Use of Intensive Insulin Therapy for the Management of Glycemic Control in Hospitalized Patients: A Clinical Practice Guideline From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Linda L. Humphrey, MD, MPH; Roger Chou, MD; Vincenza Snow, MD; and Paul Shekelle, MD, PhD, for the Clinical Guidelines Committee of the American College of Physicians*

Description: The American College of Physicians (ACP) developed this guideline to present the evidence for the link between the use of intensive insulin therapy to achieve different glycemic targets and health outcomes in hospitalized patients with or without diabetes mellitus.

Methods: Published literature on this topic was identified by using MEDLINE and the Cochrane Library. Additional articles were obtained from systematic reviews and the reference lists of pertinent studies, reviews, and editorials, as well as by consulting experts; unpublished studies on ClinicalTrials.gov were also identified. The literature search included studies published from 1950 through March 2009. Searches were limited to English-language publications. The primary outcomes of interest were short-term mortality and hypoglycemia. This guideline grades the evidence and recommendations by using the ACP clinical practice guidelines grading system.

Recommendation 1: ACP recommends not using intensive insulin therapy to strictly control blood glucose in non–surgical intensive care unit (SICU)/medical intensive care unit (MICU) patients with or without diabetes mellitus (Grade: strong recommendation, moderate-quality evidence).

Recommendation 2: ACP recommends not using intensive insulin therapy to normalize blood glucose in SICU/MICU patients with or without diabetes mellitus (Grade: strong recommendation, high-quality evidence).

Recommendation 3: ACP recommends a target blood glucose level of 7.8 to 11.1 mmol/L (140 to 200 mg/dL) if insulin therapy is used in SICU/MICU patients (Grade: weak recommendation, moderate-quality evidence).

Ann Intern Med. 2011;154:260-267.   www.annals.org
For author affiliations, see end of text.

Hyperglycemia is a common finding among medical and surgical patients with or without known diabetes during hospital admission (1, 2). Although the prevalence of hyperglycemia in hospitalized patients is not known with certainty, it is estimated to be around 40% (3). Poorly controlled hyperglycemia is associated with increased morbidity, mortality, and costs (4). Hyperglycemia is associated with poor immune response, increased cardiovascular events, thrombosis, inflammatory changes, delayed healing, and other problems (5). Achieving tight glycemic control safely in inpatients is labor intensive and often requires coordination of efforts involving a multidisciplinary team in a hospital setting (4). Most of the evidence on how to best achieve target blood glucose levels centers around the use of intensive insulin protocols.

The purpose of this American College of Physicians (ACP) guideline is to address the management of hyperglycemia and evaluate the benefits and harms associated with the use of intensive insulin therapy (IIT) to achieve tight glycemic control in hospitalized patients with or without diabetes mellitus. We defined "IIT" as use of intravenous insulin to achieve targeted blood glucose level with frequent blood glucose testing and adjustment of insulin doses. In intensive care unit (ICU) settings, the usual target of IIT is normoglycemia (blood glucose level, 4.4 to 6.1 mmol/L [80 to 110 mg/dL]), whereas targets in non-ICU settings have been more variable (ranging from normoglycemia to <11.1 mmol/L [<200 mg/dL]).

The target audience for this guideline includes all clinicians, and the target patient population comprises all adults with hyperglycemia in a hospital setting. These recommendations are based on a systematic evidence review by Kansagara and colleagues (6), from an

---

evidence report sponsored by the Department of Veterans Affairs (5).

METHODS

The objective of this guideline is to present the evidence for the following questions:

1. Does the use of IIT to achieve tight glycemic control compared with less tight glycemic control improve important health outcomes in the following settings or patient populations: surgical intensive care unit (SICU), medical intensive care unit (MICU), general surgical ward, general medicine ward, patients with myocardial infarction or acute stroke, and patients in the perioperative setting?
2. What are the harms of strict glycemic control in the above subpopulations?

The databases used for the literature search were MEDLINE and the Cochrane Database of Systematic Reviews; the search included studies published from database inception through January 2010. The literature search was supplemented by reviews of reference lists, suggestions from consulting experts, and searches on ClinicalTrials.gov for unpublished studies. Each article was reviewed by using the eligibility criteria outlined in the systematic review (6). Eligible articles were published in English and provided primary data relevant to the use of IIT in hospitalized patients. Studies evaluating fixed-dose insulin infusions, including trials of fixed-dose glucose–insulin–potassium infusions, were excluded. The primary outcome of interest was short-term mortality (preferential order: 28-day mortality, hospital mortality, ICU mortality). The major harm of interest was the rate of hypoglycemia, including effects of hypoglycemia on clinical outcomes and length of hospitalization. The quality of each study was rated as good, fair, or poor on the basis of 1) the comparability of treatment groups; 2) the adequacy of randomization; 3) whether treatment allocation was concealed; 4) whether eligibility criteria were specified; 5) whether patients, care providers, and outcome assessors were blinded; 6) whether the analysis was done on an intention-to-treat basis, conducted with postrandomization exclusions, or had extensive or differential loss to follow-up; and 7) whether clearly defined interventions and reliable outcome measurement were used. Given the importance of glucose control and hypoglycemia in assessing the effectiveness and safety of IIT, studies that did not fully report glucose levels achieved or overall hypoglycemia rates were rated as poor quality.

Three investigators reviewed the abstracts of citations identified from literature searches. When reviewers disagreed about the quality rating, consensus was reached through discussion with all authors. Details of the methods for the evidence review are provided in the evidence review (6).

Table. The American College of Physicians Guideline Grading System*

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

* Adopted from the classification developed by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) workgroup.

This guideline rates the evidence and recommendations by using the ACP's guideline grading system, which is a slightly modified version of the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system (**Table**).

BENEFITS OF IIT FOR IMPROVING HEALTH OUTCOMES
Mortality

A meta-analysis of 21 trials (14 768 participants) found no benefit associated with IIT on short-term mortality (28-day, hospital, or ICU mortality) (relative risk [RR], 1.0 [95% CI, 0.94 to 1.1]) (6). Although the trials differed with regard to target glucose levels for ITT and control groups, achieved glucose levels, IIT protocols, and medical setting (for example, ICU vs. non-ICU), there was no statistical heterogeneity ($I^2 = 0\%$). Results were similar when trials were stratified according to blood glucose level achieved, the percentage of diabetic patients, definition of short-term mortality, or study quality. Meta-analysis also showed no benefit associated with IIT for 90- or 180-day mortality (13 trials; RR, 1.1 [CI 0.99 to 1.1]; $I^2 = 0\%$). Results in specific patient subgroups are described below.

ICUs
MICUs

Evidence from 5 fair-quality trials (7–11) and 1 poor-quality trial (12) of IIT (target glucose levels of normoglycemia [4.4 to 6.1 mmol/L {80 to 110 mg/dL}] compared with control values ranging from 7.8 to 11.1 mmol/L [140 to 200 mg/dL]) consistently found no mortality benefit associated with normoglycemia as a target. The overall quality of evidence that IIT with normoglycemia as a target in patients in the MICU does not improve mortality was rated as high.

SICUs

Three fair-quality trials (7, 9, 13) and 2 poor-quality trials (14, 15) of IIT (target glucose levels of 4.4 to 8.3 mmol/L [80 to 150 mg/dL] vs. control values ranging from

10.0 to 12.2 mmol/L [180 to 220 mg/dL]) conducted in SICUs showed no benefit of IIT on mortality (7, 9, 13–15). The largest trial (2232 patients in the surgical subgroup) was the recent multicenter NICE-SUGAR (Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation) study (9), a fair-quality study with target glucose levels of 4.4 to 6.0 mmol/L (80 to 108 mg/dL) that showed an increase in mortality compared with a target less than 10.0 mmol/L (<180 mg/dL) (RR, 1.31 [CI, 1.07 to 1.61]). However, not all of the trials found no benefit. A large (1600 participants), fair-quality study showed a statistically significant reduction in all-cause ICU mortality in the IIT group (morning blood glucose level, 4.4 to 6.1 mmol/L [80 to 110 mg/dL]) compared with conventional therapy (morning blood glucose level, 10.0 to 11.1 mmol/L [180 to 200 mg/dL]); mortality rates were 4.6% and 8.0%, respectively (RR, 0.58 [CI, 0.38 to 0.78]) (16). The overall quality of evidence that IIT targeted at normoglycemia in patients in the SICU does not improve mortality was rated as moderate.

Mixed MICU and SICU Populations

Five fair-quality trials that included mixed MICU and SICU populations (glucose target for IIT ranging from 4.0 to 6.1 mmol/L [72 to 110 mg/dL] compared with control ranging from 7.8 to 11.1 mmol/L [140 to 200 mg/dL]) did not demonstrate an overall mortality benefit of IIT (7, 9, 17, 18; Mackenzie I, Blunt M, Ingle S, Palmer C. GLYcaemic Control and Outcome in GENeral Intensive Care. Unpublished report). The largest trial (6104 participants), the NICE-SUGAR study, showed that IIT with target glucose levels of 4.4 to 6.0 mmol/L (80 to 108 mg/dL) was associated with an increase in 90-day mortality compared with a target level less than 10.0 mmol/L (<180 mg/dL) (RR, 1.14 [CI, 1.02 to 1.28]); there was approximately 1 excess death per 39 patients treated with IIT (9). The overall quality of evidence that IIT targeted at normoglycemia in mixed MICU/SICU populations does not improve mortality was rated as high.

General Medicine Ward

No studies evaluated IIT in patients on the general medical ward.

Patients With Myocardial Infarction

Evidence from 3 fair-quality studies (19–21) and 2 poor-quality studies (22, 23) showed no reduction in mortality among patients with myocardial infarction who received IIT and adjustable-dose glucose–insulin–potassium infusions (target glucose levels ranging from 4.0 to 11.0 mmol/L [72 to 198 mg/dL] vs. unspecified target levels in control groups). One fair-quality trial (620 participants) that compared IIT (target glucose levels ranging from 7.0 to 11.0 mmol/L [126 to 198 mg/dL]) with long-term postdischarge insulin therapy found a mortality reduction at 1 year (18.6% vs. 26.1%, respectively; RR, 0.69 [CI, 0.49 to 0.96]; $P = 0.027$), but it was not possible to determine whether the results were due to IIT or the use of insulin after discharge (24). In addition, this trial was published about 10 years before the other trials, and given changes over time in management of myocardial infarction, its current applicability may be limited.

Variations in trial design, glucose level achieved, and concomitant therapy for myocardial infarction limit the strength of conclusions that can be drawn from these studies. The overall quality of evidence for IIT to achieve target glucose levels of 4.0 to 11.0 mmol/L (72 to 198 mg/dL) on mortality in patients with myocardial infarction was rated as low.

Patients With Stroke or Acute Brain Injury

Two fair-quality trials (25, 26) and 2 poor-quality trials (27–29) that examined the efficacy of IIT (target glucose values ranging from 4.4 to 8.0 mmol/L [80 to 144 mg/dL]) in patients with stroke or brain injury showed no mortality benefit compared with higher targets (ranging from <10.0 to <17.0 mmol/L [<180 to <306 mg/dL]). The overall quality of evidence that IIT targeted to achieve glucose levels of 4.4 to 8.0 mmol/L (80 to 144 mg/dL) in patients with stroke does not improve mortality was rated as low.

Perioperative Care

Evidence from 1 fair-quality trial (30) and 2 poor-quality trials (31, 32) that evaluated IIT (glucose targets ranging from 3.9 to 10.0 mmol/L [70 to 179 mg/dL]) versus higher or unspecified target values during the immediate perioperative period (IIT was begun before, during, or immediately after surgery and was continued for less than 24 hours after surgery) did not show a beneficial effect on mortality.

The trials included patients undergoing surgery (mainly cardiac) and had small sample sizes, low event rates, and considerable differences in interventions used and blood glucose targets. The overall quality of evidence that IIT to achieve target glucose levels of 3.9 to 10.0 mmol/L (70 to 179 mg/dL) does not improve health outcomes in patients receiving perioperative care was rated as low.

Infection

Nine fair-quality trials (7, 9, 13, 17, 30, 33–36) and 7 poor-quality trials (12, 14, 15, 29, 32, 37, 38) evaluated the effect of IIT on the incidence of infection in various patient populations. For sepsis, evidence from 9 trials (7, 9, 12–14, 16, 17, 29, 36) showed a marginally significant reduction in the risk for sepsis (RR, 0.79 [CI, 0.62 to 1.00]). Seven other studies (15, 30, 32–34, 38) reported the occurrence of wound infections, urinary tract infections, pneumonia, or a combination of these infections. A pooled analysis of these outcomes showed a non–statistically significant reduction in infection (RR, 0.68 [CI, 0.36 to 1.30]).

Length of Stay

Eight fair-quality trials (7, 9, 18, 24, 30, 33, 34; Mackenzie I, Blunt M, Ingle S, Palmer C. GLYcaemic Control and Outcome in GENeral Intensive Care. Unpublished report) and 5 poor-quality trials (15, 31, 32, 37) reported the effects of IIT on hospital length of stay. Four trials (7, 9, 18; Mackenzie I, Blunt M, Ingle S, Palmer C. GLYcaemic Control and Outcome in GENeral Intensive Care. Unpublished report) in the mixed MICU/SICU environment found a neutral effect of IIT on overall hospital length of stay (0.008 day [CI, −0.84 to 0.85 day) or ICU length of stay (−0.04 day [−0.34 to 0.26 day]; $I^2 = 0\%$). In contrast, 4 SICU studies (13–15, 39) found that IIT was associated with a reduction in ICU length of stay (−1.5 days [CI, −2.2 to −0.73 day]; $I^2 = 50\%$; $P = 0.11$). The overall quality of evidence on effects of IIT on length of hospital or ICU stay in patients in the ICU was rated as moderate.

Two fair-quality perioperative trials (33, 40) showed neutral results for hospital length of stay, and 1 fair-quality trial (34) showed on average a 1-day reduction in length of stay. The overall quality of evidence was rated as low.

Harms of Intensive Insulin Therapy: Hypoglycemia

The use of IIT was associated with an excess risk for hypoglycemia in almost all trials; critically ill patients receiving IIT aimed at achieving normoglycemia had the highest occurrence of hypoglycemia (RR, 5.32 [CI, 4.21 to 6.73]) (41–44). The overall quality of evidence that IIT is associated with hypoglycemia in all subgroups except the general medical unit (for which there were no studies) was rated as high.

The consequences of hypoglycemia in hospitalized patients are unclear because few of the studies reviewed reported adverse effects and few studies have examined the long-term consequences of hypoglycemia. There is some evidence for excess mortality or extended length of stay among patients in the MICU experiencing 1 or more episodes of severe hypoglycemia related to IIT (7, 8, 45, 46). However, it is unclear whether hypoglycemia was a causative factor or whether it was a marker for more severe disease. Some studies have suggested that hypoglycemia is associated with an increased risk for dementia in patients with type 2 diabetes (47) and a 2-fold increase in risk for mortality (48) and that it may induce transient ischemia and catecholamine surges (49–51).

Implementation of Effective and Safe Intensive Insulin Therapy

Fair-quality evidence (52–54) on the effects of different insulin infusion protocols on glycemic control differed in terms of patient characteristics, target glucose ranges, the time required to achieve the target glucose, the incidence and definition of hypoglycemia, the rationale or algorithm used for adjusting the insulin infusion rates, the methods used to assess effectiveness, and the methods of glucose monitoring. Two reviews suggested that in light of variabil-

ity among protocols, each institution should individualize protocol implementation on the basis of its patient population, institutional resources, and provider resources (52, 53). A third review concluded that protocols that incorporate such factors as the rate of change in glucose level, current blood glucose level, and insulin infusion rate may be more effective than simple sliding-scale infusion protocols in decreasing blood glucose levels while maintaining relatively low rates of hypoglycemia (54). However, this conclusion is not based on direct comparisons of protocols.

Evidence evaluating subcutaneous sliding-scale insulin regimens suggests that this regimen may be relatively ineffective in achieving lower target blood glucose values (38, 55–57).

Summary

Poorly controlled hyperglycemia is associated with increased morbidity, mortality, and worsening health outcomes in hospitalized patients. Most clinicians make efforts to prevent and control hyperglycemia in inpatient settings. However, the optimal blood glucose range to target in hospitalized patients is uncertain. Many trials have shown no effect of IIT targeted to different blood glucose levels on mortality, and pooling of trials does not suggest any trend toward benefit. Among patients in ICUs, in whom there are theoretical reasons to target normoglycemia or near-normoglycemia, the evidence also shows no mortality benefit associated with IIT for targeted glucose levels of 4.4 to 6.1 mmol/L (80 to 110 mg/dL). Although an SICU study (16) showed evidence supporting the link between reduced mortality and the use of IIT to targets of 4.4 to 6.1 mmol/L (80 to 110 mg/dL), the study used aggressive parenteral nutrition, which is not standard practice in many hospitals (16, 36, 58). Parenteral nutrition has been associated with hypertriglyceridemia, insulin resistance, increased infection rates, and increased mortality. Furthermore, this study had a relatively low event rate and was stopped early because of benefit, raising concerns that the reported treatment effect was larger than the "true" treatment effect (59). Finally, the results of this study have not been replicated in other settings. In contrast, several other trials were stopped early owing to an excess risk for hypoglycemia in the intervention groups. This raises the possibility that the lack of observed benefit may reflect inadequate power to detect health benefit (7, 8).

The consequences of severe hypoglycemia in hospitalized patients have not been well studied. There is some evidence for excess mortality or extended length of stay among patients experiencing 1 or more episodes of hypoglycemia. However, from the currently available evidence, it cannot be established whether hypoglycemia was the causative factor.

The evidence evaluating insulin protocols that have achieved normoglycemic targets with low rates of hypoglycemia is sparse. The ability to achieve glucose targets safely

Figure. The American College of Physicians guideline on the use of intensive insulin therapy for the management of glycemic control in hospitalized patients.

ACP Clinical Practice®
American College of Physicians
GUIDELINES

Summary of the American College of Physicians Guideline on the Use of Intensive Insulin Therapy for the Management of Glycemic Control in Hospitalized Patients

Disease or condition	Inpatient hyperglycemia
Target audience	Internists, hospitalists, and other clinicians
Target patient population	Adults with inpatient hyperglycemia
Interventions	Intensive insulin therapy
Outcomes	Mortality
Recommendations	*Recommendation 1:* ACP recommends not using intensive insulin therapy to strictly control blood glucose in non-SICU/MICU patients with or without diabetes mellitus (Grade: strong recommendation, moderate-quality evidence). *Recommendation 2:* ACP recommends not using intensive insulin therapy to normalize blood glucose in SICU/MICU patients with or without diabetes mellitus (Grade: strong recommendation, high-quality evidence). *Recommendation 3:* ACP recommends a target blood glucose level of 7.8 to 11.1 mmol/L (140 to 200 mg/dL) if insulin therapy is used in SICU/MICU patients (Grade: weak recommendation, moderate-quality evidence).
Clinical considerations	• This guideline refers to hospitalized patients with hyperglycemia. • Critically ill medical and surgical patients who are hyperglycemic have a higher mortality rate. • Most clinicians agree that prevention of hyperglycemia is an important intervention. • The range of optimal glucose level is controversial. A few studies show that IIT improves mortality, whereas most have shown that patients who receive IIT have no reduction in mortality and have a significantly increased risk for severe hypoglycemia.

IIT = intensive insulin therapy; MICU = medical intensive care unit; SICU = surgical intensive care unit.

probably depends on multiple factors, including the titration characteristics of the protocol, patient characteristics, staffing ratios, and provider acceptance. Characteristics of these studies suggest that several variables may be responsible for the lower rates of hypoglycemia: modest glucose targets (approximately 5.6 to 8.3 mmol/L [100 to 150 mg/dL]); an iterative, institution-based protocol development and deployment process; and innovations in insulin titration protocols.

RECOMMENDATIONS

Recommendation 1: ACP recommends not using intensive insulin therapy to strictly control blood glucose in non-SICU/MICU patients with or without diabetes mellitus (Grade: strong recommendation, moderate-quality evidence).

Current evidence does not show any reduction in mortality with a target blood glucose level of 4.4 to 10.0 mmol/L (80 to 180 mg/dL) compared with higher or unspecified targets using a variety of IIT regimens for patients with myocardial infarction, stroke, or acute brain injury or those under perioperative care. A nonsignificant reduction in the incidence of infection has also been observed. Al-

though the target blood glucose levels in the current trials ranged widely, avoiding targets less than 7.8 mmol/L (<140 mg/dL) should be a priority because harms are likely to increase at lower blood glucose targets. Although the consequences of hypoglycemia in hospitalized patients are unclear, there is some evidence for increased mortality or extended length of stay among patients experiencing 1 or more episodes of hypoglycemia. However, optimal targets in patients not receiving care in the SICU or MICU cannot be precisely defined, because IIT was associated with an excess risk for hypoglycemia in almost all trials and no clear differences in mortality were observed at any target level.

Recommendation 2: ACP recommends not using intensive insulin therapy to normalize blood glucose in SICU/MICU patients with or without diabetes mellitus (Grade: strong recommendation, high-quality evidence).

Current evidence does not show a mortality benefit associated with use of IIT to achieve a target of normoglycemia (blood glucose levels of 4.4 to 6.1 mmol/L [80 to 110 mg/dL]). Evidence from some studies showed an increase in mortality associated with IIT and hypoglycemia.

Data on the effects of IIT targeted to normoglycemia on reduction in length of ICU stay are mixed.

Recommendation 3: ACP recommends a target blood glucose level of 7.8 to 11.1 mmol/L (140 to 200 mg/dL) if insulin therapy is used in SICU/MICU patients (Grade: weak recommendation, moderate-quality evidence).

Although IIT to achieve targeted normoglycemia is not associated with improved health outcomes and increases the risk for hypoglycemia, poorly controlled hyperglycemia is associated with increased morbidity, mortality, and worsened health outcomes in patients in the ICU. While the evidence is not sufficient to give a precise range for blood glucose levels, target values of 7.8 to 11.1 mmol/L (140 to 200 mg/dL) is a reasonable option in patients in the ICU, because insulin therapy targeted at blood glucose levels of 7.8 to 11.1 mmol/L (140 to 200 mg/dL) is associated with similar mortality outcomes as IIT targeted at blood glucose levels of 4.4 to 6.1 mmol/L (80 to 110 mg/dL) and is associated with a lower risk for hypoglycemia. Current studies do not provide enough information to determine whether allowing blood glucose levels to increase above 10.0 to 11.1 mmol/L (180 to 200 mg/dL) is associated with similar outcomes to those seen at lower target levels.

Although the risk for hypoglycemia was higher in studies with lower target glucose values, hypoglycemia was also observed among patients who received insulin therapy with target blood glucose levels ranging from 7.8 to 11.1 mmol/L (140 to 200 mg/dL). Therefore, minimizing hypoglycemia associated with IIT is critical in institutions that choose to implement insulin therapy in patients in the ICU. Factors that may be associated with achievement of glucose targets with low rates of hypoglycemia include titration characteristics of the protocol, patient characteristics, staffing ratios, and clinician acceptance. Institutions that implement insulin therapy in patients in the ICU should incorporate quality improvement and training initiatives in order to achieve target glucose levels while minimizing rates of hypoglycemia.

SUMMARY OF RECOMMENDATIONS AND EVIDENCE

See the **Figure** for a summary of the recommendations and clinical considerations. The **Table** describes the ACP's guideline grading system.

From the American College of Physicians, Philadelphia, Pennsylvania; Pfizer, Collegeville, Pennsylvania; Oregon Health & Science University and Portland Veterans Affairs Medical Center, Portland, Oregon; and West Los Angeles Veterans Affairs Medical Center, Los Angeles, California.

Note: Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication, or once an update has been issued.

References

1. **Levetan CS, Passaro M, Jablonski K, Kass M, Ratner RE.** Unrecognized diabetes among hospitalized patients. Diabetes Care. 1998;21:246-9. [PMID: 9539990]

2. **Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE.** Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab. 2002;87:978-82. [PMID: 11889147]

3. **Clement S, Braithwaite S, Magee M, Ahmann A, Smith EP, Schafer RG, et al; American Diabetes Association Diabetes in Hospitals Writing Committee.** Management of diabetes and hyperglycemia in hospitals. Diabetes Care. 2004;27:553-91. [PMID: 14747243].

4. **ACE/ADA Task Force on Inpatient Diabetes.** American College of Endocrinology and American Diabetes Association Consensus statement on inpatient diabetes and glycemic control. Diabetes Care. 2006;29:1955-62. [PMID: 16873812]

5. **Kansagara D, Wolf F, Freeman M, Helfand M.** Management of inpatient hyperglycemia: a systematic review. A report by the Evidence-based Synthesis Program of Veterans Health Administration, Health Services Research & Development. Washington, DC: Veterans Health Administration; 2008.

6. **Kansagara D, Fu R, Freeman M, Wolf F, Helfand M.** Systematic review: intensive insulin therapy in hospitalized patients. Ann Intern Med. 2011;154: 268-xx.

7. **Arabi YM, Dabbagh OC, Tamim HM, Al-Shimemeri AA, Memish ZA, Haddad SH, et al.** Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. Crit Care Med. 2008;36:3190-7. [PMID: 18936702]

8. **Brunkhorst F, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, et al; German Competence Network Sepsis (SepNet).** Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358:125-39. [PMID: 18184958].

9. **NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, et al.** Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283-97. [PMID: 19318384]

10. **Van den Berghe G, Wilmer A, Milants I, Wouters PJ, Bouckaert B, Bruyninckx F, et al.** Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. Diabetes. 2006;55:3151-9. [PMID: 17065355]

11. **Savioli M, Cugno M, Polli F, Taccone P, Bellani G, Spanu P, et al.** Tight

glycemic control may favor fibrinolysis in patients with sepsis. Crit Care Med. 2009;37:424-31. [PMID: 19114908]

12. **Farah R, Samokhvalov A, Zviebel F, Makhoul N.** Insulin therapy of hyperglycemia in intensive care. Isr Med Assoc J. 2007;9:140-2. [PMID: 17402320]

13. **Bilotta F, Caramia R, Paoloni FP, Delfini R, Rosa G.** Safety and efficacy of intensive insulin therapy in critical neurosurgical patients. Anesthesiology. 2009; 110:611-9. [PMID: 19237874]

14. **Grey NJ, Perdrizet GA.** Reduction of nosocomial infections in the surgical intensive-care unit by strict glycemic control. Endocr Pract. 2004;10 Suppl 2:46-52. [PMID: 15251640]

15. **Kirdemir P, Yildirim V, Kiris I, Gulmen S, Kuralay E, Ibrisim E, et al.** Does continuous insulin therapy reduce postoperative supraventricular tachycardia incidence after coronary artery bypass operations in diabetic patients? J Cardiothorac Vasc Anesth. 2008;22:383-7. [PMID: 18503925]

16. **van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al.** Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001;345:1359-67. [PMID: 11794168]

17. **De La Rosa Gdel C, Donado JH, Restrepo AH, Quintero AM, González LG, Saldarriaga NE, et al; Grupo de Investigacion en Cuidado intensivo: GICI-HPTU.** Strict glycaemic control in patients hospitalised in a mixed medical and surgical intensive care unit: a randomised clinical trial. Crit Care. 2008;12:R120. [PMID: 18799004]

18. **Preiser JC, Devos P, Ruiz-Santana S, Mélot C, Annane D, Groeneveld J, et al.** A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. Intensive Care Med. 2009;35:1738-48. [PMID: 19636533]

19. **Cheung NW, Wong VW, McLean M.** The Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. Diabetes Care. 2006;29:765-70. [PMID: 16567812]

20. **Oksanen T, Skrifvars MB, Varpula T, Kuitunen A, Pettilä V, Nurmi J, et al.** Strict versus moderate glucose control after resuscitation from ventricular fibrillation. Intensive Care Med. 2007;33:2093-100. [PMID: 17928994]

21. **van der Horst IC, Zijlstra F, van 't Hof AW, Doggen CJ, de Boer MJ, Suryapranata H, et al; Zwolle Infarct Study Group.** Glucose-insulin-potassium infusion inpatients treated with primary angioplasty for acute myocardial infarction: the glucose-insulin-potassium study: a randomized trial. J Am Coll Cardiol. 2003;42:784-91. [PMID: 12957421].

22. **Malmberg K, Rydén L, Wedel H, Birkeland K, Bootsma A, Dickstein K, et al; DIGAMI 2 Investigators.** Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J. 2005;26:650-61. [PMID: 15728645].

23. **Rasoul S, Ottervanger JP, Timmer JR, Svilaas T, Henriques JP, Dambrink JH, et al.** One year outcomes after glucose-insulin-potassium in ST elevation myocardial infarction. The Glucose-insulin-potassium study II. Int J Cardiol. 2007;122:52-5. [PMID: 17223212]

24. **Malmberg K, Rydén L, Efendic S, Herlitz J, Nicol P, Waldenström A, et al.** Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. J Am Coll Cardiol. 1995;26:57-65. [PMID: 7797776]

25. **Azevedo JR, Lima ER, Cossetti RJ, Azevedo RP.** Intensive insulin therapy versus conventional glycemic control in patients with acute neurological injury: a prospective controlled trial. Arq Neuropsiquiatr. 2007;65:733-8. [PMID: 17952272]

26. **Bruno A, Kent TA, Coull BM, Shankar RR, Saha C, Becker KJ, et al.** Treatment of hyperglycemia in ischemic stroke (THIS): a randomized pilot trial. Stroke. 2008;39:384-9. [PMID: 18096840]

27. **Gray C, Hildreth A, Sandercock P, O'Connell JE, Johnston DE, Cartlidge NE, et al; GIST Trialists Collaboration.** Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). Lancet Neurol. 2007;6:397-406. [PMID: 17434094]

28. **Walters MR, Weir CJ, Lees KR.** A randomised, controlled pilot study to investigate the potential benefit of intervention with insulin in hyperglycaemic acute ischaemic stroke patients. Cerebrovasc Dis. 2006;22:116-22. [PMID: 16685123]

29. **Yang M, Guo Q, Zhang X, Sun S, Wang Y, Zhao L, et al.** Intensive insulin therapy on infection rate, days in NICU, in-hospital mortality and neurological outcome in severe traumatic brain injury patients: a randomized controlled trial.

Int J Nurs Stud. 2009;46:753-8. [PMID: 19232615]

30. **Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, O'Brien PC, et al.** Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial. Ann Intern Med. 2007;146: 233-43. [PMID: 17310047]

31. **Butterworth J, Wagenknecht LE, Legault C, Zaccaro DJ, Kon ND, Hammon JW Jr, et al.** Attempted control of hyperglycemia during cardiopulmonary bypass fails to improve neurologic or neurobehavioral outcomes in patients without diabetes mellitus undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2005;130:1319. [PMID: 16256784]

32. **Smith A, Grattan A, Harper M, Royston D, Riedel BJ.** Coronary revascularization: a procedure in transition from on-pump to off-pump? The role of glucose-insulin-potassium revisited in a randomized, placebo-controlled study. J Cardiothorac Vasc Anesth. 2002;16:413-20. [PMID: 12154417]

33. **Barcellos Cda S, Wender OC, Azambuja PC.** Clinical and hemodynamic outcome following coronary artery bypass surgery in diabetic patients using glucose-insulin-potassium (GIK) solution: a randomized clinical trial. Rev Bras Cir Cardiovasc. 2007;22:275-84. [PMID: 18157412]

34. **Subramaniam B, Panzica PJ, Novack V, Mahmood F, Matyal R, Mitchell JD, et al.** Continuous perioperative insulin infusion decreases major cardiovascular events in patients undergoing vascular surgery: a prospective, randomized trial. Anesthesiology. 2009;110:970-7. [PMID: 19387173]

35. **van den Berghe G, Weekers F, Baxter RC, Wouters P, Iranmanesh A, Bouillon R, et al.** Five-day pulsatile gonadotropin-releasing hormone administration unveils combined hypothalamic-pituitary-gonadal defects underlying profound hypoandrogenism in men with prolonged critical illness. J Clin Endocrinol Metab. 2001;86:3217-26. [PMID: 11443192]

36. **Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al.** Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354:449-61. [PMID: 16452557]

37. **Lazar HL, Chipkin SR, Fitzgerald CA, Bao Y, Cabral H, Apstein CS.** Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. Circulation. 2004; 109:1497-502. [PMID: 15006999]

38. **Li JY, Sun S, Wu SJ.** Continuous insulin infusion improves postoperative glucose control in patients with diabetes mellitus undergoing coronary artery bypass surgery. Tex Heart Inst J. 2006;33:445-51. [PMID: 17215967]

39. **Van den Berghe G, Wouters PJ, Kesteloot K, Hilleman DE.** Analysis of healthcare resource utilization with intensive insulin therapy in critically ill patients. Crit Care Med. 2006;34:612-6. [PMID: 16521256]

40. **Ingels C, Debaveye Y, Milants I, Buelens E, Peeraer A, Devriendt Y, et al.** Strict blood glucose control with insulin during intensive care after cardiac surgery: impact on 4-years survival, dependency on medical care, and quality-of-life. Eur Heart J. 2006;27:2716-24. [PMID: 16608860]

41. **Fischer KF, Lees JA, Newman JH.** Hypoglycemia in hospitalized patients. Causes and outcomes. N Engl J Med. 1986;315:1245-50. [PMID: 3534567]

42. **Krinsley J.** Glycemic control in critically ill patients: Leuven and beyond [Editorial]. Chest. 2007;132:1-2. [PMID: 17625075]

43. **Shilo S, Berezovsky S, Friedlander Y, Sonnenblick M.** Hypoglycemia in hospitalized nondiabetic older patients. J Am Geriatr Soc. 1998;46:978-82. [PMID: 9706886]

44. **Vriesendorp TM, van Santen S, DeVries JH, de Jonge E, Rosendaal FR, Schultz MJ, et al.** Predisposing factors for hypoglycemia in the intensive care unit. Crit Care Med. 2006;34:96-101. [PMID: 16374162]

45. **Devos P, Preiser J, Melot C.** Impact of tight glucose control by intensive insulin therapy on ICU mortality and the rate of hypoglycaemia: final results of the GLUCONTROL study. Intensive Care Med. 2007;33:S189.

46. **Krinsley JS.** Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc. 2003;78:1471-8. [PMID: 14661676]

47. **Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV.** Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA. 2009;301:1565-72. [PMID: 19366776]

48. **Svensson AM, McGuire DK, Abrahamsson P, Dellborg M.** Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. Eur Heart J. 2005;26:1255-61. [PMID: 15821004]

49. **Desouza C, Salazar H, Cheong B, Murgo J, Fonseca V.** Association of hypoglycemia and cardiac ischemia: a study based on continuous monitoring. Diabetes Care. 2003;26:1485-9. [PMID: 12716809]

50. **Lindström T, Jorfeldt L, Tegler L, Arnqvist HJ.** Hypoglycaemia and cardiac arrhythmias in patients with type 2 diabetes mellitus. Diabet Med. 1992;9:536-41. [PMID: 1643801]

51. **Spyer G, Hattersley AT, MacDonald IA, Amiel S, MacLeod KM.** Hypoglycaemic counter-regulation at normal blood glucose concentrations in patients with well controlled type-2 diabetes. Lancet. 2000;356:1970-4. [PMID: 11130525]

52. **Nazer LH, Chow SL, Moghissi ES.** Insulin infusion protocols for critically ill patients: a highlight of differences and similarities. Endocr Pract. 2007;13:137-46. [PMID: 17490927]

53. **Wilson M, Weinreb J, Hoo GW.** Intensive insulin therapy in critical care: a review of 12 protocols. Diabetes Care. 2007;30:1005-11. [PMID: 17213376]

54. **Meijering S, Corstjens AM, Tulleken JE, Meertens JH, Zijlstra JG, Ligtenberg JJ.** Towards a feasible algorithm for tight glycaemic control in critically ill patients: a systematic review of the literature. Crit Care. 2006;10:R19. [PMID: 16469124]

55. **Umpierrez GE, Smiley D, Zisman A, Prieto LM, Palacio A, Ceron M, et al.** Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). Diabetes Care. 2007;30:2181-6. [PMID: 17513708]

56. **Datta S, Qaadir A, Villanueva G, Baldwin D.** Once-daily insulin glargine versus 6-hour sliding scale regular insulin for control of hyperglycemia after a bariatric surgical procedure: a randomized clinical trial. Endocr Pract. 2007;13:225-31. [PMID: 17599852]

57. **Dickerson LM, Ye X, Sack JL, Hueston WJ.** Glycemic control in medical inpatients with type 2 diabetes mellitus receiving sliding scale insulin regimens versus routine diabetes medications: a multicenter randomized controlled trial. Ann Fam Med. 2003;1:29-35. [PMID: 15043177]

58. **Needham P, Burton A, Jayne D.** Artificial nutrition in UK intensive care units: a review of current practice. Proc Nutr Soc. 2008;67:E152.

59. **Montori VM, Devereaux PJ, Adhikari NK, Burns KE, Eggert CH, Briel M, et al.** Randomized trials stopped early for benefit: a systematic review. JAMA. 2005;294:2203-9. [PMID: 16264162]

Annals of Internal Medicine

Current Author Addresses: Dr. Qaseem: American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106.

Dr. Humphrey: Portland Veterans Affairs Medical Center, 3710 SW US Veterans Hospital Road, Portland, OR 97201.

Dr. Chou: Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239.

Dr. Snow: Pfizer, 500 Arcola Road, Collegeville, PA 19426.

Dr. Shekelle: West Los Angeles Veterans Affairs Medical Center, 11301 Wilshire Boulevard, Los Angeles, CA 90073.

Author Contributions: Conception and design: A. Qaseem, L.L. Humphrey, V. Snow, P. Shekelle.

Analysis and interpretation of the data: A. Qaseem, L.L. Humphrey, R. Chou.

Drafting of the article: A. Qaseem, V. Snow.

Critical revision of the article for important intellectual content: A. Qaseem, L.L. Humphrey, R. Chou, V. Snow, P. Shekelle.

Final approval of the article: A. Qaseem, L.L. Humphrey, R. Chou, V. Snow, P. Shekelle.

Administrative, technical, or logistic support: A. Qaseem.