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BCS Editorial

Sodium-glucose Co-transporter-2 (SGLT2) inhibitors and use in patients with acute coronary syndromes: The 5th Paradigm shift?

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Take Home Messages

- Benefits of SGLT2is in patients with type 2 diabetes mellitus (T2DM) and stable atherosclerotic cardio-vascular disease (ASCVD) are established, however, their role in acute coronary syndrome is unclear.
- There is growing evidence showing improved outcomes when initiated early post-ACS in patients with T2DM and possibly in non-diabetic patients. However, safety profile not yet clear.
- Ongoing research, including randomized controlled trials, are currently underway to assess this and potential role in patients without diabetes.
- If proven to be safe with improved outcomes, SGLT2is will lead to significant change in management of patients with ACS, especially those not deemed appropriate for intervention.

Introduction

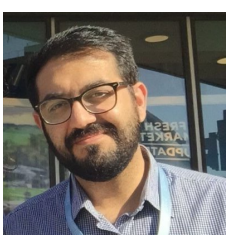
Sodium-glucose co-transporter 2 inhibitor (SGLT2i) precursors were discovered in 1835 and glycosuric effects confirmed in 1886. Subsequently, there have been four paradigm shifts in the use of SGLTIs as eloquently summarised by Eugene Braunwald (1). These medicines reduced cardiovascular mortality and development of heart failure in patients with type 2 diabetes (T2DM) and cardiovascular disease (2–4). Additionally, similar benefits were seen in patients with heart failure (reduced and preserved ejection fraction), irrespective of diabetes, and in patients with chronic kidney disease (5–9). The benefits and optimal initiation of SGLTIs in patients with acute coronary syndrome (ACS) are still not proven. Could this represent the fifth paradigm shift in the use of SGLTIs?

SGLT2is in acute coronary syndromes

Landmark trials and exclusion of patients with ACS

The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG) outcome trial was the first to assess safety of Empagliflozin in patients with T2DM and noted significant reduction in hospitalisation for heart failure, cardiovascular and overall deaths in the SGLT2i group (2). Subsequent trials performed on patients with atherosclerotic cardiovascular disease (ASCVD), and later in patients with heart failure, with reduced and preserved left ventricular systolic function, irrespective of diabetes status, found similar benefits (3–7).

About the author



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Sub-study analysis showed that patients with T2DM and previous MI, in whom SGLT2is were started with in two years of index event, had greater reduction in cardiovascular death, MI and stroke. In other words, the earlier start the greater the benefit (2,4,10,11). However, patients with ACS or myocardial infarction (MI) were excluded, with minimum time from index event to enrolment ranging from 8 weeks to 3 months. Important trials looking at SGLT2i use in ASCVD and heart failure are summarised in **Table 1** (2-4, 12) and **Table 2** (5,6,8,13,14) respectively. Therefore, the impact and safety of SGLT2i initiation in the very early phase post-MI could not be elicited from these trials.

Table 1: Sodium-Glucose co-transporter 2 inhibitors in type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

Trial/Study Name	Trial Design	Key Inclusion criteria	Number of patients	eGFR cut off *	Key ACS Exclusion criteria	Primary outcome event	Results
EMPA-REG OUTCOME 2015 (2) (Empagliflozin)	Double blind Randomised controlled trial	T2DM and established ASCVD	7020	30	ACS within 2 months prior to informed consent	Composite of CVD, Nonfatal MI and Nonfatal CVA	Significant reduction in CVD (3.7% vs 5.9%), HHF (2.7% vs 4.1%) and death from any cause (5.7% vs 8.3%)
CANVAS 2017 (3) (Canagliflozin)	Single Blind Randomised Controlled trial	T2DM and ≥30 years & symptomatic ASCVD or ≥50 & additional risk factors.	4330	30	ACS or re-vascularisation within 3 months prior to screening	Composite of CVD, Nonfatal MI and Nonfatal CVA	Significant reduction in primary outcome event rate in patients taking Canagliflozin (26.9 vs 31.5 participant event/1000 patient years)
DECLARE TIMI 58 2018 (4) (Dapagliflozin)	Double blind Randomised controlled trial	T2DM with established ASCVD or multiple risk factors including dyslipidaemia hypertension or active smoking	17160	60 (CrCL)	ACS within 8 weeks prior to randomisation	Safety outcome of adverse cardio-vascular events, cardio-vascular death and HHF	Lower incidence HHF or CVD (4.9% vs 5.8%), mainly driven by HHF
VERTIS 2020 (12) (Ertugliflozin)	Double blind Randomised controlled trial	T2DM and ≥40 years or older and established ASCVD	8246	30	ACS or re-vascularisation within 3 months prior to screening or between screening and randomisation	Time to first occurrence of composite of CVD, Nonfatal MI and Nonfatal CVA	Ertugliflozin was non-inferior to Placebo. However, no improvement secondary outcome of HHF, incidence of CVD or improvement in renal composite outcome

ACS = Acute coronary syndrome; ASCVD = Atherosclerotic cardiovascular disease; CABG = Coronary artery bypass graft; CANVAS = Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes; CrCl = Creatinine clearance; CVA = Cerebrovascular accident; CVD = Cardiovascular death; DECLARE = Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes; DKA = Diabetic ketoacidosis; EMPA-REG = Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; HHF = Hospitalisation for heart failure; LVEF = Left ventricular ejection fraction; MI = Myocardial infarction; NYHA = New York Heart Association; T2DM = Type 2 diabetes mellitus; VERTIS = Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes

** (ml/min/1.73/m2) for eGFR*

Table 2: Sodium-Glucose co-transporter 2 inhibitors in heart failure with and without type 2 diabetes mellitus

Trial/Study Name	Trial Design	Key Inclusion criteria	Number of Patients	eGFR cut off*	Key ACS Exclusion criteria	Primary outcome event	Results
DAPA HF 2019(5) (Dapagliflozin)	Double blind Randomised controlled trial	NYHA II-IV and LVEF<40%	4744	30	ACS within 12 weeks prior to enrolment	Composite of CVD, HHF or urgent review for HF	Significant reduction in primary endpoint (16.3% vs 21.2%), with and without DM
EMPEROR Reduced 2020(6) (Empagliflozin)	Double blind Randomised controlled trial	NYHA II-IV and LVEF<40%	3730	20	MI or CABG in 3 months prior to participation	Individual and composite of CVD and HHF	Significant reduction in incidence of primary end point in Empagliflozin group (19.4% vs 24.7%), with and without DM
EMPEROR Preserved 2021(14) (Empagliflozin)	Double blind Randomised controlled trial	NYHA II-IV and LVEF>40%	5988	20	MI or CABG in 3 months prior to participation	CVD or HHF	Significant reduction in incidence of primary end point in Empagliflozin group (13.8% vs 17.1%), with and without DM
SOLOIST 2021(8) (Sotagliflozin)	Double blind Randomised controlled trial	T2DM with admission or urgent review for heart failure	1222	30	ACS within 3 months of index procedure to randomisation	CVD, HHF or urgent review for HF	when started at admission or within 3 days of discharge, resulted in significant reduction incidence of primary end point (51 vs 76.3 events per 100 patient years)
DELIVER 2022(13) (Dapagliflozin)	Double blind Randomised controlled trial	NYHA II-IV and LVEF>40%	6263	25	ACS, PCI or CABG within 12 weeks of enrolment	Composite of CVD, HHF or urgent review for HF	Significant reduction in primary endpoint (16.4% vs 19.5%), with and without DM

ACS = Acute coronary syndrome; ASCVD = Atherosclerotic cardiovascular disease; CABG = Coronary artery bypass graft; CrCl = Creatinine clearance; CVA = Cerebrovascular accident; CVD = Cardiovascular death; DAPA HF = Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction; DELIVER = Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction; DKA = Diabetic ketoacidosis; DM = Diabetes mellitus, EMPEROR Preserved = Empagliflozin in Heart Failure with a Preserved Ejection Fraction; EMPEROR Reduced = Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure; HF = Heart failure; HHF = Hospitalisation for heart failure; LVEF = Left ventricular ejection fraction; MI = Myocardial infarction; NYHA = New York Heart Association; PCI = Percutaneous coronary intervention; SOLOIST = Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure; T2DM = Type 2 diabetes mellitus.
** (ml/min/1.73/m2) for eGFR*

Current evidence for SGLT2i use in ACS

Data to support early SGLT2i use post-MI in patients with diabetes is still lacking and limited to small observational studies or trials assessing surrogate parameters of cardiac function. This is even more deficient in patients without diabetes.

With regards to clinical events and outcomes from early SGLT2is use, one retrospective, observational study assessed 198 patients with T2DM and ACS. Sixty six patients were taking SGLT2i at discharge while 132 were not. Patients in the former group had reduced hospitalisation for MI and sudden cardiac death, with a mean follow up period of 23.5 ± 15.7 months (15). However, this was a small study and patients on SGLT2is were only compared to those who were not on this treatment and there was no comparison to patients who might have been started at a later date, the latter being more likely in

current clinical practice.

Studies have suggested improvement and stabilisation in surrogate markers of cardiac function. A double-blinded randomised controlled trial compared the effects of Empagliflozin with placebo, when started within 72 hours of percutaneous coronary intervention for MI in both diabetic (T2DM) and non-diabetic patients. The study demonstrated significant reduction in NT pro-BNP levels over 26 weeks evident within 12 weeks with favourable cardiac remodelling and significant early improvements in left ventricular systolic and diastolic function and reduction in end diastolic volume in the Empagliflozin group (16,17). Another non-randomised study with 44 participants assessed the impact of SGLT2is on left atrial remodelling in diabetic patients with acute MI. Empagliflozin was initiated prior to discharge and resulted in improved left atrial function (17).

Similarly, Shimizu *et al.* randomised 96 patients with T2DM to either Empagliflozin or placebo 2 weeks after MI and identified that patients taking SGLT2i had reduced cardiac sympathetic and increased parasympathetic activity, thereby possibly reducing the chances of arrhythmias which may result in sudden cardiac death (18). This points to the possible role of early SGLT2i therapy given patients are most vulnerable to arrhythmias and complications in the immediate post MI period. However, it is still unproven if improvement in these surrogate markers translate to clinically significant outcomes.

From the studies above, it can be noted that the current data on early SGLT2i use is from observational studies or trials to assess myocardial function or stability, all with small sample sizes and in diabetic patients with only one study with non-diabetic participants (16). Whether these trials translate into substantial improvement in clinical end points for patients with and without T2DM is still unclear.

Safety of SGLT2is

Evidence of safety of early use of SGLT2is in ACS is lacking. These medicines are usually tolerated well in stable patients. Most common side effects include urinary and genital tract infections and are similar across trials for respective SGLT2is apart from canagliflozin. The Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS) trial showed increased incidence of bone fracture or amputations with canagliflozin but the risk was similar of both adverse events in the Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE) trial, whereas diabetic ketoacidosis (DKA) was significantly greater with canagliflozin than placebo in the latter trial but not the former (**Table 3**) (2–6,8,11-13,19,20-23). There is a risk of development of euglycemic DKA in patients with acute illness (24). This may be missed given the usual first marker of the condition (hyperglycaemia) may not be present, leading to delayed treatment.

With regards to being initiated concomitantly with other medications for secondary prevention, there is a risk that it may lead to a significant drop in blood pressure which may be harmful especially in elderly patients. This along with higher rates of hypoglycaemia were noted when Sotagliflozin was commenced at discharge or within 3 days in patients admitted with heart failure (8). However, other evidence shows early initiation is safe and the rate of the above complications did not vary significantly between those that were treated with SGLTis and those that were not (16). More evidence is needed to provide reassurance especially for use in the elderly population.

Next steps

Two international large randomised controlled trials are currently underway to answer some of the questions above. The aim of the "Dapagliflozin Effects on Cardiovascular Events in Patients with an Acute Heart Attack" (DAPA-MI) and "A Study to Test Whether Empagliflozin Can Lower the Risk of Heart Failure and Death in People Who Had a Heart Attack" (EMPACT-MI) is to assess the impact of early SGLT2i therapy post MI on cardiovascular outcomes. Whilst DAPA-MI excludes patients with diabetes, EMPACT MI allows participation of diabetic and non-diabetic patients (**Table 4**) (25,26). This is important as diabetic patients are at greater risk of complications such as urinary tract infections and DKA. Additionally, safety and efficacy in type 1 DM will remain unanswered and will need more trials to assess this aspect. However, if proven safe and effective these trials will pave the way for greater use of SGLT2i in patients with ACS.

Table 3: Adverse events associated with various Sodium-Glucose co-transporter 2 inhibitors.

SGLT2 inhibitor	Adverse events with significantly higher incidence in SLT2i than placebo group	Adverse events with no significant difference in incidence between SGLT2i and placebo group
Canagliflozin (3,19,20)	Amputations of toes, feet and lower limbs (6.3 vs 3.4/1000 patient years) Bone Fractures (15.4 vs 11.9 / 1000 patient years) (CANVAS trial) Diabetic Ketoacidosis (2.2 vs 0.2 per 1000 patient years in CREDENCE)	Urinary / genital tract infection Hypoglycaemia Hyperkalaemia Acute kidney injury Pancreatitis Diabetic ketoacidosis (CANVAS) Amputations and bone fractures (CREDENCE trial)
Ertugliflozin(12)	Genital infections (men and women) Amputations (2.1% vs 1.6%) Diabetic ketoacidosis (0.4% vs 0.1%)	Urinary tract infections Hypoglycaemia Hypovolemia Acute kidney injury Pancreatitis Bone Fractures
Dapagliflozin (4,5,11,13,21)	Amputation Diabetic ketoacidosis (0.3% vs 0.1%) Genital infection (0.9% vs 0.1%)	Hypoglycaemia Bone Fracture Volume depletion Urinary infections Acute Kidney injury
Empagliflozin (2,6,22,23)	Genital infections (6.4% vs 1.8%) Urosepsis (0.4% vs 0.1%) Urinary tract infections (4.9% vs 4.5%) Hypotension (10.4% vs 8.6%)	Hypoglycaemia Diabetic ketoacidosis Bone Fracture Volume depletion Acute Kidney injury Amputations
Sotagliflozin(8)	Diarrhoea (6.9% vs 4.1%) Severe hypoglycaemia (1.5% vs 0.3%) Genital infections (0.8% vs 0.2%)	Urinary tract infections Hyperkalaemia Acute Kidney injury hypoglycaemia Amputation Volume depletion Bone fractures

CANVAS: Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes, CREDENCE: Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy.

Table 4: Current ongoing trials of Sodium-Glucose co-transporter 2 inhibitors in patients with acute coronary syndrome

Trial/Study Name	Trial Design	Key Inclusion criteria	Number of patients	Key ACS Exclusion criteria	Primary outcome event
DAPA MI Ongoing(26) (Dapagliflozin)	Double blind Randomised controlled trial	MI at high risk of developing heart failure and without DM (Enrolled at admission or within 10 days of MI)	6400 (Target)	ACS at admission or within 10 days to be enrolled in - inclusion criteria (Excluded if MI>10 days or eGFR <20 ml/min/1.73/m2)	Composite of CVD and HHF
EMPACT-MI Ongoing(25) (Empagliflozin)	Double blind Randomised controlled trial	MI at high risk of developing heart failure with and without DM (Enrolled at admission or within 14 days of MI)	6500 (Target)	ACS at admission or within 14 days to be enrolled in - inclusion criteria (Excluded if MI>14 days or eGFR <20 ml/min/1.73/m2)	Composite of HHF or all-cause mortality

ACS = Acute coronary syndrome; CVD = Cardiovascular death; DAPA MI = Dapagliflozin Effects on Cardiovascular Events in Patients With an Acute Heart Attack; DM = Diabetes mellitus; EMPACT MI = A Study to Test Whether Empagliflozin Can Lower the Risk of Heart Failure and Death in People Who Had a Heart Attack; HHF = Hospitalisation for heart failure; MI = Myocardial infarction.

Conclusion

Safety and efficacy of SGLT2i in patients with ASCVD and T2DM is established, however, optimal timing in patients with ACS in this group and benefits in those that are not diabetic are still not clear. Observational data suggests early initiation post ACS is safe and has better outcomes, however data from RCTs is needed to confirm this. If proven to show benefit, it will certainly provide an additional treatment option in management of patients with ACS. Truly exciting times lay ahead in the management of acute coronary syndromes with development of latest medical therapies, beyond the plumbing.

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