research

SGLT-2 inhibitors and heart failure outcomes
p 185

Adverse events in surgical inpatients
p 187

Safety of SGLT-2 inhibitors for heart failure

ORIGINAL RESEARCH Linked database study

SGLT-2 inhibitors and mortality among patients with heart failure with reduced ejection fraction

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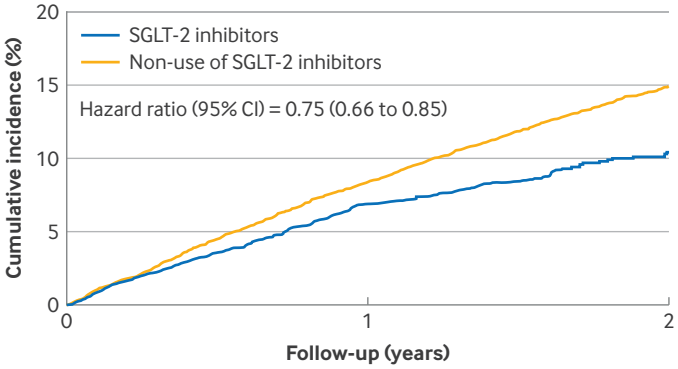
Study question Do sodium-glucose cotransporter-2 (SGLT-2) inhibitors reduce the risk of all cause mortality among patients with heart failure with reduced ejection fraction in real world clinical settings?

Methods This non-interventional database study included patients with heart failure with reduced ejection fraction (left ventricular ejection fraction ≤40%), aged ≥45 years, in Denmark (July 2020 to June 2023). It compared patients who started SGLT-2 inhibitors (dapagliflozin or empagliflozin) (n=6776) with those who remained on other standard-of-care heart failure drugs and did not use SGLT-2 inhibitors (n=14 686). The primary outcome was all cause mortality; secondary outcomes included cardiovascular mortality and admission to hospital for heart failure, both individually and combined. Analyses were adjusted using inverse probability of treatment weighting based on propensity scores.

Study answer and limitations
During follow-up, 374 deaths occurred among SGLT-2 inhibitor users (incidence rate 5.8 per 100 person years) and 1602 among non-users (8.5 per 100 person years). SGLT-2 inhibitor use was associated with a 25% lower risk of all cause mortality, compared with non-use of SGLT-2 inhibitors (weighted hazard ratio 0.75, 95% CI 0.66 to 0.85). Additionally, treatment with SGLT-2 inhibitors was associated



No at risk

SGLT-2 inhibitors		
6776	2818	550
Non-use of SGLT-2 inhibitors		
14 686	7581	4586

Weighted cumulative incidence curve for all cause mortality, truncated at two years owing to decreasing numbers of patients at risk and outcome events. CI=confidence interval; SGLT-2=sodium-glucose cotransporter-2

with a significantly lower risk of cardiovascular mortality but not of the composite outcome of cardiovascular mortality or hospital admission for heart failure or of hospital admission for heart failure alone. Despite multiple measures to enhance internal validity, unmeasured confounding cannot be ruled out.

What this study adds This study suggests that SGLT-2 inhibitors are effective in reducing mortality in routine clinical practice among patients with heart failure with reduced ejection fraction. The mortality benefit was seen in patients both with and without type 2 diabetes.

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COMMENTARY Drawing inferences from observational data with possible confounding

Heart failure is increasing in prevalence and is a major cause of morbidity and mortality worldwide,[1] with prevalence ranging from 1% to 3% of the general adult population in high income countries.[1] Limited data from low and middle income countries suggest high heart failure disease burden.[2 3] Heart failure with reduced ejection fraction, defined as a left ventricular ejection fraction of ≤40%, accounts for around 30-60% of heart failure in epidemiological studies.[1] Increasing evidence of the effectiveness of certain drugs to reduce mortality and morbidity in heart failure with reduced ejection fraction has led to strong recommendations for their use in clinical practice guidelines.[4 5] The foundational therapeutic agents for heart failure with reduced ejection fraction have been shown to improve survival, reduce the risk of readmission to hospital, and improve symptoms by targeting the renin-angiotensin-aldosterone and sympathetic nervous systems. In recent randomised controlled trials, the addition of a sodium-glucose cotransporter-2 (SGLT-2) inhibitor further reduced the risk of worsening heart failure and death from cardiovascular disease in patients with heart failure with reduced ejection fraction.[4 5] In their study, Svanström and colleagues add to this growing evidence by using real world administrative data to show a reduction in mortality but no change in heart failure related hospital admissions with SGLT-2 inhibitor use.[6]

The authors linked data in the Danish heart failure registry to the national civil registration system, including data for patients aged ≥45 years with a left ventricular ejection fraction of ≤40% treated from July 2020 to June 2023. They used a modified prevalent new user design,[7] with an intervention group including patients starting SGLT-2 inhibitors for a heart failure indication and a comparator group including patients without SGLT-2 inhibitors matched on time since diagnosis of heart failure. Results were adjusted using inverse probability of treatment weighting to account for differences in baseline characteristics. The primary outcome was all cause mortality, and secondary outcomes were a composite of cardiovascular mortality or hospital admission with heart failure and its components. The authors used proportional hazards regression to compare outcomes in the intervention and comparator groups. They reported a 25% relative risk reduction for all cause mortality and a 23% reduction in cardiovascular mortality but no change in the composite of cardiovascular mortality or hospital admissions due to heart failure associated with SGLT-2 inhibitor use compared with non-use.

Despite these limitations, these results provide assurance that no unexpected harm results from SGLT-2 inhibitors

Caveats of observational data

Given that observational data on treatment effectiveness are often confounded in ways that cannot be eliminated through risk adjustment, one must be careful in drawing conclusions.[8] Observational data can be useful in examining outcomes or subgroups that were too small to be adequately evaluated in randomised trials. If investigators can first show that the observational outcome is similar to that observed in similar patients in randomised trials, confidence in the observed result will be greater for other populations or other outcomes than for studies in which the investigators cannot reproduce the results of the clinical trials. If the clinical trial results cannot be reproduced, one must have a strong biological plausibility for why the observational studies, with their risk of confounding, are more accurate than the clinical trial results.

Unfortunately, the clinical trial data differ, as noted by Svanström and colleagues. In a meta-analysis of randomised trials of SGLT-2 inhibitors in patients with heart failure with reduced ejection fraction, all cause mortality was reduced, with an odds ratio of 0.87 (95% confidence interval 0.77 to 0.98), an effect size half that observed in the linked study.[9] By contrast, hospital admission was markedly reduced in the clinical trials (odds ratio 0.69, 0.62 to 0.78) but not in the registry. How does one reconcile these differences between the randomised controlled trials and observational studies? The authors suggest that their reliance on coding of heart failure for assigning a hospital admission due to heart failure may explain their lack of reduced admissions. Although coding is inferior to adjudication using the medical record, accuracy of coding would have to have been much poorer than has been reported to account for all of the difference.[10] Another possible explanation is that patients not treated with SGLT-2 inhibitors may have had non-heart failure disease that was more severe than their heart failure, whereas those treated had heart failure as the major condition. Although the investigators were able to match baseline demographic characteristics between the groups, the patients treated with SGLT-2 inhibitors may differ from those not treated in ways that were not considered or measured but that affect mortality, such as frailty. If risk adjustment was incomplete then these non-treated patients would have worse mortality (from non-cardiovascular causes) and be less likely to be admitted to hospital for heart failure (and presumably more likely to be admitted for non-heart failure conditions).

Despite these limitations, these results provide assurance that no unexpected harm results from SGLT-2 inhibitors when they are used for treatment of heart failure outside the clinical trial setting. Among practitioners, however, the potential for euglycaemic diabetic ketoacidosis, complexity of patients, and drug costs may lead to hesitancy to prescribe SGLT-2 inhibitors.[12] Robust implementation efforts should tackle barriers to prescribing.

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Surgical adverse events in the US

ORIGINAL RESEARCH Cohort study

Safety of inpatient care in surgical settings

Duclos A, Frits ML, Iannaccone C, et al

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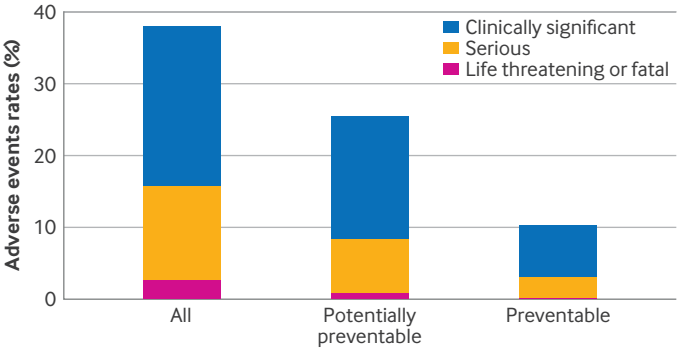
Study question What is the frequency of adverse events associated with perioperative care?

Methods In this multicentre retrospective cohort study, trained nurses and physicians comprehensively reviewed a randomly selected sample from 64 121 adult patients admitted for surgery in 11 hospitals across the US state of Massachusetts in 2018. Adverse events during inpatient perioperative care were classified as major if they resulted in serious harm requiring substantial intervention or prolonged recovery, involved a life threatening event, or resulted in death. Potentially preventable events were defined as those considered definitively, probably, or possibly preventable.

Study answer and limitations Among 1009 patients reviewed, adverse events were identified in 38.0% (95% confidence interval 32.6 to 43.4), with major adverse events occurring in 15.9% (12.7 to 19.0). Of 593 identified adverse events, 353 (59.5%) were potentially preventable and 123 (20.7%) were definitely or probably preventable. The most common adverse events were related to surgical procedures (n=292, 49.3%), followed by adverse drug events (n=158, 26.6%), healthcare associated infections (n=74, 12.4%), patient care events (n=66, 11.2%), and blood transfusion reactions (n=3, 0.5%). Adverse events were most frequent in general care units (n=289, 48.8%), followed by operating rooms (n=155, 26.1%), intensive care units (n=77, 13.0%), recovery rooms (n=20, 3.3%), emergency departments (n=11, 1.8%), and other in-hospital locations (n=42, 7.0%). Professions most involved were attending physicians (n=531, 89.5%), then nurses (n=349, 58.9%), residents (n=294, 49.5%), advanced level practitioners (n=169, 28.5%), and fellows (n=68, 11.5%). The study population was limited to Massachusetts hospitals in 2018, which may not fully represent hospitals at large.

What this study adds Adverse events were identified in more than one third of adult patients admitted to hospital for surgery, with nearly half of the events classified as major. Most of these events were potentially preventable. The findings suggest that adverse events remain frequent in perioperative care, causing substantial and preventable harm to patients.

SERGIO AZENHA/ALAMY



Severity of adverse events weighted rates for each admitted patient according to preventability. Severity was determined using an ascending ordinal classification. Adverse events were defined as clinically significant (caused unnecessary harm but resulted in rapid recovery), serious (caused harm that resulted in substantial intervention or prolonged recovery), life threatening (caused a potentially fatal situation that required immediate intervention), and fatal (resulted in death). Potentially preventable adverse events included adverse events that were assessed as definitely, probably, or possibly preventable. Preventable adverse events included adverse events that were assessed as definitely or probably preventable

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In late 1999, the US Institute of Medicine's report "To Err is Human: Building a Safer Health System" galvanised the nascent patient safety movement into action with its assertion that as many as 98 000 Americans died annually from medical error.[1] That alarming statistic was derived from the 1991 Harvard Medical Practice Study, a randomised chart review undertaken to create an evidence base for the controversy then raging around litigation against medical malpractice.[2] That study found that 3.7% of patients in a sample of hospital admissions in New York state had experienced serious adverse events, more than one fourth of which the researchers considered legally compensable. Overall, 48% of the events were associated with surgical procedures.

In their study, Duclos and colleagues set out to create an updated baseline for surgical adverse events in the US, broadly modeled on the original Harvard Medical Practice Study.[5] Data for Duclos and colleagues' study were derived from the 2023 SafeCare study, which used a "trigger" methodology to analyse a random sample of electronic inpatient records from 11 hospitals in Massachusetts.[6] In the subset of cases analysed for Duclos and colleagues' study, the authors identified adverse events in 38% (n=383/1009) of surgical admissions. Nearly half were classified as major, and more than two thirds as preventable.

Poor track record

Since the Colorado-Utah study, research examining surgical outcomes across specialties has been sparse. Duclos and colleagues' study is therefore a valuable contribution; but its findings are not encouraging. To date, around a dozen large studies have been conducted on medical harm in the US and globally, and almost all used some version of the screening

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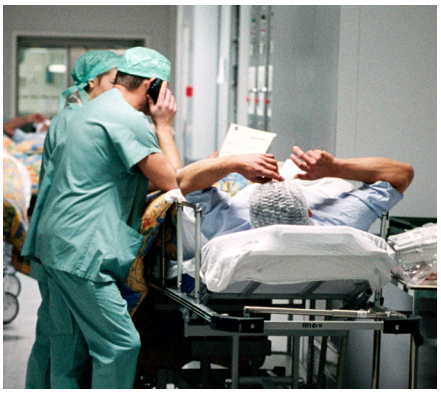

LOUISE OLIGNY/BSIP/ALAMY

Patients and families need to be empowered to weigh in on the accuracy of the accounts of their own care

methodology employed by the Harvard Medical Practice Study.[7 8] Comparison between studies is complicated by customisation and changes in the triggers used to flag events, but studies in the US have nevertheless produced remarkably consistent findings across the years. In 2010, studies of hospitals in Colorado and North Carolina found adverse event rates of 33% and 25%, respectively, with the North Carolina study showing no major improvement from 2002 to 2007.[9 10] Studies of Medicare patients by the US Health and Human Services Office of the Inspector General showed nearly unchanged rates of harm of 27% and 25% between 2008 and 2018, despite the 10 year difference.[11 12] Thus, over a period of some 17 years, medical harm may have continuously affected as many as one in three or one in four patients in US hospitals. In all these studies, surgery accounted for around one fourth of adverse events.

Patient safety at risk

Many reasons have been proposed for this failure to improve, among them a culture of disrespect, inadequate nurse staffing, ineffective implementation of proven strategies, and failure to take advantage of available technology that would allow real time detection and possibly prevention of adverse events.[13-16] All undoubtedly have played a part. The major omission in patient safety, however, is the patient. Although patient engagement is growing across other parts of healthcare, little progress has been made in including patients and families in the areas where they could contribute the most: co-creating their own history and unraveling the causes and effects of errors in their care. Information in the electronic medical records used to track adverse events is often incomplete, inaccurate, or recorded by overworked providers who may have little real knowledge of the patient's case.[5] Patients in the US can now view their medical records, a privilege not available in many countries, but they cannot comment on them, even when they spot obvious errors. When an adverse event occurs, patients and families are seldom interviewed, much less consulted, even if they are the sole witnesses. Confidential analyses of root causes and "disclosures" with confidentiality clauses may do more to hide problems about patient safety than to address them. Legal settlements silence entire swathes of people with non-disclosure agreements, and they prevent in-depth examination of the causes of harm.

Newly available tools such as large language models have the potential to transform patient safety by mining electronic records. But electronic records are only as good as the information they contain. If we are truly interested in advancing patient safety, patients and families need to be empowered to weigh in on the accuracy of the accounts of their own care and participate in finding solutions. Studies like the one by Duclos and colleagues are an important foundation for meaningful solutions, but those can only be found in tandem with patients and families.

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RETRACTION

Prioritising primary care patients with unexpected weight loss for cancer investigation: diagnostic accuracy study

This research article by Nicholson and colleagues (*BMJ* 2020;370:m2651 doi:10.1136/bmj.m2651; published in the print issue of 12 September 2020) has now been retracted by BMJ owing to the identification of an error in the authors' approach to the research. An updated version of this paper has been published in *The BMJ* (doi:10.1136/bmj-2024-080199). Please see the retraction notice (doi:10.1136/bmj.q1993) for more information.