香港中文大學
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香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Impact of SGLT2 inhibitors on CV outcomes among 19,550 diabetic patients with prior MI & stroke: Hong Kong-wide observational cohort study

Dr Wen SUN, Post-doc Fellow
Division of Cardiology, Department of Medicine and Therapeutics,
Prince of Wales Hospital & Heart & Vascular Institute,
The Chinese University of Hong Kong, Hong Kong

Background & Research Gap

- **SGLT2i & MI:**

➢ DECLARE-TIMI 58 trial:

  ➢ Dapagliflozin reduced risk of MACE by 16% in patients with prior MI but no effect in those without history of MI

  ➢ Greater benefit for MACE within 2 years after last MI.

- **SGLT2i & stroke:**

➢ CREDENCE trial:

  ➢ Ischemic stroke (HR, 0.88 [0.61-1.28]; n=111),

  ➢ Hemorrhagic stroke (HR, 0.50 [0.19-1.32]; n=18).

➢ CANVAS trial:

  ➢ no effect on ischemic stroke (HR, 0.95 [0.74-1.22]; n=253)

  ➢ hemorrhagic stroke (HR, 0.43 [0.20-0.89]; n=30).

Background & Research Gap

What is known?

- SGLT2i reduce the risk of MACE in patients with diabetes and ASCVD, of which the benefit seems more marked in patients with history of MI.

What is unknown?

- Protective effect of SGLT2i on haemorrhagic stroke was based on small number of events in RCT, therefore unpowered to conclude.
- RCT: only canagliflozin was investigated, what about dapagliflozin and empagliflozin? Inter-SGLT2i variation?
- RCT: enrolment criteria varied across studies. DM+CKD, DM + risk factors of ASCVD. What if DM + history of stroke?

Study design

- Retrospective analysis of consecutive patients with type 2 diabetes with history of cardiovascular events (MI or ischemic stroke)
- 16 public hospitals in Hong Kong between January 2015 and July 2020
- Patients with or without SGLT2i exposure were compared
- Outcome of interest: CV death, recurrent MI or stroke
- Outcomes of patients with an index (i) MI compared with (ii) stroke

Results

- 19,550 patients included, divided into 2 cohorts: post-MI & post-stroke
- Percentage of SGLT2i users:
  - 10.1% (n=832/8,230) of MI cohort (mean age 79.4±12.1, female 43.6%)
  - 3.1% (n=355/11,320) of stroke cohort (mean age 79.8±11.3, female 48.4%)
- Follow-up duration:
  - MI cohort with a median follow-up of 2.5 (IQR: 0.2-4.9) years (25,978 person-years)
  - stroke cohort with a median follow-up of 3.4 (IQR: 1.0-5.2) years (38,873 person-years)

Baseline characteristics

Demographics	MI cohort (n=8,230)			Stroke cohort (n=11,320)		
	SGLT2i users (n=832)	Non-users (n=7,398)	P value	SGLT2i users (n=355)	Non-users (n=10,965)	P value
Age	67.5±10.1	80.7±11.6	<0.01	70.9±10.0	80.1±11.2	<0.01
Female	19.5% (162)	46.4% (3,429)	<0.01	42.8% (152)	48.6% (5,327)	0.03
CHF	17.5% (146)	20.2% (1,494)	0.07	11.8% (42)	17.9% (1,959)	<0.01
Hypertension	89.3% (743)	36.3% (2,688)	<0.01	83.9% (298)	32.2% (3,536)	<0.01
Dyslipidaemia	40.6% (338)	71.4% (5,281)	<0.01	96.9% (344)	66.1% (7,251)	<0.01

Baseline characteristics (cont'd)

Non-diabetic medications	MI cohort (n=8,230)			Stroke cohort (n=11,320)		
	SGLT2i users (n=832)	Non-users (n=7,398)	P value	SGLT2i users (n=355)	Non-users (n=10,965)	P value
Antiplatelet	20.8% (173)	55.4% (4,095)	<0.01	38.9% (138)	45.3% (4,968)	0.02
Statin	26.7% (222)	71.4% (5,281)	<0.01	96.6% (343)	66.1% (7,251)	<0.01
ACEI/ARB	7.2% (60)	36.3% (2,688)	<0.01	11.5% (41)	32.2% (3,536)	<0.01
Beta blocker	17.8% (148)	16.0% (1,180)	0.17	27.6% (98)	16.1% (1,768)	<0.01

Baseline characteristics (cont'd)

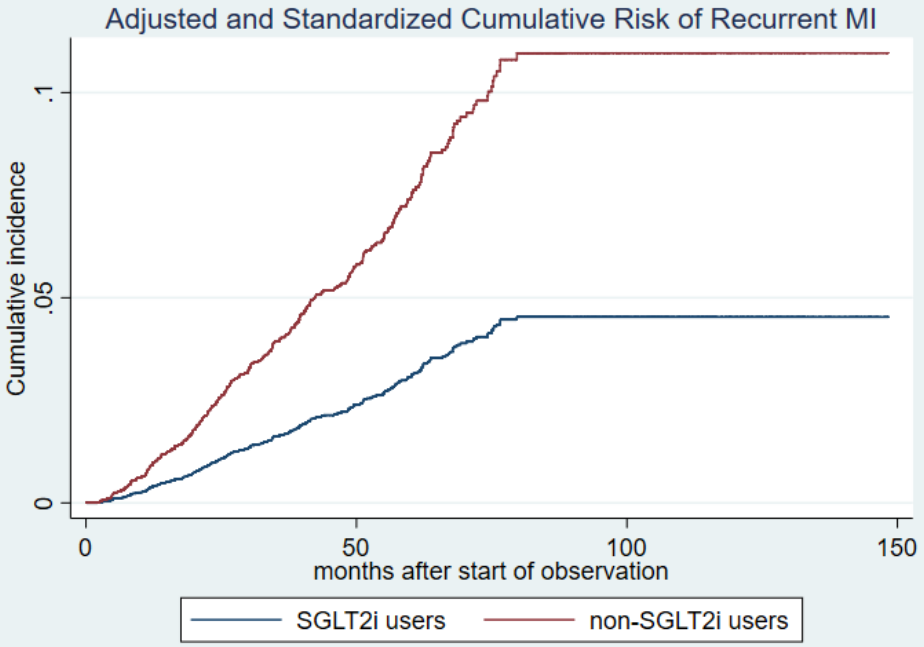
Diabetic medications	MI cohort (n=8,230)			Stroke cohort (n=11,320)		
	SGLT2i users (n=832)	Non-users (n=7,398)	P value	SGLT2i users (n=355)	Non-users (n=10,965)	P value
Insulin	8.8% (73)	31.4% (2,326)	<0.01	21.4% (76)	20.1% (2,199)	0.53
Acarbose	0.8% (7)	0.8% (60)	0.93	3.9% (14)	0.7% (81)	<0.01
Glitazone	1.2% (10)	0.6% (46)	0.05	2.8% (10)	0.6% (68)	<0.01
Gliptin	1.0% (8)	13.1% (969)	<0.01	1.4% (5)	9.4% (1,028)	<0.01
SU	34.0% (283)	53.7% (3,971)	<0.01	73.5% (261)	55.4% (6,080)	<0.01
GLP-1	0	0.1% (5)	0.59	0	0.0% (1)	0.97
Metformin	38.9% (324)	62.0% (4,586)	<0.01	93.0% (330)	76.8% (8,422)	<0.01

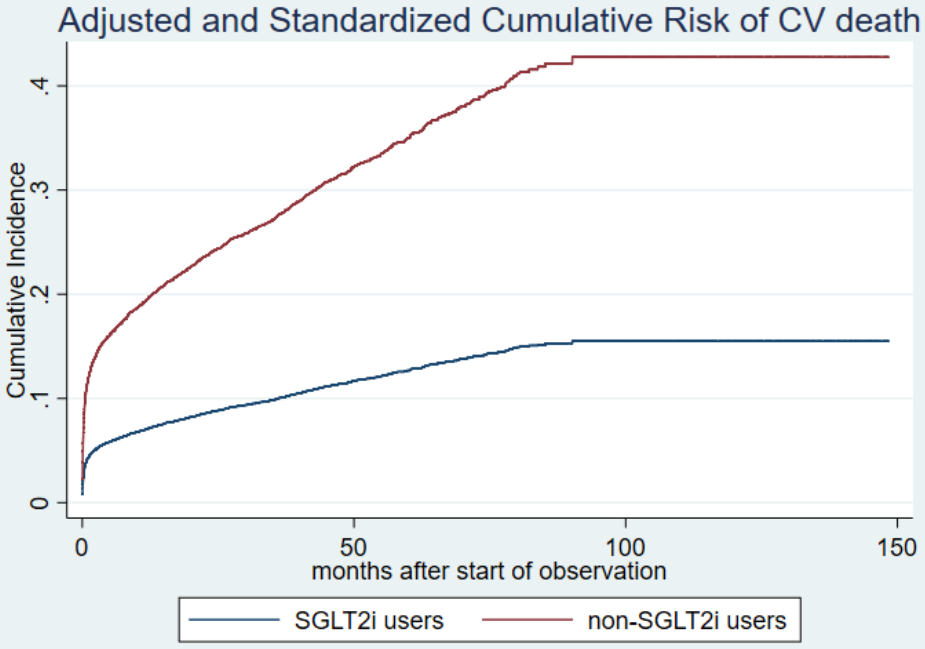
Effect of SGLT2i on outcomes

- MI cohort:

Reduction in risk of recurrent MI (AHR 0.41 (95% CI (0.18-0.97))

Reduction in risk of CV death (AHR 0.36 (95% CI (0.19-0.68))





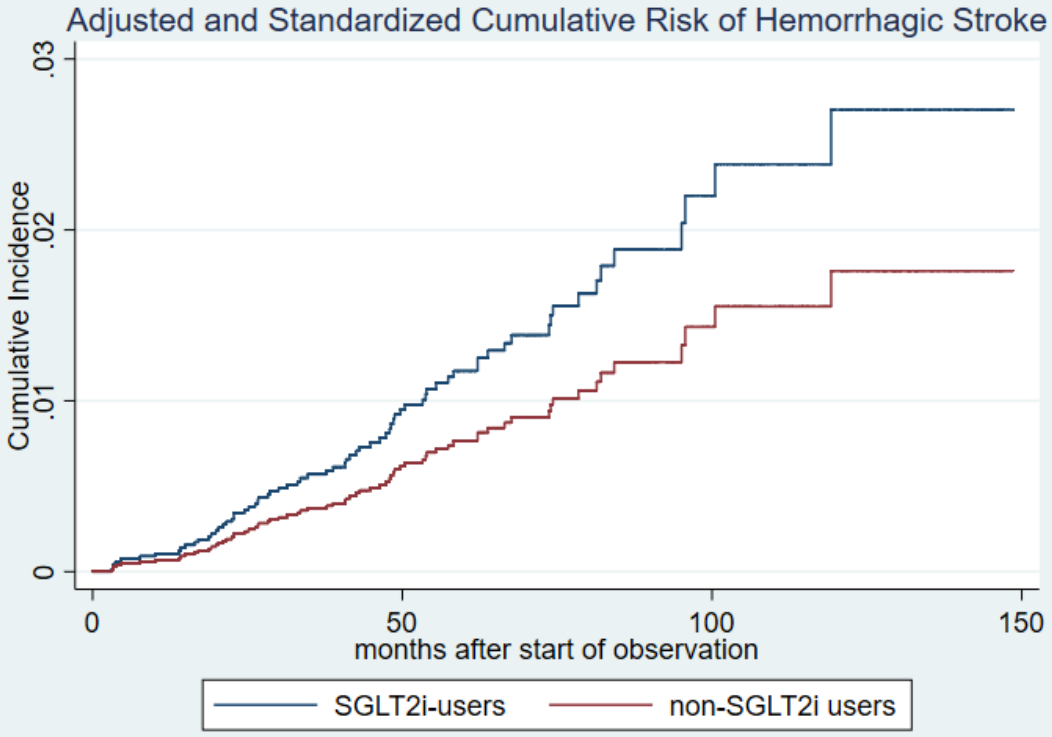
Effect of SGLT2i on outcomes

- Stroke cohort:

No difference in recurrent ischemic stroke (AHR 0.60 (95% CI (0.22-1.65))

No difference in CV death (AHR 0.69 (95% CI (0.34-1.41))

Higher risk of hemorrhagic stroke (AHR 1.51 (95% CI (1.01-7.80), P=0.049)



Limitation

MI cohort:

- RCTs suggested clinical benefit to heart failure hospitalization from SGLT2i was seen early, with time to effect reaching statistical significance being within 2 weeks from randomization, and sustained for up to 2 years. We observed superior benefit from SGLT2i in the MI cohort. However, the time to effect was not determined.
- Baseline information on index MI treatment was not collected.

Limitation (cont'd)

Stroke cohort:

- Study demonstrated inconsistent result, compared to CREDENCE and CANAS trials, with different inclusion criteria (CREDENCE: DM+CKD; CANAS: DM+risk factor of ASCVD),SGLT2i agents(canagliflozin vs. dapa/empagliflozin), and different event of interest (recurrent vs. first attack).
- Number of ICH in SGL2i users among the post-stroke cohort was few (n=14/355 in SGLT2i users, n=57/10,965 in non-users), producing a wide 95% CI (unpowered to conclude).
- Index events of the stroke cohort were mix of ischemic and hemorrhagic stroke, without discriminative analysis on recurrent of IS/ICH.
- Causes of ischemic stroke were not classified (embolic vs. non-embolic).
- SGLT2i handled as time-dependent variable, time from index-event to SGLT2i initiation contributing to non-SGLT2i group, however, the risk of recurrency after index-event changed over time.

Conclusions

- We observed superior cardiovascular outcomes benefits with SGLT2i among diabetic patients with history of myocardial infarction compared to ischemic stroke.
- Observation of increased hemorrhagic stroke risk among SGLT2i users warrants further studies.