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DEBATE

# Debate on Insulin vs Non-insulin Use in the Hospital Setting—Is It Time to Revise the Guidelines for the Management of Inpatient Diabetes?

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## Abstract

**Purpose of Review** Hyperglycemia contributes to a significant increase in morbidity, mortality, and healthcare costs in the hospital. Professional associations recommend insulin as the mainstay of diabetes therapy in the inpatient setting. The standard of care basal–bolus insulin regimen is a labor-intensive approach associated with a significant risk of iatrogenic hypoglycemia. This review summarizes recent evidence from observational studies and clinical trials suggesting that not all patients require treatment with complex insulin regimens.

**Recent Findings** Evidence from clinical trials shows that incretin-based agents are effective in appropriately selected hospitalized patients and may be a safe alternative to complicated insulin regimens. Observational studies also show that older agents (i.e., metformin and sulfonylureas) are commonly used in the hospital, but there are few carefully designed studies addressing their efficacy.

**Summary** Therapy with dipeptidyl peptidase-4 (DPP-4) inhibitors, alone or in combination with basal insulin, may effectively control glucose levels in patients with mild to moderate hyperglycemia. Further studies with glucagon-like peptide-1 (GLP-1) receptor analogs and older oral agents are needed to confirm their safety in the hospital.

**Keywords** Hospitalized patients · Inpatient · Diabetes · DPP-4 inhibitors · Incretin · Insulin

## Introduction

The association between inpatient hyperglycemia and adverse clinical outcomes in critically and non-critically ill patients is well established [1–6]. Extensive data from observational and prospective randomized controlled trials (RCTs) in hospitalized patients have reported that hyperglycemia, in patients with and without diabetes, is associated with increased hospital complications, longer length of stay (LOS), and mortality [3, 7–9]. In addition, several clinical trials in critically ill and general medicine and surgery patients have reported that improvement of glycemic control reduces LOS, risk of multiorgan failure, and systemic infections, as well as short- and long-term mortality in patients with hyperglycemia and diabetes [9–15].

Clinical guidelines from professional organizations recommend the use of insulin as the cornerstone of therapy for the management of patients with hyperglycemia (defined as blood glucose [BG] > 140 mg/dl) and diabetes in the hospital [1, 2, 16]. Initiation of insulin therapy is recommended for hospitalized patients with history of diabetes as well as those experiencing stress hyperglycemia for BG levels > 180 mg/dl during the hospital stay [1, 11, 17, 18]. The use of intravenous insulin therapy is the regimen of choice for critically ill patients [2], and subcutaneous insulin is the preferred therapy in general medicine and surgery patients with diabetes [1, 19]. Several studies have shown that the administration of basal or basal bolus insulin regimens results in improved glycemic control [1, 2, 11, 20]. Despite its efficacy, the basal bolus regimen amplifies the risk of hypoglycemia and may lead to overtreatment, particularly for those with mild to moderate hyperglycemia, which is reported in 12–30% of patients in clinical trials [1, 11]. In observational

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studies, inpatient hypoglycemia has also been consistently associated with increased length of stay and mortality [21, 22].

Practice guidelines by the American Diabetes Association (2004 and 2009) and The Endocrine Society in 2012 for the management of inpatient hyperglycemia and diabetes recommended against inpatient use of oral antidiabetic drugs (OADs) and non-insulin injectable medications due to safety and efficacy concerns [1, 2, 16]. Potential limitations to using oral antidiabetic agents in the inpatient setting relate to the delay and unpredictable onset of action of these drugs, which can prevent rapid attainment of glycemic control or dose adjustments to meet the changing needs of the acutely ill patient. It is important to indicate that when these guidelines were written the primary categories of oral agents available were insulin secretagogues (sulfonylureas and meglitinides), biguanides, and thiazolidinediones [16], and none of these had been studied in randomized controlled trials. In recent years, however, new classes of medications have been added to the armamentarium of antihyperglycemic agents used in the outpatient setting including incretin-based therapies (dipeptidyl peptidase-4 [DPP-4] inhibitors and glucagon-like peptide-1 [GLP-1] receptor agonist) and sodium-glucose cotransporter 2 inhibitors (SGLT-2i). Several studies have reported encouraging results on the safety and efficacy of incretin-based therapies compared with basal bolus insulin regimen for the management hospitalized patients with type 2 diabetes [23–28, 29•, 30•].

The use of OADs in the hospital is common in clinical practice worldwide [31–40]. Oral diabetes medications may have important non-glycemic benefits and may reduce the risk of widely fluctuating blood glucose levels during titration of insulin therapy after hospital admission [41]. Here, we review the evidence on the management of hyperglycemia with non-insulin agents in hospitalized patients. The results of five randomized controlled trials and a recent observational study indicate that the use of non-insulin agents, either in the hospital [23–30] or after hospital discharge [42], are effective in improving glycemic control in general medicine and surgery patients with mild and moderate hyperglycemia, and are associated with a significant lower risk of hypoglycemia compared with basal bolus insulin therapy [25–27, 29•, 30•]. The strength of recent data indicates that it is time for a change in the paradigm of diabetes management in the hospital and after discharge.

## Hospital Use of Older Oral Agents: Metformin, Sulfonylureas, and Thiazolidinediones

There is limited information on the use of older oral agents in the hospital setting. Recent observational studies suggest, however, that OAD use may be associated with better outcomes compared with insulin therapy. Haltmeirt et al. [38] reported an analysis including 7401 patients with DM undergoing emergency abdominal surgery, 3182 (43%) of whom were insulin treated, and 4219 (57%) treated with oral agents (patients were matched for sex, age, ASA score, BMI category, operative procedure, and preoperative acute renal failure, pneumonia, SIRS, sepsis, septic shock, and corticosteroid use). Insulin-treated patients were more likely to have postoperative complications (odds ratio [OR], 1.28; 95% confidence interval [CI], 11.12–1.46), had a higher 30-day mortality rate in patients admitted with sepsis (OR 3.421, CI 1.959–5.974), and had a longer hospital length of stay (regression coefficient [RC] 1.115, CI 1.07–1.17) and postoperative LOS (RC 1.08, CI 1.031–1.135). Postoperative urinary tract infection (5.6 vs 3.8%, $p = 0.005$), cardiac arrest (2.7 vs 1.6%, $p = 0.010$), and complications overall (35.2 vs 30.7%, $p = 0.001$) were significantly more frequent in insulin-treated patients. In addition, the median total hospital LOS (9.0 vs 8.0, $p = 0.003$) and postoperative LOS (mean 11.4 vs 10.7, $p = 0.05$) were significantly longer in insulin-treated patients. Similarly, Karamanos et al. [43] reported an increased risk for surgical site infections and postoperative cardiac arrest in insulin-treated patients compared with oral agent–treated patients with DM undergoing emergency cholecystectomy for acute cholecystitis.

### Metformin

Metformin is the first-line treatment for type 2 diabetes in the outpatient setting. In addition, metformin is the most commonly used oral agent in hospitalized patients in the USA and other countries [31–35]. It was not licensed in the USA until 1995 because of fear of lactic acidosis, a rare but fatal complication initially described with exposure to phenformin [44]. Metformin does impair gluconeogenesis from lactate [45, 46]; however, multiple cohort studies and meta-analyses have reported no increased risk of lactic acidosis. A Cochrane review found no cases of fatal or non-fatal lactic acidosis in 59,321 patient-years of metformin use [47]. In addition, metformin has important non-glycemic benefits and does not cause hypoglycemia. In clinically stable patients, there is no good evidence to support routinely stopping metformin at hospital admission. However, because the risk of lactic acidosis increases with declining renal function, metformin dosage reduction is recommended if the estimated glomerular filtration rate is 30 to 45 mL per minute per 1.73 $m^2$, and metformin should be discontinued if it is less than 30 ml per minute per 1.73 $m^2$ [48].

A recent study evaluating the effects of metformin on stroke severity and outcomes in acute ischemic stroke patients with type 2 DM reported that the administration of metformin prior to stroke onset was associated with reduced neurological severity and improved acute-phase therapy outcomes [49]. Around 355 stroke patients with type 2 DM without severe renal impairment or prestroke impairment of activities of daily

living neurological severity were assessed according to the National Institutes of Health Stroke Scale (NIHSS) score on admission [49]. On logistic regression analysis with adjustments for multiple confounding factors, pretreatment with metformin was independently associated with improved neurological symptoms (OR, 2.12; 95% confidence interval [CI], 1.09–4.10; $p = .026$). A benefit of prior metformin use was observed in patients with a prior history of stroke.

Sarfo-Adu et al. [50] recently reported the results of a retrospective study involving patients with diabetes who received enteral tube feeding during their hospitalization. In a total of 40 patients (mean age 67 (29–94) years, 60% were male, 97.5% had type 2 diabetes, and 60% were on oral hypoglycemic agents prior to admission) during enteral tube feeding, blood glucose was controlled using metformin, subcutaneous insulin, or intravenous insulin. The recommended target glycemic range of 108–216 mg/dl (6–12 mmol/l) was achieved in 66% of patients treated with metformin during enteral feeding, similar to insulin therapy [50].

A few case reports have reported a risk of lactic acidosis associated with metformin exposure in patients with established risk factors, such as severe renal or liver failure [44]. In a matched case–control analysis, the use of metformin was not associated with lactic acidosis except in the setting of concomitant acute kidney injury [51]. However, metformin should be avoided in critically ill patients with severe liver disease, renal impairment, or decompensated heart failure [36, 37]. It should be noted that the inpatient use of metformin has not been prospectively investigated in the hospital setting; therefore, current guidelines have not recommended its use in the hospital.

### Sulfonylureas

Data from inpatient settings in 659 acute-care US hospitals showed that about 1 in 5 patients is treated sulfonylureas (SU) during hospitalization [31], with higher inpatient utilization of SU reported in other countries [31–33].

Preliminary studies have indicated that sulfonylurea drugs (SUD) may confer protection against cerebral swelling and hemorrhagic transformation in severe acute ischemic stroke [52–54]. The preclinical use of SU drugs has been shown to reduce infarct volume, decrease mortality rate, and improve functional outcome in the setting of acute cerebral ischemia [53, 55]. In addition, animal models have indicated that SU may be associated with decreased rates of hemorrhagic transformation and decompressive surgery for cerebral edema in acute ischemic stroke [54, 56]. The reported benefits of SUD have been related to its inhibition of the Sur1-Trpm4 channel which is selectively expressed in ischemic neuronal tissue after stroke and regulates oncotic swelling [57]. However, a recent study among 148 patients with acute ischemic stroke with 42 (28%) cases pretreated with SU failed to demonstrate improvement on prevalence of complications and favorable outcomes between patients pretreated and non-pretreated with SU [52].

Results from a nested case–control study showed that up to 19% sulfonylurea-treated patients experienced at least 1 episode of hypoglycemia in the hospital. Age ≥ 65 years, concurrent treatment with insulin, and GFR ≤ 30 were independent predictors of hypoglycemia [58]. In a multicenter retrospective review, similar risk factors for inpatient hypoglycemia associated with SU use have been reported [34]. Patients treated with sulfonylurea actually had a lower number of hypoglycemia readings than those on insulin therapy (SU 23% vs insulin 36%). There were no differences in the percentage of participants with ≥ 5 hypoglycemic readings in those treated with insulin or sulfonylurea. Current US professional societies recommend against the inpatient use of sulfonylureas because of the potential risk of sustained hypoglycemia [59, 60].

### Thiazolidinediones

The use of thiazolidinediones (TZDs) is less documented in the inpatient setting. It has been estimated that 7–11% of patients treated with antihyperglycemic agents in the hospital receive TZDs [31, 61]. A higher utilization has been reported in India [35]. The delayed onset of action and the potential for fluid retention and risk of heart failure make TZDs less attractive for inpatient use [1, 62]. It is not known, however, if whether, in patients without heart failure already treated with TZDs, discontinuing these agents leads to worsening glycemic control. The low risk of hypoglycemia with TZD use when used as monotherapy may be beneficial in select populations. In addition, there is no need to adjust the dose of TZDs in patients with renal impairment.

In a case-matched observational study [63], the use of thiazolidinediones was associated with enhanced functional recovery of stroke patients with type 2 diabetes admitted for acute inpatient stroke rehabilitation. Improvements were observed in total functional independence measure scores and mobility sub-score compared with the control group [63]. Furthermore, among patients with insulin resistance, who had a recent ischemic stroke or transient ischemic attack (TIA), exposure to pioglitazone was associated with lower risk of stroke or myocardial infarction compared with placebo [64]. The delayed onset of action and risk of volume retention make the initiation of TZDs less attractive for inpatient use.

## Incretin-Based Therapies

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are two incretin hormones secreted in the gastrointestinal tract in response to nutrients. This response accounts for > 90% of the incretin effect, which

represents a 2- to 3-fold greater secretion of insulin from β-cells following oral versus intravenous glucose administration. These hormones also have an inhibitory effect on glucagon. Both mechanisms provide a normal physiologic response in the presence of glucose with a low risk of hypoglycemia [65, 66]. Recent clinical trials testing the efficacy of *DPP-4 inhibitors* (drugs that inhibit the degradation of incretins) as well as with native GLP-1 or receptor analogs (GLP-1 RA) have shown promising results. In addition, DPP-4 inhibitors have been shown to have a safe cardiovascular risk profile and several of the GLP-1 RA have actually been shown to reduce cardiovascular outcomes [67–70].

## Dipeptidyl-Peptidase-4 Inhibitors

Several RCT and observational studies have shown that the use of DPP-4-I alone or in combination with basal insulin is safe and effective for the management of general medicine and surgery patients with type 2 diabetes [25–28, 30•].

The first pilot RCT investigating the use of a DPP-4 inhibitor in non-critically ill patients suggested sitagliptin was effective in patients with type 2 diabetes with mild to moderate hyperglycemia [25]. In this open-labeled pilot trial, 90 patients were randomized to sitagliptin alone, sitagliptin plus basal insulin, or basal–bolus insulin. Patients included in the study were treated at home with either diet alone, oral agents, or low doses of insulin (< 0.4 units/kg/day). No differences were observed in the primary outcome of mean daily blood glucose (sitagliptin 168 ± 35; sitagliptin plus basal 154 ± 29; basal bolus 158 ± 31, $p = 0.23$) (Table 1). The total daily dose (TDD) of insulin and the number of insulin injections were lower in the sitagliptin groups compared with basal bolus. A subanalysis showed that patients with randomization BG > 180 mg/dl treated with sitagliptin alone tended to have higher mean daily BG, suggesting that monotherapy with a DPP-4 inhibitor may not be as effective for patients with moderate to severe hyperglycemia.

In a larger study (*n* 277), we compared the efficacy and safety of the combination of sitagliptin with a single dose of basal insulin compared with basal bolus in patients with a wide range of hemoglobin A1c (HbA1c) levels on admission and insulin home doses up to 0.6 units/kg/day [30•]. This study reproduced the preliminary findings of the pilot study. Treatment failure (two consecutive BG > 240 mg/dl or a mean daily BG > 240 mg/dl) occurred in 22 patients (16%), in the sitagliptin–basal group versus 26 (19%) in the basal–bolus group ($p = 0.54$). In addition, treatment failure in this study was independently associated with higher A1c levels, as previously described [75], with 30% higher odds of failing per one unit change in HbA1c (OR 1.3, 95% CI 1.2–1.5).

Recently, the glycemic efficacy and safety of linagliptin was compared with basal–bolus insulin regimen in general surgery patients with T2D [28]. This prospective open-label multicenter study randomized T2D patients undergoing non-cardiac surgery with admission blood glucose (BG) between 140 and 400 mg/dl treated with diet, oral agents, or total insulin dose (TDD) ≤ 0.5 units/kg/day to linagliptin ($n = 128$) daily or basal–bolus ($n = 122$) with glargine once daily and rapid-acting insulin before meals. Both groups received supplemental insulin for BG > 140 mg/dl. The primary endpoint was the difference in mean daily BG between groups. We reported a mean daily BG difference of 10.8 mg/dl (95% confidence interval 0.72, 22 mg/dl). In patients with randomization BG < 200 mg/dl (63% of cohort), mean daily BG was similar in linagliptin vs basal-bolus (160 ± 41 vs 157 ± 41 mg/dl, $p = 0.43$); however, patients with BG ≥ 200 mg/dl treated with linagliptin had higher BG compared with basal-bolus (196 ± 47 vs 165 ± 47 mg/dl, $p < 0.001$). Linagliptin resulted in fewer hypoglycemic events (1.6% vs 11%, $p = 0.001$, 86% relative risk reduction), similar supplemental insulin doses, and lower number of daily insulin injections (2.0 ± 3.3 vs 3.1 ± 3.3, $p < 0.001$) compared with basal–bolus.

In another clinical trial enrolling patients with very mild hyperglycemia (admission BG ~ 150 mg/dl and mean A1c < 7%), Garg et al. reported that the use of saxagliptin alone was as effective as a basal–bolus regimen in medical and surgical patients with T2D [27].

The results of these trials indicate that treatment with oral DPP-4-I alone or in combination with basal insulin is safe and effective and offers an effective alternative to the basal–bolus insulin therapy in most patients with diabetes, especially in patients who present with a BG < 200 mg/dl. In addition, the treatment with DPP-4-I results in lower rates of hypoglycemia compared with insulin therapy.

## GLP-1 Receptor Analogs

GLP-1 receptor agonists (GLP-1RA) are a commercially available class of antihyperglycemic medications that are growing in use due to their relatively strong efficacy in lowering blood glucose and low risk of hypoglycemia. These characteristics make them an attractive option for inpatient use as well. Additionally, GLP-1RA have been found to exert cardiovascular benefit in preclinical studies and clinical trials. Several pilot trials have reported that infusion of endogenous GLP-1 and GLP-1RA use may lead to improved endothelial function [76], reduced infarct size following myocardial infarction [77], and increased left ventricular function in patients with heart failure [78, 79] and in patients following coronary artery bypass graft (CABG) [80, 81]. Large randomized controlled trials have shown cardiovascular benefit associated with the use of GLP-1RAs [67–70], suggesting a class effect. Both native GLP-1 and GLP-1 receptor agonists (GLP-1 RA) have been studied in the hospital setting [76, 79, 80].

**Table 1** Recent randomized clinical trials testing the use of incretin-based therapies in the hospital

| Author (year) | Intervention arms | Population | Setting | Primary outcome | Key findings |
|---|---|---|---|---|---|
| DPP-4-i | | | | | |
| Umpierrez et al. (2013) [25] | -Sitagliptin alone<br>-Sitagliptin plus basal insulin<br>-Basal bolus | $N = 90$<br>(BG between 140 and 400 mg/dl on OAD or low-dose insulin therapy (≤ 0.4 units/kg/day) | Medical and surgical wards | Mean difference in hospital glucose | Similar glycemic control between groups. TDD and # of insulin injections were less in the sitagliptin groups compared with the basal bolus. Patients with a randomization BG > 180 mg/dl treated with sitagliptin alone had higher mean daily BG. |
| Pasquel et al. (2017) [30] | -Sitagliptin plus basal insulin<br>-Basal–bolus | $N = 277$<br>BG between 140 and 400 mg/dl on OAD or low-dose insulin therapy (≤ 0.6 units/kg/day) | Medical and surgical wards | Mean difference in hospital glucose | No significant difference in mean daily blood glucose concentrations.<br>Treatment with sitagliptin and basal insulin required a lower daily insulin dose and fewer insulin injections. |
| Garg et al. (2018) [27] | -Saxagliptin<br>-Basal–bolus | $N = 66$<br>T2D with HbA1c ≤ 7.5% on a ≤ 1 non-insulin hypoglycemic agent or HbA1c ≤ 7.0% on ≤ 2 non-insulin hypoglycemic | Medical and surgical wards | Mean daily BG level during study days 2–5 | Saxagliptin use was non-inferior to basal–bolus insulin in non-critically ill hospitalized patients with T2D controlled on 0–2 oral agents without insulin (149.8 ± 22.0 vs 146.9 ± 30.5, $p = 0.59$) |
| Vellanki et al. (2018) [26] | -Linagliptin<br>-Basal–bolus | $N = 250$<br>(BG) between 140 and 400 mg/dl on OAD or low-dose insulin therapy (≤ 0.5 units/kg/day) | Surgical ward | Non-inferiority in mean daily BG between groups | In patients with mild to moderate hyperglycemia (BG < 200 mg/dl), daily linagliptin resulted in similar glucose control with lower hypoglycemia (83% RRR). Patients with BG > 200 mg/dl at randomization had worse control compared with insulin. |
| GLP-1-based interventions | | | | | |
| Abuannadi et al. (2013) [71] | -Exenatide I.V.<br>-Historical controls<br>A. Intensive target (90–119 mg/dl)<br>B. Modified insulin infusion (100–140 mg/dl) | $N = 40$<br>Non-DM and non-insulin dependent T2D, BG 140–400 mg/dl<br>Admission for primary cardiac diagnosis | Coronary intensive care unit | Median glucose values during steady state.<br>In | Non-randomized study, major limitation. Steady-state BG was similar for exenatide and moderate insulin protocol (132 mg/dl [IQR 110, 157] vs 127 [105, 161], $p = 0.15$) but higher than in the intensive insulin group (105 [92, 128], $p$ 0.001) |
| Kohl et al. (2013) [72] | -Native GLP-1<br>-Placebo | $N = 77$<br>Non-DM and non-insulin dependent T2D undergoing elective cardiac surgery with cardiopulmonary bypass | Perioperative cardiac surgery | Mean glucose level 30 min after bypass | Mean BG was lower 30 min after bypass in GLP-1 group (113 ± 21 vs 128 ± 21, $p = 0.001$). Overall intraoperative mean BG was 12 mg/dl lower with GLP-1 ($p = 0.015$) |
| Besch et al. (2017) [73] | -Exenatide infusion<br>-Insulin infusion | $N = 104$<br>Non-DM and non-insulin-dependent T2D, undergoing CABG | Perioperative CABG surgery | Superiority in proportion of patients with ≥ 50% of time within target range of 100–139 mg/dl | Study stopped prematurely after futility analysis. The primary outcome was observed in 72% of patients in the exenatide group and 80% in the insulin group ($p = 0.3$).<br>Consumption of insulin was lower (~ 30 units less) and time before starting insulin was longer in the exenatide than insulin groups. Most patients required insulin infusion. |

**Table 1** (continued)

| Author (year) | Intervention arms | Population | Setting | Primary outcome | Key findings |
|---|---|---|---|---|---|
| Polderman et al. (2017) [74] | -Liraglutide<br>-Glucose infusion<br>-Bolus insulin | $N = 150$<br>T2D on diet, OAD or insulin < 1 u/kg, undergoing non-cardiac surgery | Perioperative non-cardiac surgery | Differences in median BG 1 h post surgery | Median BG 1 h post-op was lower in the liraglutide group (6.6 [IQR 5.6–7.7] mmol/l compared with insulin infusion 7.5 (6.4–8.3) or bolus insulin 7.6 (6.4–8.9), $p = 0.006$. More nausea was reported with liraglutide, $p = 0.007$ |
| Fayfman et al. (2019) [29] | -Exenatide<br>-Exenatide + basal<br>-Basal bolus | $N = 150$<br>T2D, BG 140–400 mg/dl on diet, OAD, or low-dose insulin (≤0.5 units/kg/day) | Medical and surgical wards | Differences in hospital mean daily BG after day 1 | Combined use of exenatide and basal insulin resulted in lower mean bg than exenatide alone (154 ± 39 vs 177 ± 41, $p = 0.02$) and was similar to basal bolus (166 ± 40 mg/dl, $p = 0.31$)<br>Exenatide plus basal resulted in higher % of BGs within target range 70–180 mg/dl than the other treatment groups (78% vs 62% vs 63%, $p = 0.023$). |

*BG* blood glucose, *OAD* oral antidiabetic drugs, *TDD* total daily dose

GLP-1 RA and native GLP-1 have also been considered in critically ill and surgical patients [71–73, 74•]. An early proof-of-concept non-randomized study in cardiac surgery patients with hyperglycemia suggested intravenous exenatide use was feasible, effective, and associated with a low risk of hypoglycemia compared with historical controls [71]. In a randomized trial, Besch et al. compared the use of IV exenatide to insulin infusion in cardiac surgery patients [73]. A total of 104 subjects (21% with DM) undergoing CABG surgery were randomized to receive exenatide bolus followed by continuous infusion or intravenous insulin infusion both starting after patients develop stress hyperglycemia (BG ≥ 140 mg/dl). Both infusions were continued for up to 48 h. The primary outcome of superiority in the proportion of patients with at least 50% of BG readings within the target range of 100–139 mg/dl was not met. They reported that 72% of the exenatide-treated subjects and 80% of the insulin-treated group ($p = 0.3$) met the target glucose concentration. Subjects in the exenatide arm received less insulin overall and had a longer time interval to initiation of insulin. In a sub-study, they reported that exenatide use did not lead to reduced myocardial reperfusion injury [82]. Similar findings were reported in pediatric burn patients where subcutaneous exenatide use resulted in similar glycemic control to treatment with intensive insulin therapy [83]. Insulin rescue therapy doses were significantly reduced in the exenatide-treated group. In a study aimed at preventing hyperglycemia with early infusion of native GLP-1 vs placebo, Kohl et al. reported a significant reduction in plasma glucose at the primary endpoint of 30 min of cardiopulmonary bypass in CABG patients (113 ± 21 vs 128 ± 21, $p = 0.0001$). Glucose levels were better controlled during the perioperative period in the GLP-1 group, and no hypoglycemic episodes occurred in either group [72].

Perioperative treatment with GLP-1 RA, liraglutide, given subcutaneously prior to non-cardiac surgery was studied by Poderman et al. [74•]. In an open-label multicenter trial, subjects with type 2 diabetes were randomized to receive either liraglutide subcutaneously starting 1 day before surgery, insulin infusion, or subcutaneous insulin with 50% of their home insulin dose given the morning of surgery. Treatment with liraglutide was associated with lower glucose levels 1 h following surgery with no differences in hypoglycemia or postoperative complications. This occurred at the expense of increased preoperative nausea rates. Liraglutide was administered subcutaneously with a low dose of 0.6 mg the night before surgery and titrated to 1.2 mg the day of surgery. A larger European multicenter trial with similar design is ongoing enrolling 274 cardiac surgery aiming at reducing the number of patients that need any insulin to achieve BG < 8 mmol/l (144 mg/dl) in the intraoperative period [84].

In a recently published study, our group evaluated the effects of subcutaneous exenatide 5 mcg administered twice daily both with and without basal insulin as compared with

standard basal–bolus insulin therapy among 150 patients with type 2 diabetes admitted to general medicine and surgery services [29•]. Patients treated with exenatide plus basal insulin in the hospital had similar mean BG to those on basal–bolus insulin (154 ± 39 vs 166 ± 40, $p = 0.31$) and had lower mean BG than those on exenatide treatment alone (177 ± 4, $p = 0.02$). We found that treatment with exenatide plus basal insulin resulted in higher percentage of blood glucose readings within the target range of 70–180 mg/dl (78%) as compared with exenatide alone (62%) or basal–bolus insulin (63%).

As expected based on side effects reported in outpatient studies, GLP-1 use was associated with increased rates of nausea [29•, 74•]. In our study of patients receiving twice daily injections of exenatide in the hospital, we observed a non-statistically significant increase in gastrointestinal side effects among those receiving exenatide [29•].

The available data supports the use of GLP-1RA in the inpatient setting, with improved glycemic control and lower rates of hypoglycemia (in the non-ICU setting). Its use, however, is limited by potential risk of gastrointestinal side effects and may need to be avoided in people who have active gastrointestinal conditions during hospitalization. However, newer long-acting agents that can be administered just once a week and have improved side effect profiles may be good candidates for future inpatient studies.

## SGLT-2 Inhibitors

SGLT-2 inhibitors are a class of oral antihyperglycemic agents that block the SGLT-2 sodium-glucose cotransporter in the renal proximal collecting tubules. This prevents glucose reabsorption by the kidneys leading to glycosuria [85]. In addition to improving glycemic control, SGLT-2i have significant cardiovascular benefit with large randomized controlled trials showing reduced CVD-related mortality and fewer hospitalizations for heart failure [86, 87]. Despite these favorable characteristics, SGLT-2i have several side effects that may limit potential for inpatient use. One major concern is that SGLT-2i have been associated with cases of euglycemic diabetic ketoacidosis. Despite the high level of concern, these cases remain rare with clinical trials reporting rates of 0.2–0.8 cases per 1,000 patient years among patients with type 2 diabetes [86, 88]. The risk, however, is increased in patients who are not eating or have an acute illness, so higher rates may be expected in hospitalized patients. Additional concerns include genitourinary infections and potential risk of rare but more serious infections (i.e., Fournier's gangrene) [48]. Patients with heart failure may be the ideal candidates for SGLT-2i use in the inpatient setting. A small pilot RCT (ClinicalTrials.gov Identifier: NCT03200860), recruiting 80 patients with acutely decompensated heart failure, is testing the safety and efficacy of empagliflozin in the inpatient setting. The primary outcomes of interest include change in dyspnea, diuretic response, weight change from baseline per 40 mg of furosemide equivalent, length of hospital stay, and change in plasma NT-proBNP. Positive findings would warrant larger clinical trials before SGLT-2i are recommended for inpatient use, given current safety concerns.

## Discussion and Conclusions

The use of oral agents has been considered a less attractive option than insulin therapy for the management of hyperglycemia in the hospital. Evidence from recent studies, however, shows that OADs are widely used in the hospital setting [31–40]. Non-insulin agents may have important non-glycemic benefits and may reduce the risk of widely fluctuating blood glucose levels after hospital admission [41]. Our review of the literature suggests that oral diabetes medications taken at home should be reviewed carefully for possible contraindications, but they may be continued in stable patients tolerating meals, and without significant renal or cardiac failure [23–28, 29•, 30•, 38, 43]. Despite these observations, further research is needed to assess comprehensively the efficacy and safety of older oral agents (i.e., metformin, SU) in the hospital. Recent results from RCTs [25–27, 30•] show that DPP-4 inhibitors are safe and effective for the management of mild to moderate hyperglycemia in non-critically ill patients. In addition, the use of GLP-1 RA also appears promising for the management of hyperglycemia in the perioperative period [72, 74•] and regular wards [29•].

Metformin is the most commonly used oral agent in the outpatient and inpatient settings. It has been associated with better glycemic control, reduced LOS, and lower rate of complications compared with insulin therapy in general medicine and surgery patients [38]. Similarly, the use of metformin in patients with type 2 diabetes admitted with acute ischemic stroke was associated with reduced neurological severity and improved acute-phase therapy outcomes [49]. Metformin-associated lactic acidosis is rare, and can be avoided with proper patient selection, avoiding its use in individuals with severe kidney or liver disease [36, 37]. Although sulfonylurea drugs are widely used in the hospital [31–33], their use in patients with poor oral intake or with kidney failure has been associated with increased risk of hypoglycemia [59, 60]. Results from a nested case–control study showed that up to 19% sulfonylurea-treated patients experienced at least 1 episode of hypoglycemia in the hospital. The use of sulfonylureas may confer protection against cerebral swelling and hemorrhagic transformation in severe acute ischemic stroke [52–54] and represents an area of active research.

A strong set of data from several randomized controlled trials as well as observational studies indicates that the use of incretin agents (particularly DPP-4 inhibitors) either in the

hospital [23–30] or after hospital discharge [42] is effective in improving glycemic control in general medicine and surgery patients, and is associated with a significantly lower risk of hypoglycemia compared with basal bolus insulin therapy [25–27, 29•, 30•]. Our clinical trials, and the study by Garg et al., clearly show that in hospitalized patients with mild to moderate hyperglycemia the use of DPP-4 inhibitors represents a reasonable alternative to complex regimens such as the basal bolus approach (Fig. 1) [26, 27]. In patients with BG levels between 140 and 400 mg/dl and a wide range of admission HbA1c, the combination of a DPP-4 inhibitor with basal insulin has been shown equally effective in achieving and maintaining BG levels, with lower number of insulin injections and lower insulin daily doses compared with basal bolus insulin regimens in medical and surgical patients [30•]. Patients with uncontrolled hyperglycemia (i.e., high BG or HbA1c on admission) and those treated with higher doses of insulin at home may respond better to a basal–bolus insulin regimen in the hospital [2, 75].

In cardiac and non-cardiac surgical patients, the use of native GLP-1 or receptor analogs may constitute an alternative to insulin therapy in the immediate perioperative period. Delayed gastric emptying, nausea, and vomiting represent potential challenges to the use of GLP-1-based interventions in critically ill patients, especially in those with altered mental status who may have a higher risk of aspiration [71]. Use of newer long-acting agents that reduce the risk of these side effects may help overcome this barrier. Studies in the ICU with incretin therapies have been limited by short duration and lack of data on glycemic control outside of the immediate perioperative period. The reported incidence in hypoglycemia has been low in the ICU setting in recent studies using incretin-based agents, but this is usually not the case after transition to the hospital floor where glycemic variability and the risk of hypoglycemia with SC insulin is much higher [12]. Prolonging incretin therapy may help maintain glucose levels throughout the hospital stay, but such studies have yet to be conducted. Results from several trials suggest that GLP-1 RA may result in acceptable glycemic control with lower incidence of hypoglycemia.

Clinical guidelines for the management of inpatient hyperglycemia and diabetes have ignored the efficacy and high utilization of oral agents worldwide, and recommended the use of insulin as the only method to achieve glycemic control in the hospital [1, 2]. Although effective in achieving glycemic control, insulin regimens, in particular the basal bolus approach, is labor intensive and is associated with significant risk of iatrogenic hypoglycemia [1, 11], a complication that has been associated with increased length of stay and mortality [21, 22].

We believe that not all patients need to be treated with insulin, in particular stable patients with good nutritional intake and preserved renal function. Solid evidence indicates that incretin therapy, particularly with DPP-4 inhibitors alone or in combination with basal insulin, is a safe and effective approach to control glucose levels (especially if initiated early) with an expected low risk of hypoglycemia (Fig. 1). Larger prospective randomized studies are needed to confirm the safety and efficacy of continuing or starting older OADs and GLP-1 RA in stable patients admitted to general medical and surgical services.

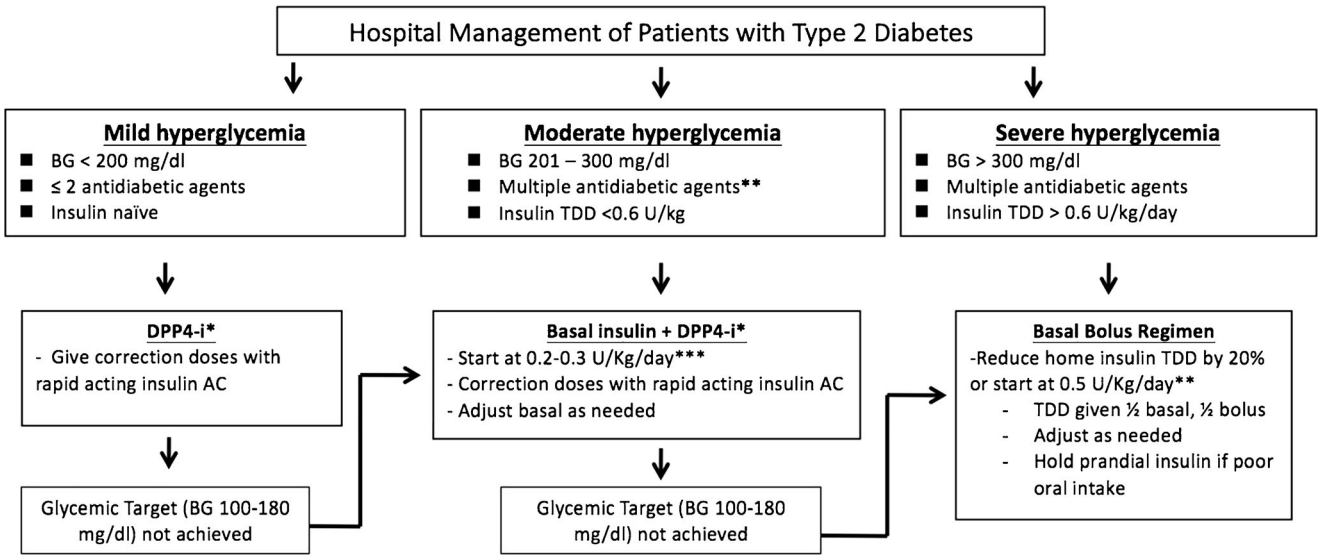


**Fig. 1** Suggested algorithm to start antihyperglycemic therapy in hospitalized patients with type 2 diabetes based on randomized controlled trials. AC: before meals, BG: blood glucose, TDD: total daily dose. *Adjust dose according to eGFR (sitagliptin or saxagliptin); no adjustment is needed with linagliptin. **Antidiabetic agents: oral agents and GLP-1-RA. ***In patients with hypoglycemia risk (frail, elderly, acute kidney injury) reduce starting dose to 0.15 U/kg/day (basal alone) or TDD 0.3 U/kg/day (basal bolus). No prospective studies have determined the efficacy of other oral antidiabetic drugs in the hospital setting

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## Compliance with Ethical Standards

**Conflict of Interest** Francisco J. Pasquel has received consulting fees and research support from Merck, and consulting fees from Boehringer Ingelheim, Lilly, and AstraZeneca.

Maya Fayfman declares no conflicts of interest.

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**Human and Animal Rights and Informed Consent** Informed consent was obtained from all individual participants included in the studies performed by the authors. This article does not contain any animal studies performed by any of the authors.

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