Role of SGLT-2 inhibitors in diabetes

RCP update, May 2025

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Declaration for Dr Danijela Tatovic

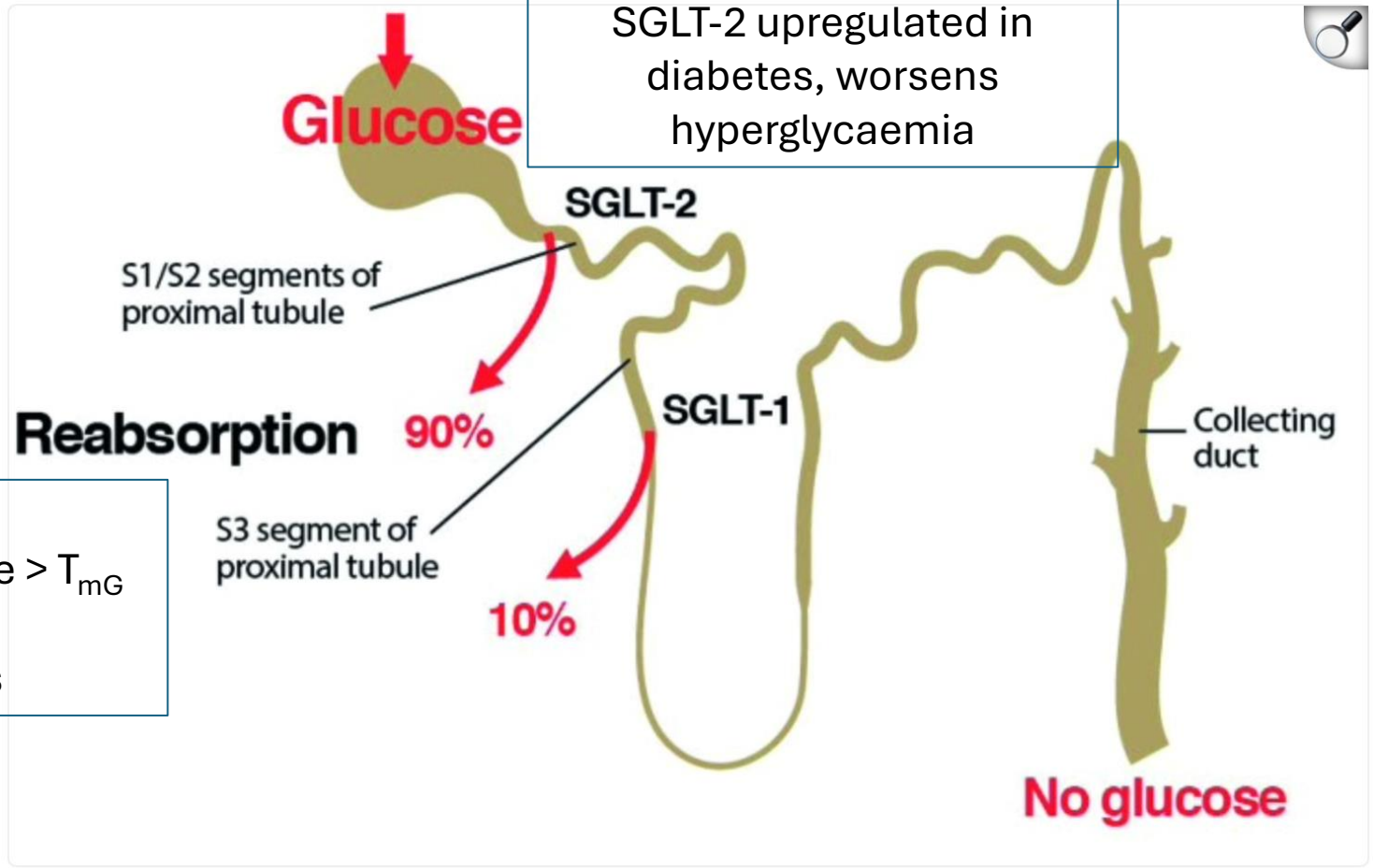
I have the following financial interest or relationship/s to disclose with regard to the subject matter of this presentation:

- Consulting fees: NA
- Research contracts: Funded by BreakthroughT1D/Steve Morgan Foundation
- Clinical trial steering committee: NA
- Owner/stockholder of healthcare company/ies: NA
- Other [please specify activity]: Trustee of NovoNordisk UK Research Foundation

Glucose filtration and reabsorption

162g/day (40 teaspoons)

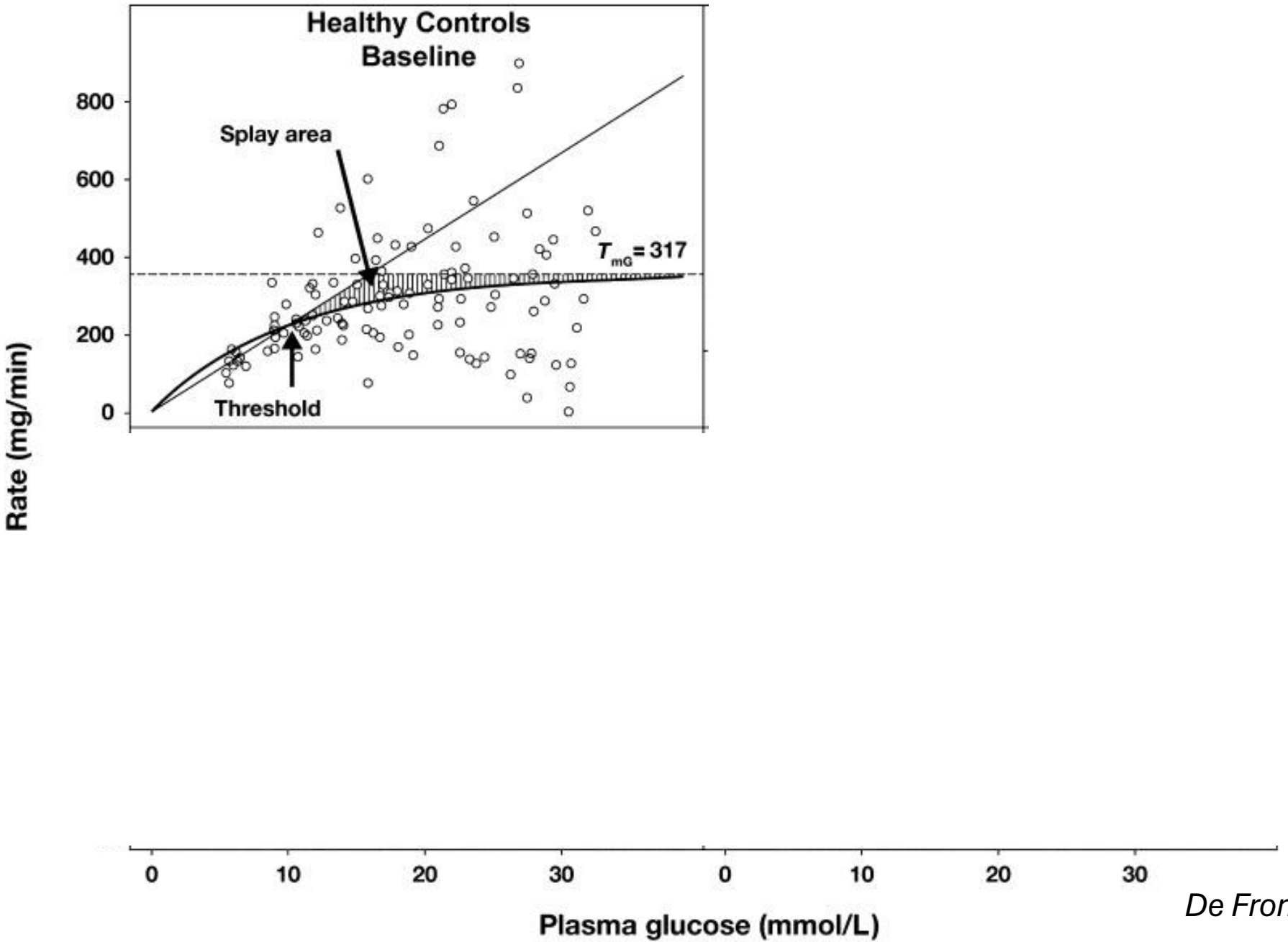
SGLT-2 upregulated in diabetes, worsens hyperglycaemia



T_{mG} 375mg/min
When filtered glucose > T_{mG}
= glycosuria
T_{mG}higher in diabetes

T_{mG} – renal glucose reabsorption capacity

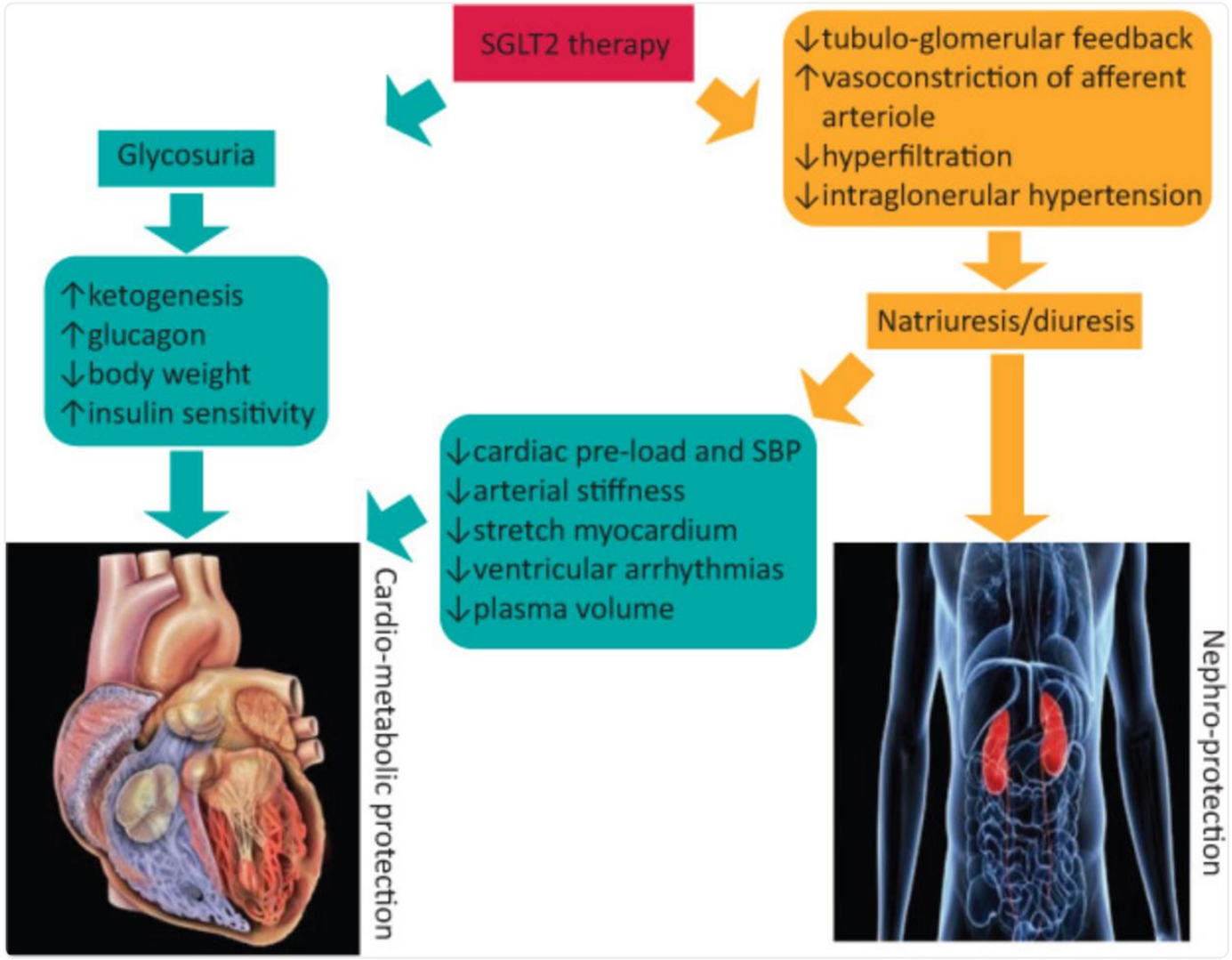
Chao. Clin Diabetes. 2014; doi:10.2337
De Fronzo Diabtes Care 2013; doi: 10.2337



SGLT-2 inh. reduced threshold <4.6-6mM

De Fronzo Diabtes Care 2013; doi: 10.2337

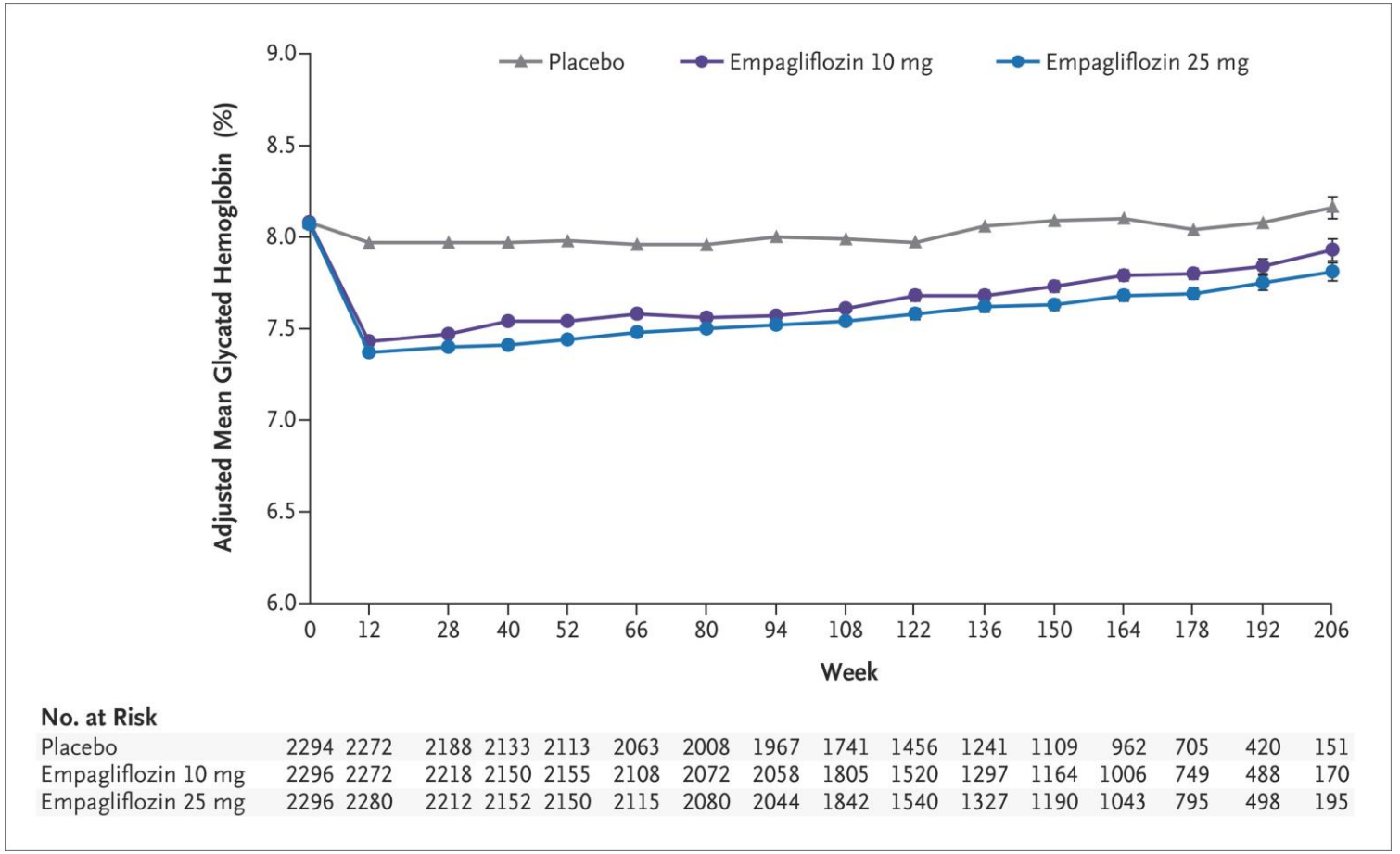
SGLT-2 inhibitors – mechanism of action



Dashora et al. Clinical Medicine 2021 doi: 10.7861/clinmed.2021-0045

SGLT-2 inhibitors in T2 diabetes

Effect of Empagliflozin on glycaemic control (EMPA-REG OUTCOME)

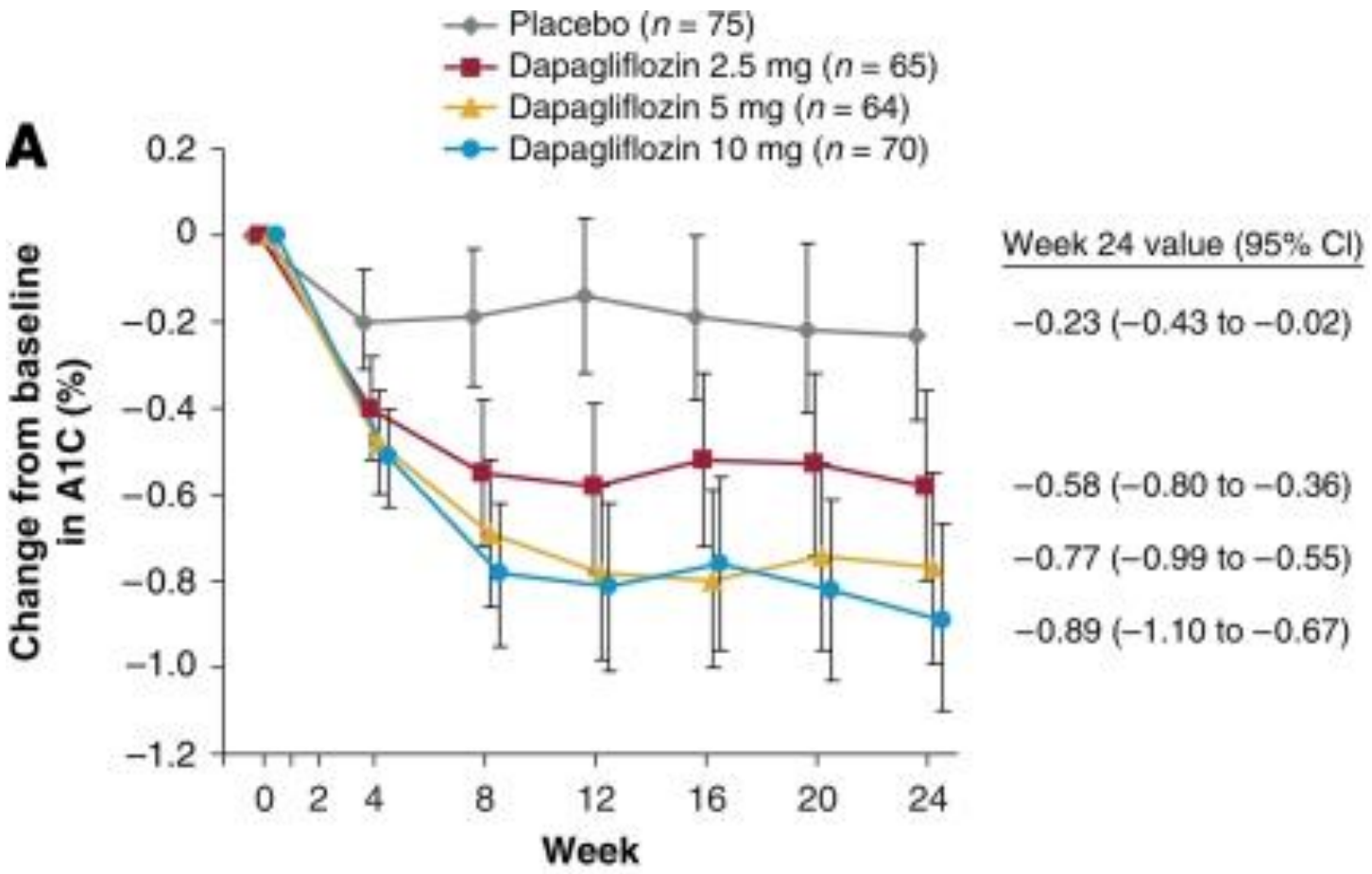


No. at Risk

Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

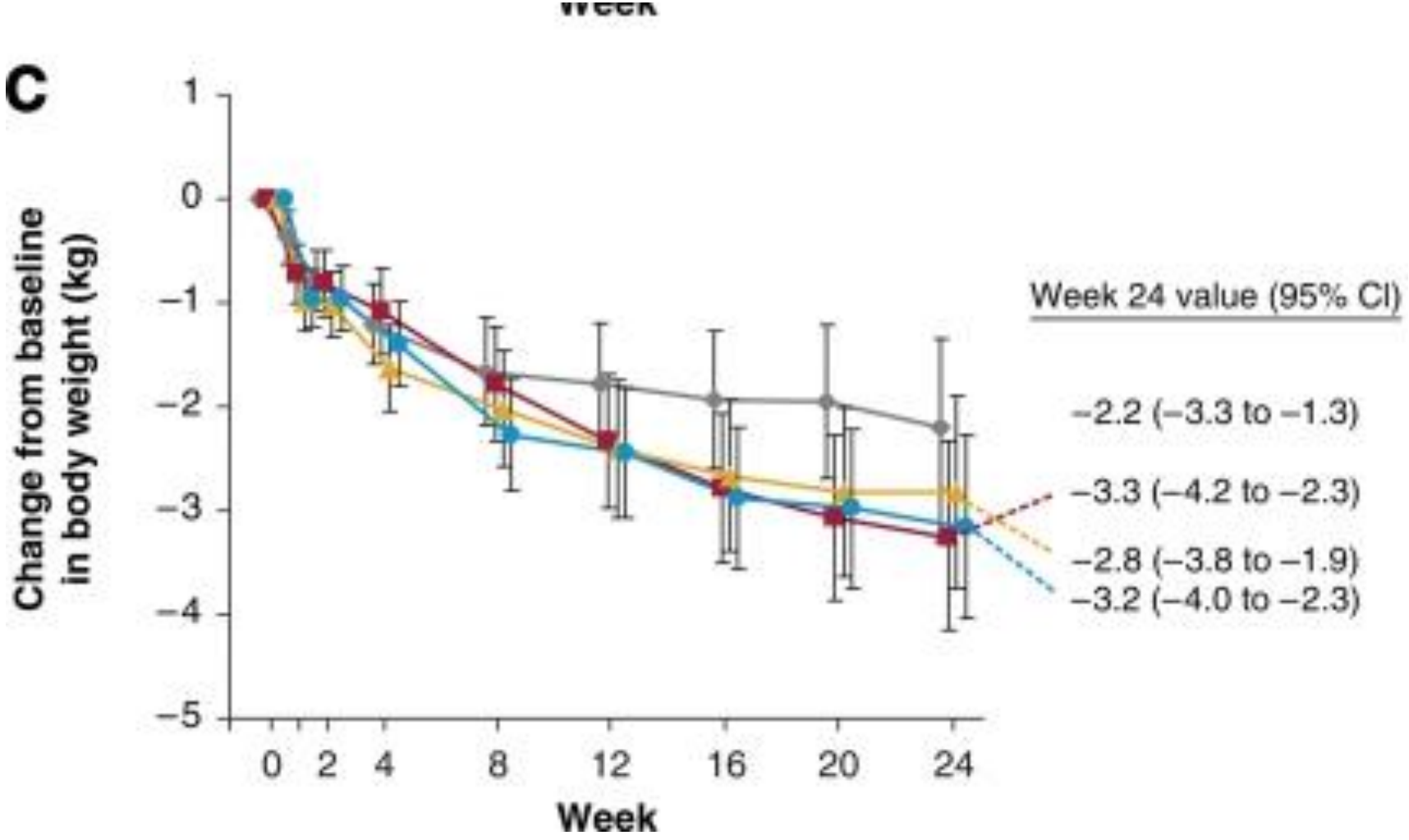
Zinman, et al. N Engl J Med 2015;doi: 10.1056

Effect of Dapagliflozin on glycaemic control



Ferrannnini, et al. Diabetes Care 2010; doi: 10.233/dc10-0612

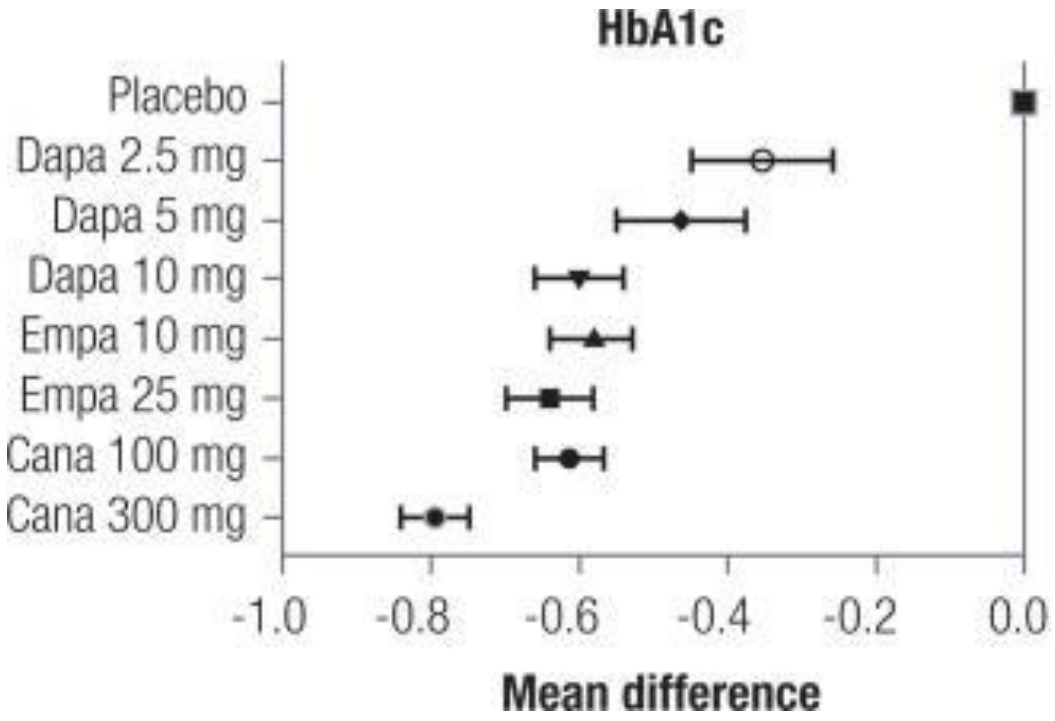
Effect of Dapagliflozin on weight



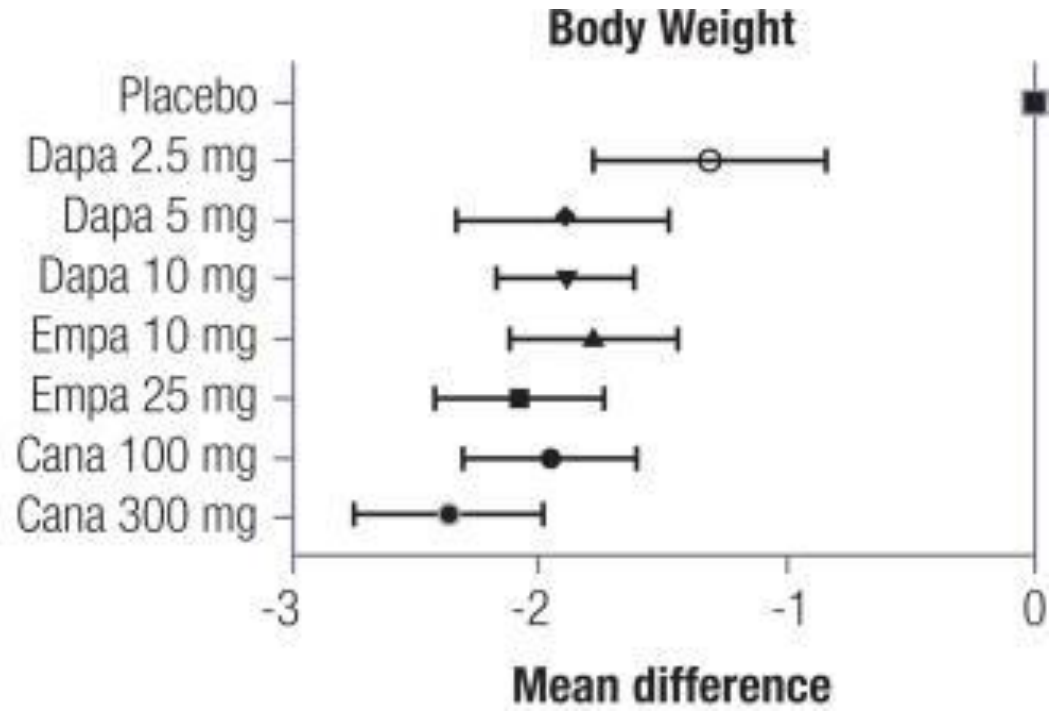
Ferrannnini, et al. Diabetes Care 2010; doi: 10.233/dc10-0612

Comparison of the effect of SGLT-2 inhibitors on HbA1c and weight

Trials were published from 2009 to 2018: 16,095 patients



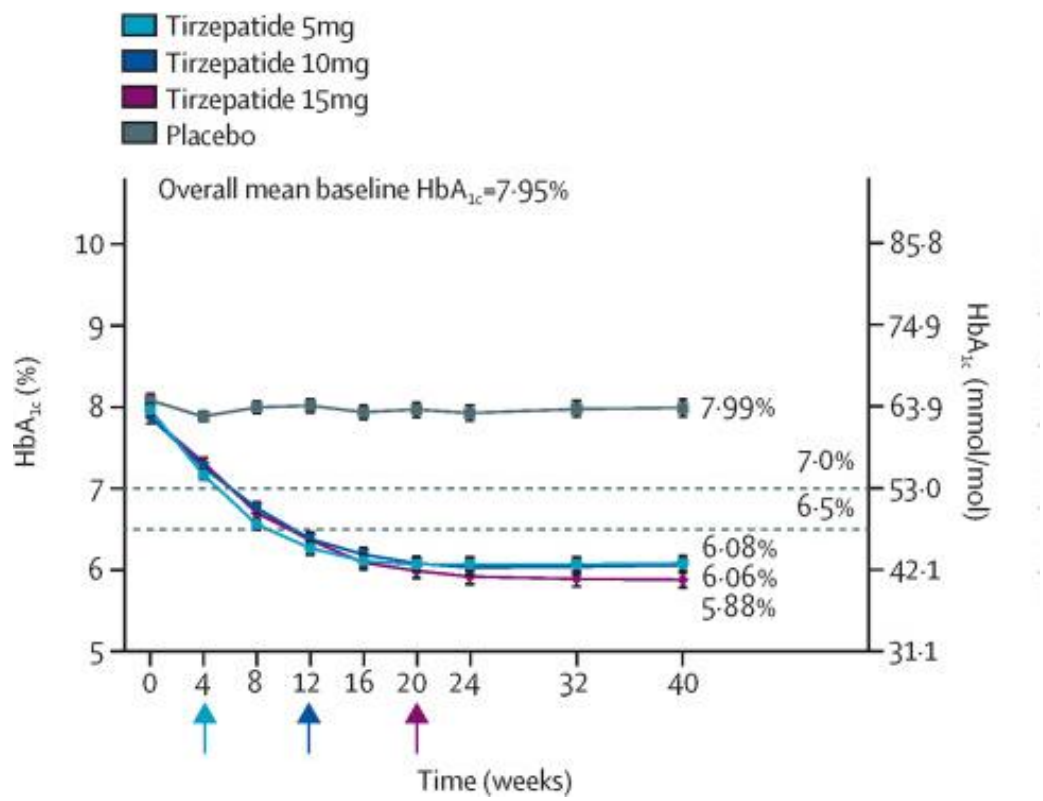
HbA1c reduction of **0.62%** (95% CI -0.66% to -0.59%)

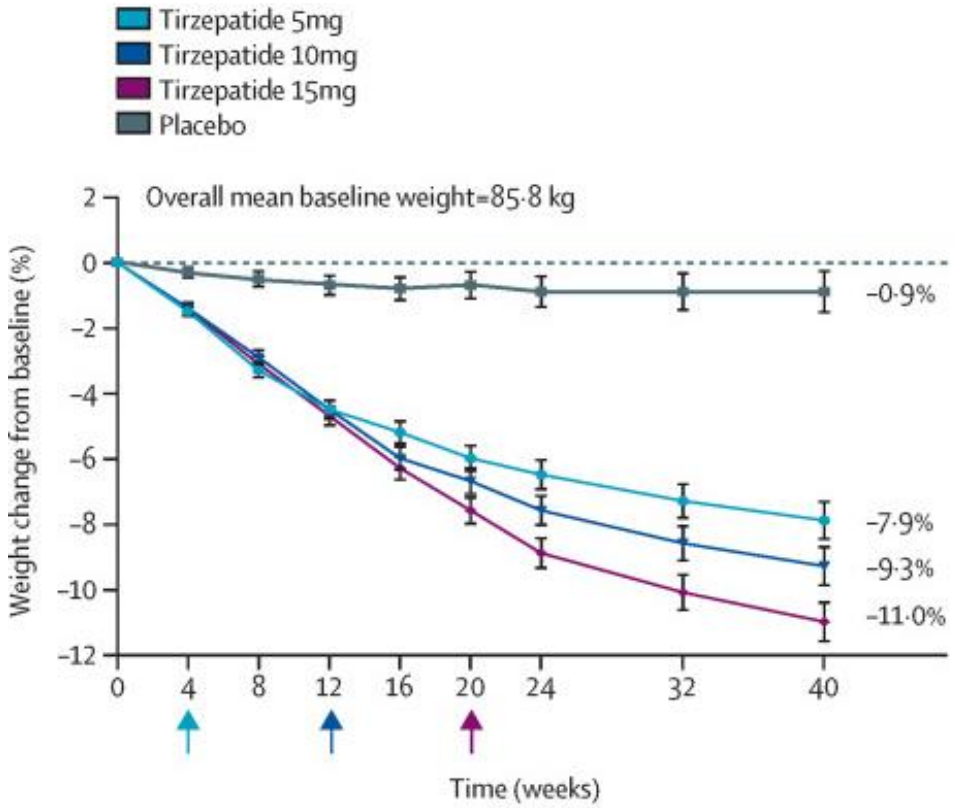


Weight reduction from -**2.36 kg** (95% CI -2.74 kg to -1.98 kg) to -**1.31 kg** (95% CI -1.78 kg to -0.84 kg)

Pinto et al. Arch Endocrinol Metab 2022; doi: 10.20945/2359-3997000000440

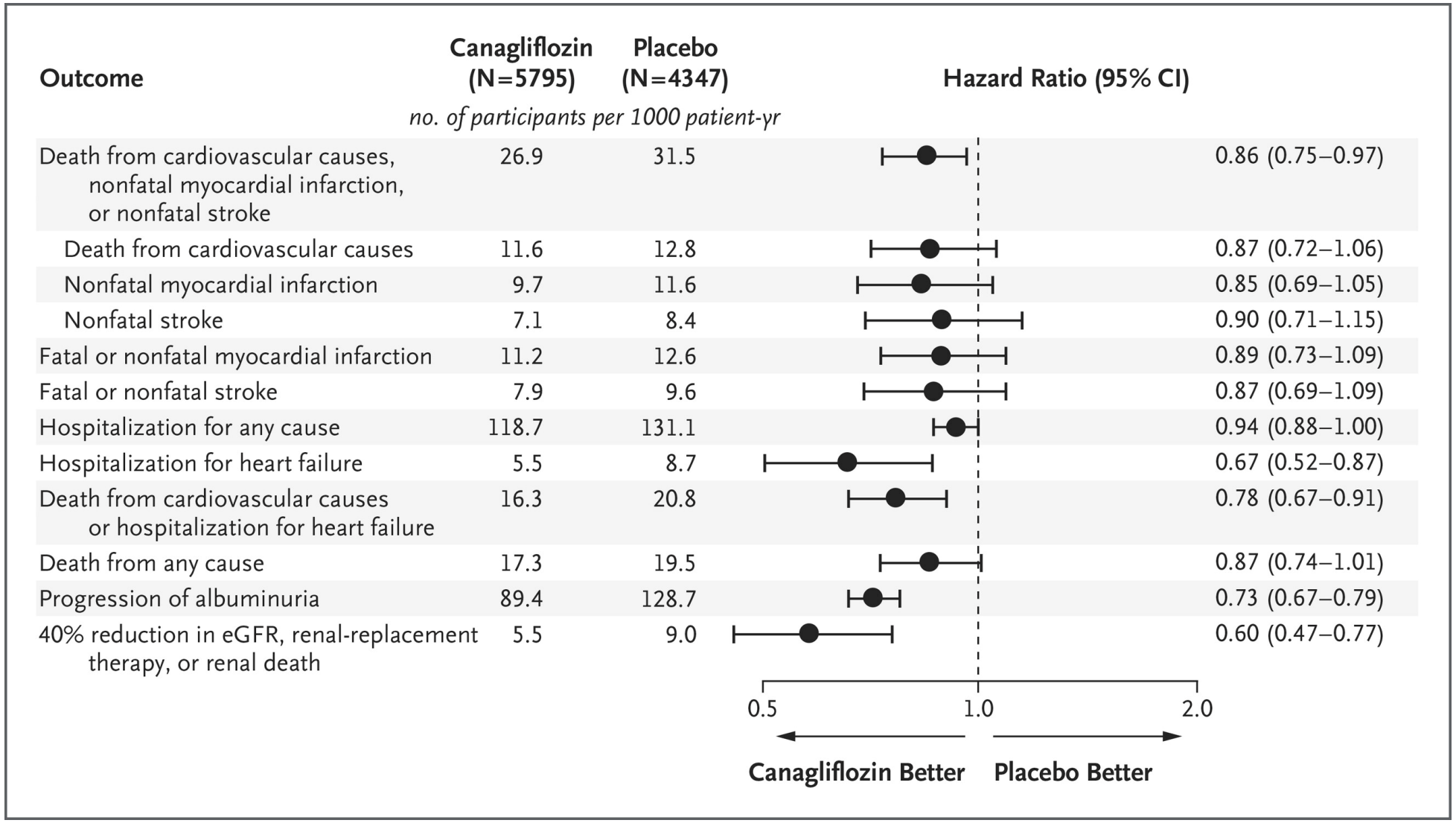
As a comparison… effect of Tirzepatide….





Rosenstock et al. Lancet 2021; doi:10.1016/S0140-6736(21)01324-6

Canagliflozin and Cardiovascular and Renal events in T2D - CANVAS



Neal et al. N Engl J Med 2017;DOI: 10.1056/NEJMoa1611925

Major sodium glucose co-transporter 2 inhibitor trials: summary of outcomes

	Cardiovascular outcome trials in type 2 diabetes				Renal outcome trials		Heart failure outcome trials	
Trial drug	CANVAS canagliflozin	DECLARE TIMI-58 dapagliflozin	EMPA-REG OUTCOME empagliflozin	VERTIS-CV ertugliflozin	CREDENCE canagliflozin	DAPA-CKD dapagliflozin	DAPA-HF dapagliflozin	EMPEROR-REDUCED empagliflozin
n	10,142	17,160	7,020	8,246	4,401	4,304	4,744	3,730
Baseline participant characteristics	65% established CVD; 35% risk factors for CVD	40% established CVD; 60% risk factors for CVD	All established CVD	All established CVD	All T2D with established diabetic kidney disease	All chronic kidney disease with or without T2D	All HFrEF II–IV with or without T2D	All HFrEF II–IV with or without T2D
Major adverse CV event (MACE)	↓14%[9]	↔	↓14%[12]	↔	↓20%[9]	n/a	n/a	n/a
CV death and hospitalisation for heart failure	↓22%[10]	↓17%[11]	↓34%[13]	↔	↓31%[9]	↓29%[15]	↓25%[16]	↓25%[17]
Major adverse renal events	↓47%[9]	↓47%[11]	↓39%[12]	↔	↓30%[9]	↓39%[15]	↔	↓50%[17]
Hospitalisation for heart failure	↓33%[9]	↓27%[11]	↓35%[12]	↓30[14]	↓39%[9]	n/a	↓30%[16]	↓31%[17]
CV death	↔	↔	↓38%[12]	↔	↔	↔	↓28%[16]	↔
All-cause mortality	↔	↔	↓32%[12]	↔	↔	↓31%[15]	↓17%[16]	↔

SGLT2 inhibitors in type 2 diabetes

A systematic review and meta-analysis of cardiovascular outcome trials balancing their benefits and risks

Benefit | Risk

?

Randomised clinical trials assessing SGLT2i on cardiovascular events in patients with type 2 diabetes

5 trials

46,969 participants

CardioVascular Outcomes Trials	CANVAS	CREDENCE	DECLARE-TIMI	EMPA-REG OUTCOME	VERTIS-CV
Sample size (*n*)	10,142	4401	17,160	7020	8246
Follow-up (years)	3.6	2.6	4.2	3.1	3
CVD* (%)	65.6	50.4	40.6	99.2	75.9

*at baseline, CVD: cardiovascular disease

1. Estimate incident rate ratio
2. Estimate spontaneous rate (placebo groups)

→ 3. Estimate absolute treatment effect

For 1000 patients treated over 3.5 years with SGLT2 inhibitors:

All-cause deaths decreased from 70 to 61 (**-9**)

MACE decreased from 104 to 95 (**-9**)

HHF decreased from 37 to 26 (**-11**)

ESRD decreased from 8 to 6 (**-2**)

Genital infection increased from 15 to 51 (**+36**)

Keto-acidosis increased from 1 to 3 (**+2**)

Amputations: unclear

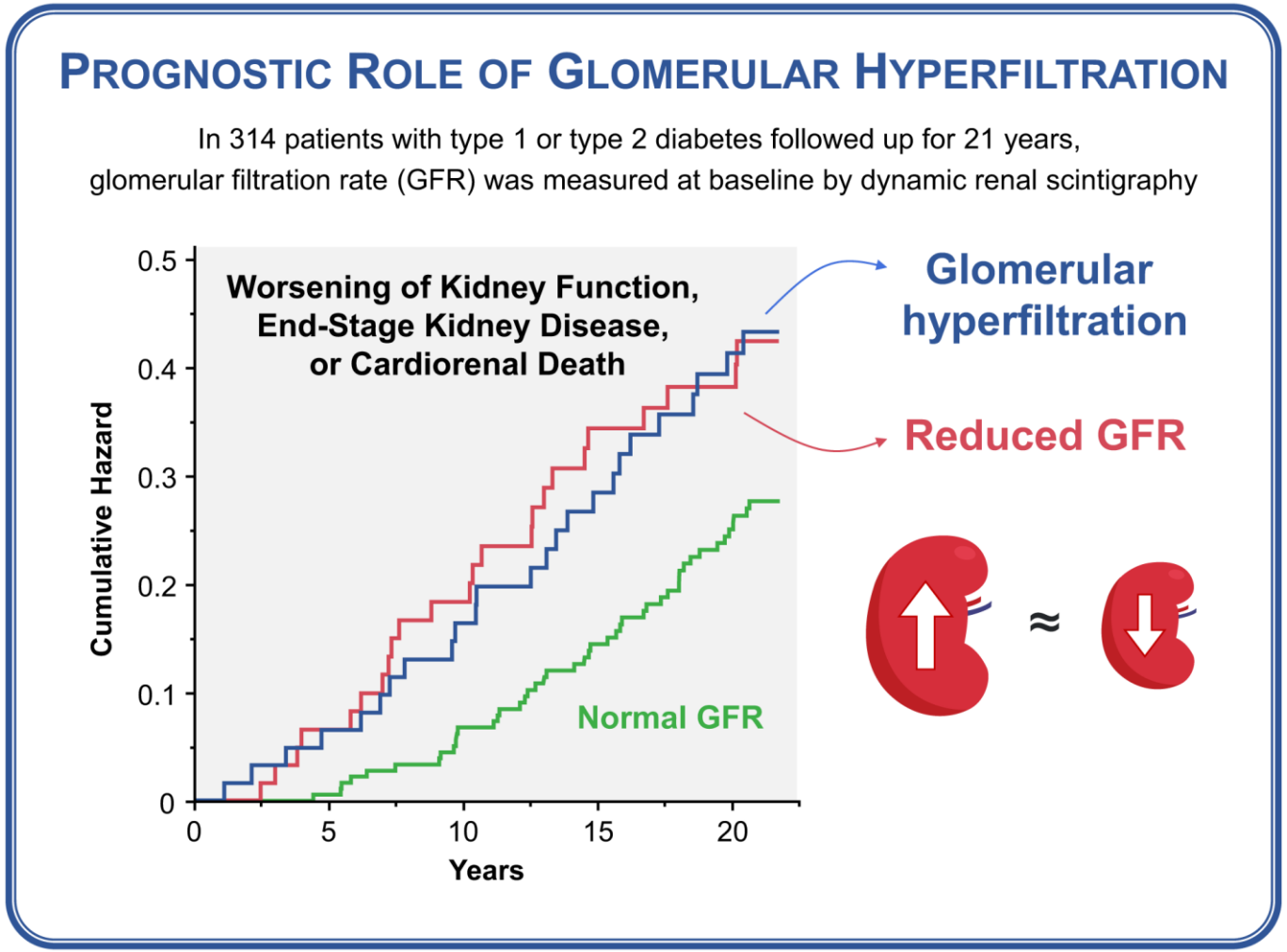
MACE: major adverse cardiovascular events, HHF: hospitalisation for heart failure, ESRD: end-stage renal disease

The risk–benefit ratio of SGLT2i remains in favour of their use in patients with type 2 diabetes and a high risk of CVD

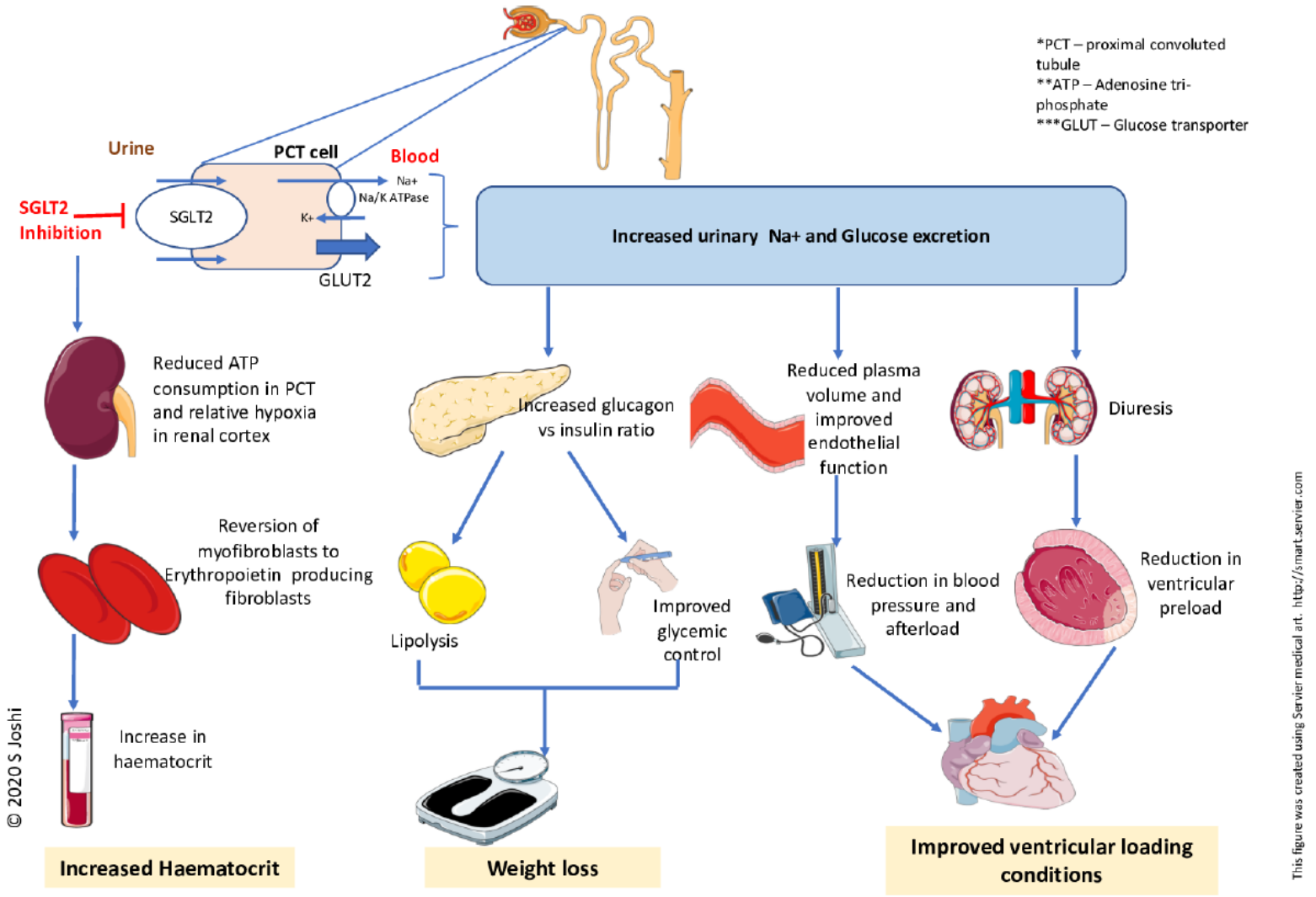
*Marilly, E., Cottin, J., Cabrera, N. et al. SGLT2 inhibitors in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials balancing their risks and benefits. Diabetologia **65**, 2000–2010 (2022). https://doi.org/10.1007/s00125-022-05773-8*

From: **Glomerular Hyperfiltration Predicts Kidney Function Decline and Mortality in Type 1 and Type 2 Diabetes: A 21-Year Longitudinal Study**

Diabetes Care. 2023;46(4):845-853. doi:10.2337/dc22-2003



Cardiovascular benefit



Joshi et al. Heart 2021 doi: 10.1136/heartjnl-2020-318060

Association of British Clinical Diabetologists (ABCD) and Diabetes UK joint position statement and recommendations for non-diabetes specialists on the use of sodium glucose co-transporter 2 inhibitors in people with type 2 diabetes (January 2021)

- Adults above 18 years with T2D and one or more of the following are likely to benefit the most:
  - established / high risk of cardiovascular disease
  - chronic kidney disease with albuminuria
  - history of heart failure
  - inadequate glycaemic control with need to minimise hypoglycaemia
  - inadequate glycaemic control with need to minimise weight gain / encourage weight loss.
- Patients with a clear understanding of the risks associated with SGLT2 inhibitors and how to reduce those risks.

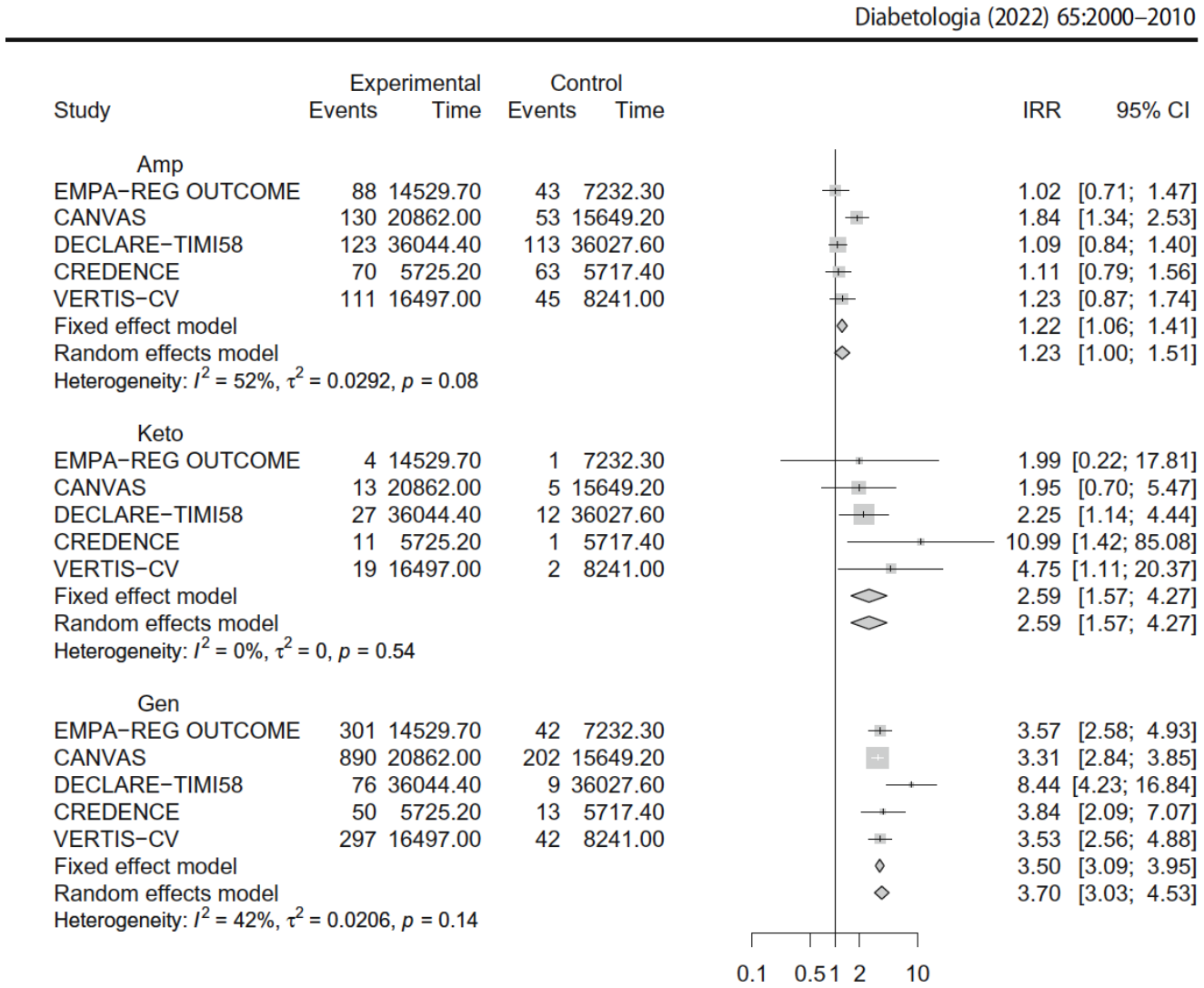
Dashora et al. Clinical Medicine 2021 doi: 10.7861/clinmed.2021-0045

SGLT-2 inhibitors - Adverse effects

Amputations

DKA

GU infections



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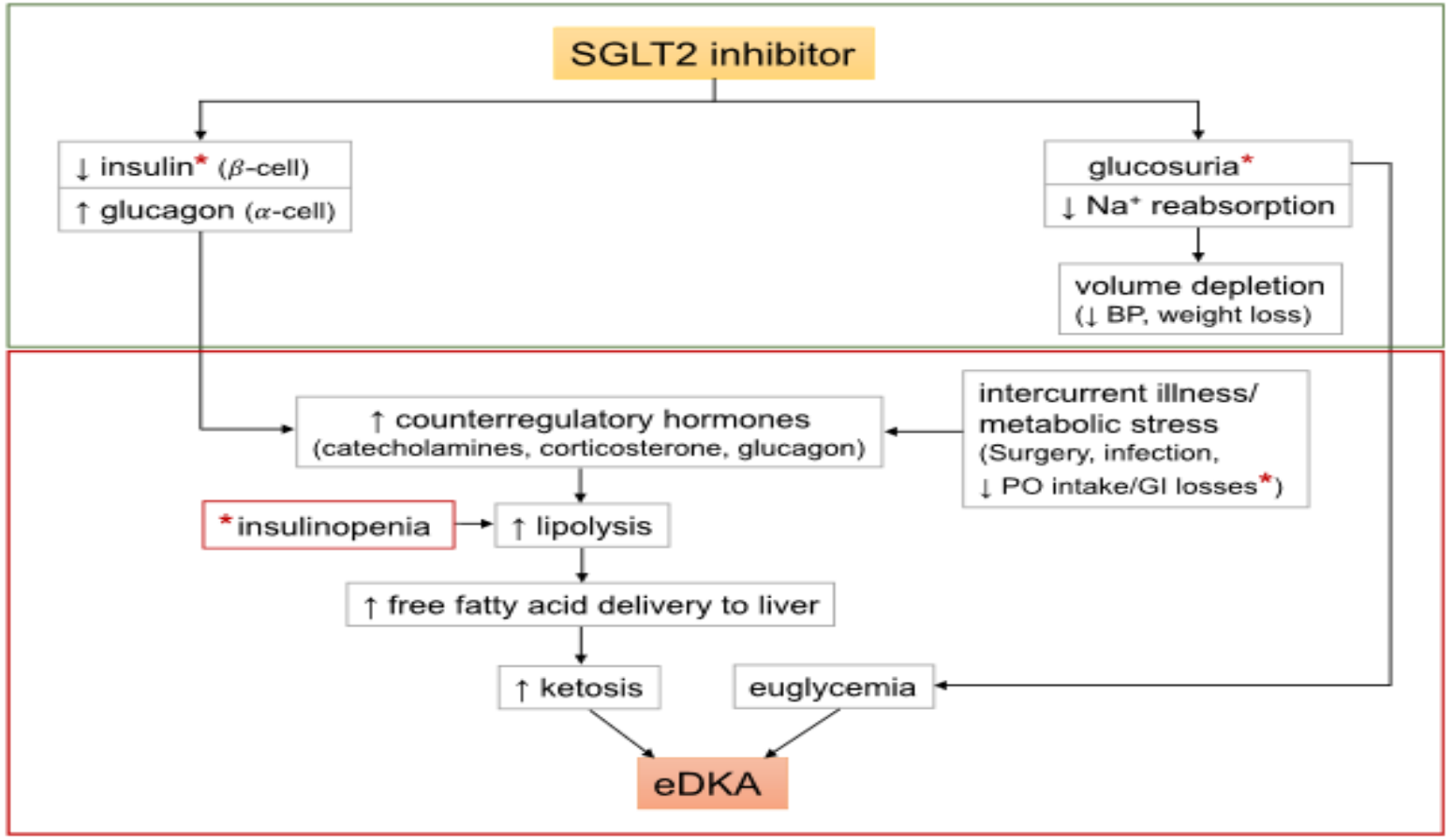
Mechanism pf Euglycaemic DKA (Eu DKA)



Kidney Med., 2020 doi: 10.1016/ j.xkme.2019.12.006

Association of British Clinical Diabetologists (ABCD) and Diabetes UK joint position statement and recommendations for non-diabetes specialists on the use of sodium glucose co-transporter 2 inhibitors in people with type 2 diabetes (January 2021)

Use with caution in the following situations:

- Ketogenic diet
- Body mass index under 25 kg/m^2
- High risk of acute effects of hyperglycaemia (such as dehydration due to non-adherence to medication)
- HbA1c >86 mmol/mol
- Frailty
- Cognitive impairment as it may interfere with the adequate understanding to take action to prevent and identify DKA
- Recent weight loss
- Long duration of diabetes (generally over 10 years from diagnosis)

Dashora et al. Clinical Medicine 2021 doi: 10.7861/clinmed.2021-0045

Association of British Clinical Diabetologists (ABCD) and Diabetes UK joint position statement and recommendations for non-diabetes specialists on the use of sodium glucose co-transporter 2 inhibitors in people with type 2 diabetes (January 2021)

•Suspend SGLT2 inhibitors in the following circumstances:

- acute medical admission including COVID-19
- admission for elective surgery or procedure requiring starvation
- vomiting
- dehydration.

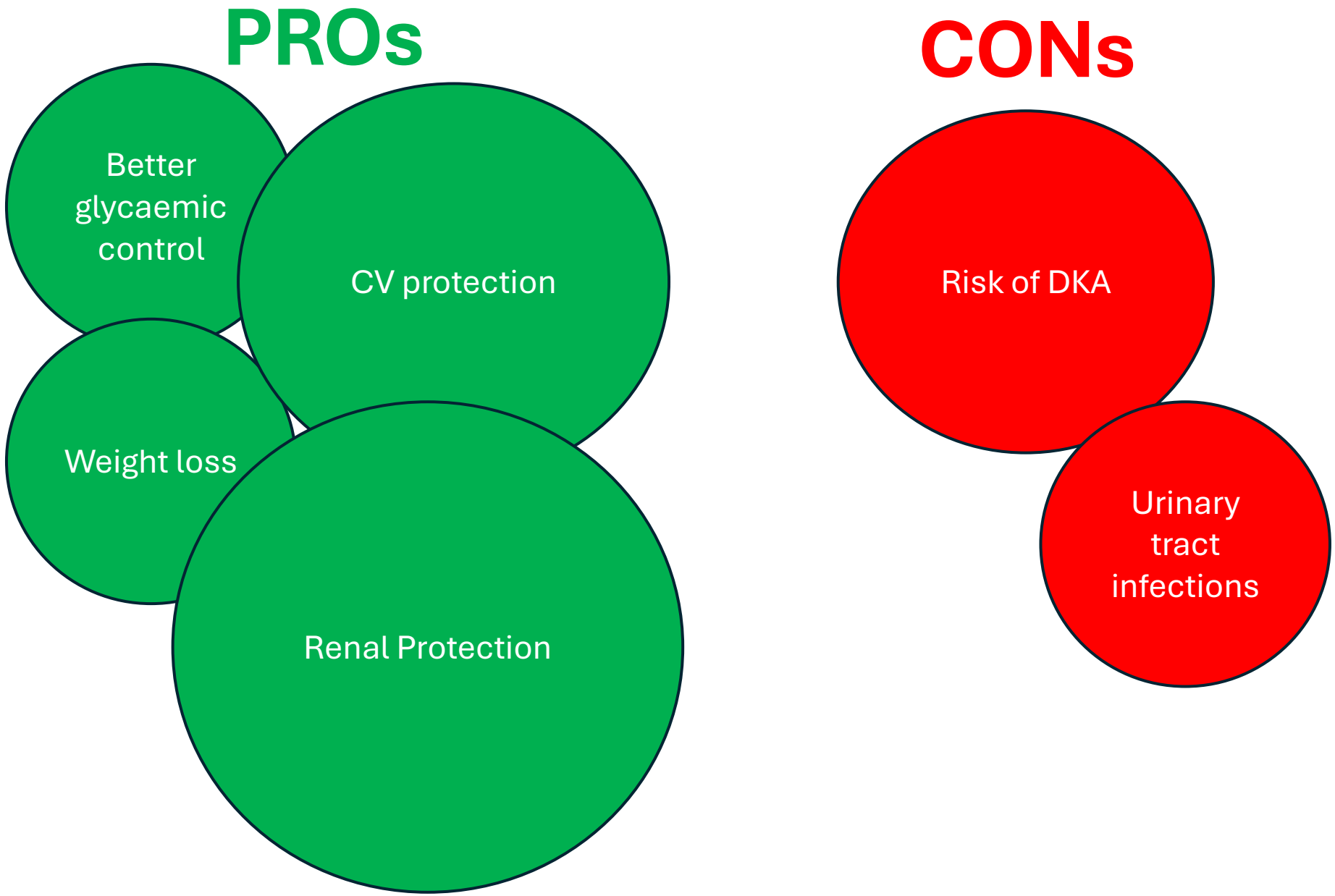
•Restart only AFTER patient has been eating normally for AT LEAST 24 hours AND no longer acutely unwell.

•Alternative diabetes treatment may be required in the interim.

Dashora et al. Clinical Medicine 2021 doi: 10.7861/clinmed.2021-0045

SGLT-2 inhibitors in T1 diabetes

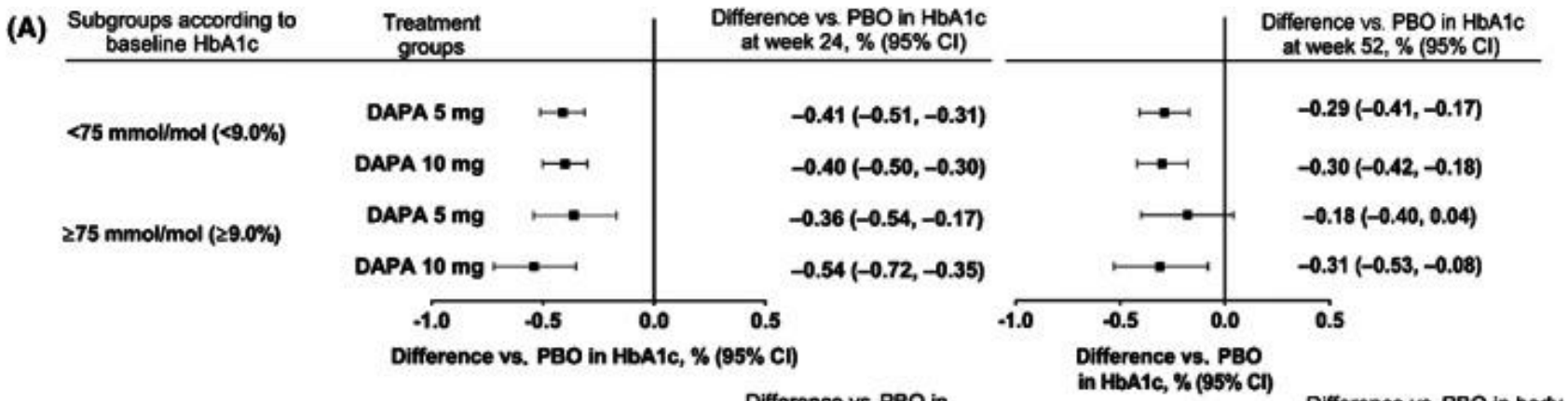
Role of SGLT-2 inhibitors in T1D patients - UNLICENCED



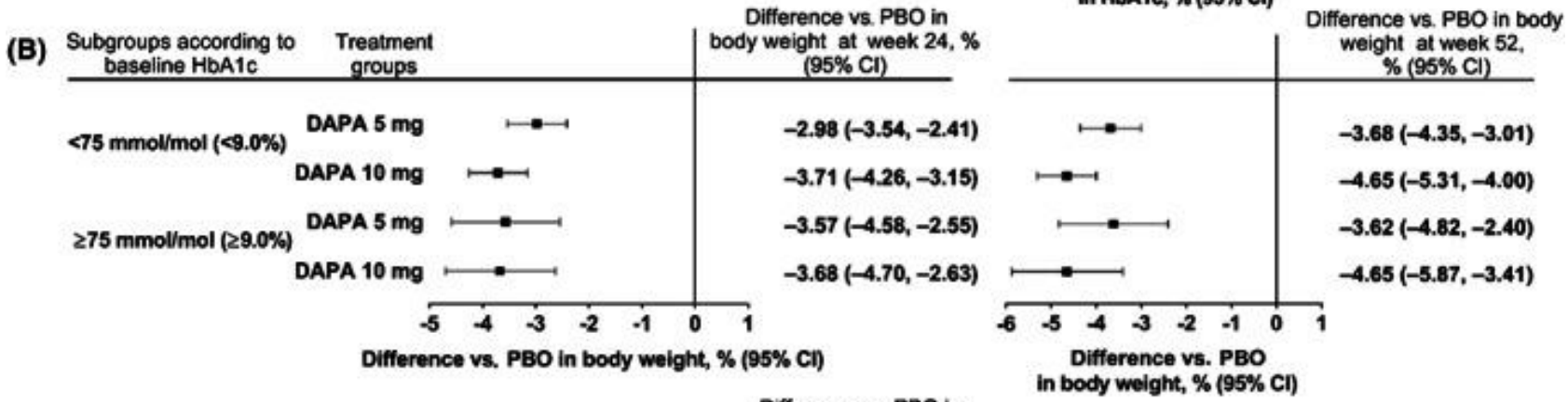
DEPICT-1 and DEPICT-2 studies

- Randomized, double-blind studies
- Adults with T1D and HbA1c 7.5%-10.5%
- Randomized (1:1:1) to receive dapagliflozin 5 mg, 10 mg or placebo.
- Efficacy analyses included 530, 529 and 532 and safety analysis included 548, 566 and 532 patients in the dapagliflozin 5 mg, 10 mg and placebo groups, respectively.

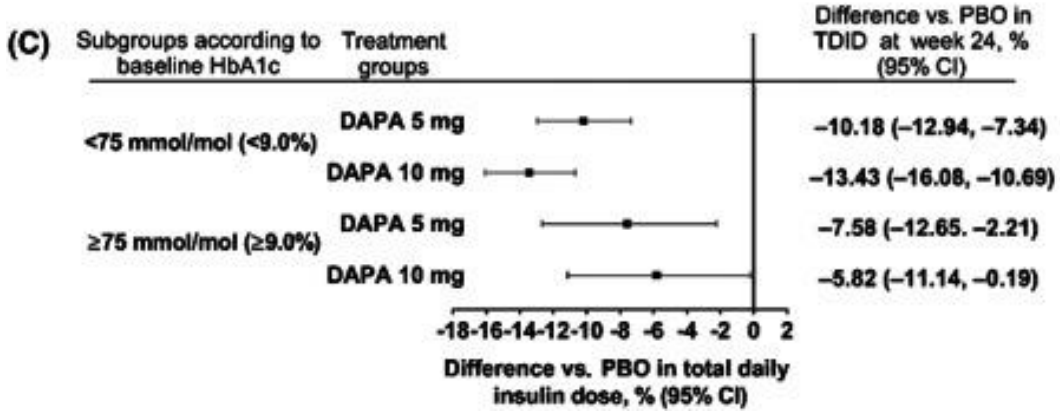
DEPICT 1 and DEPICT 2 – effect on glyc.control/insulin dose/weight by HbA1c



HbA1c



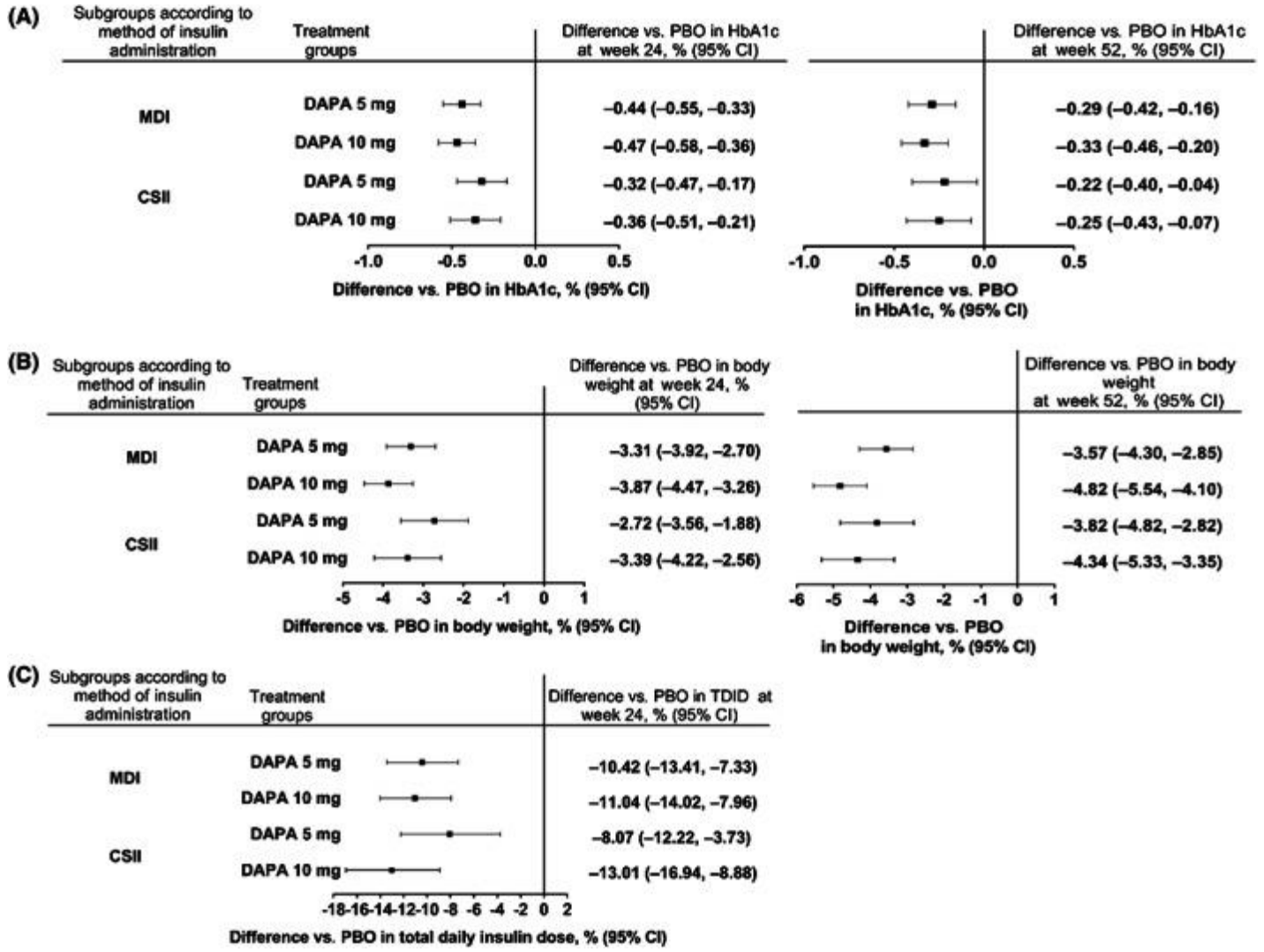
Weight



Insulin dose

Phillip et al. Diabetes Obes Metab. 2020; doi: 10.1111/dom.14248

DEPICT 1 and DEPICT 2 – effect on glyc.control/insulin dose/weight by method of insulin delivery



HbA1c

Weight

Insulin dose

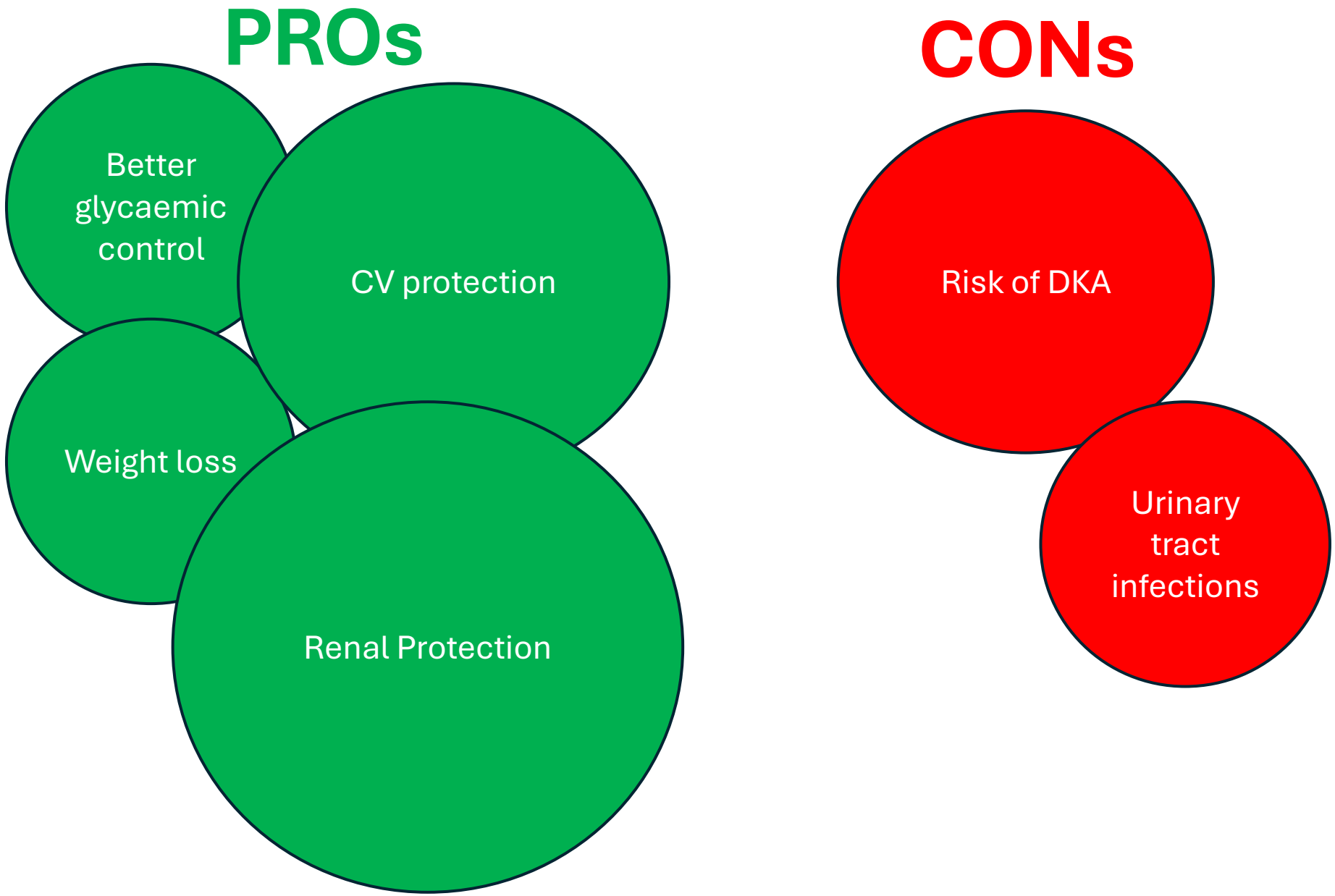
Phillip et al. Diabetes Obes Metab. 2020; doi: 10.1111/dom.14248

DEPICT 1 and DEPICT 2 – side-effects

	Week 24 (short-term period)			Week 52 (short-term + long-term period)		
	DAPA 5 mg (N = 548)	DAPA 10 mg (N = 566)	Placebo (N = 532)	DAPA 5 mg (N = 548)	DAPA 10 mg (N = 566)	Placebo (N = 532)
AE of special interest[b]						
Adjudicated CV event	2 (0.4)	5 (0.9)	2 (0.4)	2 (0.4)	5 (0.9)	4 (0.8)
Events of renal function	6 (1.1)	2 (0.4)	0	7 (1.3)	3 (0.5)	4 (0.8)
Fracture	8 (1.5)	6 (1.1)	5 (0.9)	12 (2.2)	11 (1.9)	12 (2.3)
Urinary tract infection	37 (6.8)	21 (3.7)	25 (4.7)	57 (10.4)	30 (5.3)	39 (7.3)
Male[c]	2 (0.8)	2 (0.7)	3 (1.2)	4 (1.7)	4 (1.5)	4 (1.6)
Female[d]	35 (11.3)	19 (6.5)	22 (7.8)	53 (17.0)	26 (8.9)	35 (12.5)
Genital infection	61 (11.1)	54 (9.5)	12 (2.3)	73 (13.3)	68 (12.0)	18 (3.4)
Male[c]	12 (5.1)	12 (4.4)	0	13 (5.5)	17 (6.2)	0
Female[d]	49 (15.8)	42 (14.3)	12 (4.3)	60 (19.3)	51 (17.4)	18 (6.4)
SAEs						
≥1 SAE	37 (6.8)	31 (5.5)	20 (3.8)	69 (12.6)	59 (10.4)	46 (8.6)
≥1 SAE related to study drug	18 (3.3)	12 (2.1)	3 (0.6)	23 (4.2)	20 (3.5)	6 (1.1)
SAE leading to study discontinuation	15 (2.7)	7 (1.2)	6 (1.1)	22 (4.0)	13 (2.3)	9 (1.7)
Hypoglycaemia						
≥1 SAE of hypoglycaemia	6 (1.1)	2 (0.4)	2 (0.4)	8 (1.5)	5 (0.9)	5 (0.9)
Hypoglycaemia leading to study discontinuation	3 (0.5)	0	1 (0.2)	3 (0.5)	1 (0.2)	2 (0.4)
Ketone-related events[e]						
≥1 ketone-related SAE	14 (2.6)	11 (1.9)	2 (0.4)	28 (5.1)	20 (3.5)	4 (0.8)
Ketone related SAE leading to study discontinuation	9 (1.6)	7 (1.2)	0	14 (2.6)	11 (1.9)	0
Death[f]	0	0	1 (0.2)	1 (0.2)	0	1 (0.2)

Phillip et al. Diabetes Obes Metab. 2020; doi: 10.1111/dom.14248

Role of SGLT-2 inhibitors in T1D patients - UNLICENCED



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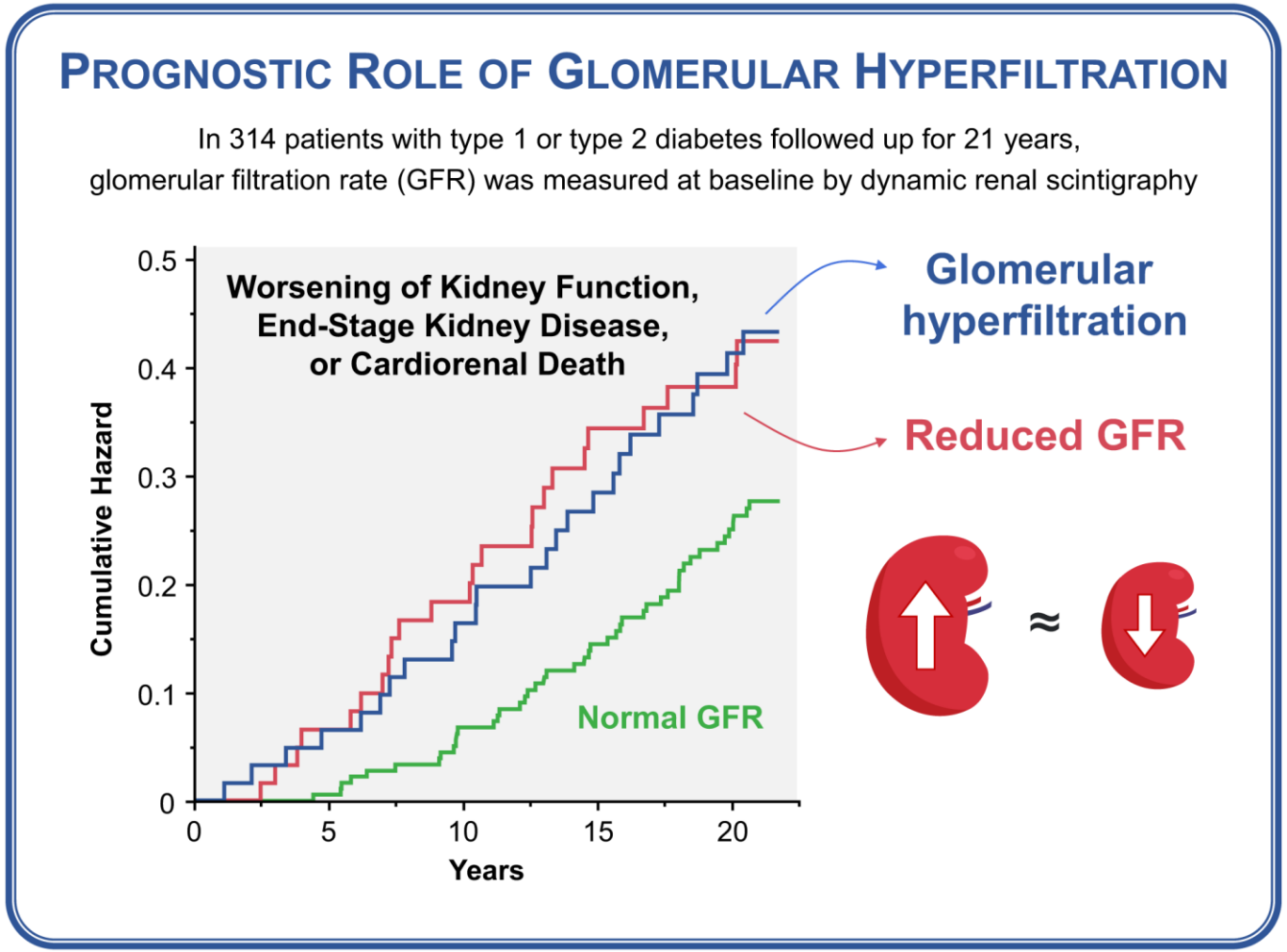


Role of SGLT-2 in T1D patients…

1. Who should be our target population?

2. Can C-peptide help?

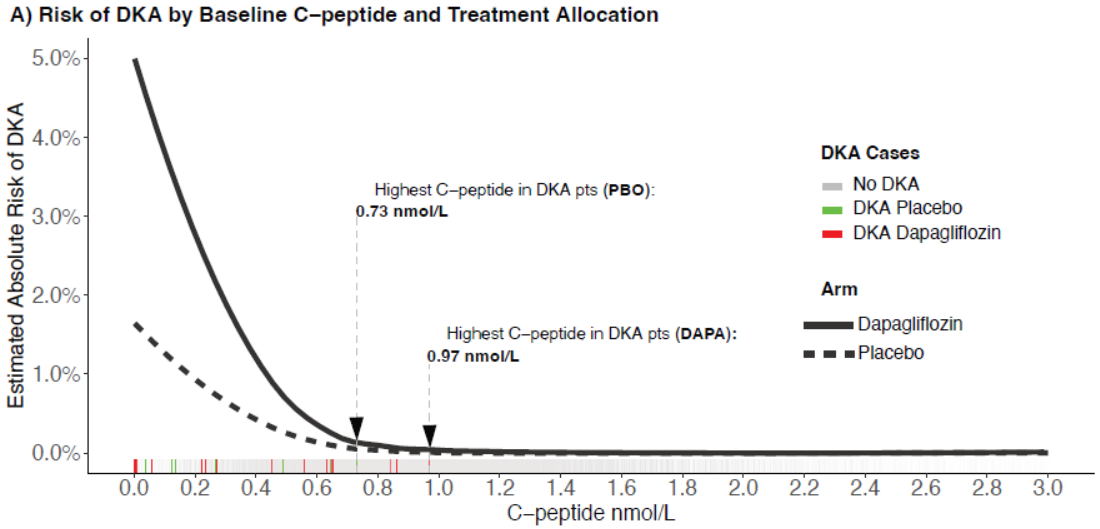
Role of SGLT-2 in T1D patients…

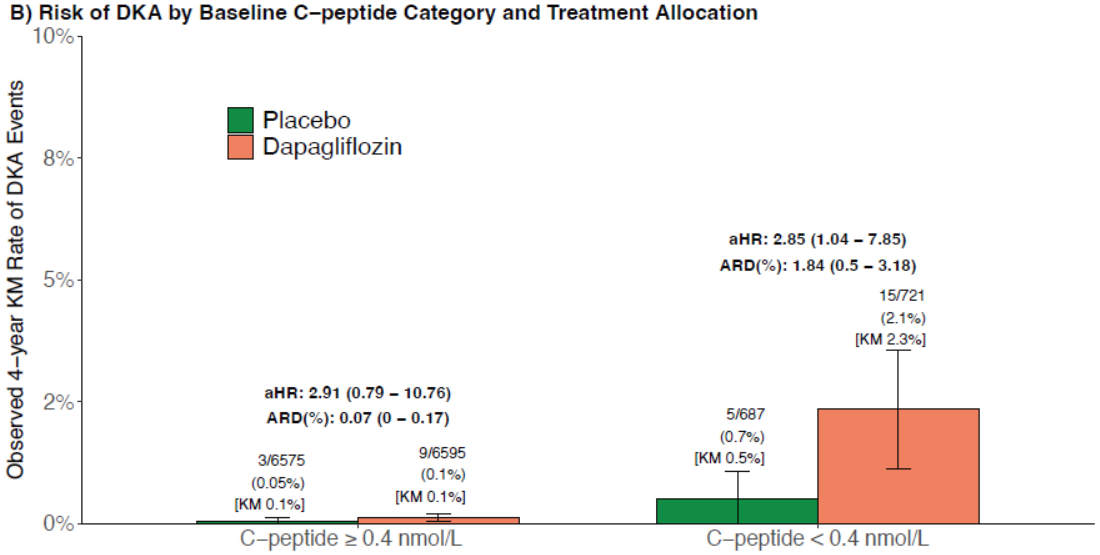
1. Who should be our target population?

2. Can C-peptide help?

From: **1896-LB: Clinical Features and C-Peptide Levels Associated with Diabetic Ketoacidosis in Patients with Type 2 Diabetes on Dapagliflozin vs. Placebo—Insights from DECLARE-TIMI 58**

Diabetes. 2024;73(Supplement_1). doi:10.2337/db24-1896-LB





For discussion...

- 40-year-old patient with T1D (15 years)
- HbA1c 55 mmol/mol
- No missed insulin doses
- Diabetic nephropathy/heart failure

- 40-year-old patient with T1D (15 years)
- HbA1c 85mmol/mol
- Heart failure

- 40-year-old patient with T1D (15 years)
- HbA1c 120mmol/mol
- Frequently missed insulin doses
- Alcohol excess
- Diabetic nephropathy

Thank you