

Glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors in type 2 diabetes

Dr Guillaume Grenet



Declarations of Conflicts of Interest

- **Conflicts of interest**
 - Relationships with commercial interests, Speakers Bureau/Honoraria, Consulting Fees
 - NONE
- **Grants/Research Support**
 - One systematic review funded by the Association Française pour la Recherche Thermale (afreth), via Lyon 1 University
 - not related to today's topic, published in BMJ Open 2025;15:e089597
- **Currently funded by UBC**
 - Research associate

Type 2 diabetes (T2D) & Cardiovascular disease (CVD)



≈ 10% of adults
≈ 500 000 people
in BC [BC diabetes care](#)

↗ risk of CVD
≈ 50% die from CVD



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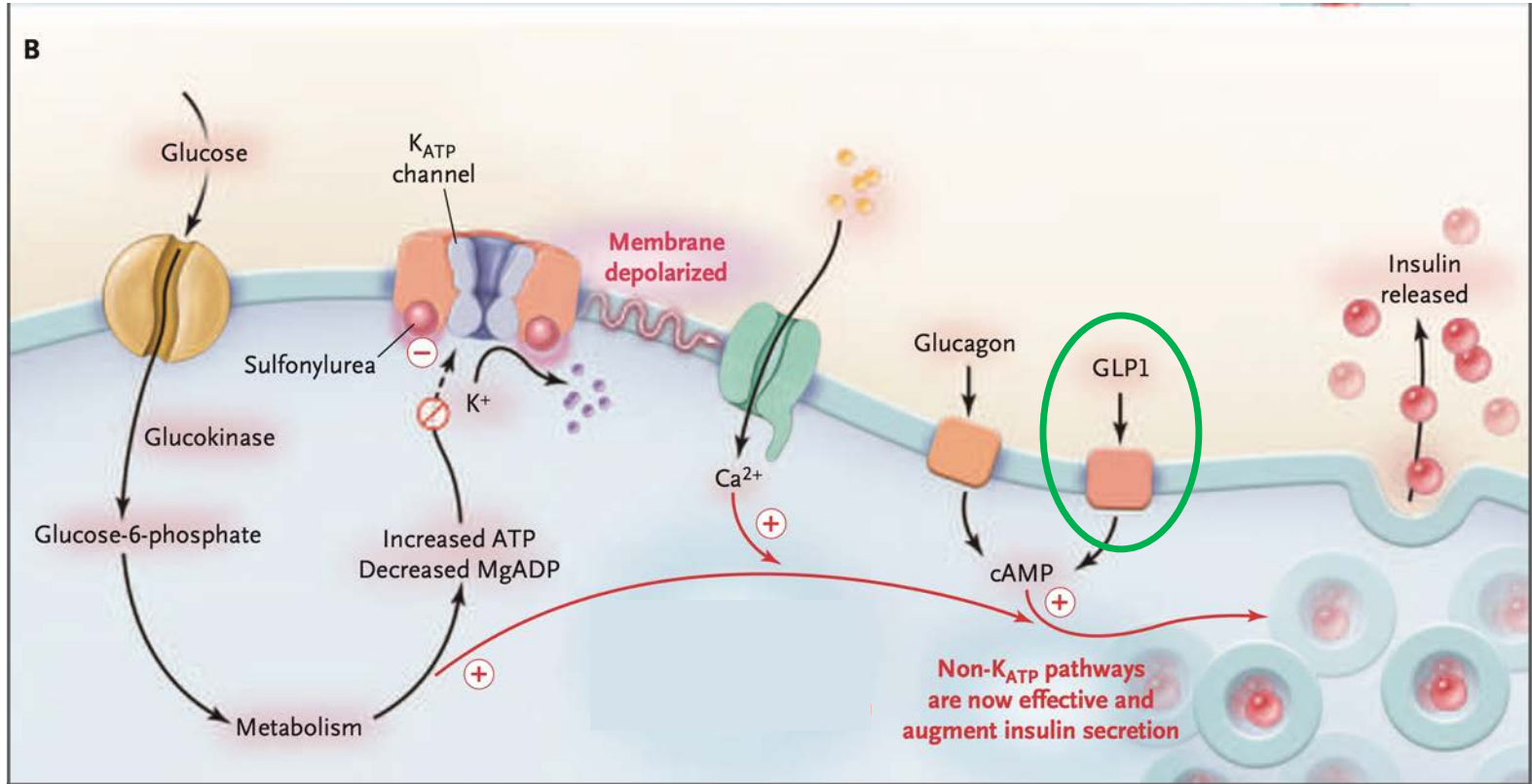
→ Recent but expensive glucose lowering drugs:



GLP-1 RA and SGLT2i

- Coverage in BC (approximate annual cost) [PAD 2024](#)
 - Limited: semaglutide_{injection} (≈ \$3,060) | empagliflozin (≈ \$1,090)
 - Regular benefit: dapagliflozin (≈ \$270)

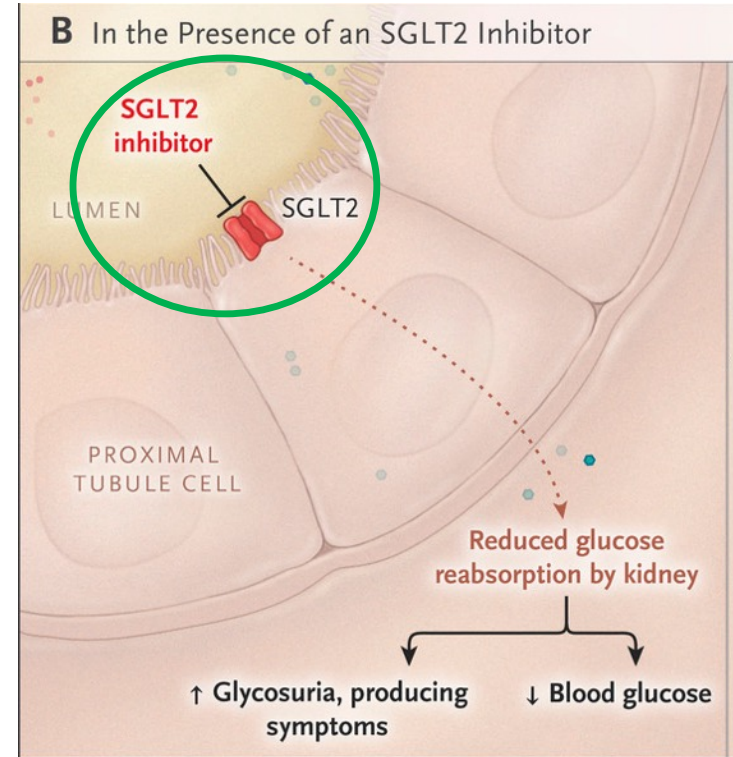
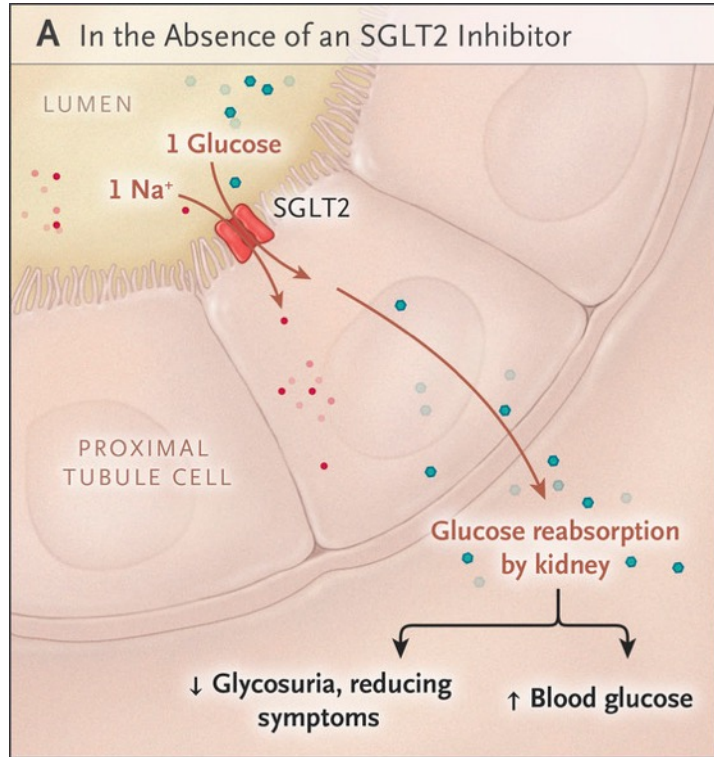
GLP-1 RA / mechanism of action



GLP-1 RA / main warnings

- **Adverse effects**
 - **Gastro-intestinal side effects**
 - **Gallbladder / biliary diseases**
 - **Pancreatitis? retinopathy worsening?**
- **Contraindications**
 - **Pregnancy**
 - **History of**
 - pancreatitis,
 - medullary thyroid carcinoma.

SGLT2i / mechanism of action



SGLT2i / main warnings

- **Adverse effects**
 - **Euglycemic ketoacidosis**
 - Do not use in type 1 diabetes +++
 - **Volume depletion**
 - Consider reducing furosemid at introduction
 - **Genital mycotic/urinary tract infections**
 - **Amputation?**
 - Especially if peripheral artery diseases?
- **Contraindication**
 - **Pregnancy**

Metabolic effects

○ ↘ **HbA1c**

- **GLP-1 RA > SGLT2i**

○ ↘ **weight**

- **GLP-1 RA > SGLT2i**

Interventions	Bodyweight change (kg)	Haemoglobin A1C (%)
Tirzepatide	-8.63 (-9.34 to -7.93)	-1.78 (-1.96 to -1.59)
Orforglipron	-7.87 (-10.24 to -5.50)	-1.82 (-2.37 to -1.26)
Semaglutide (subcutaneous)	-4.44 (-5.02 to -3.86)	-1.36 (-1.51 to -1.21)
Beinaglutide	-4.20 (-9.79 to 1.39)	-0.41 (-1.53 to 0.71)
Semaglutide (oral)	-2.89 (-3.51 to -2.26)	-1.15 (-1.31 to -0.99)
Efpeglenatide	-2.59 (-4.46 to -0.72)	-1.20 (-1.60 to -0.79)
Liraglutide	-2.34 (-2.70 to -1.97)	-0.88 (-0.97 to -0.78)
SGLT-2 inhibitors	-1.94 (-2.14 to -1.74)	-0.59 (-0.64 to -0.55)
Exenatide immediate-release	-1.86 (-2.56 to -1.16)	-0.73 (-0.90 to -0.57)
Dulaglutide	-1.64 (-2.14 to -1.15)	-0.97 (-1.10 to -0.83)
Exenatide extended-release	-1.07 (-1.74 to -0.40)	-0.83 (-1.01 to -0.65)
Metformin	-0.79 (-1.11 to -0.46)	-0.78 (-0.91 to -0.65)



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GLP-1 RA and SGLT2i: for everyone with type 2 diabetes?



- Male
- 63 years old
- BMI: 25kg/m²
- No history of
 - Cardiovascular
 - Or chronic kidney disease
- Rx:
 - Atorvastatine 20mg once daily
 - Hydrochlorothiazide 25mg once daily
 - Metformine 500mg twice daily
- HbA1c: 7.4%

Would you consider adding

- A) GLP-1 RA
- B) SGLT2i
- C) Both
- D) None



BC Guidelines for diabetes care (2021)



Diabetes AND:	→ consider:
Atherosclerotic cardiovascular disease (ASCVD)	→ GLP1-RA or SGLT2i
Chronic kidney disease (CKD) and an estimated eGFR >30 mL/min/1.73m ²	→ SGLT2i
History of HF (ejection fraction ≤ 40%)	→ SGLT2i and avoid glitazones and saxagliptin
≥ 60 years & ≥ 2 CV risk factors (tobacco, dyslipidemia, high blood pressure)	→ GLP1-RA, SGLT2i

→ Tom  

Benefit harm ratio



GLP-1 RA
SGLT2i



↘ HbA1c

GLP-1 RA > SGLT2i



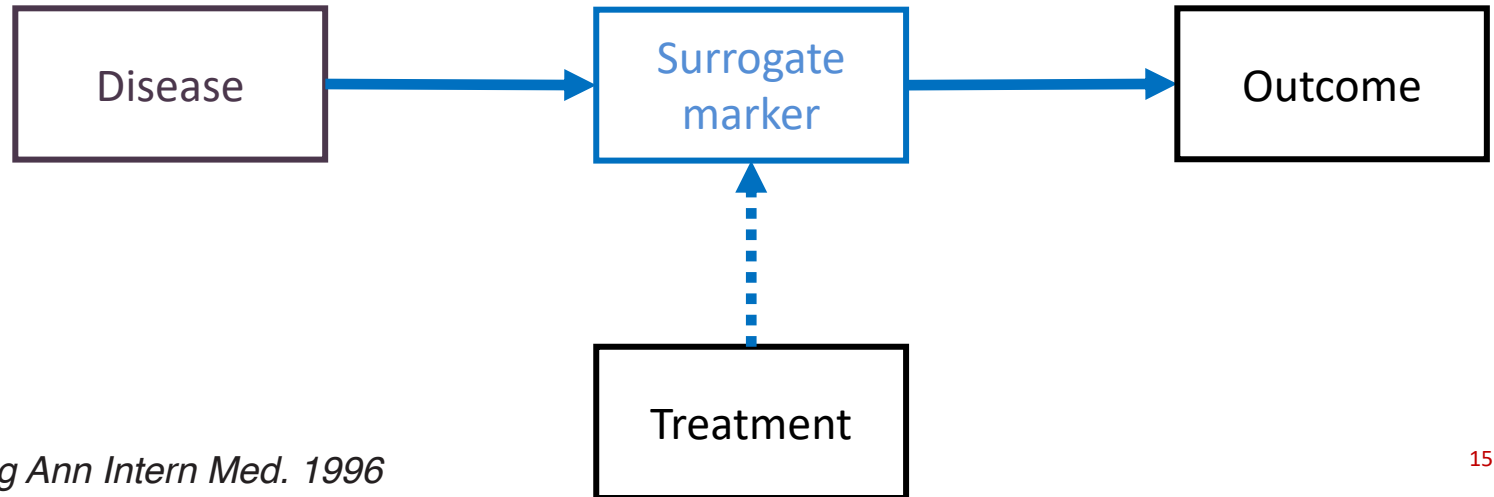
↘ Complication

Is ↘ HbA1c enough evidence?

- A marker can be correlated with the prognostic,
- Without being a predictor of the treatment effect.

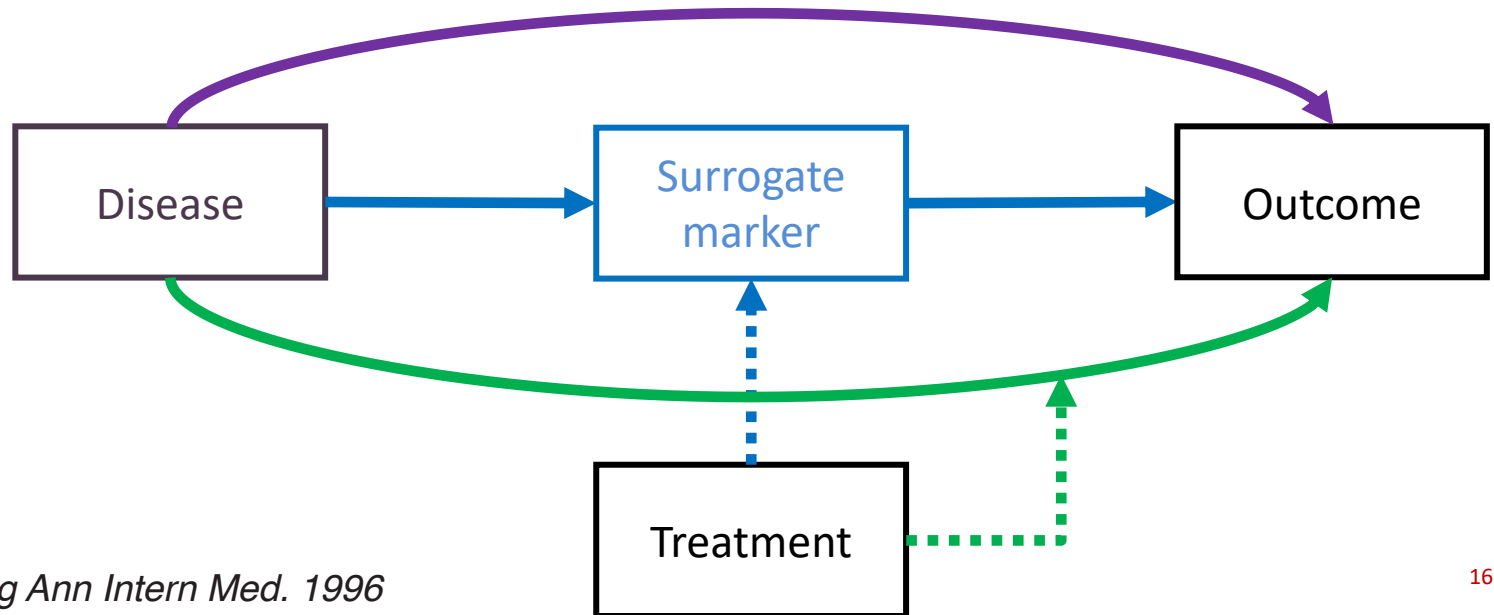
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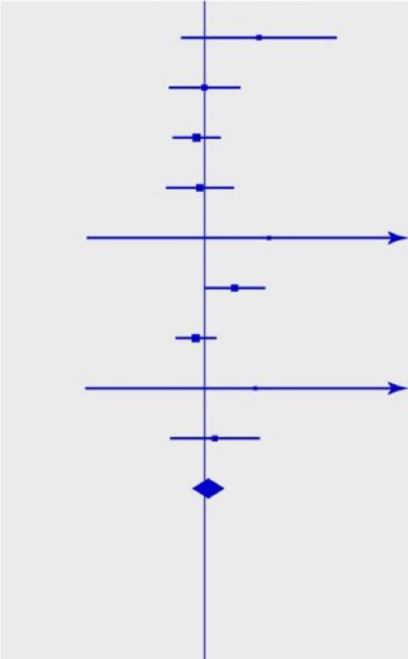


Is ↘ HbA1c enough evidence?

Study	No of events/No in group		Risk ratio Mantel-Haenszel, random (99% CI)	Weight (%)	Risk ratio Mantel-Haenszel, random (99% CI)
	Intensive treatment	Standard treatment			
All cause mortality					
UGDP ^{22 23}	64/408	21/205		4.1	1.53 (0.83 to 2.82)
UGDP ²⁴	91/204	94/210		13.0	1.00 (0.75 to 1.32)
UKPDS ²⁷	539/3071	213/1138		19.2	0.94 (0.78 to 1.13)
PROactive ²⁸	177/2605	186/2633		14.2	0.96 (0.74 to 1.25)
Dargie et al ²⁹	8/110	5/114		0.8	1.66 (0.40 to 6.91)
ACCORD ⁷	257/5128	203/5123		15.7	1.26 (1.00 to 1.60)
ADVANCE ⁶	498/5571	533/5569		22.1	0.93 (0.80 to 1.09)
HOME ³⁰	9/196	6/194		1.0	1.48 (0.39 to 5.63)
VADT ⁸	102/892	95/899		10.0	1.08 (0.77 to 1.53)
Total (99% CI)	1745/18 185	1356/16 085		100.0	1.04 (0.91 to 1.19)

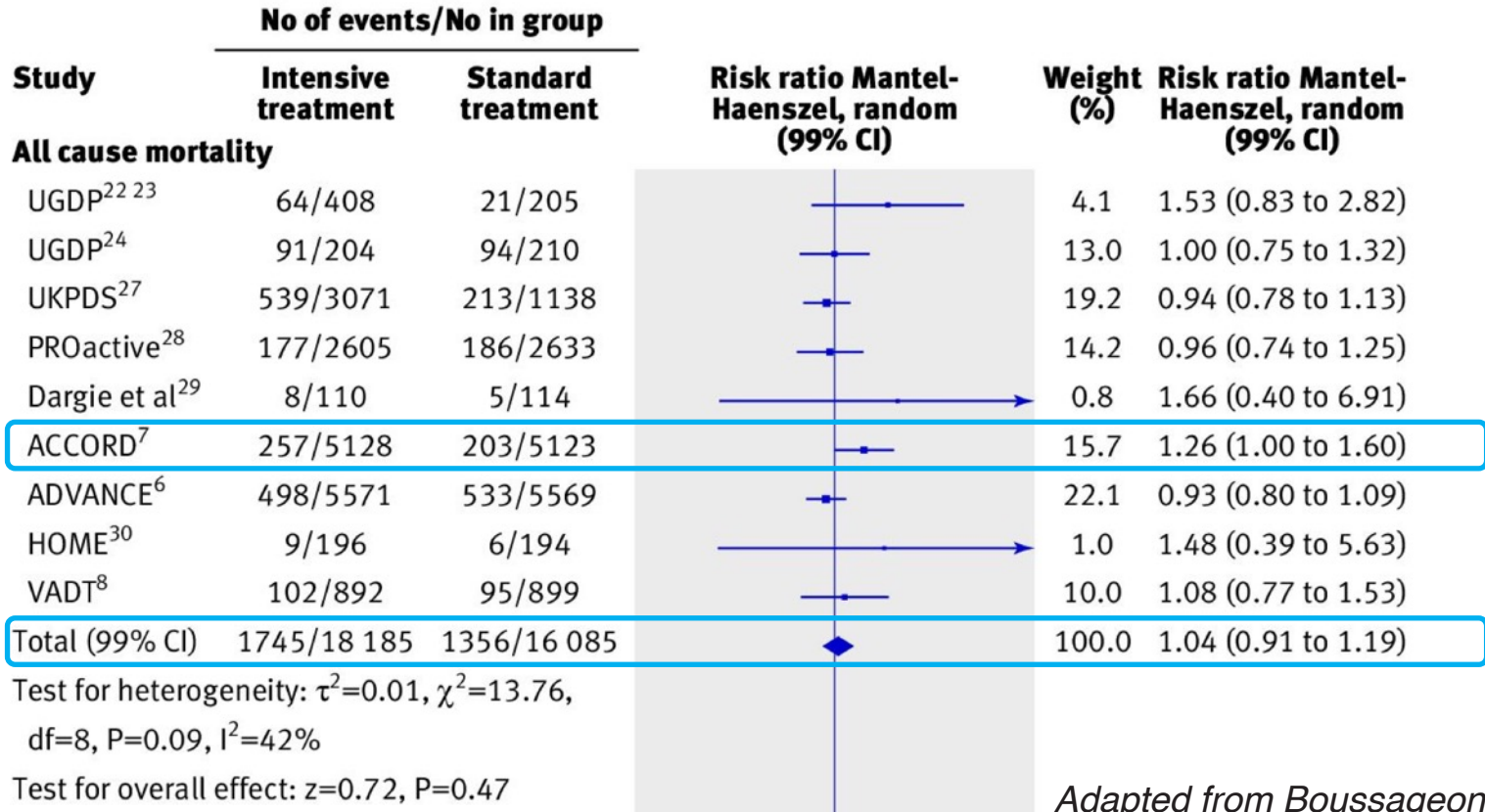
Test for heterogeneity: $\tau^2=0.01$, $\chi^2=13.76$, $df=8$, $P=0.09$, $I^2=42\%$

Test for overall effect: $z=0.72$, $P=0.47$



Adapted from Boussageon BMJ 2011

Is ↘ HbA1c enough evidence?



Unclear

Adapted from Boussageon BMJ 2011

Benefit harm ratio



GLP-1 RA
SGLT2i



GLP-1 RA: gastro-intestinal harms ...
SGLT2i: genital infection ...



↗ Harm

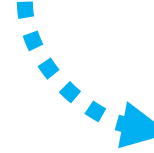


?

↘ Complication



↘ HbA1c
GLP-1 RA > SGLT2i



**Where does the clinical evidence
come from?**

Cardiovascular outcome trials (CVOT)

Big trials powered for clinical outcome

- **MACE: major adverse cardiovascular event**
 - Cardiovascular mortality
 - Non-fatal myocardial infarction
 - Non-fatal stroke

'Gold standard' methodologies

- **Randomized**
- **Double-blinded**
- **Placebo-controlled ...**

Cardiovascular outcome trials (CVOT)

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'Gold standard' methodologies

- Randomized
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But: all were industry-sponsored

- → High risk of 'sponsor bias'

Sponsor bias

- **Industry sponsorship is associated with more favorable efficacy findings than other sponsorship.**



Industry sponsorship and research outcome (Review)

Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L

GLP-1 RA/SGLT2i CVOT in T2D



- **GLP-1 RA: >10 CVOT, > 70,000 participants**
- **SGLT2i: >5 CVOT, > 50,000 participants**



- **Added to metformin**



- **Mean age from 60 to 69 years old**
- **Mean body mass index from 30 to 33 kg/m²**



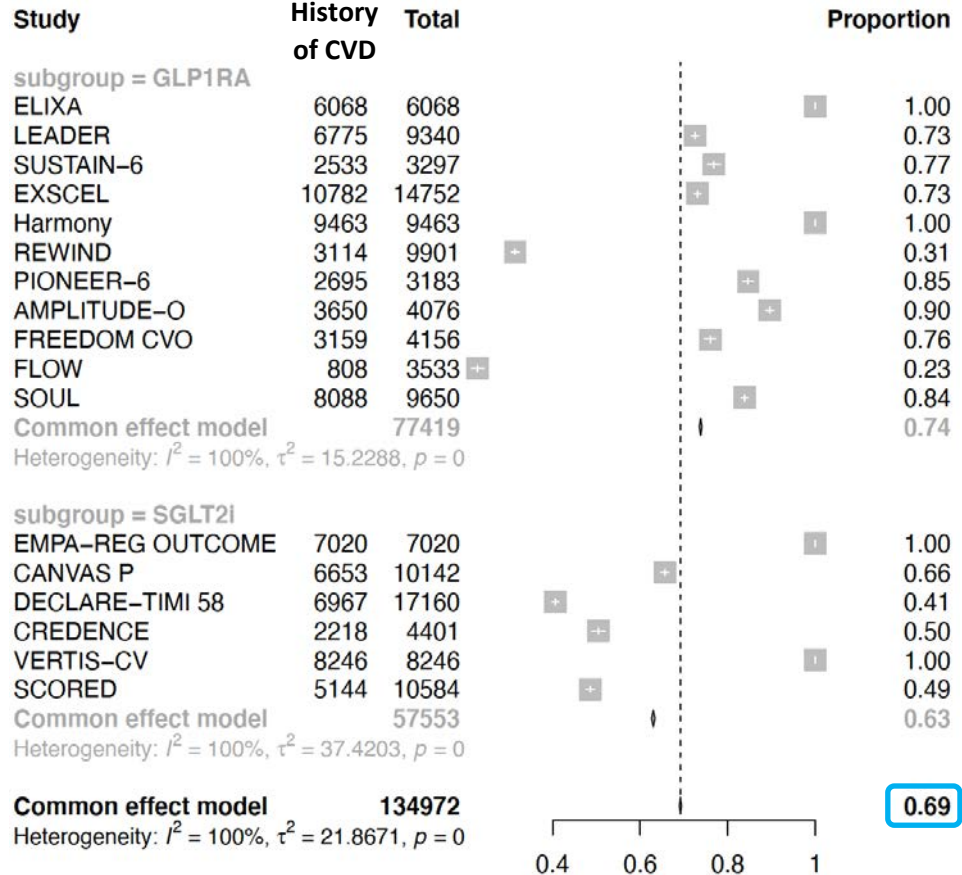
- **Mean diabetes duration from 9 to 17 years**
- **Mean HbA1c at baseline from 7 to 9 % (53 to 75 mmol/mol)**



- **Follow-up \approx 2-4 years**

Cardiovascular disease prevalence in T2D

- In CVOT, at baseline



0.69

Cardiovascular disease prevalence in T2D



- In 'real life'

Table 4 Summary of prevalence rates of cardiovascular comorbidities in persons with type 2 diabetes

Sex	Cardiovascular outcome	Studies	N	Rate ^a (%)	95% confidence interval (%)
Both	Stroke	39	3,901,505	7.6	6.6–8.6
	Myocardial infarction	13	3,518,833	10.0	7.5–12.5
	Angina pectoris	4	354,743	14.6	12.0–17.3
	Heart failure	14	601,154	14.9	13.0–16.7

Cardiovascular disease prevalence in T2D



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	Heart failure	14	601,154	14.9	13.0–16.7
	Atherosclerosis	4	1153	29.1	21.7–36.4
	Coronary artery disease	42	3,833,200	21.2	20.3–22.2
	Cardiovascular disease (any)	53	4,289,140	32.2	30.0–34.4

Primary CVD prevention was under-represented in the CVOT

$\lesssim 1/3$ in CVOT



 T2D with CVD
 T2D without CVD

$\approx 2/3$ in real life



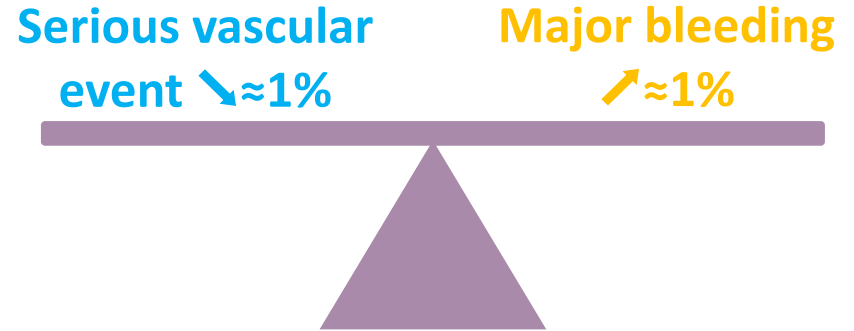
**→ Can we extrapolate the benefits from
the CVOT to the general T2D population?**

Why does it matter?

- **The previous example of aspirin for CVD prevention in T2D**
 - **The ASCEND trial**
 - 15,480 participants
 - Without history of CVD
 - Randomized to aspirin or placebo
 - Mean follow-up: 7.4 years

Why does it matter?

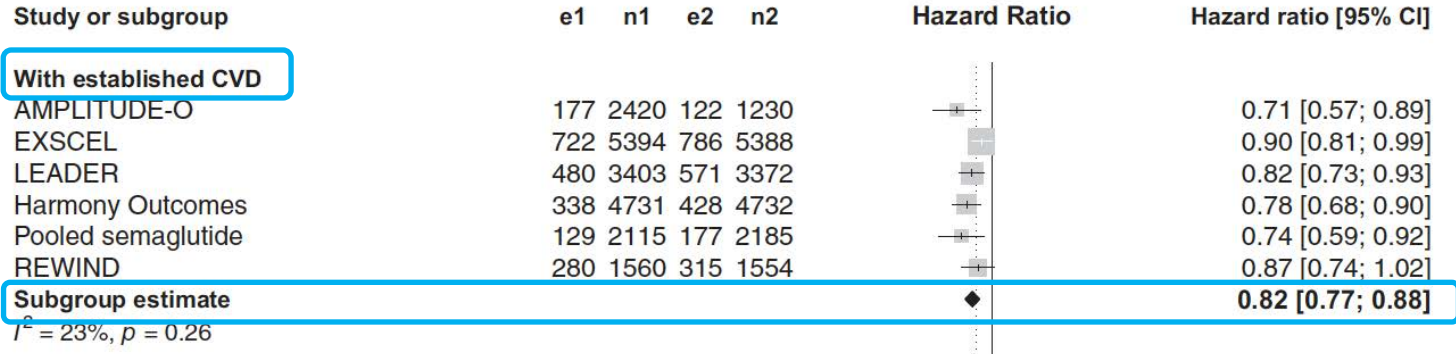
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**→ In primary CVD prevention,
the benefits of aspirin were counterbalanced by its harm...**

**For GLP-1 RA and SGLT2i in T2D,
what are the clinical evidence in primary
CVD prevention?**

Effect of GLP-1 RA on the risk of MACE

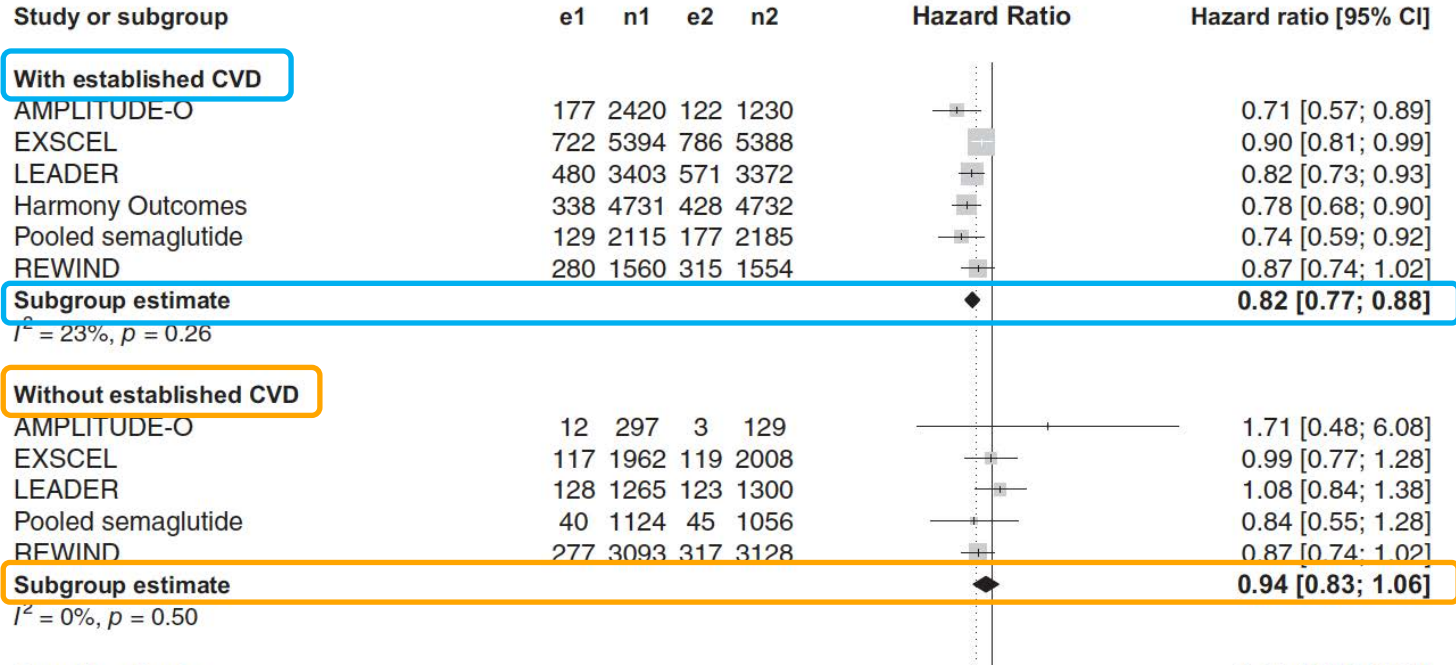


↘ risk of MACE

Favors GLP-1 RAs Favors placebo

Adapted from Karagiannis Diabetes Care 2024

Effect of GLP-1 RA on the risk of MACE



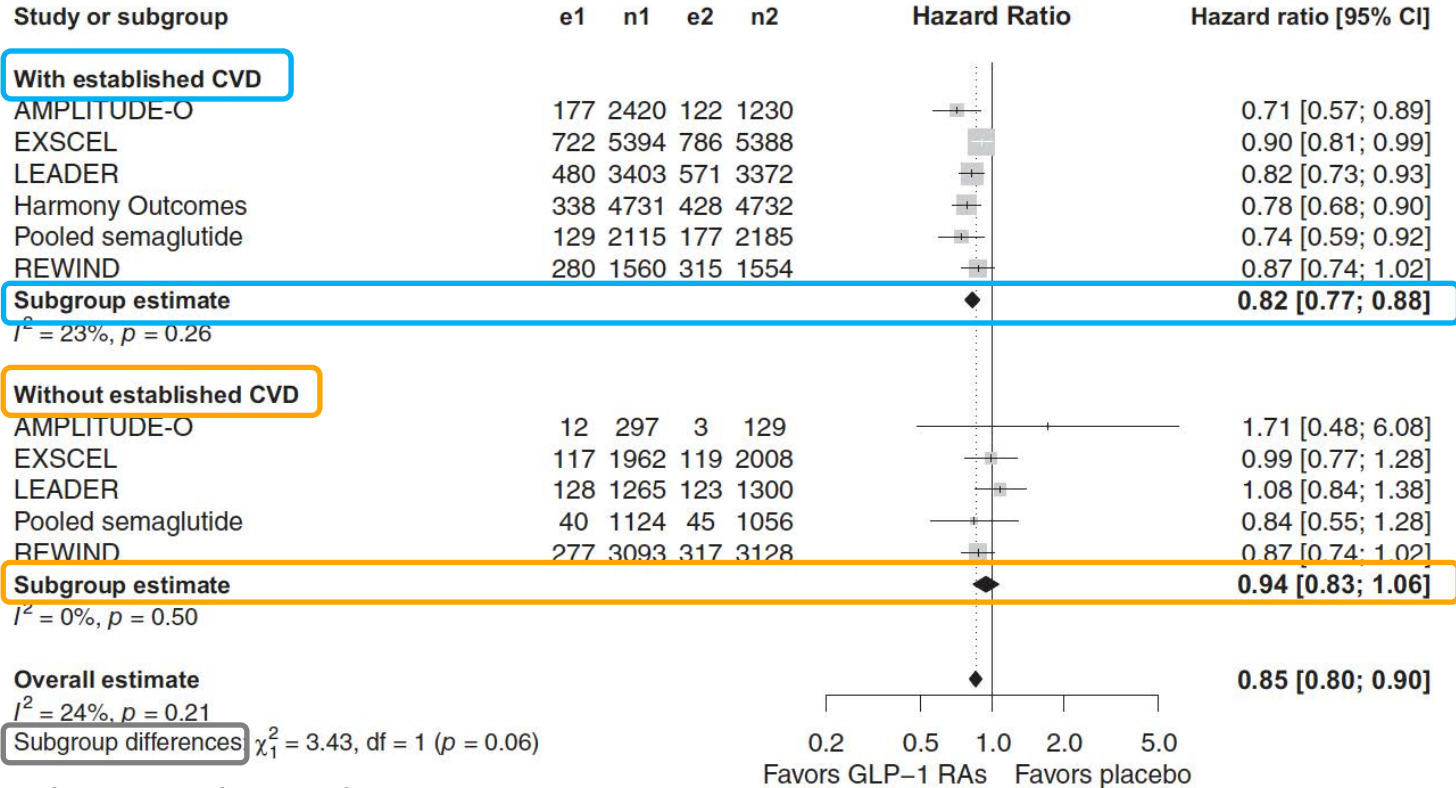
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No ↘ risk of MACE

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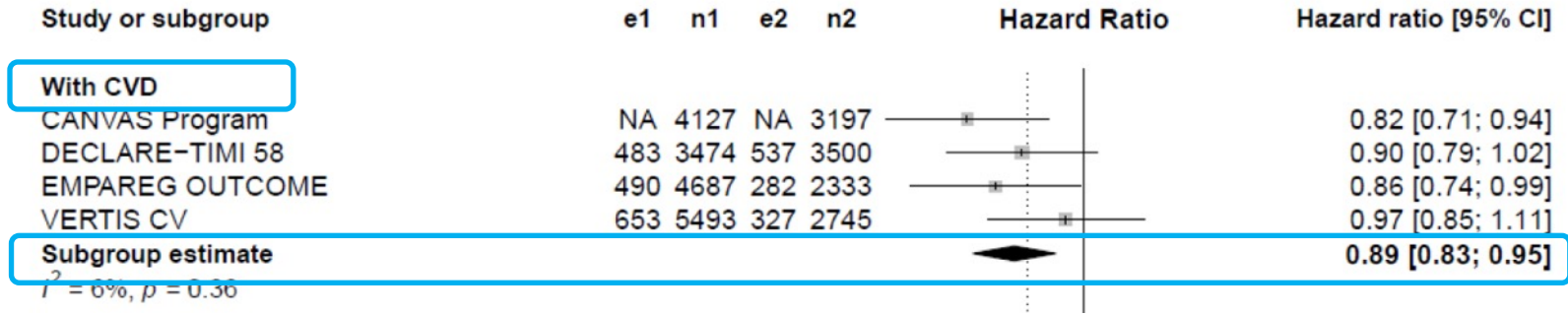
↘ risk of MACE

No ↘ risk of MACE

This test has a low power

Adapted from Karagiannis Diabetes Care 2024

Effect of SGLT2i on the risk of MACE

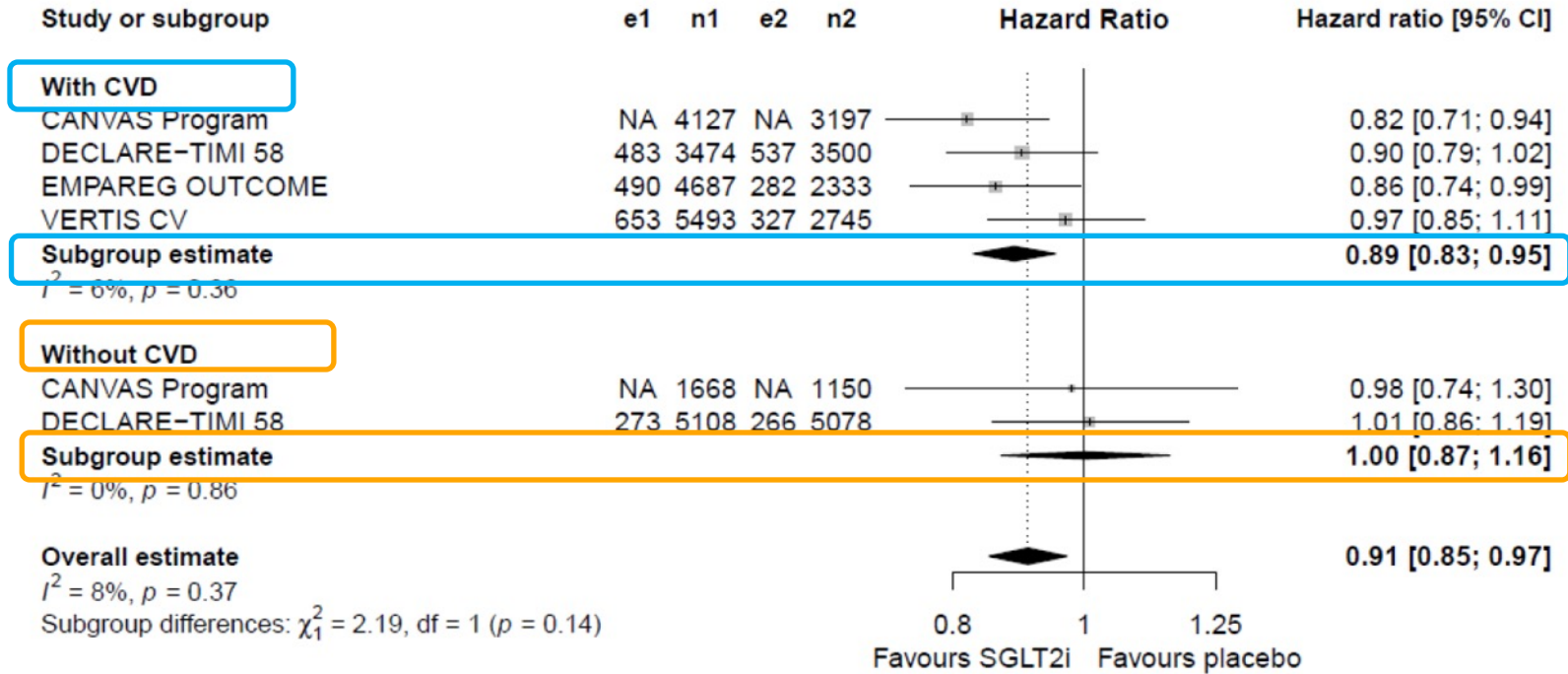


↘ risk of MACE

Subgroup differences: $\chi^2 = 2.19, df = 1 (p = 0.14)$

0.8 1 1.25
Favours SGLT2i Favours placebo

Effect of SGLT2i on the risk of MACE



↘ risk of MACE

No ↘ risk of MACE

GLP-1 RA/SGLT2i in primary CVD prevention



- **Compared to placebo,**
- **In the subgroups without previous CVD,**
- **No differences for**
 - **All cause mortality**
 - **CV mortality**
 - **Myocardial infarction**
 - **Stroke**

GLP-1 RA/SGLT2i in primary CVD prevention



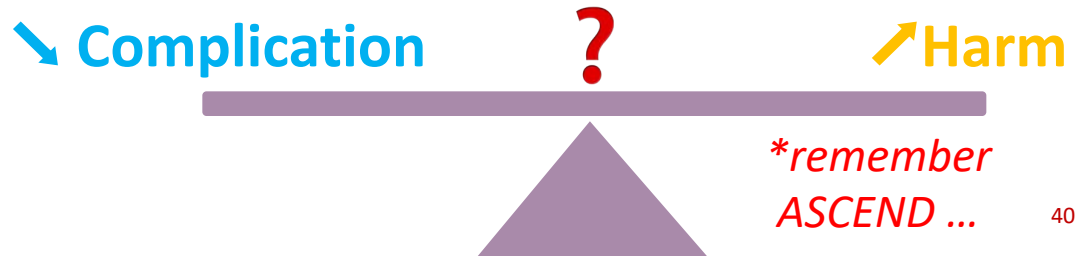
- **The available evidence for primary CVD prevention are of low certainty**
 - **High risk of sponsor bias**
 - **Low precision**
 - Lack of effect or lack of power to detect the effect? 🙄
 - ➔ need more participants in primary CVD prevention
- ➔ **No demonstration of CV benefits in this population**

GLP-1 RA/SGLT2i in primary CVD prevention

- If we extrapolate a potential benefit from secondary CVD prevention,
- Such effect would be small in primary CVD prevention
 - Risk of MACE among 1,000 patients over 3-4 years:
 - Without GLP-1 RA/SGLT2i: around $\approx 70-80$ CV events
 - *If GLP-1 RA/SGLT2i \searrow MACE risk by $\approx 15\%$*
 - *Then we would expect ≈ 10 fewer CV events*

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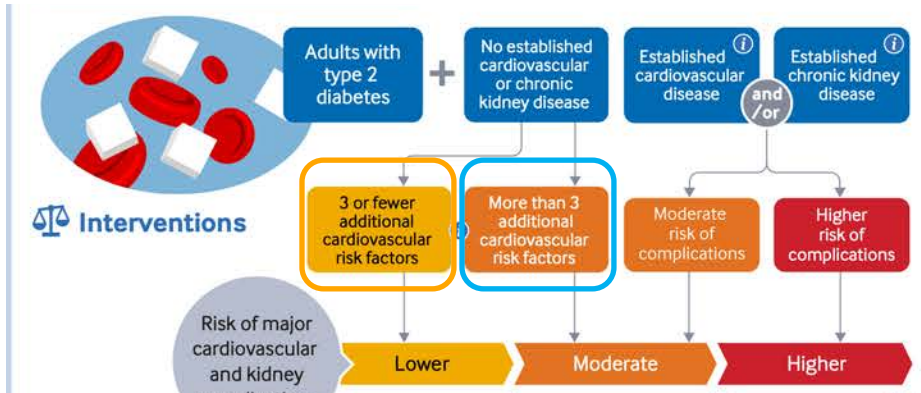
Would you consider adding

- A) GLP-1 RA
- B) SGLT2i
- C) Both
- D) None



BMJ Rapid Recommendations

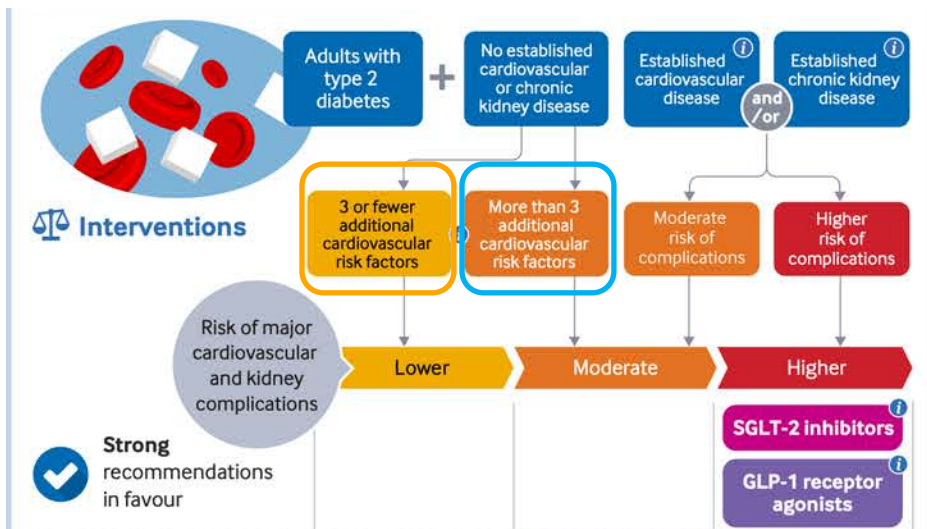
(2025)



Adapted from Agarwal BMJ 2025

BMJ Rapid Recommendations

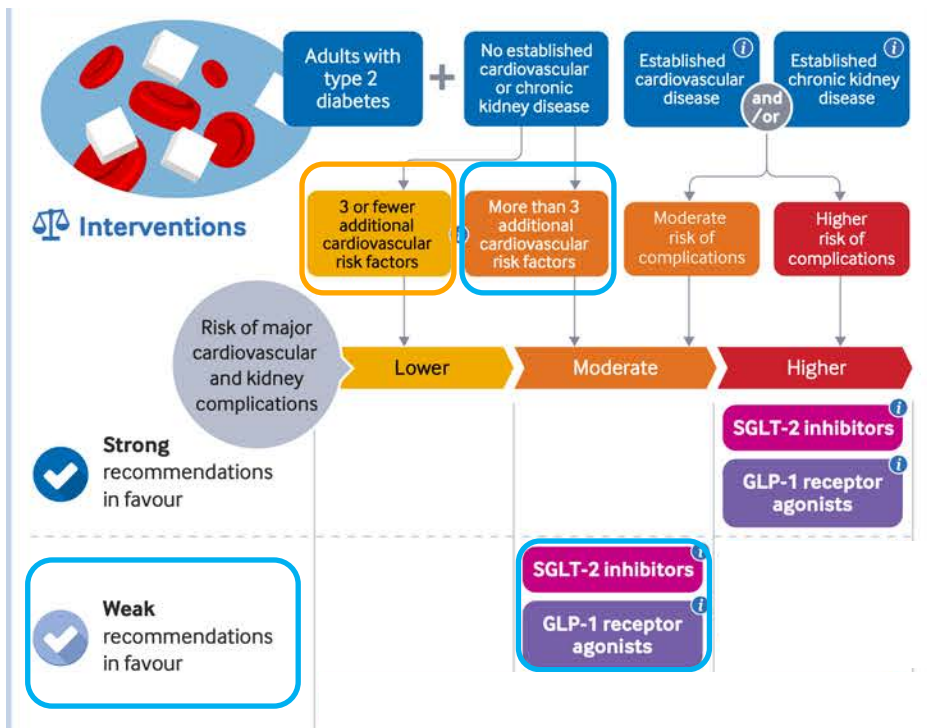
(2025)



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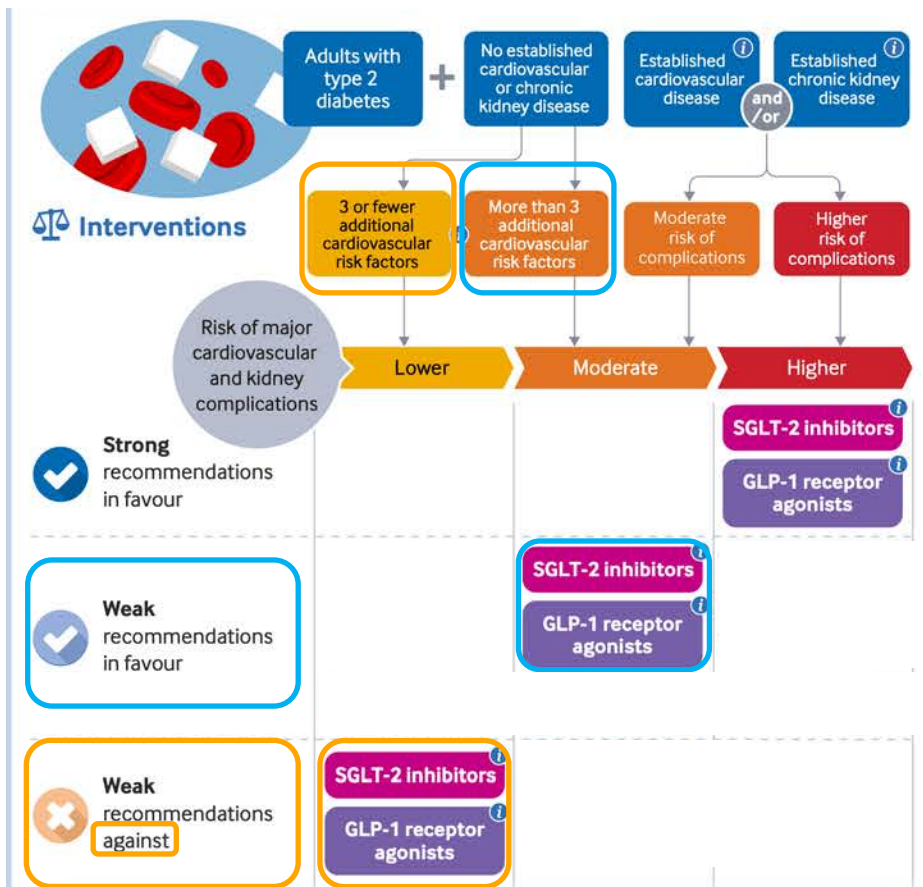
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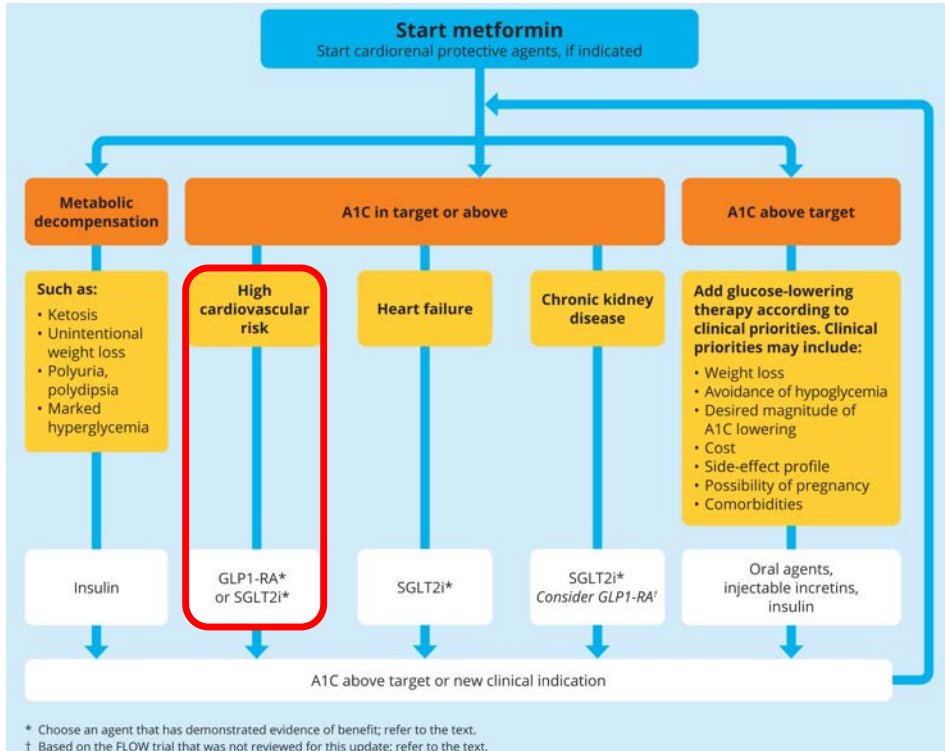
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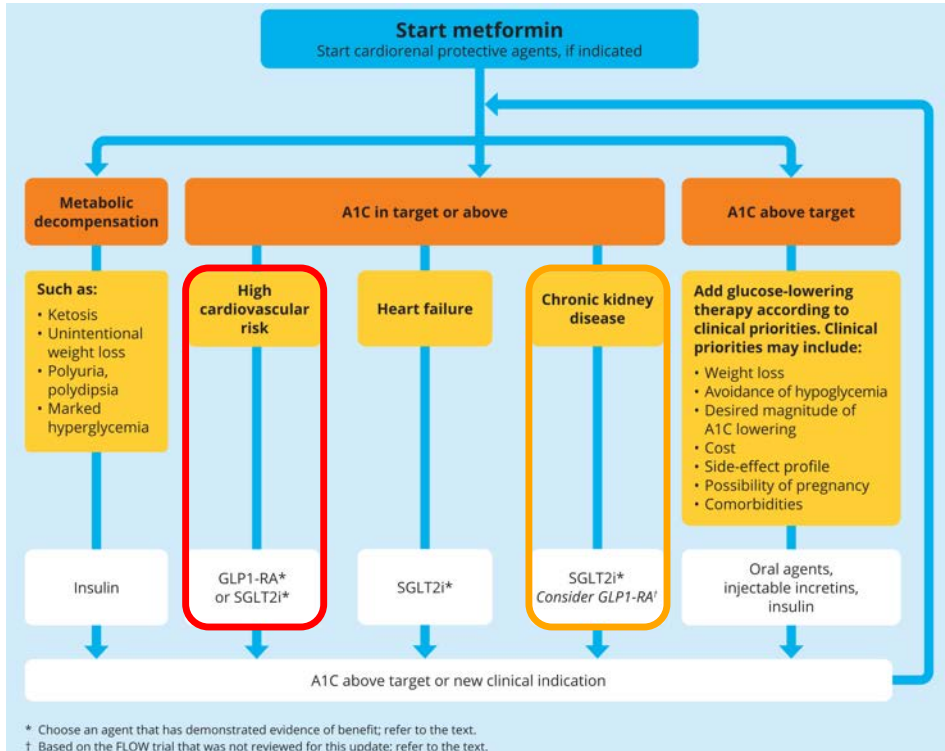
➔ Some disagreements in the guidelines regarding the population with T2D but without CVD

➔ Tom  

Adapted from Agarwal BMJ 2025






○ Definition of “high CV risk”: unclear



○ Definition of “high CV risk”:
unclear

T2D with chronic kidney disease (CKD)

Placebo controlled randomized renal outcome trial in T2D	Baseline CKD	Reported renal protection
FLOW ^{NEJM 2024} (SC sema)	eGFR 25 to 75ml.min & UAC 100 to 5000	eGFR* 
CREDENCE ^{NEJM 2019} (cana)	eGFR 30 to <90ml.min & UAC 300 to 5000	Serum creatinine level End-stage kidney disease**  

UAC: Urinary albumin (mg) to creatinine (g) ratio; eGFR: estimated glomerular filtration rate
 *: fewer ≥50% reduction; **: fewer eGFR <15ml.min or dialysis or transplantation

Take home message

GLP-1 RA and SGLT2i in type 2 diabetes

- The evidence relies mostly on patients with a history of CVD.
- In primary CVD prevention, evidence is still lacking.

Benefit-harm ratio in
the CVOTs
(high CV risk)




How is the benefit-harm
ratio in the general T2D
population
(at lower CV risk)?



Primary CVD prevention in T2D



👁️👁️ **More to come**

Expected	Trial	Comparison	Population	Outcome
2025-10	SMARTEST	dapagliflozin vs metformin	2,072  without CVD	Large composite*

*all-cause death, MACE and microvascular complications (including albuminuria)

Primary CVD prevention in T2D

👁️ **More to come**




Expected	Trial	Comparison	Population	Outcome
2025-10	SMARTTEST	dapagliflozin vs metformin	2,072  without CVD	Large composite*
2028	ASCEND PLUS	oral semaglutide vs placebo	≈ <u>20,000</u>  without CVD	MACE+**

*all-cause death, MACE and microvascular complications (including albuminuria)

** : MACE-3P + transient ischaemic attack and coronary revascularisation)

Primary CVD prevention in T2D

👁️ **More to come**

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2025-10	SMARTTEST	dapagliflozin vs metformin	2,072  without CVD	Large composite*
2028	ASCEND PLUS	oral semaglutide vs placebo	≈ <u>20,000</u>  without CVD	MACE+**
2029	PRECIDENTD	SGLT2i vs GLP-1 RA	≈6,000  , 30% without CVD	Large composite***

*all-cause death, MACE and microvascular complications (including albuminuria)

** : MACE-3P + transient ischaemic attack and coronary revascularisation)

***: total number of myocardial infarction, stroke, arterial revascularization, hospitalization for heart failure, end-stage kidney disease, kidney transplantation, and mortality

Any questions?



Thank you

<https://www.ti.ubc.ca/>

 @Drug_Evidence



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