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Net effects of SGLT2 inhibitors by diabetes status and albuminuria

Natalie Staplin on behalf of SMART-C

ASN Kidney Week 2025, High-Impact Clinical Trials - 1

Background

- There is uncertainty about the effects of SGLT2 inhibitors (SGLT2i) in certain types of patients with chronic kidney disease (CKD)
- International guidelines offering different strengths of recommendation based on diabetes status and urine albumin:creatinine ratio (uACR) of ≥200 mg/g or <200 mg/g

Recommendation 3.7.1: We recommend treating patients with type 2 diabetes (T2D), CKD, and an eGFR ≥20 ml/min per 1.73 m^2 with an SGLT2i *(1A)*.

Recommendation 3.7.2: We recommend treating adults with CKD with an SGLT2i for the following *(1A)*:
- **eGFR ≥20 ml/min per 1.73 m^2 with urine ACR ≥200 mg/g (≥20 mg/mmol), or**
- **heart failure, irrespective of level of albuminuria.**

Recommendation 3.7.3: We suggest treating adults with eGFR 20 to 45 ml/min per 1.73 m^2 with urine ACR <200 mg/g (<20 mg/mmol) with an SGLT2i *(2B)*.

- Aim of this meta-analysis is to assess the relative and absolute effects of SGLT2i in participants across the full range of efficacy and serious safety outcomes stratified by diabetes status and uACR

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Methods

Includes 8 large placebo-controlled trials that studied an SGLT2i with an indication for use in CKD, and reported longitudinal kidney outcomes with baseline albuminuria data:

- Type 2 diabetes @high atherosclerotic risk: EMPA-REG OUTCOME, CANVAS & DECLARE-TIMI-58
- Heart failure: EMPEROR REDUCED, EMPEROR-PRESERVED
- CKD: CREDENCE, DAPA-CKD, EMPA-KIDNEY

Outcomes

- **Kidney disease progression:** composite of sustained ≥40% eGFR decline from randomization, kidney failure (i.e. start of maintenance dialysis or receipt of a kidney transplant, or a sustained low eGFR [usually <15 mL/min/1.73m2]) or renal death
- **eGFR slopes (emphasizing chronic slope):** annualized rate of decline in eGFR calculated from the first post-randomization eGFR measurement to final follow-up
- **Other efficacy outcomes:** AKI and hospitalization **(**overall and for heart failure)
- **Safety:** ketoacidosis, lower limb amputation
- **Mortality:** overall, and cardiovascular vs not

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Statistical methods

- **We evaluated treatment effects in analyses stratified by diabetes and then by uACR ≥200 mg/g versus <200 mg/g**
- Inverse variance weighted meta-analysis methods
- Relative differences for slopes outcomes calculated by dividing absolute difference by the mean slope in the placebo arm
- Tests for heterogeneity by level of albuminuria (uACR ≥200 mg/g versus <200 mg/g) conducted separately in participants with and without diabetes
- Participant experienced absolute effects estimated by applying the diabetes subgroup-specific relative risk to the average event rate in the placebo arm
  - Sensitivity analyses excluding patients with heart failure and limited to eGFR <60 mL/min/1.73m^2

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Baseline characteristics

	DIABETES		NO DIABETES	
	uACR <200 mg/g	uACR ≥200 mg/g	uACR <200 mg/g	uACR ≥200 mg/g
Number of participants	35853	13093	5875	3995
Demographics				
Age at randomization (years)	65 (8)	64 (9)	70 (11)	57 (15)
Sex				
Male	64%	69%	61%	69%
Female	36%	31%	39%	31%
Race				
Asian	15%	25%	16%	43%
Black	4%	5%	5%	3%
White	78%	63%	76%	51%
Other	4%	7%	4%	3%
Past medical history				
Heart failure	21%	20%	80%	14%
Any prior cardiovascular disease	63%	55%	84%	24%
Medications				
RAS inhibitors	81%	92%	82%	91%
Mineralocorticoid receptor antagonists	9%	7%	41%	8%
GLP-1 receptor agonists	4%	4%	0%	0%
Laboratory findings				
CKD-EPI 2009 eGFR (mL/min/1.73m²)	77.8 (20.8)	55.8 (22.2)	56.5 (21.1)	42.3 (16.6)
uACR (mg/g), geometric mean (geometric SD)	15.3 (3.1)	874.2 (2.5)	17.2 (3.3)	815.3 (2.2)

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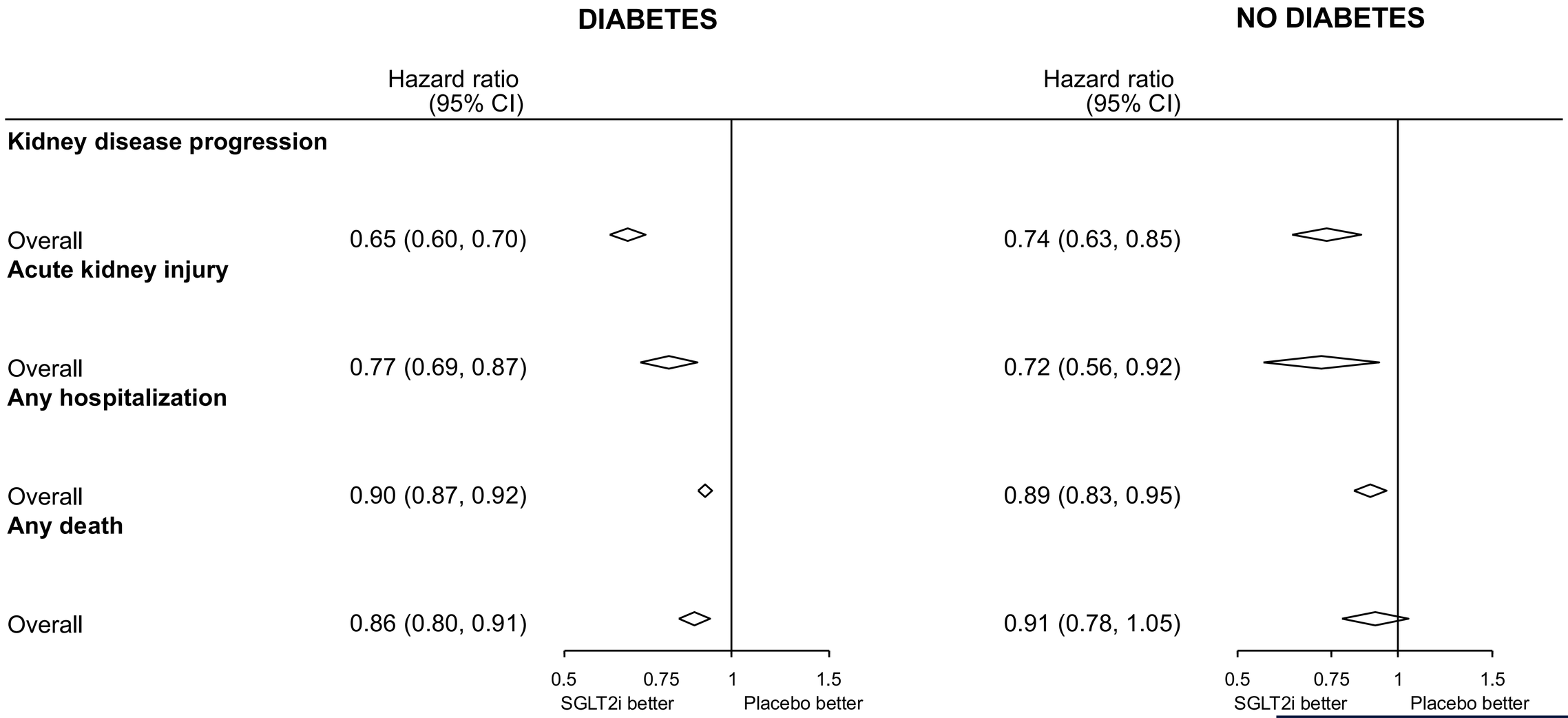
Effect of SGLT2i on selected key efficacy outcomes



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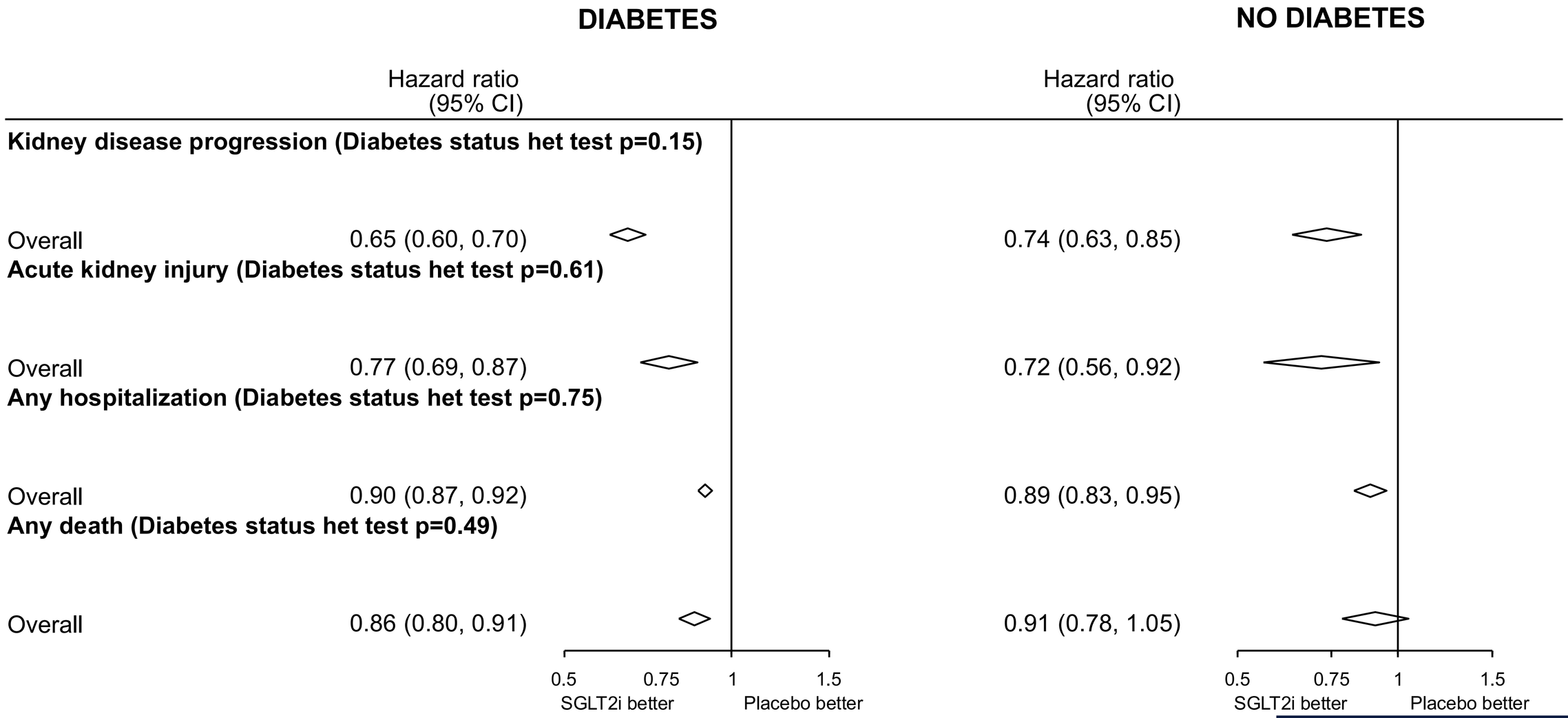

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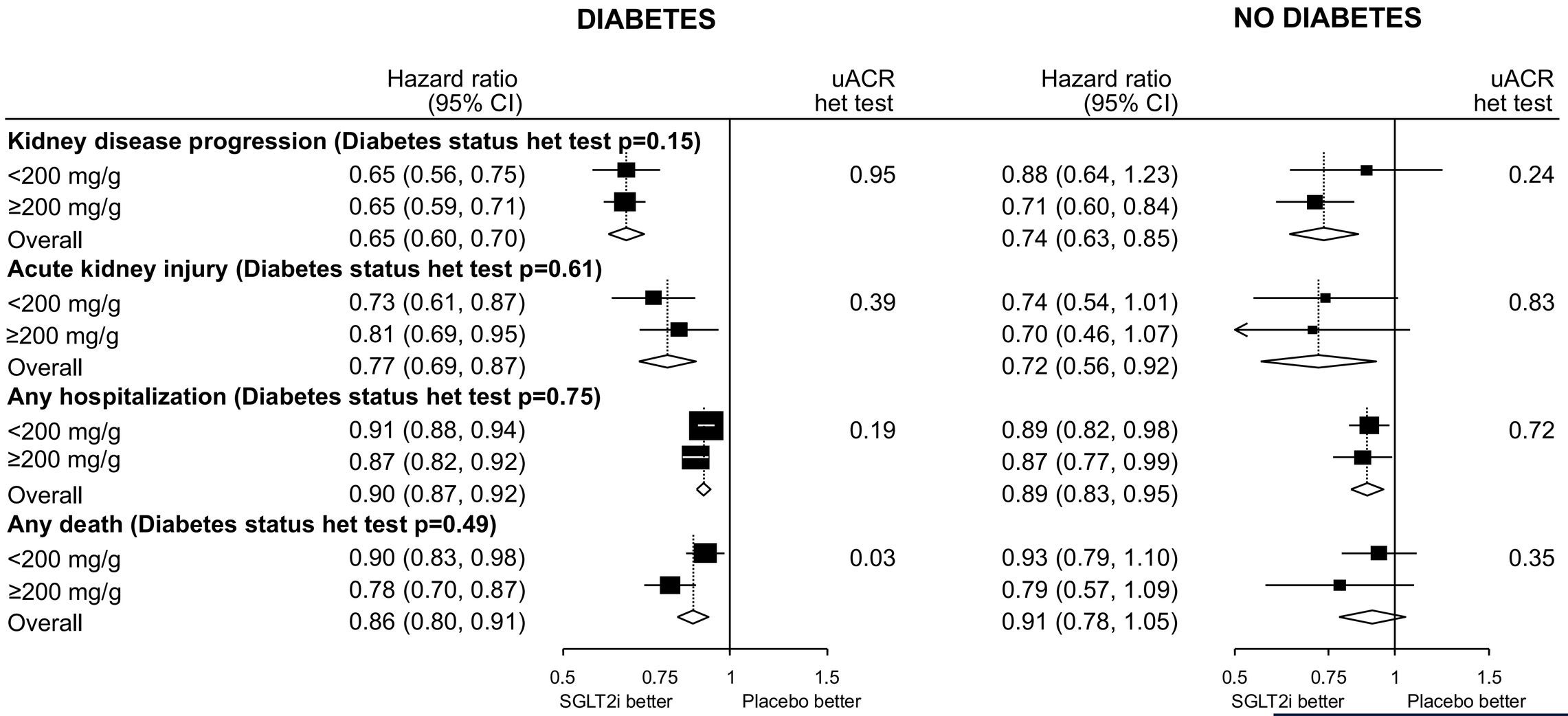

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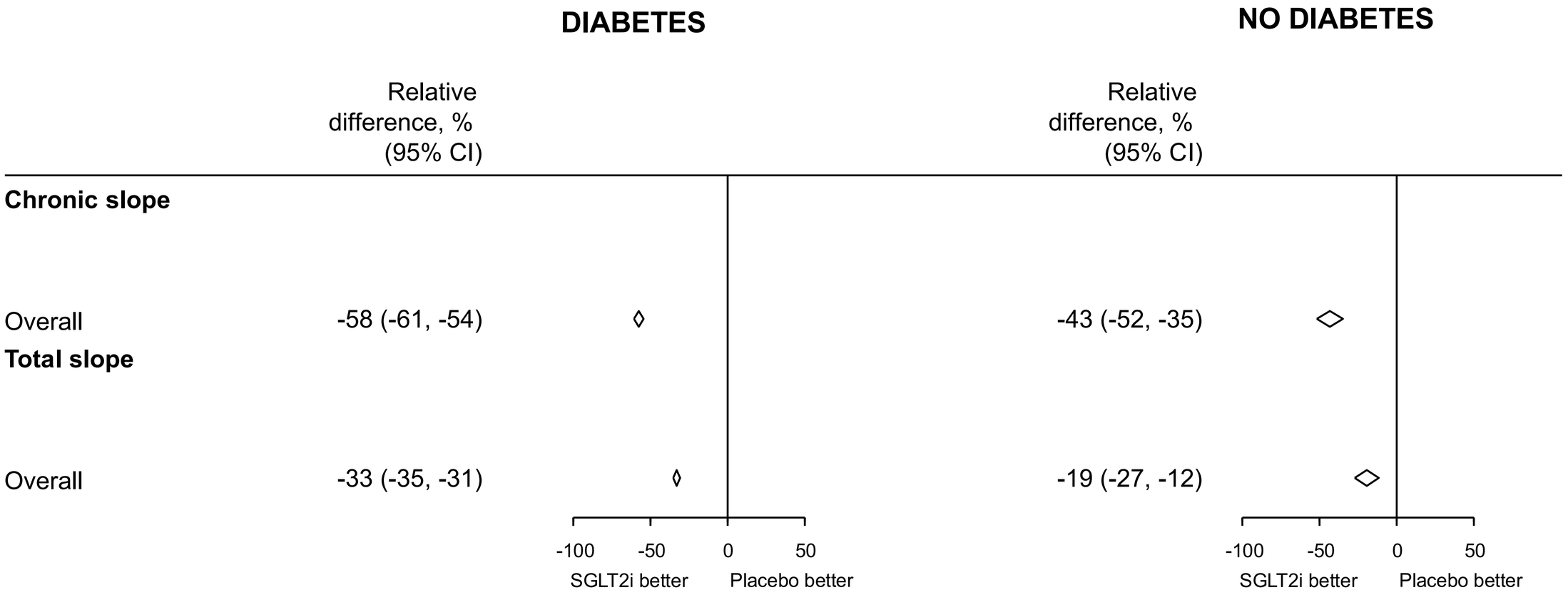
Effect of SGLT2i on chronic and total eGFR slopes



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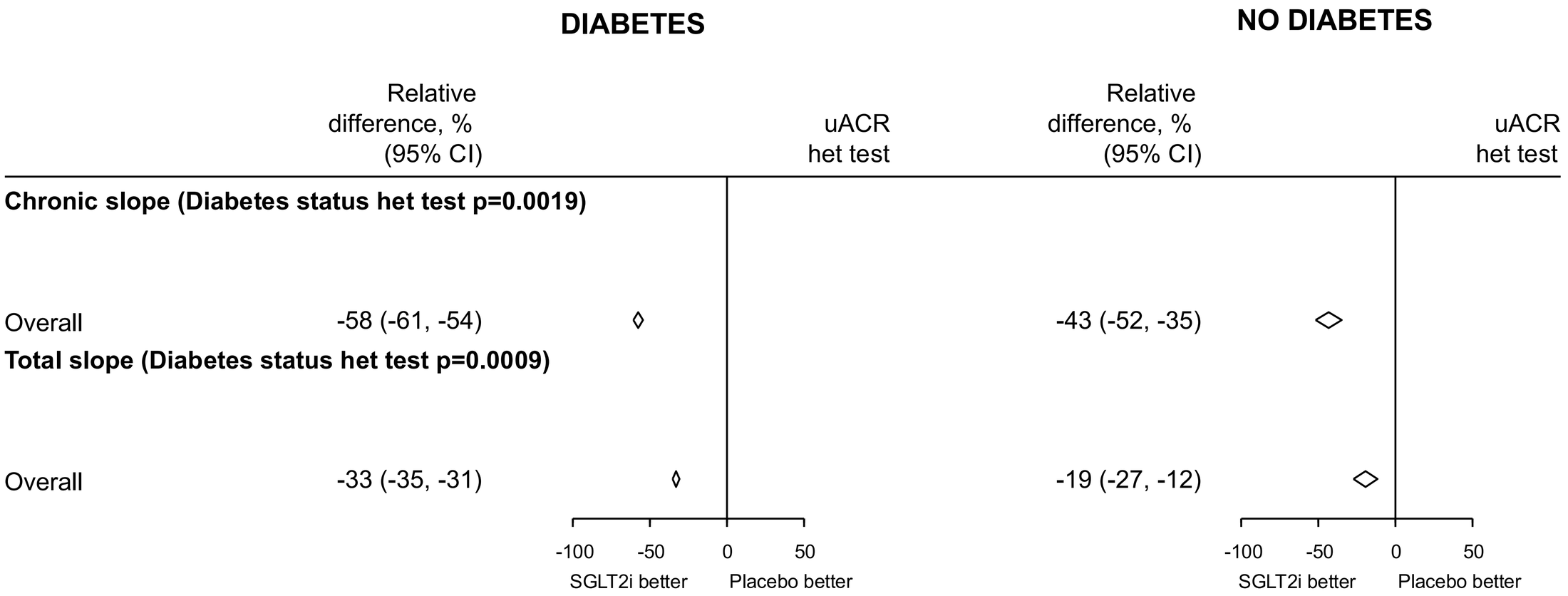

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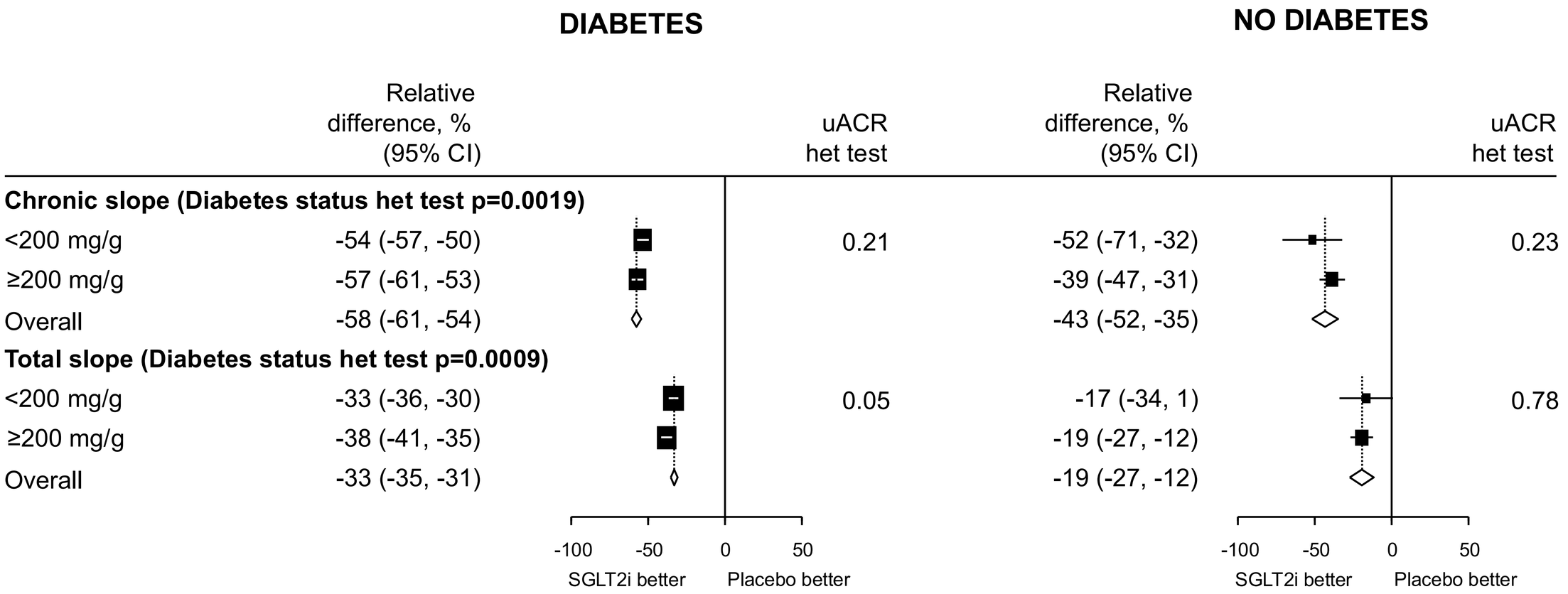

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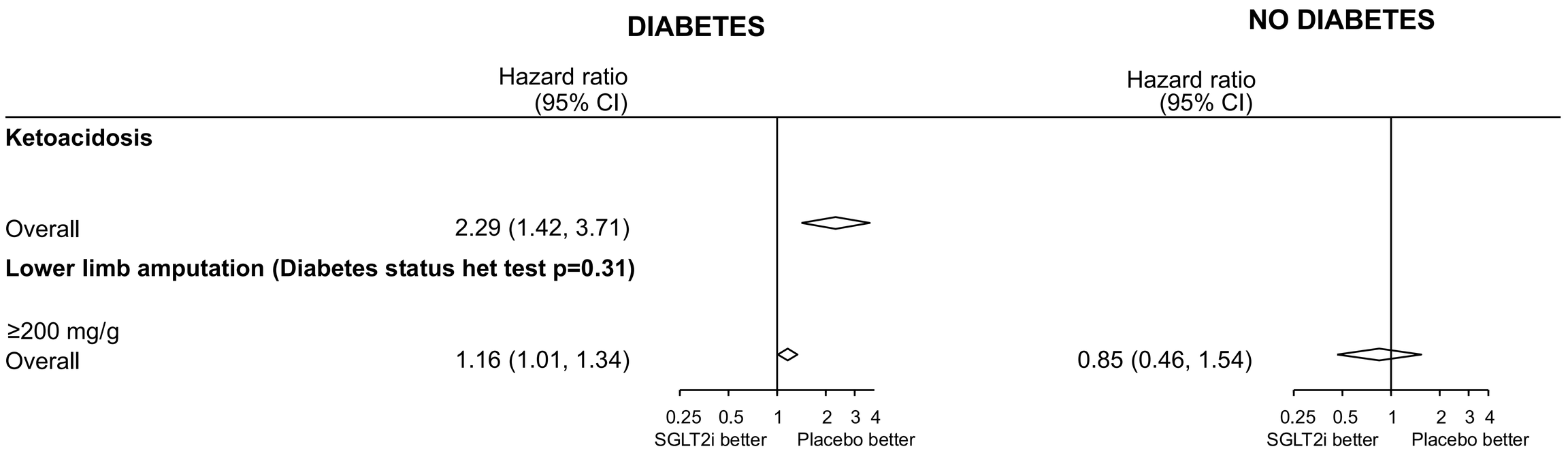
Effect of SGLT2i on safety outcomes



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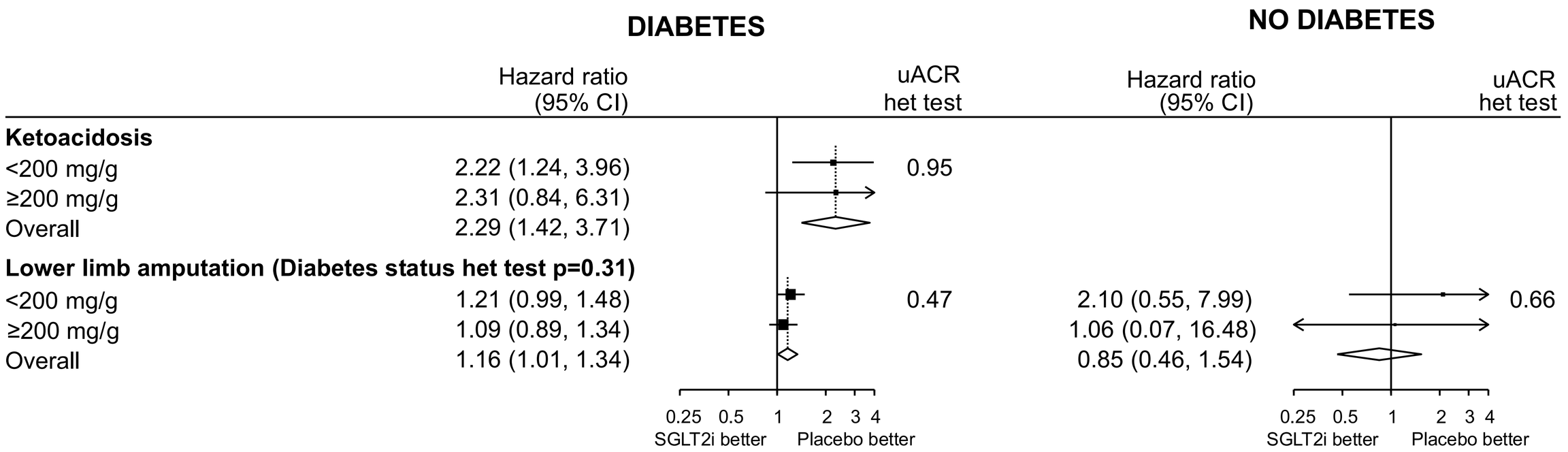
Effect of SGLT2i on safety outcomes



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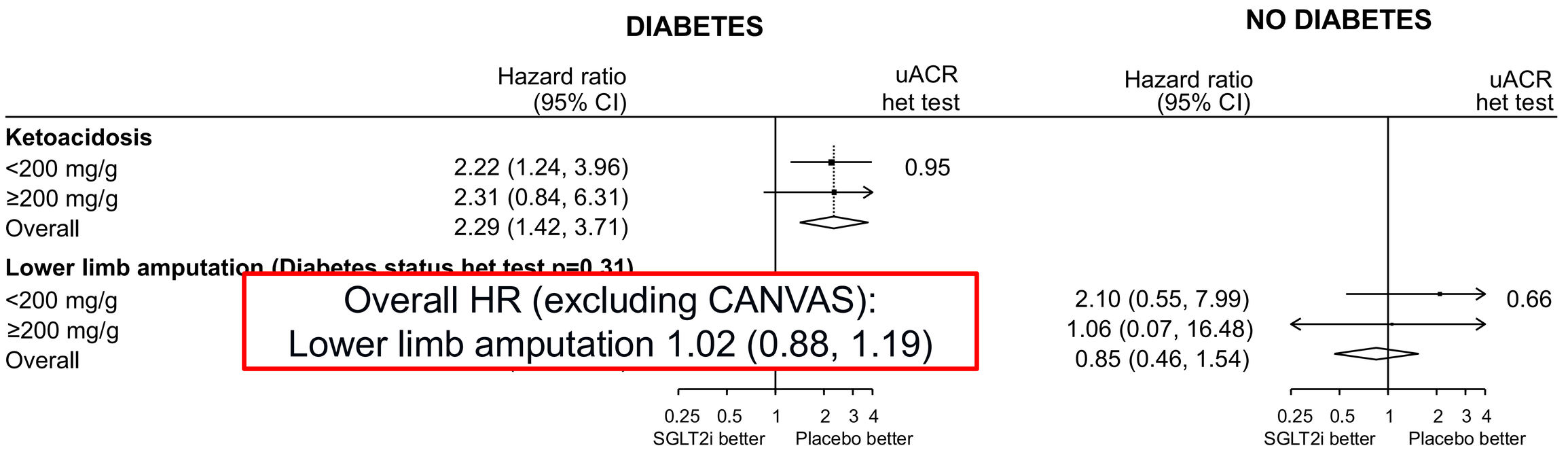
Effect of SGLT2i on safety outcomes



Overall HR (excluding CANVAS):
Lower limb amputation 1.02 (0.88, 1.19)

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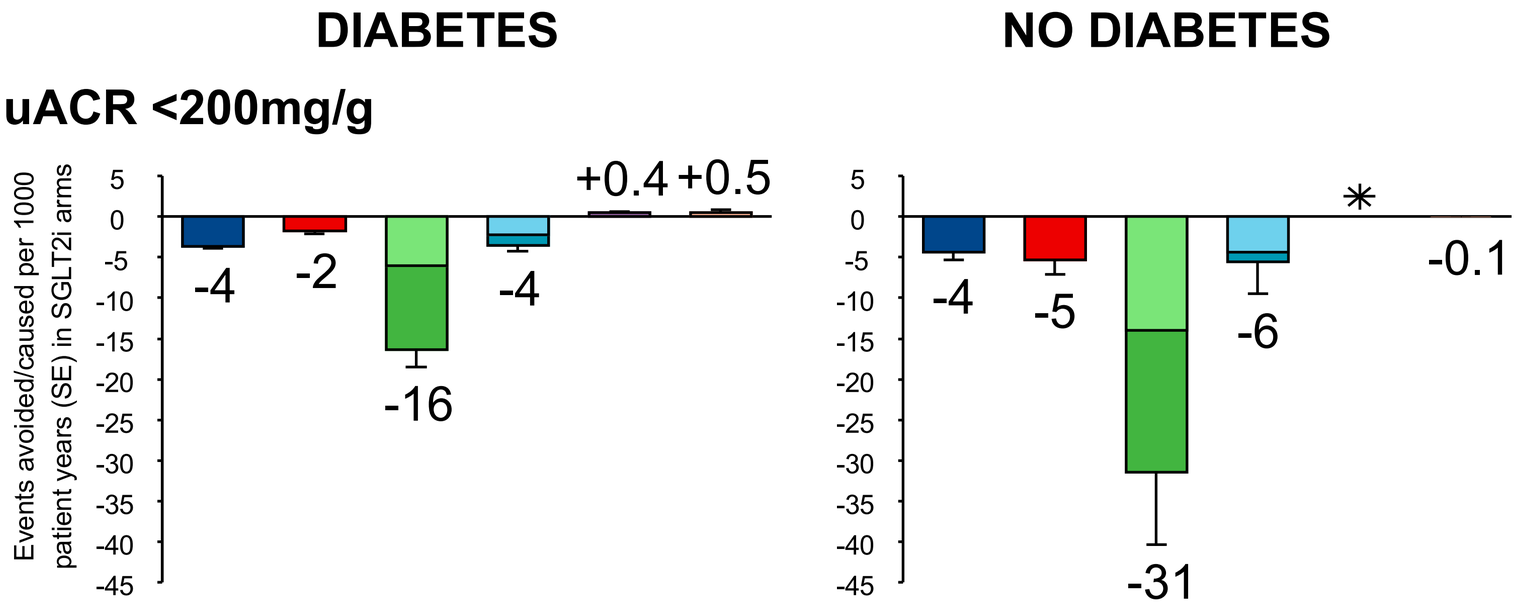
Absolute effects of SGLT2i/1000 pt years of use



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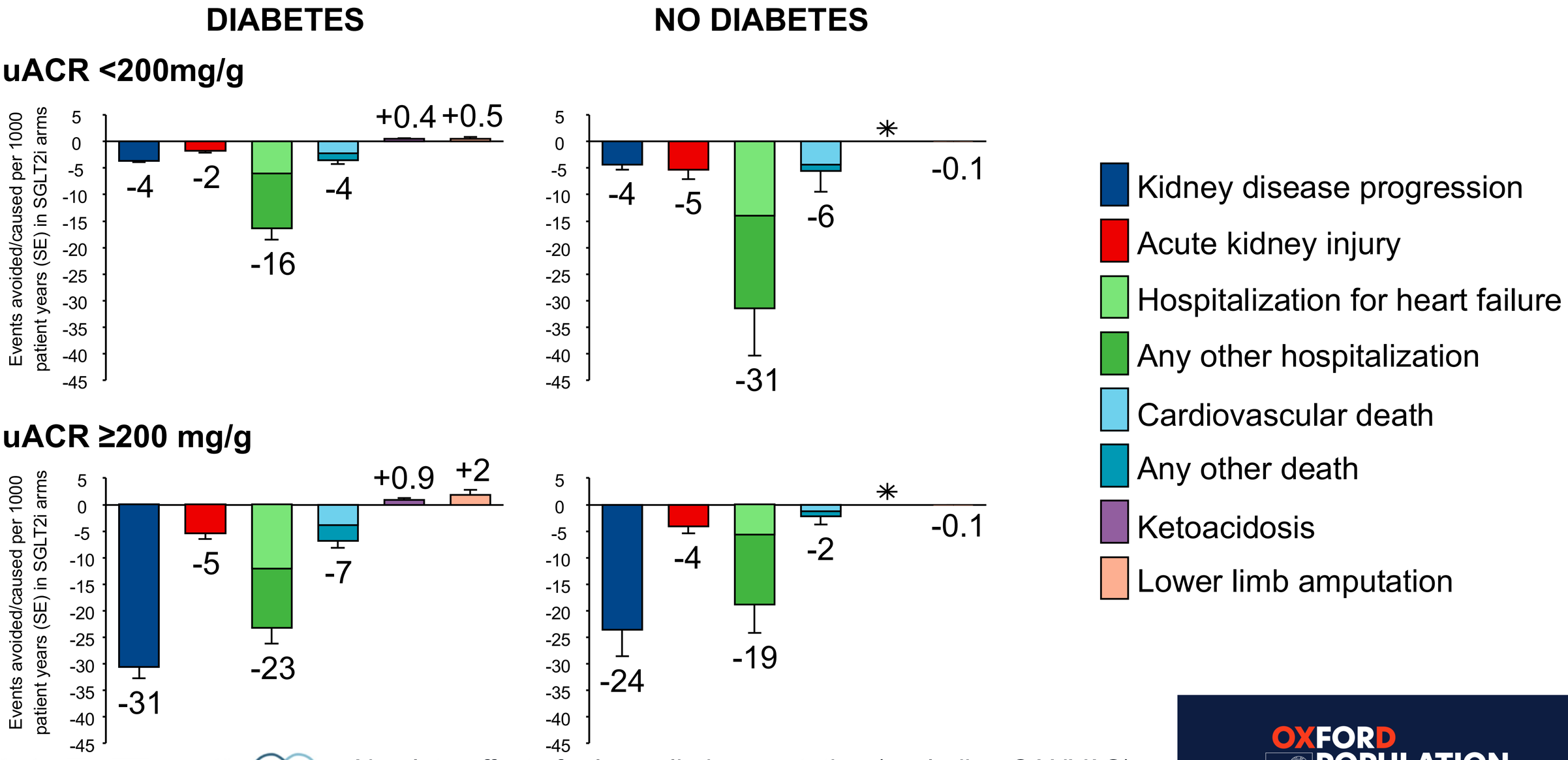

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Absolute effects for lower limb amputation (excluding CANVAS): +0.1 for uACR <200 mg/g and +0.4 for uACR ≥ 200 mg/g

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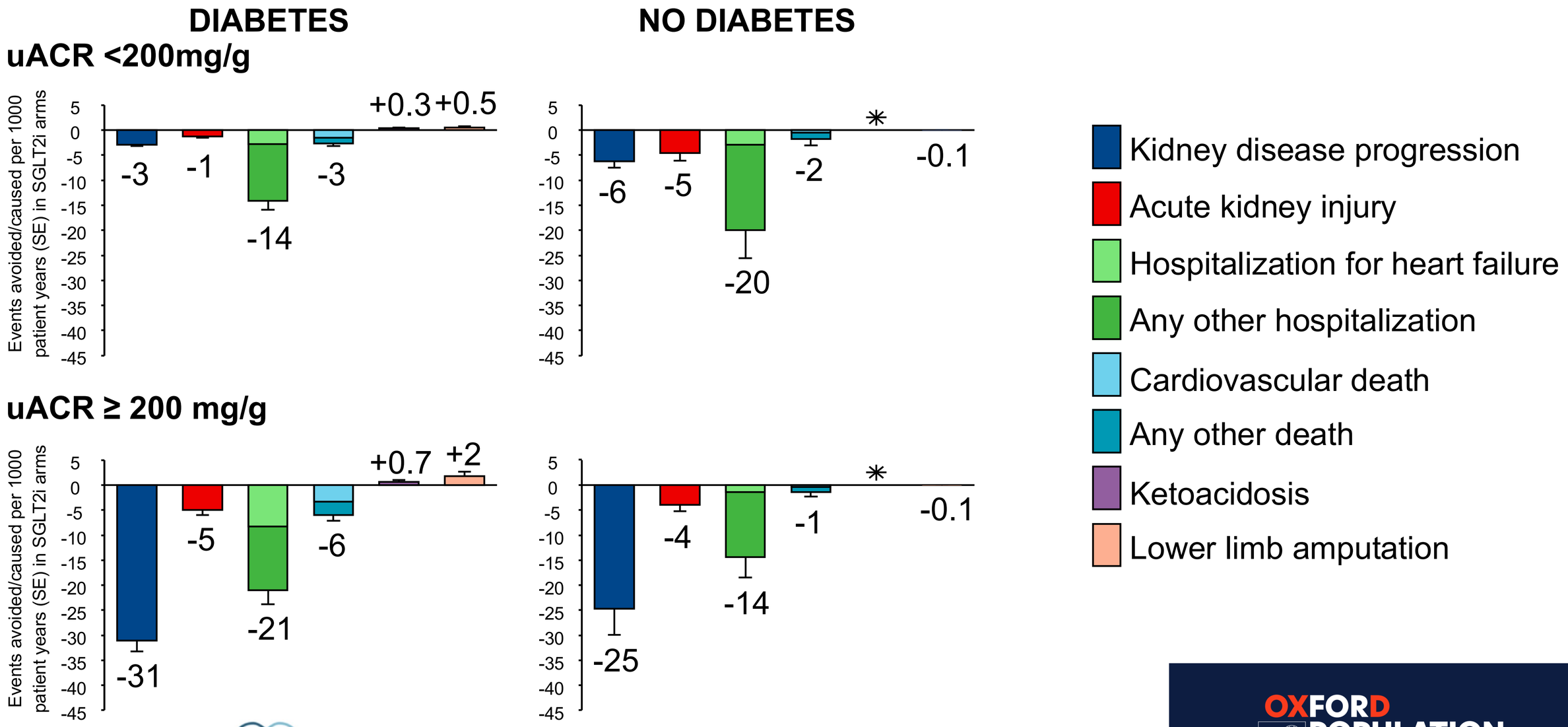
Absolute effects of SGLT2i/1000 pt years of use (excluding heart failure trials)



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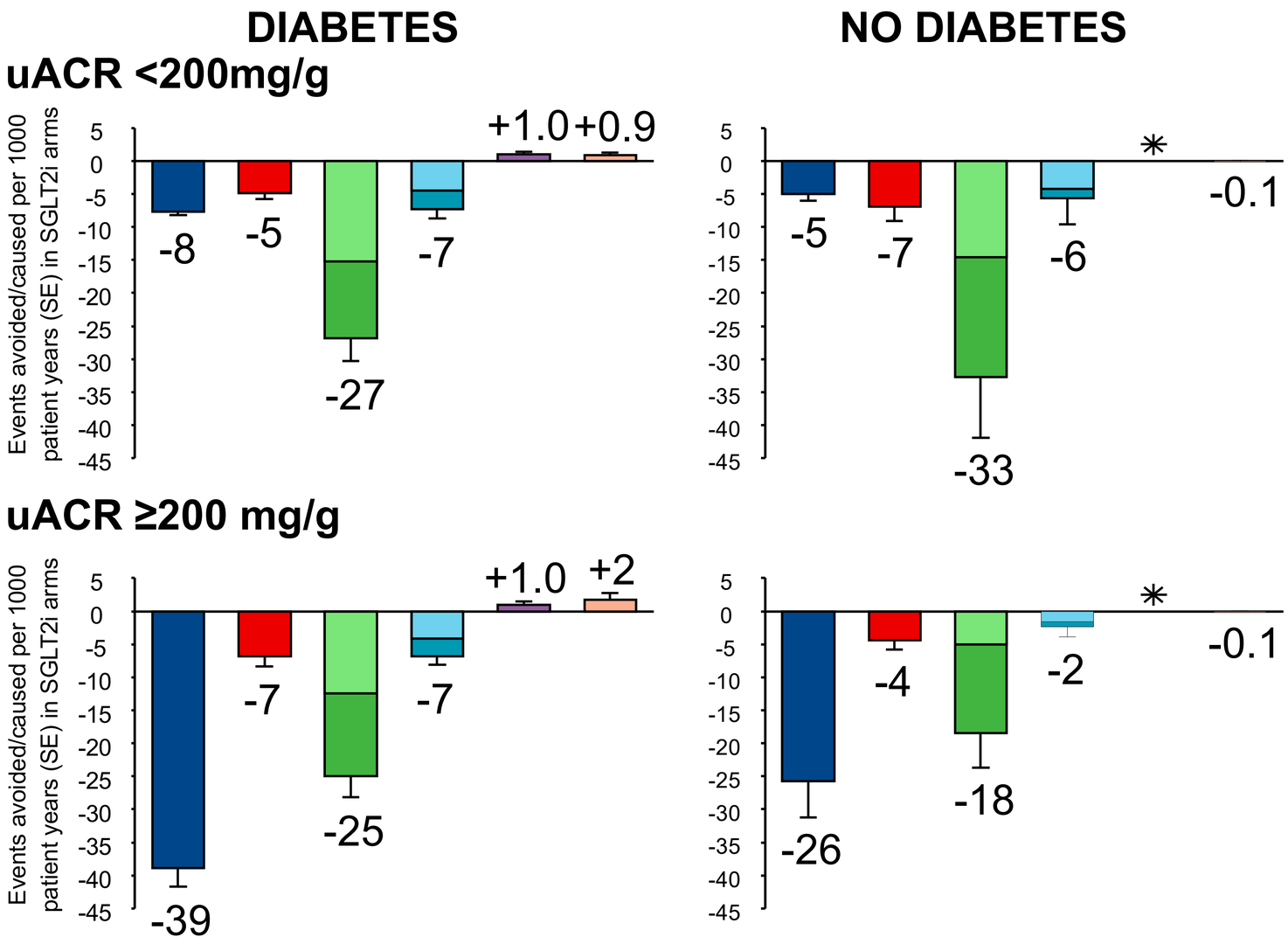
Absolute effects of SGLT2i/1000 pt years of use (eGFR <60 ml/min/1.73m^2)



- Kidney disease progression
- Acute kidney injury
- Hospitalization for heart failure
- Any other hospitalization
- Cardiovascular death
- Any other death
- Ketoacidosis
- Lower limb amputation

Absolute effects for lower limb amputation (excluding CANVAS): +0.2 for uACR <200 mg/g and +0.4 for uACR ≥ 200 mg/g

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Generalizability of absolute effects

- Presented absolute effect estimates should be interpreted as the hypothetical absolute effects of treatment with SGLT2 inhibition in a group of 1000 patients with a given baseline risk (in this case, a baseline risk equal to that of placebo-allocated participants from relevant populations in the included trials).

- In routine clinical practice, absolute effects of SGLT2 inhibitors for individuals could be estimated by calculating a patient's absolute risk for a clinical outcome using a validated risk score, and then applying the relative effect estimate for the outcome.

- This method could also be applied to eGFR slopes.

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Key conclusions from meta-analysis of ~60,000 participants from large SGLT2i trials

- **SGLT2i slow chronic rate of eGFR decline by 57% in diabetes, and 41% in patients without diabetes, and**
- **Reduce the composite of kidney disease progression based on at least a 40% decline in eGFR by 25-35%**
- **SGLT2i reduce risk of acute kidney injury by about one-fifth, and hospitalization from any cause by ~10%**

- Relative risks for efficacy or safety outcomes similar in analyses stratified by diabetes status, and then by baseline uACR ≥200 vs <200 mg/g

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Key conclusions from meta-analysis of ~59,000 participants from large SGLT2i trials

- **Substantial net absolute benefits irrespective of diabetes status or uACR, with particularly large benefits on risk of hospitalization (for heart failure or other causes)**
  - Higher absolute risk at uACR ≥200mg/g means larger absolute effects on kidney disease progression in this subgroup, otherwise patterns of absolute benefits were similar irrespective of diabetes status and uACR

- **These data support removal of stratification by level of albuminuria from guideline recommendations for use of SGLT2 inhibitors in chronic kidney disease and more widespread use.**

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