COMMENTS AND RESPONSE

Intensive Insulin Therapy in Hospitalized Patients

TO THE EDITOR: I appreciated Qaseem and colleagues’ extensive review of in-hospital glucose targets (1). Perhaps I misunderstood, but I think that the stated target blood glucose level of 7.8 to 11.1 mmol/L (140 to 200 mg/dL) includes all patients. When I looked at the references, however, most of them seemed to discuss patients who are receiving nothing by mouth because they are critically ill, are postoperative, or have had recent neurologic events.

Most of the time, if a hospitalized patient is eating, we in the medical community almost universally check the preprandial capillary glucose level. If it is 11.1 mmol/L (200 mg/dL), the postprandial blood glucose level would be higher and outside of the target range. I did not interpret Qaseem and colleagues’ article as suggesting that mealtime insulin coverage is not needed if the preprandial blood glucose level is less than 11.1 mmol/L (<200 mg/dL). This is the interpretation of many of my colleagues. My understanding is that they are recommending that all blood glucose levels, both preprandial and postprandial, be less than 11.1 mmol/L (< 200 mg/dL); please clarify this recommendation.

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Potential Conflicts of Interest: None disclosed.

Reference

TO THE EDITOR: I read with interest Qaseem and colleagues’ clinical practice guideline on intensive insulin therapy (ITT) (1). For diabetic patients who have undergone coronary artery bypass grafting (CABG), recommendations 2 and 3 are unfounded and not supported by the data cited.

Only 2 of the 14 randomized, controlled trials (RCTs) evaluated in the meta-analysis (2, 3) included patients who had undergone CABG. In both of these trials, IIT-directed tight glyceremic control (TGC) statistically significantly reduced in-hospital mortality and surgical wound infection rates. All of the remaining studies that were evaluated in the meta-analysis excluded patients who had undergone cardiac surgery by design. Those studies should not be used to broadly “overrule” the statistically significant effects of ITT-TGC that have been repeatedly proven in diabetic patients who have undergone CABG. To dilute the positive effects of these 2 cardiac surgical RCTs with 12 medical or noncardiac surgical studies of IIT-TGC that were ineffective in reducing mortality and infection and then broadly claim that IIT-TGC should not be performed in all patients—including diabetic patients who have undergone CABG—is both irresponsible and dangerous.

We first demonstrated the detrimental effects of hyperglycemia on mortality and surgical wound infections in diabetic patients who had undergone cardiac surgery in the 1990s in our large prospective observational studies from the Portland Diabetes Project (4, 5), which now includes more than 7000 patients. These detrimental effects were proven to persist for 3 full days from the time of open-heart surgery, regardless of patient location within the hospital (the surgical intensive care unit [ICU] or the non-ICU surgical ward). Eradication of hyperglycemia with ITT-TGC for 3 full days eliminated the increased risk for mortality and surgical site infection in this prominent proportion (31%) of patients who had undergone cardiac surgery.

Kirdemir and colleagues (2) subsequently confirmed these findings in an RCT. A subanalysis of patients who had undergone cardiac surgery from Vanhorebeek and colleagues’ Leuven surgical ICU study (6) reconfirmed the protective causal effects of ITT-TGC in these patients. Even the neurosurgical RCT by Bilotta and coworkers (7) confirmed the salutary effects of tight ITT on surgical wound infections.

Hypoglycemia is an obvious potential detrimental consequence of IIT, but it is highly dependent on the protocol followed, patient population studied, and hospital environment in which it is used. The Portland Protocol, at a target blood glucose level of 3.9 to 6.1 mmol/L (70 to 110 mg/dL), carries a 1.0% risk per patient for severe hypoglycemia (defined as a blood glucose level less than 2.2 mmol/L [<40 mg/dL]) in the diabetic patients who have undergone CABG in whom it is used for 3 days, even in the non-ICU ward (8). This incidence of hypoglycemia is far lower than that of any other protocol assessed in Qaseem and colleagues’ meta-analysis.

The American College of Physicians, and the Annals of Internal Medicine, should withdraw its recommended guideline for diabetic patients who have undergone CABG, reexamine all of the evidence specific to this important patient cohort, and revise these guidelines appropriately and with haste, lest more patients die or become injured because of this misguided guideline becoming widely adopted in the wrong patient population.

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Potential Conflicts of Interest: None disclosed.

References

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Increased risk for hypoglycemia, which is related to an increased risk (2). The use of ITT to achieve these targets is associated with an target blood glucose level of 4.4 to 6.1 mmol/L (80 to 110 mg/dL) consistent evidence to support strict glycemic control, defined as a treatment is based on a systematic review in which investigators found no in medical and surgical patients in the hospital. This recommendation is against IIT (1) on inpatient blood glucose level control recommends against IIT (2) in the non-ICU setting. Regardless of the diabetes status of the patient. Intensive insulin therapy is defined as the use of intravenous insulin infusion; if intravenous insulin infusion should not be used in the ICU, what should be used to keep blood glucose levels in the target range of 7.8 to 11.1 mmol/L (140 to 200 mg/dL)? Should it be oral agents, multiple subcutaneous insulin injections, or a sliding-scale insulin regimen?

Many physicians consider multiple subcutaneous insulin injections also to be a form of ITT. This is especially true in the non-ICU setting, where intravenous insulin is rarely used. Therefore, if Qaseem and colleagues’ guideline is followed, many hospitalized patients would receive only sliding-scale insulin therapy. This is potentially dangerous for all patients with type 1 diabetes and many patients with type 2 diabetes. Moreover, this guideline provides no upper limit for blood glucose levels for non-ICU patients. I think that American College of Physicians (ACP) guidelines should be more explicit and explain what should be done and not just what should not be done.

Potential Conflicts of Interest: None disclosed.

TO THE EDITOR: Qaseem and colleagues’ guideline also recommends that the upper glycemic target be changed to include blood glucose levels as high as 11.1 mmol/L (200 mg/dL) in ICU and non-ICU settings. Evidence from observational trials and RCTs (3) has shown that blood glucose levels higher than 10 mmol/L (>180 mg/dL) impair neutrophil function, increase risk for infections, prolong length of hospital stays, and increase mortality in ICU patients. In addition, recent RCTs in non-ICU patients (4) have shown that targeting preprandial and random blood glucose levels between 6.1 and 10 mmol/L (110 and 180 mg/dL), respectively, decreases the risk for infections and other complications.

The ACP guides practice for most internal medicine physicians across the United States and beyond. It raises concern that these guidelines were published without reference to either a recent consensus statement or the 2011 clinical practice recommendations for hospitalized patients (3, 5), which advocate target blood glucose levels of 7.8 to 10.0 mmol/L (140 to 180 mg/dL) for most critically ill and non–critically ill hospitalized patients. These levels can be safely achieved without increasing the risk for hypoglycemia.

We are concerned that variability in recommendations for glycemic targets by different professional organizations can result in both confusion and clinical inertia among clinicians who are responsible for guiding inpatient glycemic management. Such publications as the ACP clinical practice guidelines have the potential for misinterpretation that may weaken current efforts to achieve reasonable glycemic goals that have been demonstrated to reduce risks for undertreated hyperglycemia in hospitalized patients.

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Potential Conflicts of Interest: None disclosed.

References

TO THE EDITOR: Qaseem and colleagues’ clinical practice guideline on inpatient blood glucose level control recommends against ITT in medical and surgical patients in the hospital. This recommendation is based on a systematic review in which investigators found no consistent evidence to support strict glycemic control, defined as a target blood glucose level of 4.4 to 6.1 mmol/L (80 to 110 mg/dL) (2). The use of ITT to achieve these targets is associated with an increased risk for hypoglycemia, which is related to an increased risk for hospital complications and mortality (3).
IN RESPONSE: We thank Dr. Bentson, Dr. Furnary, Dr. Garg, and Dr. Korytkowski and colleagues for their comments on the ACP clinical guideline on inpatient glycemic control.

Dr. Bentson assumed that our guideline should not be interpreted to mean that patients on oral diets should not receive insulin therapy if their preprandial blood glucose level is less than 11.1 mmol/L (<200 mg/dL). She is correct. Although this population of hospitalized patients has not been specifically studied in terms of target thresholds of blood glucose levels, our guideline discussed the use of IIT to maintain blood glucose levels below a low threshold, such as 6.1 mmol/L (110 mg/dL), primarily in very ill, hospitalized patients receiving parenteral nutrition. This guideline should be interpreted to mean that diabetic patients receiving insulin therapy should use their normal dosage of insulin while they are hospitalized; for example, the use of preprandial insulin should be based on the preprandial blood glucose level.

We agree with Dr. Furnary that the evidence base for patients who have undergone CABG is relatively limited. However, the evidence that is available in patients who have undergone cardiac surgery specifically and operative patients more broadly does not convincingly show consistent evidence of benefit from the use of IIT to achieve very strict glucose targets, although there is some evidence of harm associated with this intervention. The surgical ICU study by van den Berghe and colleagues (1) and Vanhorebeek and coworkers (2) did, indeed, find that IIT was associated with both lower mortality and sepsis rates, but IIT was not associated with lower rates of sepsis in the subgroup of patients who had undergone cardiac surgery to whom Dr. Furnary refers, and surgical wound infection rates were not reported. The evidence report (3) describes the potential reasons for discrepancies between that surgical ICU study and subsequent studies.

Kirdemir and colleagues (4) reported a dramatic 92% reduction in the risk for sternal wound infection associated with IIT, which seems disproportionate to the very modest reductions in average blood glucose levels in the intervention group (9.5 vs. 10.8 mmol/L [172 vs. 195 mg/dL]). Of note, the quality of this study was limited by important baseline differences between groups and unclear blinding of outcome assessors. An additional poor-quality study examining 2 groups of patients who had undergone CABG (5) showed that perioperative IIT did not reduce the risk for infection. On the other hand, a prespecified subgroup analysis of operative patients in the NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) trial (6) found statistically significantly higher mortality associated with IIT titrated to very strict blood glucose targets (relative risk, 1.31 [95% CI, 1.07 to 1.61]).

The Portland Protocol (7) is an observational study and was therefore not included in the analysis of health outcome data. We agree, however, that the ability of this protocol to achieve low rates of hypoglycemia—at least in the selected patients who tolerate the protocol for 3 or more days—highlights significant lessons about the importance of gradual implementation and nursing buy-in but also may reflect selective reporting of patients who are least likely to be harmed. Such factors as protocol, hospital, and implementation characteristics probably contribute to the safety of IIT use, and these issues are summarized in the evidence report appendix and discussed in the guideline (3).

About Dr. Garg’s comments, our guideline does not mean that insulin should not be used to control blood glucose levels but rather that insulin should not be used to try to achieve “tight control” as defined in the RCTs that have assessed this, which usually means a blood glucose level consistently less than 6.1 mmol/L (<110 mg/dL). These RCTs have generally found few, if any, benefits for tight control yet certainly show an increase in the risk for hypoglycemic events.

Dr. Korytkowski and colleagues question the discrepancy among various guidelines on the upper limit of the blood glucose level. This discrepancy probably exists because no data from trials unequivocally establish the threshold above which the benefits from glucose control exceed the harms. The ACP based its choice on the blood glucose levels targeted or achieved by the “control” groups in the studies of intensive insulin infusions, most of which showed no appreciable benefits for the intervention (3). We concluded that no evidence existed to support attempting to achieve better blood glucose levels than that achieved in the “control” groups of these studies in which target blood glucose levels ranged from 7.8 to 11.1 mmol/L (140 to 200 mg/dL).

The very recently published RABBIT 2 (Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients With Type 2 Diabetes) trial (8) that Dr. Korytkowski and colleagues referenced was not designed to assess the relative benefits of a strict versus less strict target blood glucose level because the targets were the same in both groups. However, the group randomly assigned to the basal-bolus strategy did achieve lower mean blood glucose levels and seemed to have a lower incidence of wound infections at the expense of a higher risk for hypoglycemia.

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Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M10-2725.

References


**CORRECTIONS**

**Correction: Optimizing Statin Treatment for Primary Prevention of Coronary Artery Disease**

In Figure 1 of an article on statin treatment and primary prevention of coronary artery disease (1), the “Intensive NCEP [National Cholesterol Education Program] III treat-to-target approach” section, unlike the analysis, inadvertently omits the NCEP III distinction between the low-density lipoprotein (LDL) cholesterol goal (130 mg/dL) and the low-density lipoprotein cholesterol level at which to consider drug therapy (160 mg/dL) for the moderate-risk group (≥2 risk factors and a Framingham risk score ≤10%).

**Reference**


**Correction: Diagnostic Performance of Low-Radiation-Dose Coronary Computed Tomography Angiography**

In Figure 1 of a meta-analysis on diagnostic performance of low-radiation-dose coronary computed tomography angiography (1), the labels “Vessel level” and “Patient level” were reversed. The correct order of the labels is “Segment level,” “Patient level,” and “Vessel level.”

This has been corrected in the online version.

**Reference**


**Correction: Liver Transplantation From Donors With Acute Intermittent Porphyria**

The authors of a letter (1) by Dowman and colleagues should be listed in the following order: Joanna K. Dowman, MBChB(Hons); Bridget K. Gunson; Simon Bramhall, MD; Mike N. Badminton, MBChB, PhD; and Philip N. Newsome, PhD.

This has been corrected in the online version.

**Reference**