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Cardiovascular Safety of Antidiabetic Drugs in the Hospital Setting

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Abstract
Purpose of Review Patients with diabetes and/or stress hyperglycemia requires good glycemic control in the hospital setting, often requiring the use of glucose-lowering therapy. Standard-of-care dictates that non-insulin therapy be discontinued, with insulin therapy initiated using a basal-bolus approach. However, insulin is associated with a high risk for hypoglycemia and medical errors. Alternatives to insulin are needed in the inpatient setting, but the cardiovascular (CV) safety of non-insulin therapy is a concern.
Recent Findings Most studies of antidiabetic drugs have been performed in the outpatient setting, and except for insulin therapy, trials in the inpatient setting have been insufficient to establish CV safety. Randomized controlled trials support the safety of insulin with more moderate glycemic control in the hospital, when hypoglycemia is minimized. Two recent multicenter randomized controlled clinical trials support the safety of sitagliptin, a dipeptidylpeptidase-4 inhibitor (DPP4i), in hospitalized patients, although the sample sizes were likely too small to detect CV events. Small trials suggest a possible CV benefit of glucagon-like peptide-1 receptor agonist therapy. A paucity of evidence and presence of side effects and cautions with insulin secretagogues, sodium glucose-co-transporter-2 inhibitors, and metformin preclude their routine use in the hospital setting.
Summary Available evidence is inadequate to evaluate the CV safety of most antidiabetic drug classes in the hospital setting. However, preliminary data from randomized clinical trials suggest the potential safety of the DPP4i sitagliptin.

Keywords Cardiovascular · Diabetes · Hyperglycemia · Hospital · Inpatient · Insulin

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Introduction

Individuals with diabetes (diagnosed or undiagnosed) and stress hyperglycemia make up a significant proportion of hospitalized patients, and current standards of care requiring good glycemic control in the inpatient setting most often result in the use of glucose-lowering antidiabetic drugs. Current recommendations call for the discontinuation of all non-insulin diabetes medications and the institution of insulin therapy upon admission to the hospital [1, 2]. However, insulin carries significant risk for hypoglycemia, and alternative approaches have been proposed in selected patients, including the use of incretin enhancers or other agents that carry low risk for hypoglycemia. The cardiovascular (CV) safety of newer medications for diabetes has been studied intensively in the outpatient context, but data for hospitalized patients are not as extensive and often do not include CV endpoints. Clinical trial data cannot be easily extrapolated from outpatient data to the acute care setting since hospitalized patients with diabetes and hyperglycemia may be at higher risk for CV events and complications. This increased risk arises from co-existing comorbidities as well as risks for hospital-associated complications. Our goal was to review the available evidence for CV safety of insulin, metformin, insulin secretagogues, incretin enhancers (glucagon-like peptide-1 receptor agonists and dipeptidyl

peptidase 4-inhibitors), and sodium-glucose-transporter-2 inhibitors in the hospital.

Clinical Studies of Diabetes Medications in the Hospital

A recent authoritative review outlines key issues for CV disease in type 2 diabetes [3] and will not be repeated here. The CV safety of glucose-lowering medications has been reviewed elsewhere [4], but much of the data reviewed relates to the outpatient setting. The current review will highlight studies deemed especially relevant to the inpatient setting including randomized controlled trials when available, and larger retrospective analyses or meta-analyses, and will include a focus on safety and newer antidiabetes drugs. Several classes of medications will not be addressed because they are much less widely used, including thiazolidinediones (which should be discontinued upon hospital admission although their glucose-lowering effects are expected to last for days to weeks after discontinuation), pramlintide, colesevalam, and bromocriptine.

Insulin

The use of insulin in the inpatient setting to manage hyperglycemia and diabetes is the standard of care according to current and previous guidelines by major professional societies including the Endocrine Society [1], the American Diabetes Association [2], and the American College of Endocrinology/American Diabetes Association [5]. Most of the studies evaluating the safety and effectiveness of insulin in the hospital setting have been performed using regular insulin, NPH insulin, or older subcutaneous insulin analogs. There are sparse data regarding CV safety of insulin analogs in the inpatient setting, and to our knowledge, no studies have been published regarding the use of the newer insulins/insulin analogs (insulin degludec, glargine U-300, technosphere inhaled insulin) in the hospital setting, so these will not be discussed in this review. Although insulin use in the hospital setting had been studied prior [6, 7], the Diabetes Insulin-Glucose in Acute Myocardial Infarction (DIGAMI) study was a landmark randomized controlled trial examining the use of a combined glucose and insulin infusion in patients hospitalized with acute myocardial infarction with or without previously diagnosed diabetes in 19 hospitals across Sweden [8]. One might speculate that patients presenting with acute myocardial infarction are among those at highest risk for reinfarction and in whom CV safety of an antidiabetic drug would be of greatest concern. The target range for blood glucose in DIGAMI was 126–180 mg/dL, and yet the in-hospital mortality was not lower in the insulin infusion group as compared to the conventional treatment group (9.1 vs 11.1%, p = NS). However, patients randomized to insulin infusion who were not on insulin prior to admission and were considered "low cardiovascular risk" experienced a 58% reduction in in-hospital mortality ($p < 0.005$) and a reduction in 1-year mortality of 52% ($p < 0.002$) as compared to "low cardiovascular risk" patients randomized to control [9]. Furthermore, the overall mortality for the insulin-treated group after 1 year was 19% as compared to 26% in the control group ($p < 0.005$), supporting the CV benefit of insulin therapy in the acute care setting and beyond, since 72% of patients in the insulin-treated group were on insulin at 1 year as compared with 49% in the control group. A 20-year follow-up study of DIGAMI1 showed a longer median survival time in the intensive treatment group [7.0 years, interquartile (IQR) range 1.8–12.4] as compared with the control group (4.7 years, IQR 1.0–11.4 years), with a hazard ratio for mortality of 0.83, 95% CI of 0.70–0.98, $p = 0.027$ [10].

Another landmark trial of inpatient insulin therapy was performed by van den Berghe and colleagues, and enrolled patients admitted to the surgical intensive care unit (ICU) requiring ventilatory support at a single center, irrespective of diabetes diagnosis or presence of hyperglycemia [11]. Patients randomized to the intensive glycemic control arm targeting blood glucose <110 mg/dL were observed to have a marked reduction in 1-year mortality. In patients receiving intensive care for more than 5 days, in-hospital mortality occurred in only 16.8% of patients as compared with 26.3% in the conventional arm ($p = 0.01$). Furnary and colleagues compared mortality rates in 3554 patients with diabetes undergoing coronary artery bypass graft surgery receiving "sliding scale" subcutaneous insulin between 1987 and 1991 (median blood glucose 177 mg/dL), or continuous intravenous insulin infusion between 1991 and 2001 (median blood glucose 213 mg/dL) [12]. Although the study conclusions were limited by factors such as the nonrandomized nature of the study which compared sequential groups of patients over a long time period with asynchronous controls, the lower mortality rate among patients receiving insulin infusion as compared to those receiving subcutaneous insulin (2.5 vs 5.3%, $p < 0.0001$) was impressive. These and other studies accelerated the interest in glycemic control in the hospital setting and led to major changes in hospital policies and development of inpatient insulin-dosing protocols.

However, the NICE-SUGAR study, which enrolled patients at multiple centers and included both medical and surgical ICU patients, found increased 90-day (but not 28-day) mortality in patients randomized to intensive glycemic control (targeting BG of 81–108 mg/dL), with an odds ratio for mortality at 90-days of 1.14 for intensive control (95% confidence interval, 1.02 to 1.28; $p = 0.02$) [13]. The results of the NICE-SUGAR trial tempered enthusiasm for intensive glycemic control in the ICU setting and helped support a more moderate target range for glycemic control in the hospital. The recently

published BIOMarker Study to Identify the Acute Risk of a Coronary Syndrome–2 (BIOMArCS-2) Glucose Trial attempted to answer the question of whether intensive glycemic control in the setting of acute coronary syndrome would decrease infarct size [14]. A total of 294 patients presenting with acute coronary syndrome (predominantly ST-elevation myocardial infarction) and blood glucose of 140–288 mg/dL were randomized to receive intensive glycemic control (targeting blood glucose 85–110 mg/dL) versus conventional glycemic control using an intravenous insulin infusion. Patients randomized to the conventional arm were not started on insulin therapy unless a single blood glucose value exceeded 288 mg/dL within the first 72 h after onset of symptoms of acute coronary syndrome. The primary outcome of enzymatic infarct size was not reduced in the intensive-control arm, although the extent of myocardial injury as measured by myocardial perfusion scintigraphy approached statistical significance ($p = 0.07$). During the brief hospital admission period (median 3.6 days), four patients (2.9%) randomized to intensive glucose management died as compared with only one patient (0.7%) in the conventional arm ($p = 0.37$). The composite secondary endpoint of death or a second spontaneous MI occurred in eight patients (5.7%) in the intensive glycemic control arm versus one patient (0.7%) in the conventional treatment arm ($p = 0.04$).

Although the results of NICE-SUGAR [13] and BIOMArCS-2 [14] are sobering, these data do not address the specific question of CV safety of insulin per se in the inpatient setting, but rather the intensity of glycemic control. The main concern with intensive glycemic control is the markedly increased risk for hypoglycemia and severe hypoglycemia, and risk for CV and neurologic sequelae. Therefore, subsequent analyses performed examining the relationship of hypoglycemia to mortality are relevant and will be discussed briefly here [15–17]. In DIGAMI2, the rate of hypoglycemia was significantly higher in groups 1 and 2 (each receiving the glucose-insulin infusion) as compared with group 3 (treatment at the discretion of the physician), but mortality and the composite endpoint of mortality, nonfatal myocardial infarction or stroke were not different between patients with or without hypoglycemic episodes [15]. There was a higher hazard ratio for total mortality, rate of nonfatal reinfarctions, and stroke in patients experiencing symptomatic hypoglycemia, but this difference was no longer significant after adjustment for possible confounding factors. Thus, data from DIGAMI2 do not support an independent association between hypoglycemia and subsequent CV morbidity and mortality. However, further analyses of the contribution of hypoglycemia to CV endpoints in NICE-SUGAR showed that 45% of the 6026 patients in the trial had moderate hypoglycemia defined as blood glucose of 41–70 mg/dL (74.2% of the intensive-control group and 15.8% of the conventional-control group) [16]. Overall, 3.7% of patients experienced severe hypoglycemia (blood glucose of 40 mg/dL or lower), or 6.9% of the intensive-control group and 0.5% of the conventional treatment group. Whether patients experienced moderate or severe hypoglycemia, the hazard ratio for mortality was increased even after adjustment for baseline and postrandomization characteristics: moderate hypoglycemia HR 1.41 (1.21–1.62, $p < 0.001$) and severe hypoglycemia HR 2.10 (1.59–2.77, $p < 0.001$) [16]. A recent study demonstrated that hypoglycemia occurring after cardiac surgery did not increase the rate of surgical complications, but patients who experienced multiple episodes of hypoglycemia had a significantly increased risk of postoperative morbidity and all-cause mortality long-term (causes unknown) [17]. These data are extremely concerning and limit the treatment of hyperglycemia when this cannot be accomplished without hypoglycemia.

Overall, insulin therapy is the standard of care for management of hyperglycemia with or without diabetes in the hospital setting, and data support the acute CV safety of insulin. However, available data highlight CV safety concerns with glycemic control that is too intensive; this may be related at least in part to increased hypoglycemia, so antidiabetic therapies that minimize or avoid hypoglycemia while still providing glycemic control in the hospital setting are needed.

Metformin

Metformin is in the biguanide class of antidiabetes drugs and has been used for decades in the treatment of diabetes. It is considered a first-line antidiabetic drug in the treatment of type 2 diabetes. Since it is cleared by the kidney and carries a risk for lactic acidosis if used in patients at higher risk for developing lactic acidosis, it is discontinued for intravenous contrast studies and upon hospital admission. However, restarting metformin therapy may be appropriate after patients are clinically stable, nearing discharge, and barring contraindications. There has been great interest in metformin because of positive data from long-term follow-up of the UKPDS [18] and improvement in CV risk factors in numerous studies, as reviewed previously [1, 2].

An extensive PubMed search of published English language literature did not reveal any randomized controlled trials evaluating the CV safety of metformin in the inpatient setting, likely because of current and prior guidelines recommending its discontinuation at hospital admission. In the outpatient setting, clinical trials have often compared metformin with sulfonylureas rather than with placebo, and with CV risk factors or risk markers as outcomes instead of evaluating effects on CV outcomes directly.

In the United Kingdom Prospective Diabetes Study (UKPDS) of patients with newly diagnosed type 2 diabetes, overweight patients assigned to metformin in the conventional arm had a 42% risk reduction in diabetes-related death and a 36% risk reduction for all-cause mortality [19, 20]. In patients

allocated to intensive glycemic control, metformin therapy had a greater effect than sulfonylureas or insulin on all-cause mortality and stroke. Limitations to interpretation of the UKPDS include the crossover therapy occurring in both treatment arms, confounding conclusions regarding specific effects of the glucose-lowering treatments, and a relatively small number of CV events [21]. However, the 10-year follow-up study for the UKPDS [18] and subsequent nonprospective studies [22] appear to support the conclusion that metformin therapy does not increase CV risk and may have beneficial CV effects in patients with type 2 diabetes, as outlined in a systematic review [23]. For the purposes of this review of CV safety in the inpatient setting, the results of UKPDS cannot be extrapolated directly, since it was performed in the outpatient setting. Furthermore, the comparison group was taking sulfonylureas or insulin, so distinguishing between a decrease in CV risk with metformin versus an increase in risk with sulfonylureas or insulin was difficult in this study.

Kooy and colleagues examined the effect of metformin versus placebo on a background of insulin therapy in patients with type 2 diabetes on a primary outcome made up of multiple components of macrovascular and microvascular disease [24]. The composite primary outcome did not reach statistical significance after adjustment (hazard ratio, HR of 0.92, 95% CI 0.72–1.18, $p = 0.33$) [23]. The authors note that the secondary outcome of composite macrovascular disease did reach statistical significance between groups, with lower HR in the metformin-treated group (0.61; 95% CI 0.30–0.94, $p = 0.02$), but this conclusion must be interpreted with caution and considered to be hypothesis-generating only. Unfortunately, a number of key factors limit interpretation of this study to understand whether metformin has a beneficial or neutral CV effect. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was conducted in 9795 patients with type 2 diabetes treated with diet alone, metformin, or sulfonylureas in the outpatient setting and showed that the point estimates for risk of coronary heart disease events, total CV disease events, CHD mortality, CVD mortality, total mortality, coronary revascularization, and other CV endpoints were higher than with diet alone, but not significant [25]. These point estimates were higher with sulfonylureas than with metformin, but the differences were attenuated markedly yet not eliminated after adjustment for CV risk factors [25]. However, the CV safety of metformin in the outpatient setting cannot be directly translated to the inpatient setting.

Overall, the available data do not provide evidence for the safety of metformin in the inpatient setting (CV or otherwise). The incidence of metformin-associated lactic acidosis is low [26–28]. However, many of the contraindications and cautions for use of metformin with conditions that increase the risk of lactic acidosis occur in the hospital setting, such as hypoxia, liver dysfunction, heart failure, renal dysfunction, use of intravenous contrast, hypovolemia, and hypotension with resulting renal injury. Therefore, unless more data are accumulated in the hospital setting, the use of metformin cannot be recommended for most patients in the inpatient setting [29, 30], despite the April 2016 liberalization of renal function guidelines by the FDA [31]. However, in hospitalized patients at low risk for lactic acidosis, such as patients admitted electively for minor procedures or are otherwise clinically stable (e.g., on an inpatient rehabilitation unit) and/or nearing discharge, restarting metformin may be a safe option, particularly if it is initiated at a low dose and uptitrated to the goal dose.

Insulin Secretagogues

Sulfonylureas (glipizide, glyburide, glimepiride, gliclazide, tolbutamide, chlorpropamide) stimulate production of insulin by pancreatic beta cells by binding to the sulfonylurea receptor and blocking ATP-sensitive potassium channels in the cell membrane. Meglitinides (repaglinide, nateglinide) work through a similar mechanism of action. Both classes of antidiabetic drugs are thus "secretagogues" and stimulate insulin secretion regardless of blood glucose.

As noted above, there is a dearth of randomized controlled trials of sulfonylureas in the hospital setting, particularly those that include evaluation of CV outcomes and safety. A recent Cochrane database systematic review of randomized controlled trials of insulin secretagogues in the outpatient setting also revealed that only a small single trial with sulfonylureas met criteria for inclusion in the meta-analysis and included any CV endpoint [32]. The trial was deemed low-quality evidence; it examined CV mortality, which was not increased with sulfonylurea therapy versus placebo over a 3.7-year follow-up period. On the other hand, there was a large trial of the meglitinide analog nateglinide that was considered to have moderate quality evidence, consisting of 9306 patients, which showed that all-cause and CV mortality, nonfatal myocardial infarction, nonfatal stroke and congestive heart failure were not increased with nateglinide over a median follow-up period of 6.3 years in the outpatient setting. Huang and colleagues published a recent cohort study of patients with type 2 diabetes hospitalized for ischemic heart disease and showed that the risk of a composite outcome of all-cause mortality or new onset of atrial fibrillation, stroke, heart failure, or myocardial infarction was not increased with gliclazide, glyburide, or repaglinide within 30 days of hospitalization for ischemic heart disease [33]. However, the adjusted hazard ratios for glyburide (0.91; 95% CI 0.78–1.05) and repaglinide (0.80; 95% CI 0.63–1.03) as compared to gliclazide trended toward a relative benefit with glyburide or repaglinide, or conversely an increased risk with gliclazide [33].

The main concern with use of insulin secretagogues in the inpatient setting is the high risk of hypoglycemia, particularly for patients with renal or hepatic impairment. Table 1 lists relative risks for hypoglycemia of various antihyperglycemic

Table 1 Odds ratio for hypoglycemia with antidiabetic drugs

	Change in HbA1c (%)	Hypoglycemia,odds ratio
Sulfonylureas	−0.82*	8.86*
Meglitinides	−0.71*	10.51*
DPP-4 inhibitors	−0.69*	1.13
GLP-1 receptor agonists	−1.02*	0.92
Basal insulin	−0.88*	4.77*
Premixed insulin	−1.07*	17.78*

DPP-4 dipeptidyl peptidase 4, *GLP-1* glucagon-like peptide-1, *HbA1c hemoglobin A1c*

*Significant versus placebo

(With permission from: Connelly KA, et al. Circulation 2015:132:2345–2350) [34].

drug classes (excluding SGLT2i) from a network meta-analysis of trials performed almost exclusively in the outpatient setting, showing an odds ratio of 8.86 for hypoglycemia with sulfonylureas as compared with placebo. Risk factors for severe hypoglycemia include HbA1c <6%, hypoglycemia unawareness, autonomic neuropathy, cognitive impairment, renal dysfunction, previous episodes of severe hypoglycemia, and missed meals, among other factors typically present among inpatients [34]. Hypoglycemia increases the risk for CV events [35]. Potential mechanisms include abnormalities of coagulation, inflammation, endothelial dysfunction, and activation of the sympathetic nervous system leading to adverse CV outcomes.

Overall, there is very little evidence regarding CV safety of insulin secretagogues in the inpatient setting. The evidence available for the outpatient setting does not indicate an increased CV risk except possibly for gliclazide. Because of the risks of hypoglycemia, the routine use of insulin secretagogues cannot be recommended in the inpatient setting.

Incretin-Enhancing Therapy

Glucagon-like petide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) are incretin hormones secreted by the gastrointestinal tract. They bind the GLP-1 receptor (GLP-1R) and GIP receptor (GIPR), respectively, thereby stimulating glucose-dependent insulin secretion. In addition to its insulinotropic effects, GLP-1 has additional metabolic effects, and suppresses postprandial glucagon production thus decreasing hepatic gluconeogenesis, controls appetite, and delays gastric emptying [3, 4]. As plasma glucose rises, the effect of GLP-1 on insulin secretion increases. Conversely, as glucose concentration falls, its inhibitory effect on glucagon diminishes. GLP-1 receptor agonists (GLP-1RA) are a class of antidiabetic medications administered via subcutaneous injection that increase GLP-1 action. Dipeptidyl peptidase-4 (DPP4) is the proteolytic enzyme responsible for rapidly degrading endogenously secreted GLP-1 and GIP. DPP4 inhibitors (DPP4i) are taken orally and hinder the metabolism of GLP-1 and GIP, allowing for a 1.5–2-fold increase in incretin activity [36].

Dipeptidylpeptidase-4 Inhibitors

There are currently four FDA-approved DPP-4 inhibitors (DPP4i): sitagliptin, saxagliptin, linagliptin, and alogliptin. To date, three CV safety studies have been completed, all in the outpatient setting: the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 (SAVOR-TIMI 53) [37], Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) [38], and Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin (TECOS) [39]. Each trial demonstrated CV safety of the respective DPP4i. The effect of linagliptin on CV endpoints is currently under evaluation in the CARdiovascular Outcome Study of LINAgliptin versus Glimepiride in Patients with Type 2 Diabetes trial (CAROLINA), NCT01243424.

A secondary analysis of the SAVOR-TIMI 53 study showed an increased risk of hospitalization for heart failure for participants treated with saxagliptin (289, 3.5%) when compared to placebo (228, 2.8%; HR, 1.27; 95% CI, 1.07–1.51; p = 0 .007) [40]. The mechanisms underlying the increased rates of heart failure with saxagliptin are unclear. However, the increased risk for this group has been hypothesized to be due to differences in diabetes treatments between the study groups, including a higher rate of pioglitazone use in the saxagliptin arm as compared to the placebo arm, a drug class known to cause or exacerbate fluid retention. Rehman et al. completed a meta-analysis of randomized placebo-controlled studies of DPP4i and postulated that DPP4i were associated with significantly increased risk of hospitalization for severe heart failure (relative risk, RR 1.13 95%, CI 1.01–1.26) [41]. Conversely, a systematic review by Mannucci and Monami subsequently concluded that because this meta-analysis was weighted heavily by results of SAVOR-TIMI 53, it may have overstated the risk of HF with this class of medication [42•]. It is unclear whether the risk of heart failure

is a class effect or is medication-specific, possibly related to differences in specificity of inhibition of DPP-4 and/or other related enzymes [43]. However, because of these data, the FDA required warnings regarding the potential increased risk of heart failure in the labels of medication containing saxagliptin and alogliptin, and recommend that providers discontinue saxagliptin and alogliptin in patients who develop heart failure [44]. A more recent secondary analysis of TECOS examined the effect of sitagliptin in older adults (≥75 years of age) [45]. The analysis found that in well-controlled individuals with type 2 diabetes and CV disease, sitagliptin did not increase the risk for the primary outcome of major cardiac event (HR 1.1; 95% CI 0.89–1.36), death (HR 1.05; CI 0.83–1.32), heart failure hospitalization (HR 0.99; CI 0.65–1.49), severe hypoglycemia (HR 1.03; CI 0.62–1.71), or rates of acute pancreatitis and pancreatic cancer, supporting a neutral effect with no significant safety concerns [45].

The question of whether DPP4i lead to increased risk of pancreatitis awaits a definitive answer. Rehman et al. found an alarming increase in risk of acute pancreatitis with DPP4i (RR 1.79, 95% CI = 1.13–2.81) [41]. In contrast, a cohort study performed by Azoulay, et al. did not confirm a link between DDP4I and acute pancreatitis [46]. This difference in findings between the Azoulay study and the Rehman meta-analysis was attributed to differences in study populations: patients enrolled in the cohort study had a shorter duration of diabetes and significantly fewer microvascular complications than those treated in the three CV outcome trials included in the meta-analysis [41, 46].

Because of the low risk of hypoglycemia, DDP4i are a potential option for the safe treatment of diabetes in hospitalized patients. Table 2 summarizes studies of antidiabetic drugs in hospitalized patients with an emphasis on randomized controlled trials. For insulin treatment, only studies performed in the noncritical care setting were included. Inpatient hyperglycemia treatment with sitaglipitin has been studied [57••, 58]. Pasquel et al. examined glycemic and safety endpoints in a multicenter, randomized controlled clinical trial of 277 patients with type 2 diabetes admitted to medical and surgical wards and found that treatment with basal insulin plus sitagliptin was noninferior to treatment with basal-bolus insulin therapy during the study period, which lasted for up to 10 days and was limited to the duration of hospitalization. One patient in the basal-bolus group experienced a myocardial infarction whereas none occurred in the sitagliptin arm. Of note, hypoglycemia did not occur less frequently in the sitagliptin treatment arm (9 vs 12%; $p = 0.45$) [57••]. This was a surprising finding given the low risk for hypoglycemia with sitagliptin, except that both arms received correctional insulin. Similarly, Umpierrez et al. found sitagliptin to be a safe alternative to basal-bolus insulin therapy in the treatment of hyperglycemia in the non-ICU setting, albeit in a pilot study [58]. Although these data are encouraging regarding CV safety of sitagliptin in the hospital setting, CV outcomes were not specifically examined in either of these trials, and the trials may not have included sufficient sample size to answer this question adequately.

Given recent data from SAVOR-TIMI53 and EXAMINE of saxagliptin and alogliptin, respectively, enthusiasm for the use of DPP4i in the hospital setting must be tempered by the potential for increased risk for developing or exacerbating heart failure [37, 38].

We conclude that the use of saxagliptin and alogliptin for the treatment of inpatient hyperglycemia cannot be recommended at this time. Recent clinical trials of sitaglipitin in the inpatient setting suggest a potential reduction in hypoglycemia, so it may prove to be a beneficial treatment option for inpatient hyperglycemia and may be considered for use in patients with type 2 diabetes similar to the population enrolled in the recent trials [57••, 58]. Clinical trial data are not available for linagliptin, but given that dose adjustment of linagliptin is not needed even in end-stage renal disease, this may be a better option, although the CV outcome trial has not been completed. None of these agents have been studied in the ICU setting and therefore should not be used in critical illness until enough data regarding safety can be accumulated. As acknowledged in the 2017 Standards of Medical Care by the American Diabetes Association, there are insufficient data regarding the safety of incretin-enhancing therapies to recommend their use in the hospital setting [2]. More multicenter clinical trials of DPP4i therapy are needed in the hospital setting. Ideally, these would consist of randomized controlled clinical trials. However, because the feasibility of this may be limited by funding and other issues, an alternative might be pragmatic trials in the inpatient setting, ideally multi-institutional, with sufficient sample size to assess CV safety.

Glucagon-Like Peptide-1 Receptor Agonists

The currently available glucagon-like peptide-1 receptor agonists (GLP-1RA) include exenatide, exenatide extended-release, liraglutide, lixisenatide, albiglutide, and dulaglutide. Recent CV outcome trials as well as prior meta-analyses of clinical trials involving GLP-1RA support the CV safety of this class of drugs in the outpatient setting [63–67]. There are limited data regarding GLP-1RA in the inpatient setting administered via subcutaneous injection instead of via intravenous infusion (Table 2). In a small short-term study, patients with STEMI with or without diabetes were randomized in a 1:2 ratio to receive subcutaneous injection of either exenatide (10 μg SC and 10 μg IV 5 min prior to onset of reperfusion, then 10 μg twice daily for two more days) or placebo [68]. Infarct size (as measured by area under the curve for CKMB and troponin I) was significantly decreased in the exenatide group by about 40%. Cardiac magnetic resonance imaging showed that the absolute mass of delayed enhancement was

Table 2 Clinical studies of antidiabetic drugs in the hospital setting

Author/trial	Setting	Study design	Population	Intervention	Primary endpoint	CV endpoint/outcome
Insulin—ICU settings						
BIOMArCS-2, 2013 [14]	ICU	Prospective, open-label, randomized clinical trial	*n* = 294 pts. with ACS and BG 140–288 mg/day w/ or w/o hx of DM	1:1 ratio to INT (BG 80–110 mg/dL during day and 85–139 mg/dL at night) or CON (no insulin until 1 BG >288 mg/dL)	No significant differences in enzymatic infarct size between the 2 treatment groups measured by hsTropT72	Secondary CV outcomes: No difference in myocardial, left ventricular function
NICE-SUGAR, 2009 [13]	ICU	Parallel-group, randomized controlled trial	*n* = 6104 pts. requiring ICU tx for ≥3 days w/ or w/o hx of DM	Randomized to INT (BG 81–108 mg/dL) or CON (BG <180 mg/dL) by IV insulin infusion	3 month mortality increased in INT (27.5 vs 24.9%)	Secondary CV outcomes: death from CV cause more common in INT (41.6 vs 35.8%)
De La Rosa, 2008 [47]	Medical/surgical ICU	Prospective, randomized, nonblinded, single-center clinical trial	*n* = 504 pts. requiring ICU tx for ≥2 days w/ or w/o hx of DM	1:1 ratio to INT (BG 80–110 mg/dL) or SOC (BG 180–200 mg/dL) by IV insulin infusion	28 days mortality increased in INT (36.6 vs 32.4%)	None
VISEP, 2008 [48]	ICU	Multicenter, randomized, two-by-two factorial trial	*n* = 537 pts. with sepsis w/ or w/o hx of DM	Randomized to INT (BG 80–110 mg/dL) or CON (BG 180–200 mg/dL) by IV insulin infusion	28 days mortality showed no significant different between groups (INT 24.7% vs CON 26.0%)	Trial stopped early due to hypoglycemia in INT
GluControl, 2007 [49]	ICU	Prospective randomized controlled trial	*n* = 1101 pts. requiring ICU tx for >24 h w/ or w/o hx of DM	Randomized to INT (BG 80–110 mg/dL) or CON (BG 140–180 mg/dL) by IV insulin infusion	All-cause ICU mortality showed no significant different between groups (INT 17.2% vs CON 15.3%)	Trial stopped early due to high rate of unintended protocol violations
HI-5, 2006 [50]	CCU	Multicenter, open-label, randomized controlled clinical trial	*n* = 240 pts. with AMI or STEMI w/ or w/o hx of DM	Randomized to INT (BG 72–180 mg/dL) by IV insulin infusion or SOC (additional SQ insulin if BG >288 mg/dL)	No significant different in mortality between groups at 3 months (INT 7.1% vs SOC 4.4%) and 6 months (INT 7.9% vs SOC 6.1%)	Secondary CV outcomes: lower incidence of cardiac failure during the inpatient period and reinfarction within 3 months in the INT
Van den Berghe, 2006 [51]	Medical ICU	Prospective, randomized controlled study	*n* = 1200 w/ or w/o hx of DM	Randomized to INT (BG 80–110 mg/dL) or CON (BG 180–200 mg/dL) by IV insulin infusion	No significant different between groups in-hospital mortality (INT 37.3% vs CON 40%)	Secondary CV outcomes: Higher rate of cardiovascular deaths in INT vs CON (42.2 vs 33.3%)
DIGAMI 2, 2005 [52]	CCU	Double-blinded, multicenter, randomized controlled study	*n* = 1253 pts. with AMI or STEMI w/ or w/o hx of Type 2 DM	Randomized to group 1 (BG 126–180 mg/dL) with IV insulin infusion followed by SQ insulin; group 2 (BG 126–180 mg/dL) by IV insulin infusion followed by SOC; group 3 SOC	No significant 2 year mortality difference between groups 1 and 2 or between groups 2 and 3.	Secondary CV outcomes: *N* significant differences in morbidity expressed as nonfatal reinfarctions and strokes between the 3 groups
Furnary, 2003 [12]	CCU	Prospective interventional study	*n* = 3554 pts with type 2DM undergoing CABG	SQ group = insulin injections every 4 h with goal of BG <300 mg/dL or IV insulin infusion with a range of glucose targets	Overall mortality was significantly less in the IV group versus the SQ. (2.5 vs 5.3%, *p* .0001).	Same

Table 2 (continued)

Author/trial	Setting	Study design	Population	Intervention	Primary endpoint	CV endpoint/outcome
				from 100 to 200 mg/dL (goals were lowered over the 10 year study period)		
Van den Berghe, 2001 [11]	SICU	Prospective, randomized controlled study	*n* = 1548 pts. on mechanical ventilation w/ or w/o hx of DM	Randomized to INT (BG 80–110 mg/dL) or CON (BG 180–200 mg/dL) by IV insulin infusion	Significant different in ICU mortality between groups (INT 7.2% vs CON 10.9%)	Secondary CV outcomes: Markers of inflammation were less frequently abnormal in the INT vs CON
DIGAMI, 1995 [8]	CCU	Prospective, randomized controlled study	*n* = 620 pts with type 2 DM and AMI	Randomized to INT (BG 126–180 mg/dL) by IV insulin infusion or SOC	1 year mortality was lower in INT vs SOC (18.6 vs 26.1%)	Secondary CV outcomes: mortality reduction was particularly evident in patients with low cardiovascular risk profile and no previous insulin treatment
Insulin—non-ICU settings						
RABBIT 2, 2007 [53]	General medical floor	Multicenter, prospective, open-label, randomized study	*n* = 130 nonsurgical pts. with type 2 DM	Randomized to regular sliding scale insulin or a basal-bolus	Significantly better BG control in basal-bolus groups vs regular sliding scale insulin	None
RABBIT 2 Surgery, 2011 [54]	General surgical floor	Multicenter, prospective, open-label, randomized study	*n* = 211 pts. admitted for general elective or emergency surgery with type 2 DM	Randomized to regular sliding scale insulin or a basal-bolus	Significantly better BG control in basal-bolus groups vs regular sliding scale insulin	None
Basal Plus, 2013 [55]	General medicine/surgical floors	Multicenter, prospective, open-label, randomized study	*n* = 375 pts. with type 2 DM	Randomized 2:2:1 ratio to basal-bolus (bolus meal and correction doses), basal plus (bolus correction doses only), or regular sliding scale insulin	Basal-bolus and basal plus regimens resulted in similar BG control with better control than sliding scale insulin	None
Metformin						
No studies						
Insulin secretagogues						
Deusenberry, 2012 [56]	Tertiary care academic medical center	Nested case-control study	*n* = 234 pts. with type 2 DM	1:1 case match with controls (sex, # of days treated with the sulfonylurea during the hospitalization)	19% sulfonylurea-treated patients experienced at least 1 episode of hypoglycemia; Multiple regression analysis identified age ≥65, concurrent treatment with insulin and GFR ≤30 independent predictors of hypoglycemia	None

Table 2 (continued)

Author/trial	Setting	Study design	Population	Intervention	Primary endpoint	CV endpoint/outcome
Incretin Enhancers—DPP4-inhibitors						
Pasquel, 2016 [57••]	General medicine/surgical floors	Multicenter, prospective, open-label, noninferiority randomized clinical trial	*n* = 279 pts. with type 2 DM	Randomized 1:1 to sitagliptin plus basal or basal-bolus regimen	Glycemic control and LOS were similar for both groups	None
Umpierrez, 2013 [58]	General medicine/surgical floors	Pilot, multicenter, open-label, randomized study	*n* = 90 pts. with type 2 DM	Randomized sitagliptin alone, sitagliptin plus basal or basal-bolus regimen	Glycemic control and LOS were similar for all groups	None
Read, 2010 [59]	Pts having dobutamine stress test	Randomized control trial	*N* = 14 h/o CAD, dobutimine stress ECG; w/ or w/o hx of DM	Sitagliptin 100 mg vs placebo	Improved global and regional LV performance in response to stress; mitigated postischemic stunning	Same
Incretin enhancers—GLP1-RA						
Abuannadi, 2013 [60]	Cardiac ICU	Prospective, single-center, open-label, nonrandomized pilot study	*n* = 173 w/ or w/o hx of DM	Exenatide IV bolus followed by continuous infusion up to 48 h compared to two historical insulin infusion cohorts	No difference in mean steady-state BG between groups	None
Lonborg, 2012 [61]	Cardiac ICU	Randomized, double-blind, placebo-controlled trial	*n* = 172 p/w STEMI treated with PCI w/ or w/o hx of DM	Randomized to exenatide infusion vs placebo	Exenatide treatment was associated with a 30% decrease in final infarct size when administered ≤132 min of symptom onset	Same
Mecott, 2010 [62]	Pediatric burn ICU	Single-center, open-label, controlled study	*n* = 24 w/ or w/o hx of DM	Randomized to exenatide infusion or insulin infusion	No differences in BG or glycemic variability between groups significantly lower insulin need in exenatide group	None
SGLT2-inhibitors						
No studies						

ACS acute coronary syndrome, *AMI* acute myocardial infarction, *BG* blood glucose, *CABG* coronary artery bypass grafting, *CCU* coronary care unit, *CON* conventional, *CV* cardiovascular, *DM* diabetes mellitus, hsTropT72 high-sensitivity troponin T value 72 h after admission, *hx* history of, *ICU* intensive care unit, *INT* intensive, *IV* intravenous, *LOS* length of stay, *n* number, *pts.* patients, *SOC* standard of care, *SQ* subcutaneous, *STEMI* ST-segment elevation myocardial infarction, *tx* treatment, *w/* with, *w/o* without

significantly reduced in the exenatide group (12.8 ± 11.7 vs 26.4 ± 11.6 g; $p < 0.01$) [68]. In another study, 92 patients were randomized to receive liraglutide versus placebo via SC injection for 7 days after percutaneous coronary intervention for STEMI. Liraglutide treatment resulted in a small improvement in change in left ventricular (LV) ejection fraction of 4.1% (95% CI +1.1% to +6.9%; $p < 0.001$) [69]. Nozue et al. retrospectively evaluated the effects of liraglutide on LV remodeling in 15 patients with type 2 diabetes presenting with acute myocardial infarction (MI). Surprisingly, A1c and plasma glucose were not different between groups at 6 months. However, the liraglutide-treated group exhibited less LV remodeling and lower LV mass index than the standard treatment group [70].

Continuous infusion of GLP1-RA in a controlled setting has been shown to decrease glucose excursions caused by glucagon and glucocorticoids. For example, IV infusion of exenatide was demonstrated to have a positive impact on glycemic control after a mixed meal in eight healthy individuals with steroid-induced hyperglycemia [71]. The primarily postprandial hyperglycemic effects of steroids occur in part through a mechanism that can be overcome by the GLP-1 pathway in the beta cell [72]. It has been suggested that GLP-1RA may improve CV outcomes by decreasing hypoglycemic events [73].

Several large GLP1-RA CV outcome trials have been performed in the outpatient setting, and several more are expected to be published in the near future. The LEADER study was performed in 9340 patients taking liraglutide versus placebo over a median of 3.8 years [63]. The primary outcomes were death from CV causes, nonfatal MI, and nonfatal stroke and occurred in fewer patients randomized to liraglutide as compared with placebo (13 vs 14.9% respectively, HR 0.87, 95% CI, 0.78 to 0.97, $p < 0.001$ for noninferiority and $p = 0.01$ for superiority). The rate of all-cause mortality was lower in the liraglutide group (8.2%) versus placebo group (9.6%) (HR, 0.85, p5% CI, 0.74 to 0.97; $p = 0.02$). The SUSTAIN-6 study was performed in 3297 patients taking once weekly semaglutide versus placebo for 104 weeks [64]. The primary outcomes were death from CV causes, nonfatal MI, and nonfatal stroke, and occurred in fewer patients randomized to semaglutide than placebo (6.6 vs 8.9%, respectively, HR 0.74, 95% CI, 0.58–0.95; $p < 0.001$ for noninferiority) [64]. A reduction in stroke was the major contributor to the primary outcome. This study supported the CV noninferiority of semaglutide as compared with placebo. The ELIXA study followed 6068 patients on lixisenatide versus placebo for a median of 25 months [65]. The primary endpoint (CV death, MI, stroke, or hospitalization for unstable angina) occurred in 13.4% of patients randomized to lixisenatide, and 13.2% of patients randomized to control (HR 1.02, 95% CI, 0.89–1.17) [65], and supports the CV noninferiority of lixisenatide ($p < 0.001$). Several similar studies that are yet unpublished include EXSCEL (exenatide weekly, NCT01144338), REWIND (dulaglutide, NCT01394952), and HARMONY (albiglutide, NCT02465515). These have the potential to strengthen the findings of CV safety and possible benefit of GLP1-RA.

The safety of currently available GLP-1RA has not been examined systematically in the inpatient setting in an adequate number of patients, and more hospital-based, large-scale clinical trial and pragmatic trial data are urgently needed, since this class of medications may prove to be a good alternative to insulin in selected acute care patient populations. This drug class may also have the potential to provide cardiac protection, but there are not enough data available to make this conclusion. However, contraindications and precautions regarding their use exist. GLP-1RA should not be used for patients with thyroid cancer, multiple endocrine neoplasia, pancreatitis, or procedures that carry an increased risk for pancreatitis (e.g., Whipple procedure). Given the signal for increased risk biliary disease with liraglutide in LEADER, caution must be exercised regarding the use of GLP-1RA in patients with nephrolithiasis or gallbladder disease [63]. In a review of a US commercial health insurance claims database of antidiabetes drug-related adverse events from February 2010 to March 2013, reported events of pancreatitis, pancreatic cancer, and thyroid cancer were examined [74]. The incidence of reported pancreatitis with liraglutide was not significantly higher than for non-GLP-1-based therapies (adjusted RR 1.10; CI 0.81–1.49). The pancreatic cancer incidence rate compared with non-GLP-1 based therapies was 19.9 versus 33.0, also not significant (adjusted RR 0.65; 95% CI 0.26–1.60). Elashoff et al. examined the FDA database of reported adverse events from 2004 to 2009 and found that pancreatitis was reported more than six times more frequently for exenatide users when compared with other drug class therapies (OR = 10.68; 95% CI 7.75–15.1, $p < 10^{-16}$), pancreatic cancer was 2.9 times greater ($p = 9 \times 10^{-5}$) compared with other drug class therapies, and thyroid cancer was also increased (OR = OR = 4.73; $p = 0.004$) [75].

Renal precautions regarding the GLP-1RA include the following: exenatide should not be used in patients with estimated glomerular filtration rate (eGFR) <30 mL/min. Liraglutide is not recommended for use in moderate to severe renal impairment. Lixisenatide is not recommended for eGFR <15 mL/min. Dulaglutide and albiglutide do not have renal contraindications, but caution is recommended should be used with initiating or escalating doses. The major side effect of GLP-1RA is nausea. The incidence of nausea associated with exenatide ranges from 36 to 51%, while it ranged from 10.5 to 40% with liraglutide; in both cases, the nausea tends to subside in the weeks following initiation of therapy [44]. Rates of nausea specific to GLP infusion in the inpatient setting vary widely 0–40%, with a lower incidence often found in very small, short-term studies [60, 76–78]. Hospitalized patients are also often at higher risk for nausea because of need for anesthesia, gastrointestinal procedures, increased risk for ileus, and side effects of narcotics and

other medications. The potential side effect of nausea may limit the proportion of eligible patients who would benefit from this class in the hospital setting, and future studies must include examination of rates of nausea associated with injections of GLP-1RA in the hospital setting.

Sodium Glucose Transporter-2 Inhibitors (SGLT-2i)

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are the newest class of antihyperglycemic agents and decrease plasma glucose by promoting glucose excretion by the proximal renal tubule cells. The majority of glucose reabsorption occurs in this location and is facilitated by SGLT2 in the upper proximal tubule, and sodium-glucose co-transporter-1 (SGLT1) in the distal portion of the proximal tubule. Under physiologic conditions, SGLT2 plays a larger role in renal glucose reabsorption than SGLT1. SGLT2 inhibition has been demonstrated to be an effective way to impede renal glucose reabsorption, leading to increased renal glucose excretion, and lower plasma glucose levels [79, 80]. Currently, the FDA has approved the following SGLT2 inhibitors (SGLT2i) for the treatment of type 2 diabetes in adults: canagliflozin, dapagliflozin, and empagliflozin.

Cardiovascular benefits of SGLT2i have been the focus of several clinical trials since this class of medication was FDA approved for use. These have not occurred in the inpatient setting but will be discussed briefly here in the context of CV safety. The recently completed EMPA-REG OUTCOME trial was a large multicenter randomized controlled trial evaluating CV morbidity and mortality in patients with type 2 diabetes and established CV disease randomized to receive empagliflozin versus placebo for approximately 3 years [81]. Baseline HbA1c was 8%, with almost all patients enrolled in the study already being treated with diabetes standard of care therapies, including: metformin, antihypertensive therapy, and lipid-lowering agents. Approximately half (48%) of patients were on an insulin regimen prior to enrollment in the study. The primary outcome measured in this study was death from CV causes, nonfatal MI, or nonfatal stroke. The study provided evidence for the CV safety of empagliflozin, and in fact demonstrated a significantly lower rate of death from CV causes in the cohort receiving empagliflozin, regardless of dose. Additionally, the empagliflozin group had a lower rate of hospitalization for heart failure, lower rate of death from any cause, lower HbA1c levels, increased weight loss, decreased waist circumference, and a decrease in systolic and diastolic blood pressures when compared to placebo. The empagliflozin group did, however, experience a small increase in LDL and HDL cholesterol levels, and increased rate of genital infections. Although these findings support the potential beneficial CV effects of empagliflozin, these benefits cannot necessarily be extrapolated to other patients at lower CV risk, with a presumably higher number-needed-to-treat. The benefits of this medication were seen in a very high risk population with well-established CV disease at baseline. Although the mechanisms have yet to be elucidated, it is likely that extra-glycemic effects of this medication played major roles in the CV outcomes. Overall, it is unclear if similar CV effects would be seen in patients without established CV disease who take empagliflozin. The large number of hospitalized patients with well-established CV disease make empagliflozin a very attractive potential therapy for this particular setting. However, the acuity and highly dynamic status of hospitalized patients limit the extrapolation of these data to the inpatient setting. More data regarding the safety of this antidiabetic drug class and its CV effects in the inpatient population would be needed to support its use [60, 82].

The CANagliflozin cardioVascular Assessment Study (CANVAS; trial number NCT01032629) was a postmarketing FDA requirement to assess risk for major adverse cardiac events in patients with type 2 diabetes treated with canagliflozin. The study compared placebo to canagliflozin with regard to CV death, myocardial infarction, and stroke in patients with poorly controlled type 2 diabetes either with a history of CV events or who are at very high risk for an event. The results were presented and published in June 2017 and show decreased of the primary composite cardiovascular endpoint with canagliflozin [83, 84]. The Dapagliflozin Effect on CardiovascuLAR Events study (DECLARE-TIMI 58; trial number NCT01730534) is also underway and projected to be completed by April 2019. Similar to the above studies, this trial aims to evaluate the effectiveness of dapagliflozin in decreasing CV events such as myocardial infarction, ischemic stroke, and CV-related death as compared to placebo. This study also requires participants to have been diagnosed with type 2 diabetes prior to enrollment, and be at high risk for experiencing a CV event [84].

All of the previously mentioned studies on the CV safety of SGLT2i's are limited to the ambulatory setting. Although outcomes demonstrated in trials such as EMPA-REG show great promise and potential for significant CV advantages with this class of medication, it is unclear if these benefits extend beyond patients with established CV disease or if these benefits can be expected in the acute care patient group. Therefore, these studies alone are insufficient in demonstrating the safety of SGLT2i's for either glycemic control or CV health in the hospitalized patient.

The use of SGLT2i in certain patient populations is contraindicated. For example, patients with type 1 diabetes, type 2 diabetes that is ketosis prone, and those with an estimated glomerular filtration rate <60 mL/min (dapagliflozin), or <45 mL/min (canagliflozin and empagliflozin) should not be prescribed this class of medication. This is particularly important for hospitalized patients with potentially fluctuating renal status, and an increased likelihood of requiring IV contrast studies or medication therapies that can impede renal function [79]. An increased rate of urinary tract infections and balanitis has also

been reported with SGLT2i, some with potentially fatal urosepsis, which limits its use in the hospital setting [79]. The osmotic diuresis and subsequent orthostatic hypotension that can occur with SGLT2i increase risk for falls. Hospitalized patients are already at higher risk for falls, thus a medication that could increase this risk must be used only with extreme caution [79]. Reports of diabetic ketoacidosis in patients presenting with euglycemic plasma glucose levels has also occurred at higher rates in patients taking SGLT2i. In May of 2015, the FDA released a "Drug Safety Communication" regarding the increased risk of ketoacidosis with SGLT2i in both patients with type 1 and type 2 diabetes. All of the cases required hospitalization, and most presented with euglycemia or blood glucoses levels that are typically inconsistent with ketoacidosis (<250 mg/dL) [85].

SGLT2i are not considered a first-line treatment for type 2 diabetes and should not be utilized in this capacity either in the ambulatory or inpatient setting. The data available provides evidence to support the use of SGLT2i in certain patient populations as a monotherapy, dual or triple therapy, and in conjunction with insulin in the ambulatory setting only. The dynamic status of hospitalized patients and the many contraindications decrease the suitability of SGLT2i for most inpatient scenarios. Starting a hospitalized patient on these medications may only be appropriate for those who have been established on them as an outpatient, are stable on floor status, are preparing for immediate discharge, and who do not meet any of the above contraindications for administration.

Balancing Benefits Versus Risks—Clinical Recommendations

Unfortunately, the level of evidence for CV risk of most antidiabetic drugs for the hospitalized patient is low. However, a suggested algorithm for antidiabetes drug therapy in the

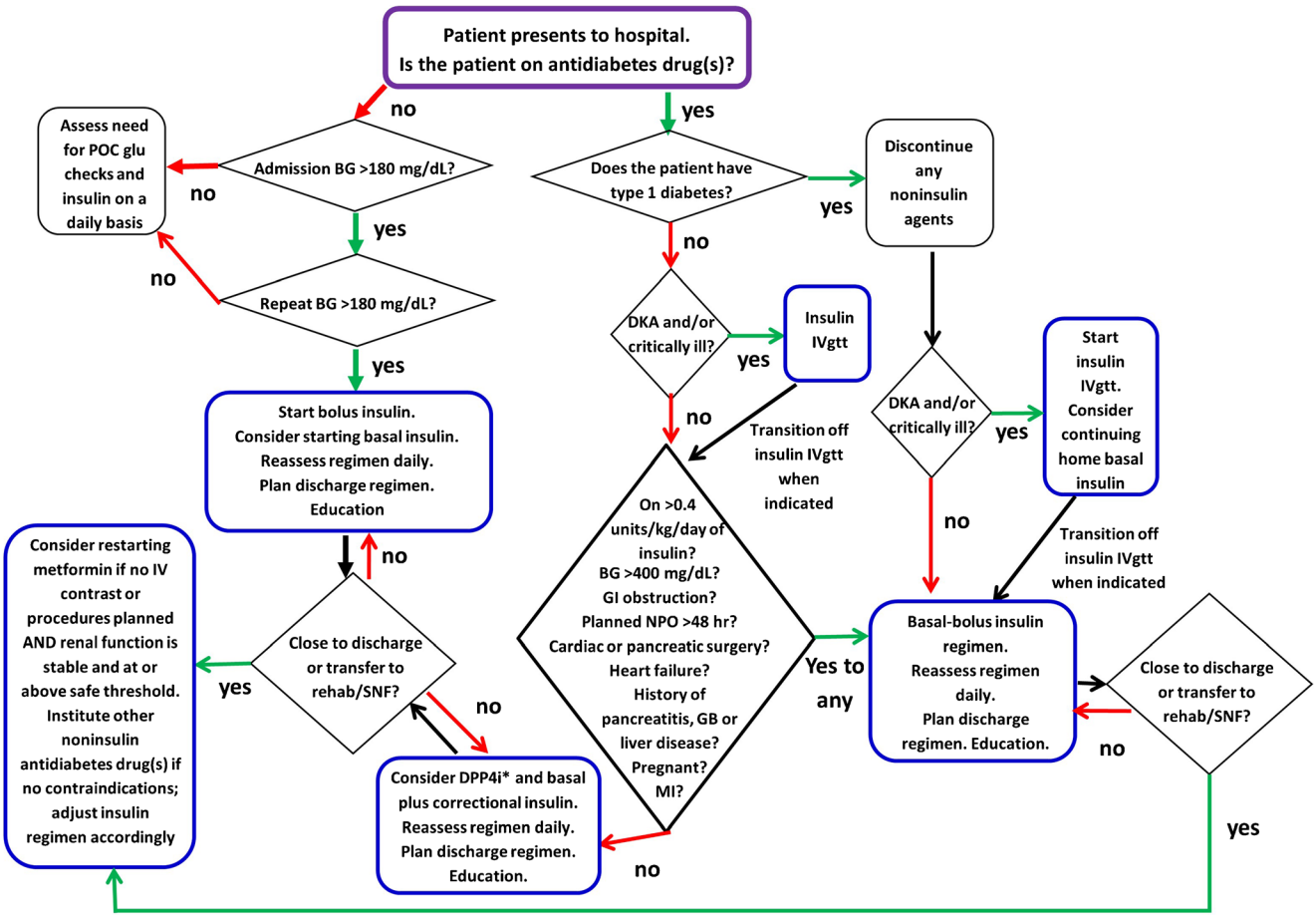

Fig. 1 Schematic of an algorithm suggested by the authors for use of antidiabetes drugs in the hospital setting. *Evidence for dipeptidylpeptidase-4 inhibitor (DPP4i) therapy is still limited and must be used with caution. DPP4i must be dose-adjusted for renal function except for linagliptin. The use of saxagliptin or alogliptin would not be recommended in the setting of known or suspected heart failure until further clinical trial information is available. Restarting metformin may be considered in select patients who are nearing discharge who are not at high risk for metabolic acidosis or are clinically stable on an inpatient rehabilitation or psychiatric unit. *BG* blood glucose, *DKA* diabetic ketoacidosis, *DPP4i* dipeptidylpeptidase-4 inhibitor, *GB* gallbladder, *IVgtt* intravenous drip, *MI* myocardial infarction, *NPO* nil per os, *POC* point-of-care, *rehab* rehabilitation facility, *SNF* skilled nursing facility

hospital setting is presented in Fig. 1 and represents the authors' opinions based on the available evidence, as well as clinical experience. The authors agree that insulin is and should be the mainstay treatment for inpatient diabetes control, as recommended by current guidelines [1, 2]. Improved insulin infusion protocols with use of computerized algorithms, continuous process improvement regarding timing of insulin dosing with meals, modification of doses for NPO status, hospital-wide staff education, and conservative dosing in acute kidney injury and elderly patients are among the many strategies that need to be implemented to minimize and avoid hypoglycemia, thus reducing the risk of harmful CV effects [13, 14, 47, 48]; insulin protocols with prevention of hypoglycemia have been shown to constitute safe treatment for hyperglycemia in both the ICU [11, 12, 49–52] and non-ICU settings [53–55].

Incretin-enhancing therapy provides an alternative/amendment to insulin use in the inpatient setting. These drug classes can improve glycemic control, decrease the need for insulin, and are associated with lower risk of hypoglycemia in the absence of insulin or sulfonylureas. Robust outpatient studies demonstrate CV safety, and some studies even show possible CV benefit [62]. Recent randomized controlled trials have shown a potential role for DPP-4i in the non-ICU setting. Limited studies have shown that the use of GLP-1RA in the hospital may provide cardioprotective benefits that are worth pursuing, along with the benefit of decreased hypoglycemia in patients with diabetes and stress/steroid-induced hyperglycemia, although this drug class may be limited by nausea [56, 65–70]. The American Diabetes Association guidelines for inpatient diabetes management states that while there hope for use of incretins in the inpatient setting, the proof of incretin safety and efficacy compared with standard therapies awaits the results of further randomized controlled trials [2].

Although the use of metformin is not recommended upon admission to the hospital or ICU, re-instituting metformin therapy may be considered in patients who are nearing discharge and are clinically stable with good renal function, pulmonary, and cardiac status without increased risk for metabolic acidosis, or on an inpatient rehabilitation or psychiatry unit.

For clinically stable patients who are eating, do not require or are not good candidates for basal-bolus insulin therapy, and whose discharge plan includes sulfonylurea therapy, instituting sulfonylurea therapy prior to discharge may assist with assessment of glycemic control on a proposed home diabetes regimen [59].

SGLT2i are currently not recommended in the inpatient setting. Although a CV benefit of empagliflozin was demonstrated in the EMPA-REG OUTCOME and the CANVAS trials [81, 84], this was in patients with type 2 diabetes with established CV disease or at high CVD risk in the outpatient setting only [81]. Overall, SGLT2i have typically been shown to produce a moderate improvement in glycemic control, weight loss, decrease in systolic blood pressure, and have a low risk of hypoglycemia (unless combined with another agent prone to hypoglycemia, such as a sulfonylurea). However, this class of medication is also associated with higher rates of genital and urinary tract infections (more common in women) can cause hypotension and hypovolemia secondary to osmotic diuresis, are high in cost, and are associated with ketoacidosis in some patients, lessening the enthusiasm for the use of this class of antidiabetic drugs in the hospital setting.

Conclusions

A plethora of new treatments for diabetes have become available in the last 15 years. While most of these antidiabetic drugs have undergone extensive clinical trials in the outpatient setting, very few (if any) randomized controlled studies have been performed to validate their use in the ICU or non-ICU hospital setting. Furthermore, available studies were not necessarily designed to examine the benefits/risks of the pharmacologic treatment per se versus degree of glycemic control. We conclude that in a select inpatient population, use of a DPP4i may be a good option to reduce risk for hypoglycemia while maintaining glycemic control when used alongside bolus insulin. As patients approach discharge, it may be feasible to restart home oral antidiabetic agents such as metformin and/or insulin secretagogues to better assess glycemic control on a proposed home regimen as part of a personalized discharge plan [2]. More multicenter clinical trials of glucose-lowering therapies are needed in the hospital setting. Ideally, these would consist of randomized, controlled, clinical trials. However, an alternative might be pragmatic trials in the inpatient setting, ideally multi-institutional, with sufficient sample size to assess overall safety and effectiveness for improving clinical outcomes.

Compliance with Ethical Standards

Conflict of Interest Stacey A. Seggelke, Mark C. Lindsay, Ingrid Hazlett, Rebecca Sanagorski, Robert H. Eckel, and Cecilia C. Low Wang declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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