SGLT2 Inhibitors and Major Adverse Cardiovascular Events in Patients with Diabetes at High Risk For Atherosclerotic Cardiovascular Disease, Heart Failure or Chronic Kidney Disease: A SMART-C Collaborative Meta-Analysis

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BACKGROUND

- SGLT2i have been clearly demonstrated to reduce the risk of adverse HF and kidney outcomes.
- Treatment effects of SGLT2i on MACE have been more modest, with differences observed across trials.
- Uncertainty exists regrading the effect of SGLT2i on MACE, particularly the individual MACE components, across several important patient subgroups.

METHODS

- Collaborative meta-analysis of the SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists Consortium (SMART-C) – includes all large, phase 3, pbo-controlled clinical outcome RCTs of SGLT2i across three primary pt populations:
  1. DM at high risk for ASCVD: EMPAREG Outcome, CANVAS, DECLARE-TIMI 58, VERTIS-CV
  2. Heart failure: DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DELIVER
  3. Chronic kidney disease: CREDENCE, DAPA-CKD, EMPA-KIDNEY
- Trial-level summary data, overall and by subgroup, provided by SMART-C investigators
- Outcomes of interest = MACE composite of CV death, MI and stroke, individual MACE components (inclusive of fatal & non-fatal events), death subtypes
- Trial effect estimates were meta-analyzed in each of the 3 primary pt populations using FE and pooled using RE
- Effect modification across subgroups was examined using RE meta-regression

RESULTS

- A total of 78,607 patients were included across 11 RCTs: 54%, 26% and 20% were included from the DM at high risk for ASCVD, HF and CKD trials, respectively.

Fig 1. MACE Composite

Trial Type	Events, n	n/N Rate, %	Overall HR (95% CI)
DM at High Risk for ASCVD	4445	10.4	0.91 (0.86, 0.97)
Heart Failure	2489	12.0	0.94 (0.86, 1.01)
Chronic Kidney Disease	1042	6.8	0.87 (0.77, 0.98)
Overall	7976	10.1	**0.91 (0.87, 0.96)**

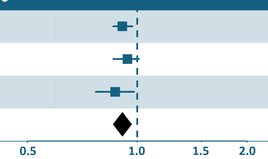

Fig 2. Individual MACE Components

Outcome	Events, n	n/N Rate, %	Overall HR (95% CI)
CV Death	4148	5.3	0.86 (0.81, 0.92)
Myocardial Infarction	2819	3.6	0.95 (0.87, 1.04)
Stroke (any)	2220	2.8	0.99 (0.91, 1.07)

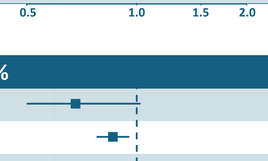

Fig 3. CV Death Subtypes

Subtype of Death	Events, n	n/N Rate, %	Overall HR (95% CI)
Heart Failure Death	743	0.9	0.68 (0.46, 1.02)
Sudden Cardiac Death	1745	2.2	0.86 (0.78, 0.95)
Other CV Death	626	0.8	0.88 (0.75, 1.03)
Fatal MI	347	0.4	0.95 (0.76, 1.17)
Fatal Stroke	308	0.4	0.99 (0.78, 1.24)

Fig 4A. MACE By Subgroups

MACE	HR (95% CI)	p-int
Overall	**0.91 (0.87, 0.96)**	
ASCVD		0.60
Yes	0.92 (0.88, 0.97)	
No	0.90 (0.82, 0.99)	
Prior MI		0.35
Yes	0.90 (0.84, 0.96)	
No	0.93 (0.88, 0.98)	
Diabetes		0.40
Yes	0.91 (0.86, 0.95)	
No	0.95 (0.85, 1.06)	
Hx of HF		0.20
Yes	0.94 (0.88, 1.00)	
No	0.90 (0.84, 0.95)	
CKD		0.76
Yes	0.91 (0.85, 0.98)	
No	0.92 (0.87, 0.98)	
Albuminuria		0.31
Yes	0.90 (0.84, 0.96)	
No	0.94 (0.87, 1.02)	

Fig 4B. CV Death By Subgroups

CV Death	HR (95% CI)	p-int
Overall	**0.86 (0.81, 0.92)**	
ASCVD		0.94
Yes	0.86 (0.80, 0.93)	
No	0.86 (0.76, 0.97)	
Prior MI		0.59
Yes	0.85 (0.76, 0.94)	
No	0.88 (0.81, 0.95)	
Diabetes		0.62
Yes	0.86 (0.80, 0.92)	
No	0.88 (0.77, 1.00)	
Hx of HF		0.32
Yes	0.88 (0.81, 0.95)	
No	0.83 (0.74, 0.93)	
CKD		0.96
Yes	0.87 (0.79, 0.95)	
No	0.86 (0.79, 0.94)	
Albuminuria		0.02
Yes	0.80 (0.72, 0.88)	
No	0.99 (0.89, 1.11)	

RESULTS (Continued)

- Overall, 80% had DM, 36% had HF, 37% had eGFR <60 mL/min/1.73m^2; 59% had established ASCVD (trial-specific definition) with 29% having prior MI at baseline.
- A total of 7,976 patients experienced MACE, with 4,148, 2,819 and 2,220 experiencing CV death, MI or stroke during f/u (ranging from 1.3-4.2 y).
- SGLT2i reduced the risk of MACE (HR 0.91 [0.87-0.96], p<0.0001), with consistent Rx effect across all trial types (I^2 = 0%) (**Fig 1**).
- Benefit driven primarily by a reduction in CV death (HR 0.86 [0.81-0.92], p<0.0001), with no clear effect on MI in the overall population (HR 0.95 [0.87-1.04], p=0.29), and no effect on stroke (HR 0.99 [0.91-1.07], p=0.77) (**Fig 2**).
- Reduction in CV death driven primarily by a reduction in HF death & SCD, without clear effect on fatal MI or stroke (**Fig 3**).
- Rx effects on MACE were consistent across subgroups (**Fig 4A**), with generally consistent effects on CV death with possible exception of albuminuria (**Fig 4B**).

CONCLUSIONS

- SGLT2i consistently reduce the risk of MACE across a broad range of patient populations (irrespective of ASCVD, DM, kidney function).
  - Driven primarily by reduction in CV death, particularly HF death & SCD, without clear effect on MI or stroke.
- These data may help inform the selection of SGLT2i therapies across the spectrum of cardiovascular-kidney-metabolic disease.

DISCLOSURE OF FACULTY RELATIONSHIPS:
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