Prasad, PhD, Dina Mansour Aly, MSc, Peter Almgren, MSc, Ylva Wessman, MSc, Nael Shaat, PhD, Peter Spégel, PhD, Prof Hindrik Mulder, PhD, Eero Lindholm, PhD, Prof Olle Melander, PhD, Ola Hansson, PhD, Ulf Malmqvist, PhD, Prof Åke Lernmark, PhD, Kaj Lahti, MD, Tom Forsén, PhD, Tiinamaija Tuomi, PhD, Anders H Rosengren, PhD, Prof Leif Groop, PhD

† Contributed equally

Published: 01 March 2018

1	577 (6.4)	Early disease onset (at a young age), essentially corresponds with type 1 diabetes and LADA, relatively low BMI, poor metabolic control, insulin deficiency (impaired insulin production), GADA+	Severe autoimmune diabetes (SAID)
2	1575 (17.5)	Similar to cluster 1 but GADA–, high HbA_{1c}, highest incidence of retinopathy	Severe insulin-deficient diabetes (SIDD)
3	1373 (15.3)	Insulin resistance, high BMI, highest incidence of nephropathy	Severe-insulin resistant diabetes (SIRD)
4	1942 (21.6)	Obesity, younger age, not insulin resistant	Mild obesity-related diabetes (MOD)
5	3513 (39.1)	Older age, modest metabolic alterations	Mild age-related diabetes (MARD)

A1C Targets

2018

≤6.5	Adults with type 2 diabetes to reduce the risk of CKD and retinopathy **if at low risk of hypoglycemia**
≤7.0	**MOST ADULTS WITH TYPE 1 OR TYPE 2 DIABETES**
7.1 ↓ **8.5**	**7.1-8.0%**: Functionally dependent* **7.1-8.5%:** • Recurrent severe hypoglycemia and/or hypoglycemia unawareness • Limited life expectancy • Frail elderly and/or with dementia**
Avoid higher A1C to minimize risk of symptomatic hyperglycemia and acute and chronic complications	
End of life	A1C measurement not recommended. Avoid symptomatic hyperglycemia and any hypoglycemia

* Based on class of antihyperglycemic medication(s) utilized and person's characteristics
** see Diabetes in Older People chapter

DIABETES CANADA

TEAMWORK AND FLEXIBILITY

"It's always 'Sit,' 'Stay,' 'Heel'—never 'Think,' 'Innovate,' 'Be yourself.'"

What's urgent what's important-

An open letter to diabetes educators

Virginia Peragallo-Dittko

- Appreciate the art and science of diabetes education
- Be as student and teacher- use beginners eyes
- If you cannot lift someones burden try and lighten the load
- Be inventive and creative- use humour and have fun

“Neither evidence nor clinical judgment alone is sufficient.

Evidence without judgment can be applied by a technician.

Judgment without evidence can be applied by a friend.

But the integration of evidence and judgment is what the healthcare provider does in order to dispense the best clinical care.”

(Hertzel Gerstein, 2012)

consequences

“Sorry, but I’m cheating on my diet and I don’t like loose ends.”