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The clinical impact of discontinuation of sodium-glucose transport protein 2 inhibitors (SGLT2is): A targeted literature review

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Introduction

- There are five SGLT2is that have been approved by the United States (US) Food and Drug Administration (FDA) to date with indications in type 2 diabetes mellitus (T2DM), T2DM with established cardiovascular disease (eCVD), heart failure (HF), and chronic kidney disease (CKD).[1]
- Despite approvals and access to SGLT2is since 2013 (T2DM),[1] proposed changes to reimbursement and formulary positioning could lead to lack of treatment initiation, or temporary or permanent discontinuation, of SGLT2is among individuals in whom these treatments are indicated.[2]
- The clinical implications following discontinuation of treatment with an SGLT2i are unclear; therefore, a review of the literature is warranted.

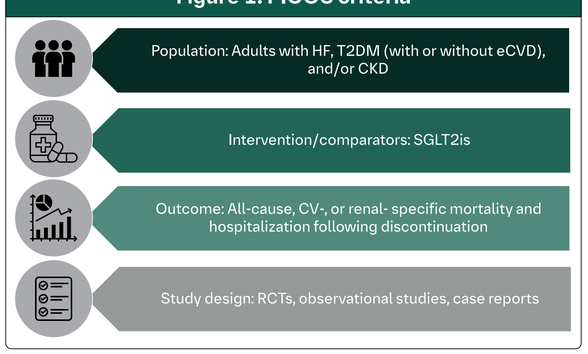
Objective

To summarize evidence on the risk of key clinical events following the discontinuation of treatment with an SGLT2i.

Methods

- Keyword searching – using terms for outcomes and interventions of interest – in PubMed and Google Scholar was performed to identify manuscripts published before September 2024.
- Articles were screened against the Population, Intervention, Comparator, Outcomes, Study design (PICOS) criteria guiding the targeted literature review (TLR; Figure 1).
- The risk (hazard ratios [HR], incidence rate ratios [IRR], 95% confidence intervals [CI]) and time to key clinical events following discontinuation were summarized.

Figure 1. PICOS criteria



Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; eCVD, established cardiovascular disease; HF, heart failure; SGLT2i, sodium-glucose transport protein 2 inhibitors; PICOS, population/intervention/comparator/outcomes/study design; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus.

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Results

- Nine studies were identified that matched the PICOS criteria: a pooled EMPEROR trials-based analysis,[3] three single-center studies,[4-6] three database analyses,[7-9] and two case reports (Table 1).[10,11]

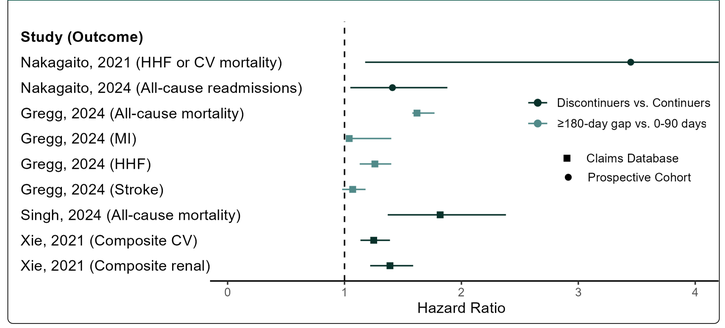
Table 1. Overview of included studies

Author, year	Country	Data source	Study period	Population	SGLT2i	Sample size	Discontinuation definition	Outcome following discontinuation
Clinical trial								
Packer, 2023[3]	Multinational	Pooled analysis	2017-2021	Chronic HF (NYHA II, III or IV) for ≥3 months	Empagliflozin	3,418	Prospective (per protocol) blinded withdrawal	CV mortality or HHF within 30 days
Cohort study								
Nakagaito, 2021[4]	Japan	Single center	2016-2019	T2DM ; starting an SGLT2i at index HHF	Any SGLT2is	30 discontinued; 56 continued	Cessation of treatment during index HHF; at discretion of physician	HHF or CV mortality within 12 months post HHF
Nakagaito, 2023[5]			2016-2021	Hospitalized for HF (mostly NYHA III/IV); starting an SGLT2i at index HHF		19 discontinued; 140 continued		HHF or CV mortality within 12 months post HHF
Nakagaito, 2024[6]			2016-2022			49 discontinued; 240 continued		All-cause readmissions within 12 months post HHF
Claims database								
Gregg, 2024[7]	US	VA	2005-2022	CKD; new SGLT2i or GLP-1 users	Any SGLT2is*	35,953 with ≥1 discontinuations	≥180-day gap vs. 0-90 days gap	All-cause mortality, MI, HHF, stroke within gap
Singh, 2024[8]			2013-2021	Hospitalized for T2DM; SGLT2i use pre-admission		30,569 discontinued; 5,936 continued	Cessation of treatment during hospitalization	All-cause mortality during hospitalization
Xie, 2021[9]			2015-2019	New antihyperglycemic users		7,998 discontinued; 28,640 continued	>90-day gap; within 6 months of initiation	Composite CV† or renal outcome‡ within gap
Case reports								
Amole, 2021[10]	US	-	2021	T2DM	Empagliflozin	1	Cessation of treatment after running out of medication	HF signs and symptoms within 1 month
Busuttil, 2024[11]			2024	End stage HF			Cessation of treatment after UTI	CV mortality after 20 days

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; GLP-1, glucagon-like peptide-1; HF, heart failure; HHF, hospitalization for heart failure; m, months; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; pts, patients; SGLT2i, sodium-glucose transport protein 2 inhibitors ; T2DM, type 2 diabetes mellitus; US, United States; UTI, urinary tract infection; VA, Veteran Affairs; yr, year. Footnotes: *99% of patients were taking empagliflozin; ‡Composite renal outcome: eGFR decline >50% from treatment initiation, end-stage kidney disease, or all-cause mortality; †Composite CV outcome: nonfatal MI, nonfatal stroke, HHF, or all-cause mortality.

- In the pooled analysis following prospective (per protocol) withdrawal:[3]
  - The annualized risk (events per 100 patient-years) of CV mortality or HHF was 17.0 (95% CI, 12.6–22.1) among patients withdrawn from empagliflozin and was 14.1 (95% CI, 10.1–18.8) among patients withdrawn from placebo.
  - The HR for the change in annualized risk among patients withdrawn from empagliflozin compared to patients on empagliflozin during the trial period was 1.75 (95% CI, 1.20–2.54; p=0.0034).
- In one case report, HF symptoms in a patient with T2DM within one month following empagliflozin discontinuation was described;[10] in the other case report, a patient experienced HF exacerbation leading to death 20 days following the discontinuation from treatment with empagliflozin.[11]
- The six additional studies (cohorts and claims databases) highlighted the risk of cardiorenal events, readmissions, and mortality following the discontinuation of treatment with an SGLT2i (Table 1, Figure 2).[4-9]
  - For example, compared to the discontinuation of treatment with an SGLT2i , continued use was associated with a reduced risk of CV (HR 0.80; 95% CI, 0.72-0.88) and renal (HR 0.72; 95% CI, 0.63-0.82) events in one database analysis (Figure 2);[9] and in another database analysis, was associated with a reduced risk of all-cause mortality among patients with CKD (HR 0.52; 95% CI, 0.47-0.56; Figure 2)[7] and T2DM (IRR 0.55; 95% CI, 0.42–0.73).[8]

Figure 2. Risk of key clinical events following the discontinuation of an SGLT2i in RWE



Abbreviations: CV, cardiovascular; HF, heart failure; HHF hospitalization for heart failure; MI, myocardial infarction; RWE, real world evidence; SGLT2i, sodium-glucose transport protein 2 inhibitors. Footnote: Signh et all reported on IRR.

Discussion and Limitations

- This synthesis highlights clinical events occurring after the discontinuation of treatment with an SGLT2i, to provide context for potential outcomes that may be observed among those with temporary or permanent discontinuation.[3]
- Limitations of this study include the targeted nature of the review (e.g., some relevant studies on this topic may have been missed).
- Identified studies have fundamental differences in inclusion criteria, discontinuation procedure, and outcome definitions that preclude any quantitative synthesis or comparison.
- Claims database analyses may be prone to bias due to unobservable confounding factors.
- Reasons for discontinuation were infrequently reported,[4-6] as this is difficult to ascertain in claims analysis.[7-9]
- Certain patient subgroups were more likely to discontinue treatment with an SGLT2is. For example, in one study Black and Hispanic patients were more likely to discontinue treatment, which may lead to health inequalities.[7]

Conclusion

- Evidence is emerging characterizing the clinical impacts following the discontinuation of treatment with an SGLT2i.
- A gap in the literature exists for studies quantifying the direct cost burden of SGLT2i discontinuation in the US.
- Formulary restrictions have the potential to negatively impact compliance and lead to increased healthcare resource use and associated costs.

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