

REVIEW ARTICLE

Preventing all-cause hospitalizations in type 2 diabetes with sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists: A narrative review and proposed clinical approach

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Abstract

Patients with type 2 diabetes (T2D) are at increased risk for hospital admissions, and acute hospitalizations are associated with a worse prognosis. However, outcomes related to all-cause hospital admissions (ACHAs) were often overlooked in trials that demonstrated the cardiovascular and kidney benefits of sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs). This review includes a contemporary literature summary of emerging data regarding the effects of SGLT2 inhibitors and GLP-1RAs on ACHAs. The role of SGLT2 inhibitors in preventing ACHAs was shown in exploratory investigations of several randomized controlled trials (RCTs) and was further supported by real-world evidence (RWE). However, the association between GLP-1RA use and lower ACHA risk was mainly shown through RWE, with minimal available RCT data. We also discuss the advantages and challenges of studying ACHAs. Finally, we propose an easily memorized (“ABCDE” acronym) clinical approach to evaluating T2D status and treatment in admitted patients, as they transition from hospital to community care. This systematic approach may assist clinicians in recognizing possible pitfalls in T2D management, thereby preventing subsequent hospitalizations and improving patient prognoses. While acute admission can sometimes be perceived as a management failure, it should also be viewed as an opportunity to take action to prevent the next hospitalization.

KEYWORDS

antidiabetic drug, diabetes complications, GLP-1 analogue, SGLT2 inhibitors, type 2 diabetes

1 | INTRODUCTION

Patients with diabetes comprise approximately a quarter of annual hospital admissions in the United States, and approximately 14% of hospitalization days are attributed to diabetes and its complications.¹

The estimated costs of diabetes-related preventable hospitalizations in the United States increase at a 1.6% annual rate, derived mainly from higher diabetes prevalence.² Cardiovascular-, infectious- and nervous-system-related aetiologies comprise the main portion of acute hospitalizations in patients with type 2 diabetes (T2D).^{3,4}

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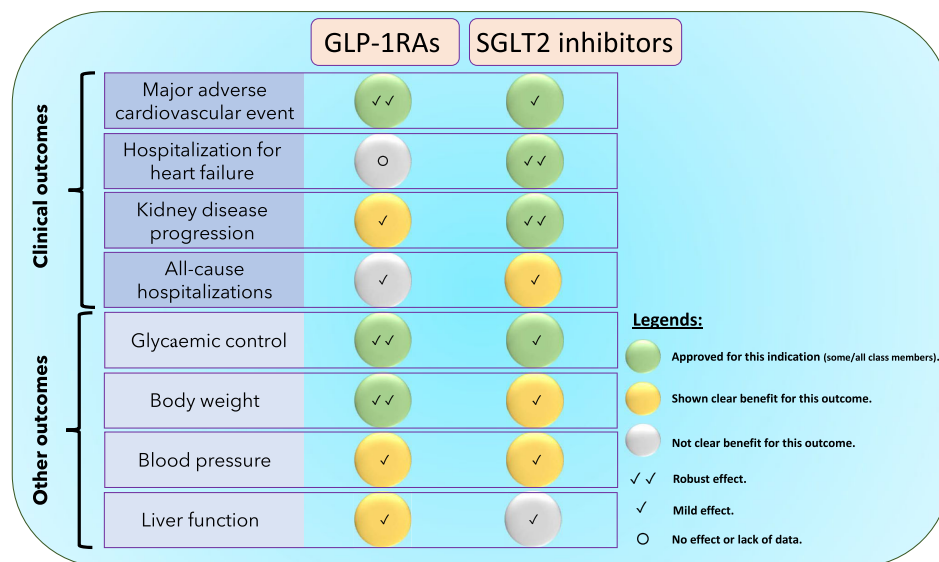


FIGURE 1 The effect of sodium glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs; diabetes-/disease-modifying drugs), on different cardiometabolic risk factors and clinical outcomes, including all-cause hospital admissions

However, the presence of diabetes is associated with a higher risk of hospitalizations for various other reasons. These include some that are not traditionally considered diabetes-related (eg, certain cancers and noninfectious noncancerous respiratory conditions).⁵ Recurrent hospitalizations are common in patients with diabetes and are associated with a worse prognosis.^{6–8} Thus, all-cause hospital admissions (ACHAs) serve as an indispensable marker for disease state and progression. Moreover, hospital admissions have significant implications for individual patients' quality of life and overall burden on healthcare systems and payers.²

Despite that, ACHA outcomes have been less studied relative to other adverse clinical outcomes, such as incidence of major adverse cardiovascular events (MACE), hospitalizations due to HF (hHF), all-cause mortality, among others. ACHA-based outcomes are often limited by lack of specificity, difficulty in sorting emergency versus elective hospitalizations, reporting inconsistencies, seasonal fluctuation and pandemics, alterations due to sociodemographic status, and regional variations in treatment approaches, healthcare systems and regulations. Endpoints related to ACHAs are not standardized and may include first or recurrent hospitalization event rate,^{3,4,9,10} percent of admitted patients,⁸ time to hospital admission,^{10,11} days-alive-and-out-of-hospital (DAOH), or percent of DAOH out of potential follow-up.⁸ These endpoints differ in how they address hospitalization duration or other competing risk events (eg, death). It is also challenging to assess hospitalization severity, which could be partly derived from length of stay or intensive care requirement. Furthermore, each endpoint may be applicable in different populations; DAOH, for example, is especially relevant in populations at high risk of recurrent hospitalization. Overall, the prognostic value and economic implications for each definition remain to be determined.

While older glucose-lowering agents (GLAs) had mostly glycaemic control properties, sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) exert additional benefits. Most importantly, the majority of them have clinical cardiovascular or kidney protective effects, earning them the term diabetes-/

disease-modifying drugs (DMDs)^{9,12–35} (Figure 1). Specifically, some GLP-1RAs protect from MACE (usually composed of cardiovascular death or nonfatal stroke or myocardial infarction)^{21,23,25,26,30} and SGLT2 inhibitors reduce hHF and improve kidney outcomes.^{9,13–19,27–29,36} Some evidence indicates that specific SGLT2 inhibitors also reduce MACE rate^{9,14,37} and GLP-1RAs reduce proteinuria and may improve kidney outcomes in T2D.^{22,24,38–40} GLP-1RAs were also shown to increase the likelihood of nonalcoholic steatohepatitis resolution.^{33,35} SGLT2 inhibitors were suggested to improve liver enzyme values in patients with T2D and non-alcoholic fatty liver disease (NAFLD).^{34,41} Of note, there is no clear evidence that SGLT2 inhibitors or GLP-1RAs improve neuropathy or retinopathy outcomes in patients with T2D. However, both DMDs were suggested to delay, to some degree, the onset of T2D in populations at risk.^{42,43}

This review aims to provide a contemporary summary of emerging exploratory data from randomized controlled trials (RCTs) and real-world evidence (RWE), indicating a role for SGLT2 inhibitors and GLP-1RAs in preventing ACHA outcomes, primarily in patients with T2D. Based on the findings, we outline a systematic clinical approach that could assist hospitalists and primary care practitioners in evaluating patients' diabetes status during the peri-discharge period.

2 | METHODS

This narrative review covers RCTs or RWE with comparable treatment arms, with either SGLT2 inhibitors or GLP-1RAs, that reported an outcome related to ACHA. An electronic search was carried out on January 5, 2022. The following terms were searched in PubMed: SGLT2 inhibitors all cause admissions; SGLT2 inhibitor all cause admissions; SGLT2 inhibitors “all-cause hospitalizations”; SGLT2 inhibitors “all-cause” “hospitalizations”; GLP-1 receptor agonists “all-cause hospitalizations”; GLP-1 receptor agonists all-cause hospitalizations; GLP-1 receptor agonists “all-cause” “hospitalizations”; GLP-1 receptor agonists “all-cause” “admissions”; GLP-1 receptor agonists all-cause admissions. The main

manuscripts and appendices of the cardiovascular and kidney outcome trials with SGLT2 inhibitors or GLP-1RAs were also searched. In addition, the papers linked to these studies in ClinicalTrial.gov were also scanned. Finally, papers from the personal library of the authors that are relevant to this topic were also included. Only articles published in English were considered.

3 | RESULTS

3.1 | SGLT2 inhibitors and all-cause hospital admissions

The associations of SGLT2 inhibitor use with risk of ACHA were tested in predefined and post hoc analyses of cardiovascular outcome trials (CVOTs) as well as some RWE (Table 1). Overall hospital admission was tested in a post hoc analysis of the EMPA-REG OUTCOME study, comprising patients with T2D and established cardiovascular disease (CVD). In that study, 13.7%, 8.9% or 6.2% had at least one hospitalization due to a cardiac disorder, infectious disease, or a nervous-system-related aetiology, respectively.⁴ Empagliflozin use was associated with a lower rate of both first (12% reduction) and total (17% reduction) all-cause hospitalization events.⁴ In a time-to-event analysis, the risk reduction for ≥ 3 , ≥ 4 , ≥ 5 or ≥ 6 ACHA events with empagliflozin compared with placebo was 21% (95% confidence interval [CI] 6-33), 34% (95% CI 17-48), 43% (95% CI, 22-58) or 53% (95% CI 30-69), respectively.^{4,10}

In the CANVAS programme, which included populations with high risk for or established CVD, the risk for any hospitalization, a predefined secondary outcome, was 0.94 (95% CI 0.88-1.00) in the canagliflozin-treated arm compared with placebo.⁹ In a post hoc analysis, there was an 8% (95% CI 2-14) reduction in the rate of acute hospitalization (first and recurrent) in canagliflozin compared with placebo, which seemed to be consistent in populations with high risk of CVD and those with established CVD ($P_{\text{interaction}} = 0.66$).³ Also in this study, the three most common hospitalization aetiologies were cardiac disorders (23.7% of all hospitalizations), infections and infestations (15.0%), and nervous system-related disorders (9.0%). The between-arm differences in risk for cardiac-, infectious-, and nervous-system-related hospitalizations were 0.81 (95% CI 0.75-0.88), 0.94 (95% CI 0.86-1.02) and 0.96 (95% CI 0.88-1.05), respectively.³

The SOLOIST-WHF study tested the SGLT2 + 1 inhibitor sotagliflozin in patients with T2D and a recent worsening of heart failure (HF); assessment of the number of DAOH was included in the protocol. This endpoint considers the length of all hospital admissions and the competing outcome of death. Numbers of DAOH were slightly higher in the sotagliflozin compared with placebo group (rate ratio 1.03 [95% CI 1.00-1.06]; $P = 0.027$). Compared with placebo, the sotagliflozin arm had fewer patients requiring recurrent hospitalization (22.1% vs. 16.3%, respectively; $P = 0.009$).⁸

Finally, in the EMPEROR-Preserved study, involving patients with HF and preserved ejection fraction (HFpEF; ejection fraction > 40%) with and without T2D, the number of ACHAs was a prespecified

secondary outcome. No significant difference was observed with empagliflozin versus placebo (hazard ratio [HR] 0.93 [95% CI 0.85-1.01]).³⁶

Data from RWE expanded the association between SGLT2 inhibitor use and lower risk of ACHA to broader populations with T2D. Furthermore, SGLT2 inhibitor use in real-world settings was associated with reductions in the number of emergency room and outpatient visits (Table 1).⁴⁴⁻⁴⁷ Importantly, these studies used an active comparator design. Thus, SGLT2 inhibitor initiators were at lower risk of ACHA compared with initiators of other GLAs, mainly dipeptidyl peptidase-4 (DPP-4) inhibitors.⁴⁴⁻⁴⁷

3.2 | GLP-1RAs and all-cause hospital admission

Adverse event reporting from the REWIND trial did not find a lower rate of patients with overall hospitalizations in the dulaglutide arm or placebo arm (41.7% and 42.6%, respectively; $P = 0.18$).²⁵ We are unaware of a more comprehensive analysis of hospitalization aetiologies or durations in CVOTs involving GLP-1RAs. A cohort study from 2007 found no difference in the rate of overall hospitalizations amongst exenatide users, compared with insulin.⁴⁸ However, two later studies found that patients with T2D initiating exenatide had a lower risk of overall hospitalizations compared with initiators of other GLAs⁴⁹ or when directly compared with insulin glargine.^{50,51} In another study, patients treated with basal insulin ($n = 6718$) who initiated a GLP-1RA were less likely to be hospitalized in the following year compared to those who started rapid-acting insulin (13.6% vs. 18.6%, respectively; $P < 0.0001$).⁵² However, no statistically significant difference between groups was observed in another study of a similar design involving a smaller sample of patients ($n = 1111$; 14.1% and 15.9% in the GLP-1RA and rapid-acting insulin arms).⁵³ A more recent cohort study found that liraglutide-adherent patients were less likely to be hospitalized than a matched non-adherent cohort.⁵⁴

3.3 | SGLT2 inhibitors compared with GLP-1RAs and ACHAs

Two RWE studies used inverse probability of treatment weighting to directly compare ACHA in patients treated with SGLT2 inhibitors or GLP-1RAs. In one study, patients who initiated empagliflozin ($n = 14148$) had a significantly lower risk for all-cause hospitalization compared to those initiating liraglutide ($n = 12\ 628$; HR 0.93 [95% CI 0.90-0.98]).⁵⁵ Another smaller study involved initiators of DPP-4 inhibitors ($n = 4762$), SGLT2 inhibitors ($n = 2492$) and GLP-1RAs ($n = 1982$). Compared with DPP-4 inhibitors, initiators of either SGLT2 inhibitors or GLP-1RAs had a lower risk for ACHA (HR 0.85 [95% CI 0.75-0.95] or HR 0.89 [95% CI 0.78-0.98], respectively). No significant difference was observed between SGLT2 inhibitor initiators compared with GLP-1RAs (HR 0.92 [95% CI 0.80-1.07]).⁴⁷

TABLE 1 Analysis from randomized controlled trials and real-world evidence testing the effect of diabetes-/disease-modifying drugs on all-cause hospitalizations

SGLT2 inhibitors or GLP-1RAs	RCT/RWE	Study	Participants and comparators	Effect on overall hospitalization (main findings)
SGLT2 inhibitors	RCT	CANVAS programme Neal, 2017 ⁹	Patients with T2D and risk for or established CVD. Canagliflozin (n = 5795 patients) vs. placebo (n = 4347 patients) Prespecified outcome	Risk of hospitalization for any cause with canagliflozin (118.7/1000 patient-years) compared with placebo (131.1/1000 patient-years); HR 0.94, 95% CI 0.88-1.00
	RCT	EMPA-REG OUTCOME McGuire, 2020 ⁴	Patients with T2D and established CVD. Empagliflozin (n = 4687) vs. placebo (n = 2333) Post hoc analysis	Lower rate of all-cause admission to the hospital with empagliflozin compared with placebo for the first events (rate ratio 0.88, 95% CI 0.81-0.96) and for total events (rate ratio 0.83, 95% CI 0.76-0.91). Similar findings in time to event analysis (HR 0.89, 95% CI 0.82-0.96)
	RCT	SOLOIST-WHF Szarek, 2021 ⁸	Patients with T2D and recent worsening due to HF. Sotagliflozin (n = 608 patients) vs. placebo (n = 614 patients) Prespecified analysis	Mean days alive and out of hospital was higher in sotagliflozin (rate ratio 1.03, 95% CI 1.00-1.06; P = 0.027) Patients with ≥1 hospitalization: Sotagliflozin, n = 234 (38.5%); placebo, n = 254 (41.1%); P = 0.30 Patients with ≥2 hospitalizations: Sotagliflozin, n = 99 (16.3%); placebo, n = 136 (22.1%); P = 0.009
	RCT	EMPEROR-preserved Anker, 2021 ^{3,6}	Patients with HFpEF, with and without T2D. Empagliflozin (n = 2997 patients) vs. placebo (n = 2991 patients) Prespecified outcome	Total number of all-cause hospitalizations: Empagliflozin (n = 2566) vs. placebo (n = 2769); HR 0.93, 95% CI 0.85-1.01
	RCT	CANVAS programme Feng, 2021 ³	Patients with T2D and risk for or established CVD Canagliflozin (n = 5795 patients) vs. placebo (n = 4347 patients) Post hoc analysis	Lower rate of total (first and recurrent) hospitalizations with canagliflozin compared with placebo (rate ratio 0.92, 95% CI 0.86-0.98), with no interaction between those with (rate ratio 0.93, 95% CI 0.86-1.01) or without (rate ratio 0.90, 95% CI 0.80-1.02) established CVD at baseline (P _{interaction} = 0.66) Tested also different aetiologies (cardiac, infectious or nervous), overall and by baseline CVD history
	RCT	EMPA-REG OUTCOME Kaku, 2021 ¹⁰	Patients with T2D and established CVD (same cohort as in McGuire, 2020 ⁴) Specific focus on patients self-identified as Asian. Empagliflozin (n _{overall} = 4687; n _{Asians} = 1006) vs. placebo (n _{overall} = 2333; n _{Asians} = 511) Post-hoc analysis	In the overall participants, the HR (95% CI) for ≥1, ≥2, ≥3, ≥4, ≥5 or ≥6 all-cause hospitalizations events with empagliflozin compared with placebo was 0.89 (0.82-0.96), 0.89 (0.79-1.00), 0.79 (0.67-0.94), 0.66 (0.52-0.83), 0.57 (0.42-0.78), or 0.47 (0.31-0.70), respectively Empagliflozin's reduction in total hospitalizations event rate was consistent in Asian and non-Asian subgroups (P _{interaction} = 0.65)
	RWE	Cahn, 2018 ⁴⁴	Patients with T2D, initiators of SGLT2 inhibitors vs. DPP-4 inhibitors (matched populations, 3464 pts each)	Compared to DPP-4 inhibitors, initiators of SGLT2 inhibitors were less likely to experience any hospitalization (OR 0.66, 95% CI 0.56-0.78), or hospitalization due to AKI (OR 0.47, 95% CI 0.27-0.80)

TABLE 1 (Continued)

SGLT2 inhibitors or GLP-1RAs	RCT/RWE	Study	Participants and comparators	Effect on overall hospitalization (main findings)
	RWE	Li, 2021 ⁴⁵	Patients with T2D and HfpEF, initiators of SGLT2 inhibitors (89 patients) or sitagliptin (161 patients), PS-matched	Lower risk of all-cause hospitalization in SGLT2 inhibitors group (HR 0.48, 95% CI 0.33-0.70)
	RWE	Sheu, 2021 ⁴⁶	Patients with T2D, initiators of empagliflozin vs. DPP-4 inhibitors (matched populations 28 712 patients each)	Compared to DPP-4 inhibitors, rate of all-cause hospitalizations (RR 0.73, 95% CI 0.67-0.79), risk for first hospitalization (HR 0.77, 95% CI 0.73-0.81), rate of emergency room visit (RR 0.88, 95% CI 0.83-0.94), and rate of outpatient visits (RR 0.96, 95% CI 0.96-0.97) were lower in initiators of empagliflozin
GLP-1RAs	RCT	REWIND Gerstein, 2019 ²⁵	Patients with T2D and risk for or established CVD. Dulaglutide (n = 4949 patients) vs. placebo (n = 4952) Adverse event reporting	Dulaglutide -2062 (41.7%); Placebo -2108 (42.6%); P = 0.18
	RWE	Segal, 2007 ⁴⁸	Patients on-treatment with exenatide (n = 3225) matched with patients treated with insulin	Based on data, the projected monthly hospitalization frequency with exenatide would be no different than insulin (relative odds 1.02, 95% CI 0.33-1.98)
	RWE	Best, 2011 ⁴⁹	Patients with T2D initiating exenatide (21 754 pts) compared with oGLAs (361 771 patients)	Exenatide initiators had a lower risk of all-cause hospitalization (HR 0.94, 95% CI 0.91-0.97) or CVD-related hospitalizations (HR 0.88, 95% CI 0.79-0.98)
	RWE	Pawaskar, 2011 ⁵⁰	Patients with T2D initiating exenatide (compared with insulin glargine [2506 patients each, PS-matched])	Exenatide-treated patients had lower likelihood of all-cause hospitalizations (OR 0.81, 95% CI 0.68-0.95), or hospitalization due to macrovascular complications (OR 0.70, 95% CI 0.54-0.90), but not for microvascular complications (OR 0.92, 95% CI 0.62-1.37)
	RWE	Dalal, 2015 ⁵²	Patients with T2D treated with basal insulin initiating either RAI (n = 5013) or a GLP-1RA (n = 1705). PS-matched 3:1. Follow-up duration of up to 1 year for each patient	In the GLP-1RA arm, there was a smaller proportion of patients with ≥1 event of all-cause and diabetes-related hospitalization, compared with the RAI arm (13.6% vs. 18.6%, and 11.8% vs. 15.7% of participants, respectively; P < 0.0001).
	RWE	Levine, 2017 ⁵³	Patients with T2D treated with basal insulin and with inadequate glycaemic control. Propensity matching (1:3) of initiators of GLP-1RA (n = 312) or RAI (n = 799). In a second comparison GLP-1RA (n = 320) vs. basal insulin dose adjustment (n = 815). Follow-up duration of up to 1 year for each patient	Proportion of patients with ≥1 all-cause hospitalization was 14.1% and 15.9% in the GLP-1RA and RAI arm, and 13.1% and 14.4% in the GLP-1RA and basal insulin dose adjustment arm, respectively. No significant difference between groups was detected
	RWE	Melzer-Cohen, 2019 ⁵⁴	Patients with T2D. Patients adherent to liraglutide were compared to those discontinuing within 12 months. (882 patients each cohort, PS-matched)	Liraglutide continuers were less likely to experience an ACHA than discontinuers (18.6% vs. 22.8%; P = 0.034), during 12-24 months post-index date No significant between-arm difference was observed in hospitalizations defined as diabetes-related (6.5% vs. 8.6; P = 0.104)

(Continues)

TABLE 1 (Continued)

SGLT2 inhibitors or GLP-1RAs	RCT/RWE	Study	Participants and comparators	Effect on overall hospitalization (main findings)
SGLT2 inhibitors vs. GLP-1RAs	RWE	Thomsen, 2021 ⁵⁵	Patients with T2D initiating empagliflozin (n = 14 148) or liraglutide (n = 12 628). IPTW was used for comparison	Empagliflozin initiators had a lower risk for a composite of ACHA or death (HR 0.93, 95% CI 0.90-0.97), or for ACHA alone (HR 0.93, 95% CI 0.90-0.98)
	RWE	Lyu, 2021 ⁴⁷	Patients with T2D, who initiated SGLT2 inhibitors (n = 2492), GLP-1RAs (n = 1982) or DPP-4 inhibitors (n = 4762). IPTW was used for comparison	Compared with DPP-4 inhibitors, initiation of SGLT2 inhibitors or GLP-1RAs was associated with a lower risk of ACHA (HR 0.85, 95% CI 0.75-0.95 or HR 0.89, 95% CI 0.78-0.98, respectively). No significant difference was observed between SGLT2 inhibitors and GLP-1RAs (HR 0.92, 95% CI 0.80, 1.07)

Similar findings were observed for CVD hospitalizations, defined as either hHF, MI or stroke (HR_{SGLT2 inhibitors vs. DPP-4 inhibitors} 0.61, 95% CI 0.47, 0.79; HR_{GLP-1RA vs. DPP-4 inhibitors} 0.77, 95% CI 0.60, 0.99 and HR_{SGLT2 inhibitors vs. GLP-1RA} 0.79, 95% CI 0.58, 1.08)

Abbreviations: AKI, acute kidney injury; CV, cardiovascular; CVD, cardiovascular disease; CI, confidence interval; DMD, diabetes-/disease-modifying drug; DPP-4, dipeptidyl peptidase-4; GLA, glucose-lowering agent; GLP-1RA, glucagon-like peptide-1 receptor agonist; HFpEF, heart failure and preserved ejection fraction; hHF, heart failure hospitalization; HR, hazard ratio; IPTW, inverse probability of treatment weighting; MI, myocardial infarction; oGLA, other glucose-lowering agent; OR, odd ratio; PS, propensity score; RAI, rapid-acting insulin; RCT, randomized controlled trial; RWE, real-world evidence; SGLT2, sodium-glucose cotransporter 2; T2D, type 2 diabetes.

4 | DISCUSSION

Support for a role for SGLT2 inhibitors in preventing ACHA comes from post hoc analyses of RCTs data. Most studies demonstrated a lower rate of ACHA in patients with T2D treated with SGLT2 inhibitors compared with controls. However, data regarding the effect of GLP-1RAs on overall hospitalizations comes mainly from RWE, with limited data from RCTs. Nonetheless, in most of these RWE analyses, participants who used GLP-1RAs had significantly better ACHA outcomes compared with their controls.

The formerly mentioned drawbacks in studying ACHA, especially lack of outcome specificity, seem to underlie the lack of statistical significance in some ACHA endpoints. More specific endpoints that also consider recurrent hospitalizations often result in more robust between-arm differences. These limitations also contribute to the small magnitude of relative risk reduction with SGLT2 inhibitors (up to 5-20%), compared to a more substantial effect on other clinically relevant outcomes, such as hHF (reaching approximately 30% risk reduction)⁵⁶. Nonetheless, due to a higher event rate, the magnitude of SGLT2 inhibitor-mediated risk change in absolute scale was numerically higher for ACHA than for hHF (although the reduction in ACHA did not always achieve statistical significance). For example, the number of participants with an event per 1000 patient-years in canagliflozin versus placebo group was 118.7 versus 131.1 for ACHA, compared to 5.5 versus 8.7 for hHF (CANVAS programme⁹). This results in an absolute difference with canagliflozin of -12.4 for ACHA, and -3.2 for hHF (participants/1000 patient-years). Even in EMPEROR-Preserved, which included patients with HF with or without T2D, there was an absolute difference with empagliflozin compared to placebo, of -203 ACHA events, and -134 hHF events (2566 vs. 2769, and 407 vs. 541 events, respectively³⁶). These numbers highlight the possible value of testing drug effects on ACHA.

4.1 | Hospital admission as an opportunity to prevent recurrent hospitalization: ABCDE acronym

Although sometimes perceived as a management failure, acute hospitalization is an opportunity to reassess a patient's diabetes status, thereby facilitating actions that would prevent the next hospitalization. In the next section, we propose an easily memorized clinical approach (acronym "ABCDE") that can be relevant both to hospitalists at the peri-discharge period and to primary care practitioners at the first clinic follow-up visit. In short, a hospitalization episode should prompt a thorough **A**ssessment of diabetes status, including glycaemic **B**alance, the presence of diabetes-related **C**omplications, and adequate use of **D**MDs. **E**xposure to possibly harmful GLAs should be avoided (Figure 2). Importantly, we do not mean to replace comprehensive society guidelines but rather we aim to provide a working framework for physicians that may assist in recognizing possible management pitfalls that may underlie recurrent hospitalizations.

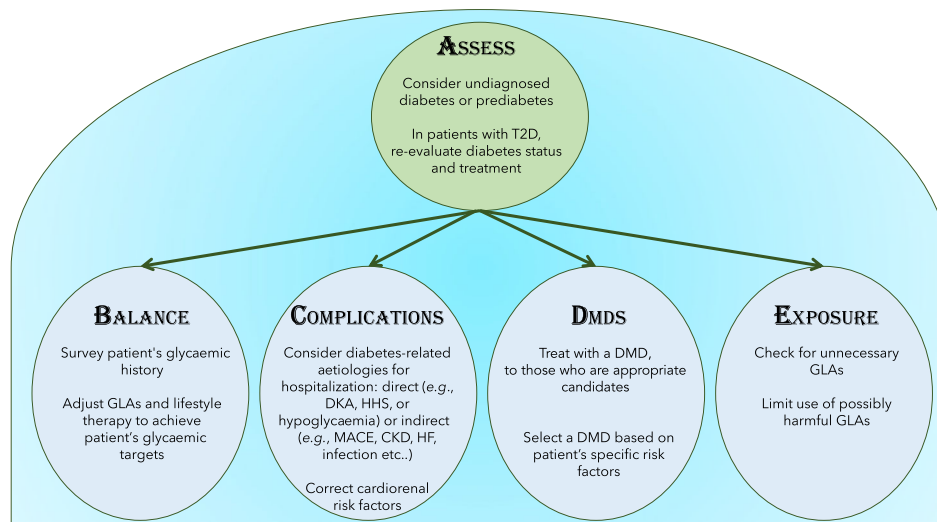


FIGURE 2 Systematic evaluation of patient's diabetes status during the peri-discharge period to prevent subsequent hospitalization (“ABCDE” acronym). A, Hospitalization period should prompt a thorough **Assessment** of the patient's diabetes status. This includes evaluating the patient's risk of having undiagnosed prediabetes or type 2 diabetes (T2D). B, Glycaemic **Balance** should be surveyed based on recent glycated haemoglobin value, followed by adequate recommendations to meet patients' glycaemic targets. C, Does a diabetes **Complication** underlie or contribute to the present hospitalization? Possible attributes include direct endocrine conditions or indirect aetiologies. Patients' treatment should be adjusted to reduce the risk for complication while properly addressing concomitant risk factors. Identification of hospitalization as a complication of diabetes may motivate the patient to improve adherence to the treatment plan. D, **Diabetes-/disease-modifying drugs** (DMDs; ie, SGLT2 inhibitors or GLP-1RAs with shown cardiovascular or kidney efficacy) prescription should be independent of glycaemic control and/or metformin use. Besides their direct cardiovascular and/or kidney benefits, DMDs may also reduce the risk of subsequent hospitalization. E, Search for **Exposure** to possibly harmful glucose-lowering agents (GLAs) and discontinue unnecessary treatment. GLA side effects sometimes underlie hospitalization aetiology. CKD, chronic kidney disease; DKA, diabetes ketoacidosis; HF, heart failure; HHS, hyperosmolar hyperglycaemic state; MACE, major adverse cardiovascular event

4.2 | Glycaemic control and all-cause hospitalization

Prediabetes and T2D are too often underdiagnosed; the International Diabetes Federation report estimated that 50% of global patients with diabetes are undiagnosed.^{57,58} Random plasma glucose screening is recommended in most admitted patients, independent of a previous diabetes diagnosis. In some high-risk or obese populations, targeted investigation (eg, fasting plasma glucose or glycated haemoglobin [HbA1c]) should be considered during hospitalization.^{59,60} In admitted patients with hyperglycaemia and/or diabetes, an HbA1c test is warranted if not performed in the prior 3-month period.⁶¹

Most data regarding the effect of glycaemic control in patients with T2D on ACHA outcomes comes from RWE. Analyses of 10 002 patients with T2D in Canada found a higher rate of emergency room visits and hospital admissions in patients with higher baseline HbA1c levels.⁶² In a larger UK cohort (n = 97 689), higher HbA1c was associated with a slight but significant increase in risk of all-cause and diabetes-related hospitalizations (3% and 8% higher risk per each 1% unit increase in baseline HbA1c, respectively).⁶³ Another study found a nonlinear relationship between HbA1c and ACHA risk, with a threshold estimated at HbA1c of 61 mmol/mol (7.7%). Above this threshold, each 11 mmol/mol (1%) baseline HbA1c increase was associated with a 6.3% higher rate of hospitalizations.⁶⁴ In the ADVANCE RCT, intensive blood glucose control (targeting $\leq 6.5\%$) resulted in a

lower risk for a composite endpoint of major adverse microvascular and macrovascular events, yet patients in this group had a higher risk for ACHA, one of the prespecified secondary outcomes (44.9%, vs. 42.8%; HR 1.07 [95% CI 1.01-1.13]).⁶⁵ This was accompanied by an increase in hospitalizations due to hypoglycaemia (1.1% vs. 0.7%; odds ratio 1.52 [95% CI 1.01-2.28]). Nonetheless, these findings were observed with older GLAs, while newer GLAs (ie, DPP-4 inhibitors, SGLT2 inhibitors and GLP-1 RAs) have favourable adverse events profiles with lower risk for hypoglycaemia and weight gain. Moreover, patients and caregivers were not blinded to arm allocation. All in all, there are limited high-quality RCT data linking glycaemic targets with ACHA, while in RWE poor glycaemic control may mark general poor treatment compliance. Additionally, older age and frailty contribute to ACHA outcomes to a significantly greater extent,⁶³ possibly diluting the effects of glycaemic control.

4.3 | Preventing diabetes complications and appropriate use of DMDs

T2D often coincides with other cardiometabolic risk factors, for example, obesity, hyperlipidaemia, hypertension, and more. Over half of the global population with T2D have NAFLD,⁶⁶ approximately a third have established CVD,⁶⁷⁻⁶⁹ a quarter have chronic kidney disease,⁶⁹⁻⁷¹ and 10% to 15% have HF.⁶⁷⁻⁶⁹ In patients with diabetes,

follow-up directed by guidelines (including measurement of HbA1c, cholesterol, kidney markers, blood pressure, body mass index, smoking status assessment, foot care, and more) was recently associated with a lower mortality risk.⁷²

Diabetes-/disease-modifying drugs improve adverse cardiovascular and kidney outcomes in patients with T2D.¹² Position statements recommend DMD treatment independently of glucose control or background metformin use in patients with T2D and increased cardiorenal risk,⁷³⁻⁷⁵ yet their use amongst appropriate patients remains low.^{68,76,77} Cumulating post hoc analyses of RCTs and RWE suggest that DMDs can also improve prognosis in those with T2D and lower cardiorenal risks^{17,24,25,40,78-83} (Figures 1 and 2).

A complete review of the in-hospital treatment of T2D is beyond the scope of this paper. However, data regarding the use of SGLT2 inhibitors in a hospital setting are briefly discussed, as it may provide a mean to increase their subsequent continuous use in those who are appropriate candidates.^{68,76,77} SGLT2 inhibitor use in admitted patients initially raised safety concerns regarding the possibility of diabetic ketoacidosis (DKA), urinary tract infection and acute kidney injury (AKI; although more recent data indicate a protective role for SGLT2 inhibitors against AKI^{44,84-86}). The recent DARE-19 study compared dapagliflozin and placebo in 1250 noncritically ill patients hospitalized with COVID-19 and at least one cardiometabolic risk factor. Dapagliflozin use was associated with a numerically lower, but nonsignificant reduction in the risk for the primary composite multi-organ-based outcome (HR 0.80 [95% CI 0.58-1.10]). No safety concerns were found, including no significant increase in risk of AKI (3.4% and 5.5% in the dapagliflozin and placebo arms, respectively) or DKA (0.3% in the dapagliflozin arm).⁸⁷ Practically, the American Diabetes Association (ADA) standards of care state that basal insulin is the preferred GLA during hospitalization, while continuation of home regimens may be appropriate only under certain circumstances.⁶¹ However, recent consensus statements list SGLT2 inhibitors as a possible GLA in hospitalized patients with moderate COVID-19, along with GLP-1RAs, DPP-4 inhibitors and insulin.^{88,89}

It is possible that SGLT2 inhibitor initiation before discharge is associated with better clinical outcomes. In the SOLOIST-WHF trial, treatment with sotagliflozin or placebo was initiated in patients hospitalized due to worsening HF (49% of participants) or immediately after discharge. Sotagliflozin treatment resulted in a lower risk of the composite primary outcome of cardiovascular death or re-hospitalization or an urgent visit due to HF.²⁷ In a small study ($n = 80$), empagliflozin initiation within 24 hours after presenting with acute decompensated HF was safe and associated with a lower risk of the secondary composite clinical endpoint of in-hospital worsening HF, re-hospitalization for HF, or all-cause death at 60 days ($P = 0.014$). However, the trial's clinical and laboratory-based primary endpoints were not achieved (EMPA-RESPONSE-AHF).⁹⁰ The recently presented EMPULSE study ($n = 530$) showed clinical benefit for empagliflozin over placebo when initiated after initial stabilization during hospitalization due to HF (NCT04157751⁹¹). Other ongoing RCTs continue to test the use of SGLT2 inhibitors in subjects hospitalized due to HF. The

DICTATE-AHF study tests dapagliflozin's initiation within the first 24 hours of admission until discharge,⁹² and other studies test its initiation throughout hospitalization and continuation after that (NCT04249778 and NCT04363697 [DAPA ACT HF-TIMI 68]). In addition, the DELIVER study tests dapagliflozin in patients with HFpEF during hospitalization or within 30 days post discharge (NCT03619213⁹³). Thus, in upcoming years we expect to have cumulating RCT data regarding the safety and efficacy of SGLT2 inhibitor initiation and use at different stages of hospitalization due to HF.

Initiation of GLP-1RAs in hospitalized patients effectively improved glucose control, and was relatively safe, with some increases in gastrointestinal side effects, as expected.^{94,95} We are unaware of RCTs that tested the effect of GLP-1RA initiation during hospitalization on long-term cardiorenal outcomes.

The decision to change the GLA regimen during hospitalization depends on the patient's characteristics, the practitioner's preference, and local practice. Sometimes financial and insurance considerations limit DMD treatment during hospitalization, while in other cases, hospitalists encounter lower bureaucratic restrictions, and healthcare providers take their recommendations more seriously. Thus, DMD initiation for those who are appropriate candidates should be the primary goal, rather than exact timing.

4.4 | Medication side effects

Side effects of GLAs may lead to or contribute to hospitalization. Acute hospitalizations provide an opportunity to review patients' GLA regimens and discontinue potentially inappropriate medications. Table 2 outlines the side effects of commonly used GLAs; some of them may lead to urgent outpatient visits or hospitalization.⁷⁴

Insulin, sulphonylureas (SUs) and glinides are associated with hypoglycaemic events and increased body weight,⁷⁴ and their use was implicated in emergency hospitalizations of older adults.⁹⁶ In the CAROLINA trial, compared to the glimepiride arm, participants receiving linagliptin had a significantly lower risk of hypoglycaemia outcomes, including hospitalization due to hypoglycaemia (HR 0.07).⁹⁷ Increased hypoglycaemic events were also observed when comparing SUs with pioglitazone (the pragmatic TOSCA.IT study)⁹⁸ or with liraglutide (GRADE study; ADA 2021 conference). RWE data suggested worse cardiovascular and kidney outcomes in patients treated with SUs compared with DMDs, or even other GLAs.^{40,99} Thus, although some patients can benefit from SUs (which are often less costly), there is emerging agreement in the field that SU use should be limited.^{12,74,100} Updated position statements suggest that GLP-1RAs should be the first-line injectable GLA, and basal insulin alone should be considered only in those that cannot tolerate GLP-1RAs or have uncontrolled hyperglycaemia.^{12,74} Short-acting insulin is associated with a higher risk of hypoglycaemia and weight gain and should be limited.

Metformin is associated with lactic acidosis, requiring dosage adjustment or avoidance of its use in patients with estimated glomerular filtration rate (eGFR) of <45 or $30 \text{ mL/min/1.73 m}^2$,

TABLE 2 Main side effects and contraindications for the major classes of glucose-lowering agents

GLA class	Side effects	Caution/ contraindications	References
Biguanides	Lactic acidosis GI side effects Vitamin B12 deficiency Metallic taste	Dose reduction in eGFR <45 mL/min/1.73 m ² ; and contraindicated in <30 mL/min/1.73 m ² . Some suggest holding for 24 hours before and 48 hours after injection of iodinated contrast dyes	74,114,115
DPP-4 inhibitors	Pancreatitis? Joint pain Heart failure? (saxagliptin)	History of pancreatitis	74,104,105,116
GLP-1RAs	GI side effects Pancreatitis? Medullary thyroid carcinoma? Increase heart rate	History of pancreatitis MEN, type 2 Personal or family history of medullary thyroid carcinoma	74
Insulin	Weight gain Hypoglycaemic events Lipo-atrophy/hypertrophy at injection sites		74
Sulphonylureas Meglitinides	Weight gain Hypoglycaemic events	Avoid use in patients with history of hypoglycaemic unawareness or severe liver disease. eGFR adjustment is needed for specific drugs	40,74,97,99
SGLT2 inhibitors	(Euglycaemic) DKA Genitourinary tract infections For sotagliflozin (SGLT2+1 inhibitor) – Diarrhoea and hypoglycaemic events Fournier gangrene? Amputations? (only CANVAS trial)	Do not initiate if eGFR <25-45 mL/min/1.73 m ² (depending on the drug and local regulations) Stop if ESKD present	9,27,28,74 110,112,113 .117
TZDs	Fluid retention/oedema Heart failure Weight gain Bone fractures Macular oedema Anaemia Bladder cancer? Increased LDL? (rosiglitazone)	HFrEF Caution in patients with significant elevation in liver enzymes	74,101-103

Abbreviations: DKA, diabetes ketoacidosis; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GI, gastrointestinal; GLA, glucose-lowering agent; GLP-1RA, glucagon-like peptide-1 receptor agonist; HFrEF, heart failure with reduced ejection fraction; LDL, low-density lipoprotein; MEN, multiple endocrine neoplasia; SGLT2, sodium-glucose cotransporter 2; TZD, thiazolidinedione.

respectively.⁷⁵ Thiazolidinediones were associated with increased risk of weight gain, fractures, anaemia, oedema (including macular oedema), and hHF.^{74,101-103}

Although under debate, incretin use may be associated with pancreatitis, especially of the idiopathic form.⁷⁴ Saxagliptin was associated with a higher risk of hHF, mainly in those with eGFR ≤ 60 mL/min/1.73 m², however, RCTs with other DPP-4 inhibitors did not report similar findings.^{74,104,105} GLP-1RAs are associated with gastrointestinal adverse events such as nausea, diarrhoea, constipation and vomiting, which may lead to dehydration and subsequent hospitalization.⁷⁴ The GLP-1RA regimen should be initiated with a low dose and increased gradually, while paying attention to the possible emergence of adverse events.^{106,107}

Use of SGLT2 inhibitors reduces eGFR levels by an average of 4 to 6 mL/min/1.73 m² immediately upon treatment initiation.^{13,15,17} However, a smaller than 30% acute eGFR decrease in patients with diabetic kidney disease was not associated with a higher risk of adverse safety outcomes.¹⁰⁸ DKA is a relatively rare yet clinically

important adverse event that has been linked to SGLT2 inhibitor treatment.^{109,110} It may present as euglycaemic DKA, which is not a direct-forward diagnosis, requiring clinicians' awareness. RCT and RWE data observed a higher risk for genitourinary infections with SGLT2 inhibitors.¹¹¹ Whether SGLT2 inhibitor treatment is associated with a higher risk of Fournier's gangrene is hard to determine.^{112,113} Sotagliflozin, a SGLT2 + 1 inhibitor, was associated with diarrhoea and hypoglycaemia, possibly related to SGLT1 expression in the gastrointestinal system.^{27,28}

4.5 | Concluding remarks

This contemporary literature review of available evidence from RCTs and RWE found that SGLT2 inhibitors may improve outcomes related to ACHA. Only limited knowledge is available regarding the effect of GLP-1RAs on overall hospitalizations, although existing data also indicate a beneficial effect. Future studies using available data already

gathered in cardiovascular and kidney outcome trials may provide more information regarding different ACHA-related endpoints with DMDs in various populations. Pursuing this line of research may result in better characterization of the different ACHA endpoints, thereby facilitating their utility as candidate clinical outcomes in future studies.

Treatment inertia presents a significant obstacle in the management of T2D, and may sometimes result in recurrent hospitalizations. Thus, the hospitalization period should prompt a reassessment of the patient's diabetes status. Inpatient wards bring together a broad multidisciplinary team, for example, dietitians, diabetes-specialized nurses, pharmacists, social workers, treating physicians and diabetes experts. Such a skilled team can help recognize and overcome hidden obstacles that interfere with T2D management, as simple as demonstrating to patients how to use insulin or GLP-1RA injection. The stress and inconvenience associated with hospital admission may facilitate behavioural and conceptual changes in patients' disease perception, leading to a new lifestyle and medical strategies. Although some may see an acute hospitalization as failure in patient management, we hope that the "ABCDE" acronym, along with an effective use of DMDs, may transform it into an opportunity to overcome treatment inertia and improve patient prognoses.

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CONFLICT OF INTEREST

Ofri Mosenzon has served on Advisory Boards for Novo Nordisk, Eli Lilly, Sanofi, Merck Sharp & Dohme, Boehringer Ingelheim, Novartis, AstraZeneca, Merck and BOL Pharma, has received research grant support through Hadassah Hebrew University Hospital from Novo Nordisk and AstraZeneca, and has served on a Speaker's Bureau for AstraZeneca, Novo Nordisk, Eli Lilly, Sanofi, Merck Sharp & Dohme, Boehringer Ingelheim and Jansen. Meir Schechter and Matan Fischer have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

PEER REVIEW

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