CLINICAL GUIDELINE | Annals of Internal Medicine

Intensive Insulin Therapy in Hospitalized Patients: A Systematic Review

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Background: The benefits and harms of intensive insulin therapy (IIT) titrated to strict glycemic targets in hospitalized patients remain uncertain.

Purpose: To evaluate the benefits and harms of IIT in hospitalized patients.

Data Sources: MEDLINE and Cochrane Database of Systematic Reviews from 1950 to January 2010, reference lists, experts, and unpublished sources.

Study Selection: English-language randomized, controlled trials comparing protocols titrated to strict or less strict glycemic targets.

Data Extraction: Two reviewers independently abstracted data from each study on sample, setting, glycemic control interventions, glycemic targets, mean glucose levels achieved, and outcomes. Results were grouped by patient population or setting. A random-effects model was used to combine trial data on short-term mortality (≤28 days), long-term mortality (90 or 180 days), infection, length of stay, and hypoglycemia. The Grading of Recommendations Assessment, Development, and Evaluation system was used to rate the overall body of evidence for each outcome.

Data Synthesis: In a meta-analysis of 21 trials in intensive care unit, perioperative care, myocardial infarction, and stroke or brain injury settings, IIT did not affect short-term mortality (relative risk, 1.00 [95% CI, 0.94 to 1.07]). No consistent evidence showed that IIT reduced long-term mortality, infection rates, length of stay, or the need for renal replacement therapy. No evidence of benefit from IIT was reported in any hospital setting, although the best evidence for lack of benefit was in intensive care unit settings. Data combined from 10 trials showed that IIT was associated with a high risk for severe hypoglycemia (relative risk, 6.00 [CI, 4.06 to 8.87]; $P < 0.001$). Risk for IIT-associated hypoglycemia was increased in all hospital settings.

Limitations: Methodological shortcomings and inconsistencies limit the data in perioperative care, myocardial infarction, and stroke or brain injury settings. Differences in insulin protocols and patient and hospital characteristics may affect generalizability across treatment settings.

Conclusion: No consistent evidence demonstrates that IIT targeted to strict glycemic control compared with less strict glycemic control improves health outcomes in hospitalized patients. Furthermore, IIT is associated with an increased risk for severe hypoglycemia.

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Hyperglycemia is common among medical and surgical inpatients with and without known diabetes (1, 2) and is associated with poor outcomes across various inpatient subpopulations (1, 3–7). Hyperglycemia may be a marker of severe, acute illness or may worsen outcomes by contributing to inflammation, oxidative stress, poor immune function, and endothelial dysfunction (8, 9). Initial studies of adjustable insulin infusions to decrease blood glucose levels raised interest in inpatient glycemic control strategies (10, 11), and several organizations called for implementing intensive insulin therapy (IIT) strategies using adjustable insulin infusions titrated to strict glycemic targets in the intensive care unit (ICU) (9, 12). Despite early evidence of benefit from IIT (13–16), many subsequent trials, including the largest IIT trial to date (17), have not found a consistent benefit.

We conducted a systematic review of studies evaluating the use of IIT to achieve glycemic control in hospitalized patients. The objectives of this review are to evaluate the benefits and harms of IIT and to discuss reasons for discrepancies in the literature. The American College of Physicians will use this review to guide recommendations for management of inpatient hyperglycemia.

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Methods

The U.S. Department of Veterans Affairs' Evidence-based Synthesis Program commissioned the full report on which this review is based (18). This review updates the previous review and addresses 2 key questions: 1) Does the use of IIT to achieve strict glycemic control compared with less strict glycemic control improve health outcomes in inpatients in surgical intensive care, medical intensive care, general medicine ward, and perioperative settings or in inpatients with acute myocardial infarction (MI) or acute stroke? 2) What are the harms of strict glycemic control in these subpopulations?

Data Sources and Searches

We searched MEDLINE and the Cochrane Database of Systematic Reviews for literature published from database inception in 1950 through January 2010. We obtained additional articles from consultation with experts and from reference lists of pertinent studies, reviews, and editorials. Table 1 in the **Supplement** (available at www.annals.org) describes the search strategies in detail. We searched ClinicalTrials.gov for information about unpublished studies. All citations were imported into the electronic database EndNote X2 (Thomson Reuters, New York, New York).

Study Selection

Three investigators reviewed the abstracts of citations identified from literature searches. We retrieved full-text articles of potentially relevant abstracts for further review. Each article was reviewed by using the eligibility criteria shown in Table 2 in the **Supplement**. Eligible articles were published in English and provided primary data on the use of IIT in hospitalized patients. We excluded studies that evaluated fixed-dose insulin and glucose–insulin–potassium infusions.

To evaluate the efficacy of and risk for hypoglycemia associated with IIT in hospitalized patients, we included randomized, controlled trials that reported at least one of the following prespecified outcomes: death, cardiovascular events, congestive heart failure, disability, wound infection, sepsis, or renal failure requiring hemodialysis. We defined "perioperative trials" as those in which IIT was begun before, during, or immediately after surgery and was discontinued less than 24 hours after surgery. We included studies of patients with MI during the postthrombolytic era (that is, 1995 or later).

Because the safety of IIT may vary on the basis of intervention and implementation characteristics, we evaluated hypoglycemia rates in controlled and uncontrolled studies of IIT protocols, even if the studies did not report other health outcomes (see the **Appendix**, available at www.annals.org, for study selection details).

Data Extraction and Quality Assessment

From each study, we abstracted the following characteristics: study design, objectives, setting, demographics (sex, age, baseline illness), participant eligibility and exclusion criteria, number of participants, years of enrollment, duration of follow-up, study and comparator interventions, method used to monitor blood glucose levels, target range for blood glucose level control, outcomes measured, analytic method used, variables adjusted in the analysis, results of the study and mean blood glucose levels achieved in each group, information on concomitant therapy or nutrition, occurrence of hypoglycemia in each group, and any other adverse events.

The quality of each study was rated as good, fair, or poor on the basis of U.S. Preventive Services Task Force criteria (see Table 3 in the **Supplement**) (19). When reviewers disagreed about quality rating, consensus was reached through discussion with all authors.

Data Synthesis and Analysis

The primary outcome of interest was short-term mortality, defined as death occurring within 28 days of or during the ICU or hospital stay. If studies reported more than 1 of these outcomes, we preferentially used 28-day mortality for the analysis, followed by hospital or ICU mortality. We conducted a sensitivity analysis based on the definition of short-term mortality. Secondary outcomes included 90- or 180-day mortality, infection, length of stay, and hypoglycemia. For each outcome, we abstracted the number of events and total participants from each treatment group and obtained a pooled estimate of relative risk (RR) by using a random-effects model (20). Statistical heterogeneity was assessed by using the Cochran Q test and the I^2 statistic (21). All analyses were done by using Stata software, version 10.0 (StataCorp, College Station, Texas).

We conducted prespecified subgroup analyses comparing ICU studies with non-ICU studies and did sensitivity analyses on the following aspects: 1) the proportion of diabetic patients included, which we calculated by using 25% as a cut point based on a natural division in the included studies; 2) the mean blood glucose level achieved in the intervention group, which we calculated by using a blood glucose level of 6.7 mmol/L (120 mg/dL) as the cut point because a lower threshold (≤6.1 mmol/L [≤110 mg/dL]) would have yielded only 1 study; and 3) study quality.

Rating the Body of Evidence

We assessed the overall quality of evidence for outcomes by using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system (22). The overall quality of evidence for each outcome is rated as high, moderate, low, or very low on the basis of the risk for bias, consistency, precision, directness, and other characteristics of the body of evidence.

Role of the Funding Source

The U.S. Department of Veterans Affairs Health Services Research and Development Service supported this review but had no role in the design, conduct, analysis, or submission of the manuscript for publication.

Results

Literature Flow

Our literature search (**Appendix Figure 1**, available at www.annals.org) identified 3055 publications, including 3 unpublished or ongoing trials (23–25). Of the 461 articles that we selected for full-text review, 31 trials conducted among perioperative or critically ill patients or patients with acute MI or stroke were included. We also found 29 insulin protocol studies not reporting health outcomes (**Appendix**).

Study Limitations

Because IIT requires intensive nursing care and monitoring, none of the trials was blinded. Therefore, unintended co-interventions that could influence patient outcomes, such as wound care, catheter care, or ventilator weaning, were possible. Because no trial reported sufficient nursing care information to decrease this risk for bias, no study was assigned a quality rating of good. Ten trials had additional methodological flaws that further increased the risk for bias (**Table 1** and Tables 4 to 6 in the **Supplement**). For example, 3 ICU trials had important differences in baseline patient characteristics and incompletely reported patient selection, allocation, blinding, or description of outcome assessment, which suggested that the groups were not comparable and that outcomes may have been differentially assessed (26–28). We also considered whether blood glucose levels achieved or rates of hypoglycemia were not reported, because these data were important in understanding the balance of benefits and harms (29–34).

Effects of IIT on Mortality

Across and within subgroups, IIT had an overall neutral effect on mortality, although the strength of the evidence varied among subgroups. Twenty-one randomized, controlled trials that comprised 14 768 inpatients reported at least 1 short-term mortality event in the treatment or control group. A meta-analysis of these trials (**Figure**) shows that IIT did not affect short-term mortality (RR, 1.00 [95% CI, 0.94 to 1.07]), with no statistical heterogeneity among studies ($I^2 = 0.0\%$; $P = 0.46$). Stratifying trials according to the blood glucose level achieved in the treatment group (<6.7 mmol/L [<120 mg/dL]) or whether the percentage of diabetic patients was less than 25% (RR, 1.02 [CI, 0.95 to 1.10]) or more than 25% (RR, 0.90 [CI, 0.77 to 1.06]) did not significantly change results (**Appendix Figure 2**, available at www.annals.org). Sensitivity analyses showed no effect of short-term mortality or study quality on the results, after exclusion of studies rated as poor quality (RR, 1.00 [CI, 0.94 to 1.07]; $I^2 = 20.2\%$).

Thirteen studies found that IIT did not reduce 90- or 180-day mortality (RR, 1.06 [CI, 0.99 to 1.12), with no statistical heterogeneity ($I^2 = 0.0\%$; $P = 0.57$) (**Appendix Figure 3**, available at www.annals.org). Subgroup results are discussed below.

ICU Settings

Of the 13 trials conducted in ICUs (**Table 1**), 6 reported data on critically ill patients in the surgical ICU (SICU) (16, 17, 26, 27, 35, 36), 6 reported data on critically ill patients in the medical ICU (MICU) (17, 28, 35, 37–39), and 3 included a mixed SICU and MICU population for whom specific ICU subgroup data were not available (40–42). A meta-analysis of all 12 ICU trials (**Figure**) found that IIT did not affect short-term mortality (RR, 0.98 [CI, 0.89 to 1.09]; $I^2 = 36.0\%$; $P = 0.10$).

Patients in the SICU. Four trials rated as fair quality conducted in patients in the SICU showed no mortality benefit of using IIT to achieve normal blood glucose levels (5.1 to 6.9 mmol/L [92 to 125 mg/dL]) (17, 26, 35, 36). In the largest of these trials, the multicenter NICE-SUGAR (Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) study (17), IIT was associated with excess 90-day mortality in patients in the SICU (RR, 1.31 [CI, 1.07 to 1.61]).

Conversely, Van den Berghe and colleagues' trial involving patients in the SICU (16) was discontinued early after all-cause ICU mortality was found to be significantly lower in the IIT treatment group (4.6% vs. 8%; RR, 0.58 [CI, 0.38 to 0.78]) (**Table 1**). The short-term mortality benefit was limited to the subgroup of patients who required 5 or more days of ICU care (10.6% vs. 20.2%; $P = 0.005$), and long-term mortality, defined as death that occurs within 90 or 180 days of the ICU or hospital stay, did not differ between the 2 groups (43). A recent small, poor-quality trial (27) found a mortality benefit (2% vs. 5%; $P = 0.044$) associated with a very modest decrease in blood glucose level.

Patients in the MICU. Among 5 fair-quality trials and 1 poor-quality trial involving patients in the MICU (17, 28, 35, 37–39), only 1 study (28) showed a benefit from achieving strict glycemic control (6.2 to 6.4 mmol/L [111 to 115 mg/dL]). Five trials (17, 28, 35, 37, 38) excluded patients who were not expected to require prolonged intensive care. In 1 trial (37), in-hospital mortality decreased in the subgroup of patients who remained in the ICU for at least 3 days (RR, 0.82 [CI not given]; $P = 0.009$), whereas a trend toward increased mortality was seen in patients with shorter ICU stays (RR, 1.09 [CI, 0.9 to 1.32]).

Mixed ICU Populations. Five fair-quality trials (17, 35, 40–42) that included mixed MICU and SICU populations also demonstrated no overall mortality benefit by using IIT to achieve normal blood glucose levels of 6.3 to 6.7 mmol/L (113 to 120 mg/dL). Two of these trials had MICU and SICU subgroup–specific information reported earlier (17, 35). The large multicenter NICE-SUGAR trial found that IIT was associated with an increase in 90-day mortality (RR, 1.14 [CI, 1.02 to 1.28]), with approximately 1 excess death for 39 patients treated with IIT.

Patients Receiving Perioperative Care

Four fair-quality trials (44–47) and 3 poor-quality trials (29–31) evaluating perioperative IIT in patients mainly undergoing cardiac surgery (Table 1 in the **Supplement**) found no short-term mortality benefit, but mortality rates were low.

Table 1. **Trials in Intensive Care Units**

Study, Year (Reference)	Sample Size, *n*	Participants With Diabetes Mellitus, %	Target Blood Glucose Level, *mmol/L (mg/dL)*	Glucose Monitoring Method	Inpatient Blood Glucose Level Achieved, *mmol/L (mg/dL)*	Mortality	Other Reported Outcomes*	Nutrition	Quality
SICU									
Van den Berghe et al, 2001 (16)	1548	13	TG: 4.4–6.1 (80–110) CG: 10.0–11.1 (180–200)	Arterial blood samples	TG: 5.7 (103)† CG: 8.5 (153)† $P < 0.001$	ICU mortality: TG: 4.6% CG: 8% RR, 0.42 (95% CI, 0.22–0.62) Hospital mortality: TG: 7.2% CG: 10.9% RR, 0.66 (CI, 0.48–0.92)	Renal replacement: TG: 4.8% CG: 8.2% $P = 0.007$ Sepsis: TG: 4.2% CG: 7.8% $P = 0.0003$	85.2% received majority of calories through parenteral nutrition‡	Fair
Grey and Perdrizet, 2004 (26)	61	15	TG: 4.4–6.7 (80–120) CG: 10.0–11.1 (180–220)	NR	TG: 6.9 (125)§ CG: 9.9 (179)§ $P < 0.001$	Hospital mortality: TG: 11% CG: 21% RR, 0.53 (CI, 0.17–1.69)	Infection: TG: 12.5% CG: 47.5% $P < 0.05$	NR	Poor‖
Arabi, 2008 (35)	88	NR	TG: 4.4–6.1 (80–110) CG: 10.0–11.1 (180–200)	Arterial and capillary blood samples	TG: 6.4 (115)§ CG: 9.5 (171)§ $P < 0.001$	ICU mortality: TG: 7.0% CG: 11.1% RR, 1.07 (CI, 0.67–1.72)	–	77%–81% received calories enterally	Fair
Kirdemir et al, 2008 (27)	200	100	TG: 5.6–8.3 (100–150) CG: <11.1 (<200)	NR	TG: 9.5 (172)§ CG: 10.8 (195)§ $P < 0.001$	ICU mortality: TG: 2.0% CG: 5.0% $P = 0.044$	Infection: TG: 1.0% CG: 12.0% $P = 0.003$ Renal replacement TG: 2% CG: 2% $P = 1.00$ Stroke/TIA: TG: 2% CG: 3% $P = 1.00$	NR	Poor‖
Bilotta et al, 2009 (36)	483	NR	TG: 4.4–6.1 (80–110) CG: 10.0–11.1 (180–200)	Arterial blood samples	TG: 5.1 (92)§ CG: 7.9 (143)§ $P < 0.001$	6–mo mortality: TG: 74.0% CG: 72.0% $P = 0.82$	Sepsis: TG: 2.9% CG: 3.3% P = NS Long-term disability: TG: 40.2% CG: 41.1% $P = 0.98$	NR	Fair
NICE-SUGAR study, 2009 (17)	2232	NR	TG: 4.4–6.0 (80–108) CG: <10.0 (<180)	Arterial blood samples	TG: 6.4 (115)¶ CG: 8.0 (144)¶ $P < 0.001$	90-d mortality: TG: 24.5% CG: 19.8% RR, 1.31 (CI, 1.07–1.61)	–	70%–72% received calories enterally	Fair
MICU									
Van den Berghe et al, 2006 (37)	1200	16	TG: 4.4–6.1 (80–110) CG: 10.0–11.1 (180–200)	Arterial and capillary blood samples	TG: 6.2 (111)† CG: 8.5 (153)† $P < 0.001$	ICU mortality: TG: 24.2% CG: 26.8% $P = 0.31$ Hospital mortality: TG: 37.3% CG: 40.0% RR, 0.93 (CI, 0.81–1.08) 90-d mortality: TG: 35.9% CG: 37.7% $P = 0.53$	Infection: TG: 0.7% CG: 0.8% P = NS Renal replacement TG: 20.8% CG: 22.7% $P = 0.50$	85.2% received majority of calories through parenteral nutrition‡	Fair
Farah et al, 2007 (28)	89	TG: 48.8 CG: 68.8 P = NS	TG: 6.1–7.8 (110–140) CG: 7.8–11.1 (140–200)	NR	TG: 7.9 (142)§ CG: 9.6 (174)§ $P < 0.001$	ICU mortality: TG: 39% CG: 31.3% P = NS 28-d mortality: TG: 53.6% CG: 45.8% RR, 1.17 (CI, 0.77–1.78)	Sepsis: TG: 26.8% CG: 35.4% P = NS Cardiovascular events TG: 12.2% CG: 39.6% $P = 0.004$	NR	Poor‖

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Table 1—**Continued**

Study, Year (Reference)	Sample Size, *n*	Participants With Diabetes Mellitus, %	Target Blood Glucose Level, *mmol/L (mg/dL)*	Glucose Monitoring Method	Inpatient Blood Glucose Level Achieved, *mmol/L (mg/dL)*	Mortality	Other Reported Outcomes*	Nutrition	Quality
Brunkhorst et al, 2008 (38)	537	30	TG: 4.4–6.1 (80–110) CG: 10.0–11.1 (180–200)	Arterial and capillary blood samples	TG: 6.2 (112)† CG: 8.4 (151)† $P < 0.001$	28-d mortality: TG: 24.7% CG: 26% RR, 0.95 (CI, 0.70–1.28) 90-d mortality: TG: 39.7% CG: 35.4% $P = 0.31$	Renal replacement: TG: 27.5% CG: 22.5% $P = 0.001$	Approximately 40%–55% received calories enterally	Fair
Savioli et al, 2009 (39)	90	13	TG: 4.4–5.5 (80–100) CG: 10.0–11.1 (180–200)	NR	TG: 6.2 (112)§ CG: 8.8 (159)§	ICU mortality: TG: 20% CG: 18% $P = 0.82$ 90-d mortality: TG: 31% CG: 29% $P = 0.82$	–	NR	Fair
Arabi et al, 2008 (35)	435	NR	TG: 4.4–6.1 (80–110) CG: 10.0–11.1 (180–200)	Arterial and capillary blood samples	TG: 6.4 (115)§ CG: 9.5 (171)§ $P < 0.001$	ICU mortality: TG: 14.8% CG: 18.4% RR, 0.50 (CI, 0.09–2.91)	–	77%–81% received calories enterally	Fair
NICE-SUGAR study, 2009 (17)	3789	NR	TG: 4.4–6.0 (80–108) CG: <10.0 (<180)	Arterial blood samples	TG: 6.4 (115)¶ CG: 8.0 (144)¶ $P < 0.001$	90-d mortality: TG: 29.3% CG: 28.0% RR, 1.07 (CI, 0.93–1.23)	–	70%–72% received calories enterally	Fair
Mixed MICU/SICU									
Mackenzie et al, 2008 (40)	240	14–19	TG: 4.0–6.0 (72–108) CG: 10.0–11.0 (180–198)	Whole-blood monitoring	TG: 7.0 (126)† CG: 8.4 (151)† TG: 6.3 (113)¶ CG: 8.0 (144)¶ $P < 0.001$	ICU mortality: TG: 19% CG: 22.7% $P = 0.53$ Hospital mortality: TG: 32.2% CG: 39.5% RR, 0.82 (CI, 0.58–1.15)	Renal replacement: TG: 0 patient-days CG: 0 patient-days Sepsis: TG: 0% CG: 0%	NR	Fair
Preiser et al, 2009 (41)	1101	TG: 16.5 CG: 21.8 $P = 0.031$	TG: 4.4–6.1 (80–110) CG: 7.8–10.0 (140–180)	Arterial and capillary blood samples	TG: 6.5 (117)§ CG: 8.0 (144)§ $P < 0.001$	ICU mortality: TG: 17.2% CG: 15.3% $P = 0.41$ Hospital mortality: TG: 23.3% CG: 19.4% $P = 0.11$ 28-d mortality: TG: 18.7% CG: 15.3% $P = 0.14$	Renal replacement: TG: 519 patient-days CG: 523 patient-days $P = 0.75$	Percentage (±SE) of days on parenteral nutrition: TG: 26% ± 44% CG: 27% ± 44%	Fair
Arabi et al, 2008 (35)	523	TG: 32 CG: 48 $P < 0.001$	TG: 4.4–6.1 (80–110) CG: 10.0–11.1 (180–200)	Arterial and capillary blood samples	TG: 6.4 (115)§ CG: 9.5 (171)§ $P < 0.001$	ICU mortality: TG: 13.5% CG: 17.1% RR, 1.09 (CI, 0.70–1.72)** Hospital mortality: TG: 27.1% CG: 32.3% RR, 0.84 (CI, 0.64–1.09)**	Renal replacement: TG: 11.7% CG: 12.1% $P = 0.89$** Sepsis: TG: 36.9% CG: 40.9% $P = 0.35$	77%–81% received calories enterally	Fair
De La Rosa et al, 2008 (42)	504	TG: 12.6 CG: 11.6 P = NS	TG: 4.4–6.1 (80–110) CG: 10.0–11.1 (180–200)	Arterial blood samples	TG: 6.7 (120)§ CG: 8.3 (149)§ $P < 0.001$	ICU mortality: TG: 33.1% CG: 31.2% RR, 1.06 (CI, 0.82–1.37) 28-d mortality: TG: 36.6% CG: 32.4% RR, 1.1 (CI, 0.85–1.42)	Infection: TG: 27.2% CG: 33.2% P = NS Renal replacement: TG: 10.8% CG: 13% $P = 0.45$	94.5% of patients received enteral nutrition exclusively	Fair

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Table 1—**Continued**

Study, Year (Reference)	Sample Size, *n*	Participants With Diabetes Mellitus, %	Target Blood Glucose Level, *mmol/L (mg/dL)*	Glucose Monitoring Method	Inpatient Blood Glucose Level Achieved, *mmol/L (mg/dL)*	Mortality	Other Reported Outcomes*	Nutrition	Quality
NICE-SUGAR study, 2009 (17)	6104	20.1	TG: 4.4–6.0 (80–108) CG: <10.0 (<180)	Arterial blood samples	TG: 6.4 (115)¶ CG: 8.0 (144)¶ $P < 0.001$	28-d mortality: TG: 22.3% CG: 20.8% RR, 1.09 (CI, 0.96–1.23) 90-d mortality: TG: 27.5% CG: 24.9% RR, 1.14 (CI, 1.02–1.28)	Renal replacement: TG: 15.4% CG: 14.5% $P = 0.34$ Sepsis: TG: 12.8% CG: 12.4% $P = 0.57$	70%–72% received calories enterally	Fair

CG = comparison group; ICU = intensive care unit; MICU = medical intensive care unit; NICE-SUGAR = Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation; NR = not reported; NS = not statistically significant; RR = relative risk; SICU = surgical intensive care unit; TG = treatment group; TIA = transient ischemic attack.
* "Infection" includes wound infection, urinary tract infection, pneumonia, or a combination of these conditions. The incidence of infection is also shown in **Appendix Figure 4** (available at www.annals.org).
† Morning blood glucose value.
‡ Data from combined analysis of Van den Berghe and colleagues' SICU and MICU trials (55); data not reported in individual trials.
§ Average of blood glucose measurements, not otherwise specified.
‖ Incomplete reporting of patient selection and allocation, important differences in baseline patient characteristics, and lack of blinding or incomplete description of outcome assessment suggested that groups did not achieve comparability and outcomes may have been differentially assessed.
¶ Time-weighted mean blood glucose value.
** Adjusted for chronic liver disease, traumatic brain injury, Acute Physiology and Chronic Health Evaluation II score, and international normalized ratio.

Patients With MI

In 5 of 6 trials including patients with acute MI (32, 48–51), IIT was not associated with a mortality benefit (Table 5 in the **Supplement**). A frequently cited older trial that may be only minimally applicable to current patients with MI (13) compared insulin infusion plus long-term postdischarge insulin therapy with usual care and found a mortality reduction at 1 year (18.6% vs. 26.1%; RR, 0.69 [CI, 0.49 to 0.96]; $P = 0.027$). Whether the benefit was related to the acute intervention or the longer-term insulin therapy remains uncertain. A trial designed to address this uncertainty (51) found no mortality benefit, but important baseline characteristics were not comparable among groups, resulting in a poor quality rating.

Patients With Stroke and Acute Brain Injury

Among the few relevant studies involving patients with stroke and acute brain injury (33, 34, 52–54), use of IIT showed no mortality benefit (Table 6 in the **Supplement**). The largest trial of patients with stroke (33) reported blood glucose data for less than 50% of the participants, and 1 trial (34) reported no data on blood glucose levels achieved using ITT.

Patients in General Medicine Wards

No trials evaluated the effects of IIT on health outcomes in patients in general medical wards.

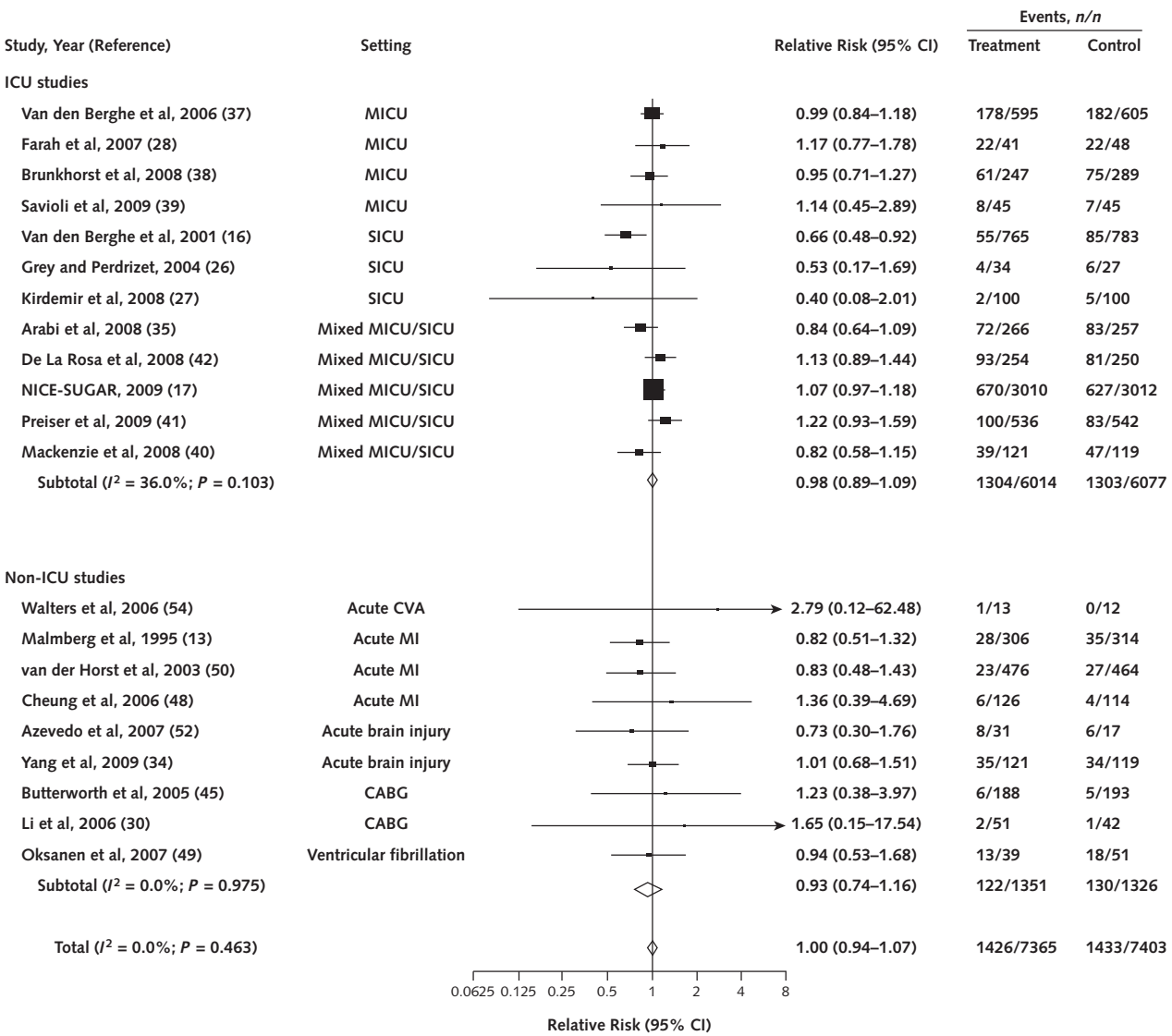
Effects of IIT on Infection

Sixteen trials evaluated the effects of IIT on the incidence of infection (**Appendix Figure 4**, available at www.annals.org). The definition of *infection* varied across studies. Nine studies reported sepsis as an outcome and found a marginally significant 21% decrease in the risk for sepsis with IIT (RR, 0.79 [CI, 0.62 to 1.00]), although heterogeneity among trials was significant ($I^2 = 53.1\%$; $P = 0.029$). A sensitivity analysis suggested that the benefit and heterogeneity were derived solely from Van den Berghe and colleagues' trial of patients in the SICU (16) (RR, 0.89 [CI, 0.74 to 1.09]; $I^2 = 29.0\%$; $P = 0.20$). Most other trials, including the large NICE-SUGAR study (17), found no effect of IIT on sepsis. A pooled analysis of the other 7 studies reporting the occurrence of wound infections, urinary tract infections, pneumonia, or a combination of these events found a neutral effect of IIT on infection (RR, 0.68 [CI, 0.36 to 1.30]), although heterogeneity among these studies was also significant ($I^2 = 56.3\%$; $P = 0.033$) (**Appendix Figure 4**).

Effects of IIT on Inpatient Length of Stay

The effects of IIT on hospital and ICU length of stay are uncertain. Trial results were heterogeneous ($I^2 = 95.3\%$ and $P < 0.001$ in 13 trials; $I^2 = 69.9\%$ and $P < 0.001$ in 17 trials), and results within subgroups were conflicting. Trials in mixed MICU and SICU settings, including the NICE-SUGAR study (17, 35, 40–42), found that IIT did not affect hospital length of stay (combined effect size, 0.008 day [CI, −0.836 to 0.853 day]; $I^2 = 0.0\%$; $P = 0.93$) or ICU length of stay (combined effect size, −0.039 day [CI, −0.335 to 0.257 day]; $I^2 = 0.0\%$; $P = 0.76$). However, 4 trials of patients in the SICU (26, 27, 36, 55) found a decrease in ICU length of stay with IIT

Figure. **Short-term mortality in studies of intensive insulin therapy, by inpatient setting.**



Short-term mortality includes death occurring within 28 d of or during the ICU or hospital stay; we used 28-d mortality in the meta-analysis when a study reported >1 outcome. *Events* is the number of deaths among participants in the treatment and control groups. CABG = coronary artery bypass graft; CVA = cerebrovascular accident; ICU = intensive care unit; MI = myocardial infarction; MICU = medical intensive care unit; NICE-SUGAR = Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation study; SICU = surgical intensive care unit.

(combined effect size, −1.484 days [CI, −2.233 to −0.734 day]; I^2 = 50.0%; P = 0.112).

Effects of IIT on Other Outcomes

The effects of IIT on other outcomes were largely neutral (**Table 1** and Tables 4 to 6 in the **Supplement**). Eight of 9 trials (17, 27, 35, 37, 38, 40–42) showed that IIT had no effect on the need for new renal replacement therapy. However, Van den Berghe and colleagues' trial of patients in the SICU (16) showed that IIT was associated with a reduced need for new renal replacement (4.8% vs. 8.2%; $P < 0.007$). One trial in patients with stroke (34) found significantly fewer patients in the IIT group who were severely disabled 6 months later, but no effects on long-term disability were shown in 3 other trials in patients with stroke or acute brain injury (33, 52, 53) or in 2 trials in neurosurgical (36) or perioperative (45) patients.

The effect of IIT on cardiovascular events was mixed. Four trials (13, 27, 50, 51) reported no differences between treatment groups in cardiovascular events. Four trials (28, 29, 47, 48) reported a decrease in cardiovascular events in the IIT intervention group, but the risk reduction in 1 of the trials seemed disproportionate compared with the modest and brief blood glucose level differential achieved (47). Conversely,

more strokes occurred in the IIT treatment group in 1 perioperative trial (46).

Effects of IIT on Hypoglycemia

Intensive insulin therapy was associated with an increased risk for hypoglycemia in all settings (**Table 2**). A meta-analysis of 10 trials (**Appendix Figure 5**, available at www.annals.org) found that IIT was associated with a 6-fold increased risk for severe hypoglycemia, defined as a blood glucose level less than 2.2 mmol/L (<40 mg/dL). However, the absolute risk varied across studies (RR, 6.00 [CI, 4.06 to 8.87]; $I^2 = 57.9\%$; $P < 0.001$). The addition of 11 trials with higher cut points defining hypoglycemia produced similar results (RR, 4.43 [CI, 2.30 to 8.53]; $I^2 = 94.5\%$; $P < 0.001$). Risk for hypoglycemia did not significantly differ between trials achieving treatment group blood glucose levels less than 6.7 mmol/L (<120 mg/dL) compared with those achieving levels of 6.7 mmol/L or greater (≥120 mg/dL) (RR, 5.99 vs. 4.28; $P = 0.39$ for the comparison between groups).

To examine the safety characteristics of various approaches to IIT, we reviewed an additional 29 studies not evaluating health outcomes that reported the safety of insulin infusions (**Appendix**). These studies were mostly small, single-center studies of iteratively developed protocols in carefully selected patient populations. Almost all of the centers that achieved blood glucose levels greater than 6.7 mmol/L (>120 mg/dL) also had low rates of hypoglycemia. Centers achieving levels less than 6.7 mmol/L (<120 mg/dL) had mixed results: Several centers safely achieved these levels by using sophisticated insulin protocols incorporating multiple variables or computerized algorithms, whereas other centers had very high rates of hypoglycemia.

A small number of in-hospital adverse effects of hypoglycemia were reported during IIT (**Table 2**). However, many critically ill patients included in these studies were sedated, which limited event detection. Three trials involving patients in the MICU (35, 38, 56) found excess mortality or extended length of inpatient stay among patients treated with IIT who experienced at least 1 episode of severe hypoglycemia. In 1 trial (35), the mortality risk in patients treated with IIT who had hypoglycemia was double that in control patients with hypoglycemia (25.0% vs. 12.5%; $P < 0.05$). Another trial (38) found that patients treated with IIT who had hypoglycemic events were significantly more likely to require prolonged hospitalization (2.4% vs. 0.3%; $P = 0.05$). One study (40) reported a case of cardiac asystole related to treatment-induced hypoglycemia.

Discussion

In a synthesis of evidence from randomized, controlled trials, we found that use of IIT to achieve strict glucose control compared with less strict control did not reduce mortality or length of hospital stay but did substantially increase the risk for severe hypoglycemia in various hospital settings. Although strict glucose control was associated with a marginally significant reduction in septicemia, our sensitivity analysis found that the marginal benefit was entirely caused by Van den Berghe and colleagues' trial of patients in the SICU (16). Furthermore, a larger, more recent trial including patients in the SICU (17) found no association between glucose control and septicemia. Using the GRADE system (**Table 3**), we summarized the strength of evidence supporting these findings in each of the hospital settings that we evaluated and found the strongest body of evidence in ICU settings.

Subsequent trials (57, 58) have not replicated the initial encouraging findings from Van den Berghe and colleagues' trial of patients in the SICU (16). Several factors may account for this discrepancy. Parenteral nutrition was used routinely only in Van den Berghe and colleagues' trials of patients in the SICU and MICU (16, 37) and may be associated with adverse effects in critically ill patients, including an increased risk for infection (59, 60). Therefore, the observed benefits of IIT in these patients may actually reflect a reduction in harm from aggressive nutrition practices.

Capillary blood sampling is the more commonly used method for monitoring blood glucose levels but is less dependable than arterial blood sampling (61), which was routinely used in Van den Berghe and colleagues' trial of patients in the SICU (16). Most ICU trials achieved a slightly smaller differential in blood glucose levels between the intervention and control groups than that in Van den Berghe and colleagues' trial. Lower blood glucose level targets for control groups in recent trials (17, 56), and different blood glucose reporting methodologies, such as measuring mean glucose versus morning glucose levels, may partly explain this discrepancy. However, despite the slightly higher blood glucose levels achieved with IIT in recent trials, the risk for severe hypoglycemia remained consistently and substantially elevated.

Several trials that showed no mortality benefit from IIT in critically ill patients were discontinued early because of an excess risk for hypoglycemia in the intervention groups, which suggested that the lack of observed benefit may reflect inadequate power (35, 38, 56). However, these trials did not demonstrate a consistent trend toward benefit. Furthermore, the inability to implement the insulin infusion protocol in various clinical trial settings without causing high rates of hypoglycemia may underscore the complexity of IIT and problems with generalizability across institutions.

Although many experts acknowledge the lack of convincing evidence showing benefit from IIT targeted to very strict ranges of blood glucose level, they are reluctant to discontinue glycemic control because of the potential complications of hyperglycemia (9, 62). However, the benefits of achieving more moderate blood glucose targets have not

Table 2. **Hypoglycemia Risk in Trials of Intensive Insulin Therapy**

Study, Year (Reference)	Intervention	Target Blood Glucose Level, *mmol/L (mg/dL)*	Hypoglycemia Definition, *mmol/L (mg/dL)*	Participants With ≥1 Episode of Hypoglycemia, %	Adverse Events Resulting From Hypoglycemia
SICU					
Kirdemir et al, 2008 (27)	TG: insulin infusion through at least postoperative day 3 CG: subcutaneous SSI	TG: 5.5–8.3 (100–150) CG: <11.1 (<200)	NR	TG: 0 CG: 0	None
Van den Berghe et al, 2001 (16)	Both groups: insulin infusion*†	TG: 4.4–6.1 (80–110) CG: 10.0–11.1 (180–200)	<2.2 (<40)	TG: 5 CG: 0.76 RR, 6.65 (95% CI, 2.83–15.62)	NR
Grey and Perdrizet, 2004 (26)	Both groups: insulin infusion*†	TG: 4.4–6.6 (80–120) CG: 10.0–12.2 (180–220)	<3.3 (<60)	TG: 32 CG: 7.4 RR, 4.37 (CI, 1.06–18.06)	None
Bilotta et al, 2009 (36)	Both groups: insulin infusion*	TG: 4.4–6.1 (80–110) CG: 10.0–11.1 (180–200)	<2.8 (<50)	TG: 93.8 CG: 62.8 $P < 0.001$	NR
MICU					
Van den Berghe et al, 2006 (37)	Both groups: insulin infusion*†	TG: 4.4–6.1 (80–110) CG: 10.0–11.1 (180–200)	<2.2 (<40)	TG: 18.7 CG: 3.1	NR
Farah et al, 2007 (28)	Both groups: insulin infusion*†	TG: 6.1–7.8 (110–140) CG: 7.8–11.1 (140–200)	<2.2 (<40)	Episodes per group: TG: 23 CG: 23	None
Brunkhorst et al, 2008 (38)	Both groups: insulin infusion*†	TG: 4.4–6.1 (80–110) CG: 10.0–11.1 (180–200)	<2.2 (<40)	TG: 17 CG: 4.1 RR, 4.11 (CI, 2.21–7.63)	More episodes (TG vs. CG) described as life-threatening (5.3 vs. 2.1; $P = 0.05$) and requiring prolonged hospitalization (2.4 vs. 0.3; $P = 0.05$)
Savioli et al, 2009 (39)	Both groups: insulin infusion*†	TG: 4.4–6.1 (80–110) CG: 10.0–11.1 (180–200)	<3.3 (<60)	TG: 2.1 CG: 0.3	NR
Mixed MICU/SICU					
NICE-SUGAR study, 2009 (17)	Both groups: insulin infusion*‡	TG: 4.4–6.0 (80–108) CG: <10.0 (<180)	<2.2 (<40)	TG: 6.8 CG: 0.5 OR, 14.7 (CI, 9.0–25.9)	None
De La Rosa, 2008 (42)	Both groups: insulin infusion*‡	TG: 4.4–6.1 (80–110) CG: 10.0–11.1 (180–200)	<2.2 (<40)	TG: 8.3 CG: 0.8	One seizure associated with hypoglycemia in the TG
Arabi et al, 2008 (35)	Both groups: insulin infusion*†	TG: 4.4–6.1 (80–110) CG: 10.0–11.1 (180–200)	<2.2 (<40)	TG: 28.6 CG: 3.1 $P < 0.001$	ICU mortality in patients with hypoglycemia: TG: 23.8% CG: 13.7% $P = 0.02$ Among patients with hypoglycemia, higher mortality in intensive insulin infusion group vs. CG (25.0% vs. 12.5%)
Mackenzie et al, 2008 (40)	Both groups: insulin infusion*†	TG: 4.0–6.0 (72–108) CG: <11.0 (<198)	<2.2 (<40)	TG: 41.3 CG: 7.6 $P < 0.001$	One case of cardiac asystole associated with rescue dextrose infusion in a hypoglycemic patient
Preiser et al, 2009 (41)	Both groups: insulin infusion*†	TG: 4.4–6.1 (80–110) CG: 7.8–10.0 (140–180)	<2.2 (<40)	TG: 8.7 CG: 2.7	ICU mortality in patients with hypoglycemia: TG: 32.2% CG: 13.6% $P < 0.01$

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Table 2—**Continued**

Study, Year (Reference)	Intervention	Target Blood Glucose Level, *mmol/L (mg/dL)*	Hypoglycemia Definition, *mmol/L (mg/dL)*	Participants With ≥1 Episode of Hypoglycemia, %	Adverse Events Resulting From Hypoglycemia
Acute myocardial infarction/ventricular fibrillation survivors					
Malmberg et al, 1995 (13)	TG: insulin infusion*‡ for 24 h, multidose insulin regimen for at least 3 mo CG: usual care	TG: 7.0–11.0 (126–198) CG: not specified	<3.0 (<54)	TG: 15.0 CG: 0 $P < 0.001$	NR
Cheung et al, 2006 (48)	TG: insulin infusion* for 24 h CG: usual care, supplemental insulin if glucose level >16.0 mmol/L (>288 mg/dL)	TG: 4.0–10.0 (72–180) CG: not specified	<3.5 (<63)	TG: 10.3 CG: 1.8 $P = 0.02$	NR
Malmberg et al, 2005 (51)	TG: intervention 1, insulin infusion*‡ plus outpatient multidose insulin; intervention 2, insulin infusion only CG: usual care	TG: 7.0–10.0 (126–180) CG: not specified	<3.0 (<54)	Group 1: 12.7 Group 2: 9.6 Group 3: 1.0	One third of hypoglycemic patients were symptomatic; no reported adverse clinical events
Rasoul et al, 2007 (32)	TG: adjustable high-dose GIK* CG: usual care	TG: 6.0–10.0 (108–180) CG: not specified	NR	NR	NR
van der Horst et al, 2003 (50)	TG: adjustable high-dose GIK*‡ CG: usual care	TG: 7.1–11.0 (128–198) CG: not specified	NR	TG: 0 CG: 0	NR
Oksanen et al, 2007 (49)	TG: insulin infusion in both groups, no protocol	TG: 4.0–6.0 (72–108) CG: 6.0–8.0 (108–144)	<3.0 (<54)	TG: 18 CG: 2	NR
Stroke/acute brain injury					
Gray et al, 2007 (33)	TG: adjustable GIK infusion* CG: saline infusion, insulin if blood glucose level >17.0 mmol/L (>306 mg/dL)	TG: 4.0–7.0 (72–126) CG: <17.0 (<306)	<4.0 (<72) for >30 min	TG: 15.7 CG: NR§	None
Azevedo et al, 2007 (52)	TG: insulin infusion† CG: regular insulin if glucose level >10.0 mmol/L (>180 mg/dL); lower-carbohydrate enteral formula	TG: 4.4–6.6 (80–120) CG: <10.0 (<180)	<2.2 (<40)	TG: 6.4 CG: 5.8	NR
Yang et al, 2009 (34)	TG: Insulin infusion (algorithm NR) CG: insulin infusion if blood glucose level >11.9 mmol/L (>215 mg/dL)	TG: 4.4–6.1 (80–110) CG: 10.0–11.1 (180–200)	<2.2 (<40)	TG: 3.3 CG: 2.5	None
Bruno et al, 2008 (53)	TG: insulin infusion*‡ CG: regular SSI for blood glucose level >11.1 mmol/L (>200 mg/dL)	TG: 5.0–7.2 (90–130) CG: <11.1 (<200)	<3.3 (<60)	TG: 35 CG: 0	4 of 11 hypoglycemic patients had transient autonomic symptoms or brief cognitive slowing

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Table 2—**Continued**

Study, Year (Reference)	Intervention	Target Blood Glucose Level, *mmol/L (mg/dL)*	Hypoglycemia Definition, *mmol/L (mg/dL)*	Participants With ≥1 Episode of Hypoglycemia, %	Adverse Events Resulting From Hypoglycemia
Walters et al, 2006 (54)	TG: insulin infusion* CG: usual care, supplemental insulin if blood glucose level >15.0 mmol/L (>270 mg/dL)	TG: 5.0–8.0 (90–144) CG: <15.0 (<270)	NR	Overall rate NR	One episode of symptomatic hypoglycemia in TG
Perioperative (CABG, cardiac surgery, vascular surgery)					
Li et al, 2006 (30)	TG: insulin infusion*‡ CG: subcutaneous insulin	TG: 8.3–11.1 (150–200) CG: 8.3–11.1 (150–200)	NR	NR	NR
Butterworth et al, 2005 (45)	TG: intraoperative insulin infusion* CG: saline infusion	TG: 3.9–5.5 (70–100) CG: not specified	<3.9 (<70)	TG: 11.7 CG: 6.2 $P = 0.07$	NR
Gandhi et al, 2007 (46)	TG: intraoperative insulin infusion* CG: intravenous bolus of insulin if blood glucose level >11.1 mmol/L (>200 mg/dL); infusion if >13.9 mmol/L (>250 mg/dL) Both groups: 24-h postoperative insulin infusion in ICU	TG: 4.4–5.5 (80–100) CG: <11.1 (<200)	<3.3 (<60)	TG: 1 CG: 1 $P = 1.00$	NR
Lazar et al, 2004 (29)	TG: intraoperative and 12-h postoperative GIK infusion* CG: subcutaneous SSI	TG: 7.0–11.1 (126–200) CG: <13.9 (<250)	NR	NR	NR
Smith et al, 2002 (31)	TG: intraoperative and 6-h post-operative GIK infusion* CG: dextrose placebo infusion, with no blood glucose monitoring	TG: 4.9–9.9 (89–179) CG: not specified	NR	NR	NR
Barcellos Cda et al, 2007 (44)	TG: intraoperative and 12-h postoperative GIK infusion* CG: subcutaneous SSI	TG: 7.0–11.1 (126–200) CG: <11.1 (<200)	<3.9 (<70)	TG: 32.0 CG: 16.0	None
Subramaniam et al, 2009 (47)	TG: intraoperative and 48-h postoperative insulin infusion* CG: intravenous SSI	TG: 5.5–8.3 (100–150) CG: <8.3 (<150)	<3.3 (<60)	TG: 8.8 CG: 4.1 $P = 0.14$	None

CABG = coronary artery bypass grafting; CG = comparison group; GIK = glucose–insulin–potassium; ICU = intensive care unit; MICU = intensive care unit; NICE-SUGAR = Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation; NR = not reported; OR = odds ratio; RR = relative risk; SICU = intensive care unit; SSI = sliding-scale insulin; TG = treatment group.

* Insulin infusion rate was based on current blood glucose levels.

† Factors included in insulin infusion rate calculations were not reported, or protocol allows for dosing based on provider discretion.

‡ Rate of change in glucose level was also included in adjusting insulin infusion rate.

§ Rate based on the number of participants requiring rescue dextrose; glucose values for overall group not available.

been established; therefore, it is imperative that any glycemic control strategy also minimizes harms.

Glucose targets are a key determinant of safety, although other factors also may be important. Previous reviews of insulin protocols stressed that, given the various factors influencing the safety of IIT implementation, each institution should individualize its protocol on the basis of its patient population as well as its institutional and provider resources (63–65). These reviews speculate that safer protocols should incorporate bolus insulin doses, account for the direction and rate of changes in blood glucose levels, and allow "off-protocol" adjustments (64, 65).

Our review of insulin protocol studies also suggests that protocol characteristics are important but perhaps less so than the blood glucose level target itself (**Appendix**). We found that use of sophisticated protocols did not consistently decrease the risk for hypoglycemia when glucose levels less than 6.7 mmol/L (<120 mg/dL) were achieved. Observational studies also show an increased risk for hypoglycemia when institutions implement stricter blood glucose level targets over time (66, 67). In addition, nearly all institutions that achieved blood glucose levels greater than 6.7 mmol/L (>120 mg/dL) also had low rates of hypoglycemia. Furthermore, the relatively low rates of hypoglycemia in the IIT trial control groups, which generally used target blood glucose levels ranging from 7.8 to 11.1 mmol/L (140 to 200 mg/dL), suggest that higher target blood glucose levels are safer.

Table 3. **Summary of the Evidence for the Effects of Intensive Insulin Therapy, by Outcome and Inpatient Setting**

Outcome, by Subgroup	Effect	GRADE Classification*	Comment
Short-term mortality			
MICU	Mixed findings/no effect	High	None of the 6 trials found a benefit.
SICU	Mixed findings/no effect	Moderate	One trial showed benefit, 4 showed no effect, and 1 found that intensive insulin therapy was associated with an increased risk for long-term mortality.
Perioperative	Mixed findings/no effect	Low	Seven trials found no benefit, but the body of evidence is hampered by small sample sizes, low event rates, and methodological weaknesses. There were considerable differences in interventions used and blood glucose targets across trials.
Myocardial infarction	Mixed findings/no effect	Low	Inconsistent results and variation in trial design, achievement of recruitment goals, glucose level achieved, and concomitant therapy for myocardial infarction limit the strength of the conclusions that can be drawn from these 6 trials.
Stroke/brain injury	Mixed findings/no effect	Low	Inadequate glucose data reporting in the 2 largest trials limit this body of evidence.
General medicine wards	No evidence		No evidence.
Infection			
MICU	Mixed findings/no effect	High	Three large, fair-quality trials found no benefit.
SICU	Benefit or mixed findings/no effect	Low	The evidence of benefit is based on 1 fair-quality trial but not confirmed in others.
Perioperative	Mixed findings/no effect	Low	The quality of included trials and clinical heterogeneity limit the body of evidence.
Brain injury	Benefit	Low	Evidence limited to 1 poor-quality trial.
Myocardial infarction, stroke, general medical	No evidence		No evidence.
Length of stay			
MICU/SICU	Mixed findings/no effect	High	Based on 4 (hospital length of stay) and 5 (ICU length of stay) trials.
SICU	Benefit or mixed findings/no effect	Moderate (ICU length of stay); very low (hospital length of stay)	Evidence on ICU length of stay is limited by quality of 2 of the trials; only 1 poor-quality trial reported hospital length of stay.
Perioperative	Mixed findings/no effect	Low	Body of evidence is limited by study quality and inconsistent results.
Myocardial infarction, stroke/brain injury, general medical	Harm or no evidence	Very low	No evidence other than 1 older myocardial infarction study showing an increase in length of stay associated with intensive insulin therapy.
Hypoglycemia			
All subgroups (except general medical)	Harm	High	Trials in all settings found an increased risk; evidence is strongest in ICU settings.

GRADE = Grading of Recommendations Assessment, Development, and Evaluation; ICU = intensive care unit; MICU = medical intensive care unit; SICU = surgical intensive care unit.

* GRADE classification: high = further research is very unlikely to change our confidence on the estimate of effect; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain.

The consequences of inpatient hypoglycemia are unclear. In several trials, hypoglycemia was associated with excess mortality; however, whether hypoglycemia is a causative factor or simply a marker of more severe disease remains uncertain, and recent observational studies attempting to clarify this issue have yielded conflicting results (68, 69). One recent cohort study of diabetic patients found that severe hypoglycemia was associated with an increased risk for incident dementia, and another study found that inpatient hypoglycemia was associated with increased long-term mortality in diabetic patients with the acute coronary syndrome (70, 71).

Two previous reviews focused on ICU settings, whereas we examined the effects of IIT in various hospital settings (57, 58). We reached conclusions similar to those reached in previous studies of the risk for hypoglycemia and lack of benefit associated with IIT in ICU settings. We also found that this lack of benefit and possible harm was less well studied but extended to other hospital settings. Our broader evaluation strengthens the finding that IIT is difficult to implement safely and that initial benefits seen in Van den Berghe and colleagues' trial of patients in the SICU (16) subsequently have not been realized despite attempts to do so in various settings. Finally, because of continued interest in glucose control strategies to reduce the perceived harm of hyperglycemia, our review also adds to findings from previous reviews by examining the safety of various insulin infusion programs.

Our review has several potential limitations. Studies were grouped according to hospital setting, but overlap may occur in some of the subgroups. For instance, patients with MI may receive care in an MICU setting. However, results were consistent across subgroups. No study could isolate the effects of the IIT intervention itself. The increased intensity of nursing care associated with IIT implementation in the intervention groups may have caused unintended co-interventions, such as improved catheter care or earlier attempts at ventilator weaning. The beneficial effects of these co-interventions therefore could potentially overshadow the harmful effects of the IIT intervention itself. The generalizability of results from the included studies may be limited by patient characteristics, event rates, concomitant therapy, institution characteristics, and monitoring methodology. Most studies were conducted in a single center, yet the relative success or failure of an insulin-based intervention may depend, in part, on characteristics that are unique to a particular institution or health system. Finally, the included trials usually relied on blood glucose measurements from a defined reference time rather than from 24-hour blood glucose levels achieved and therefore could obscure the inherent variability in glucose control through the course of intensive care (72, 73).

Many institutions are likely to pursue less aggressive glycemic control, but the health benefits of achieving moderate blood glucose level targets, such as 7.8 to 11.1 mmol/L (140 to 200 mg/dL), should be examined. Future studies also should evaluate the cost and patient, nurse, and physician acceptance of implementing insulin infusion protocols in hospitalized patients. Individual institutions describing their experience implementing intensive insulin protocols suggest that the increase in nursing workload and fear of hypoglycemia were significant although potentially surmountable barriers to implementation (74–76). Moreover, evaluating the feasibility and safety of transitioning patients from insulin infusion to subcutaneous insulin and ultimately to a safe outpatient regimen is warranted.

In summary, no consistent evidence shows that IIT improves health outcomes in hospitalized patients. However, this intervention may be associated with a high risk for severe hypoglycemia, especially when the blood glucose level target is less than 6.7 mmol/L (<120 mg/dL). The consequences of severe hypoglycemia in hospitalized patients have not been well studied. However, given the lack of compelling evidence for benefit, the potential for serious harm should forestall efforts to routinely implement very strict targets for blood glucose control in hospitalized patients.

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Appendix

Background

Over the past decade, numerous trials have evaluated how decreasing blood glucose levels by using IIT has affected health outcomes in various inpatient settings. Despite initial encouraging evidence from a study of patients in the SICU (16), subsequent trials have shown no consistent evidence that IIT decreases mortality, length of stay, or infection rates. Moreover, IIT interventions in these trials were associated with a nearly 6-fold increased risk for hypoglycemia.

Although the health outcome benefits of more moderate glucose control (for example, blood glucose levels targeted to 7.8 to 10.0 mmol/L [140 to 180 mg/dL]) have not been studied, the association of increased blood glucose levels with an increased risk for infection, dehydration, and poor hospital outcomes has caused many centers to pursue moderate degrees of blood glucose control. Given the lack of evidence showing that moderate glycemic control provides health outcome benefits, it is imperative that this intervention minimizes the risk for hypoglycemia. To evaluate the relative safety of various IIT approaches, we reviewed controlled and uncontrolled clinical trials of IIT, including trials reporting only intermediate outcomes (such as glucose control) as well as observational studies.

Methods

We searched MEDLINE and the Cochrane Database of Systematic Reviews for literature published from database inception through January 2010. Table 1 in the **Supplement** provides the search strategies in detail. We obtained additional articles from systematic reviews, reference lists of pertinent studies, reviews, and editorials and by consulting experts. We also searched for information about unpublished studies on ClinicalTrials.gov. All citations were imported into an electronic database (EndNote 9.0).

To assess the risk for hypoglycemia associated with IIT, we included controlled and uncontrolled studies that evaluated IIT protocols in hospitalized patients, even if the studies did not report health outcomes. We excluded IIT studies that did not report rates of hypoglycemia (10, 77–87). To avoid studies with potential selection bias, we excluded prospective cohort studies in which patients were not consecutively enrolled or that had excessive loss to follow-up (87–96). We also excluded studies in which the intervention was evaluated over a short period (defined as ≤6 months), because tight glycemic control strategies require personnel training and institutional acceptance and we believed that these studies were less likely to provide externally valid results (97–102).

Results

We reviewed 3054 abstracts and retrieved 460 articles for full-text review. We also included 31 trials that reported at least 1 prespecified health outcome (mortality, infection, cardiovascular events, disability, or need for renal replacement therapy) in our accompanying meta-analysis on the benefits and harms of IIT in hospitalized patients. In the paragraphs below, we report the results of studies not designed to evaluate a prespecified health outcome other than hypoglycemia: specifically 29 studies reporting on the safety of insulin infusions and 4 studies reporting on the safety of subcutaneous insulin regimens.

Insulin Infusions

In 10 studies, the intervention groups achieved a mean blood glucose level of 6.7 mmol/L or less (≤120 mg/dL) (Table 7 in the **Supplement**). The definition of hypoglycemia differed across studies. Four studies reported relatively low rates of severe hypoglycemia; 3 of these studies used a complex computerized algorithm (103–105), and 1 study used a sophisticated insulin infusion protocol that incorporated insulin sensitivity estimates (106). However, 4 studies reported high rates (defined as affecting >5% of participants) of severe hypoglycemia; 2 of these studies used a computerized algorithm (107, 108), and 2 studies used a relatively simple infusion protocol (109, 110).

Participants in 10 studies achieved more modest glucose control, defined as a mean blood glucose level of 6.7 to 7.8 mmol/L (120 mg/dL to 140 mg/dL), and almost all of these studies reported low rates of severe hypoglycemia. Most of these studies used relatively simple infusion protocols, and 1 study used a computerized algorithm (111). Of note, 1 small study (112) (the pilot study used to prepare for the NICE-SUGAR trial [17]) used a very simple infusion protocol and found a very high rate of severe hypoglycemia, whereas the phase 2 pilot study reported improved safety (110).

Two observational studies evaluated the safety of transitioning to progressively stricter blood glucose level targets over time. One of these trials was a very large single-center retrospective study evaluating the effects of an increasingly aggressive IIT policy in the ICU. The investigators found a nearly 4-fold increase in the incidence of hypoglycemia as the institution transitioned from no insulin protocols to using IIT to achieve a target blood glucose level of 4.4 to 7.2 mmol/L (80 to 130 mg/dL) and finally using this therapy to achieve a target blood glucose level of 4.4 to 6.1 mmol/L (80 to 110 mg/dL) (66). The infusion protocol details were not available. A second study of a relatively simple infusion protocol reported that the rate of severe hypoglycemia

doubled as the blood glucose level target increased from 6.7 to 8.3 mmol/L (120 to 150 mg/dL) to 4.4 to 7.2 mmol/L (80 to 110 mg/dL); however, the overall rate of severe hypoglycemia remained at less than 5% (67).

We had excluded studies in which the intervention was evaluated for 6 months or less because we believed that they were less likely to provide externally valid results than longer studies. In these shorter-term studies, the definition of hypoglycemia varied and rates of hypoglycemia ranged from 4% to 14%.

Subcutaneous Insulin

Most trials evaluating health outcomes have used insulin infusions to achieve blood glucose control. However, subcutaneous insulin is used more often in clinical settings, especially in the general medicine ward. Subcutaneous sliding-scale insulin (SSI) regimens have numerous theoretical disadvantages when used as the sole method of achieving inpatient glycemic control, and researchers have called for a reduction in the widespread use of subcutaneous SSI (113).

Very few controlled trials have compared SSI with more intensive insulin regimens, and none of these trials has evaluated health outcomes other than hypoglycemia. Several small, single-center trials in general medical populations (114, 115) and gastric bypass recipients (116) found that SSI was less effective in lowering blood glucose levels than basal-bolus insulin regimens, although safety was similar between groups. A recent small randomized, controlled trial in general medical ward patients receiving enteral nutrition found that SSI and basal-bolus insulin treatment groups achieved similar blood glucose levels and had similar rates of hypoglycemia (117).

Discussion

The safety of IIT implementation probably depends on multiple factors. We reviewed dozens of insulin protocols and found that they differed in patient characteristics, target blood glucose ranges, the time required to achieve the target blood glucose levels, the incidence and definition of hypoglycemia, the rationale or algorithm used for adjusting the insulin rates, the methods used to assess effectiveness, and the methods of glucose monitoring. We found that IIT protocols using higher blood glucose targets generally were associated with lower rates of hypoglycemia. Several studies reported blood glucose levels less than 6.7 mmol/L (<120 mg/dL) with relatively low rates of hypoglycemia. In general, protocols that safely achieved this degree of glucose control were iteratively developed at single institutions and used complex protocols incorporating insulin sensitivity information and computerized algorithms. However, we did find exceptions, such as centers that reported high hypoglycemia rates despite using relatively sophisticated protocols. Moreover, observational studies suggest that adopting more aggressive IIT protocols over time is associated with a concomitant increase in rates of hypoglycemia.

Previous reviews speculated that better protocols would incorporate bolus insulin doses, account for the direction and rate of glucose change, and allow for "off-protocol" adjustments; however, this conclusion is not based on direct comparisons of protocols (64, 65). Given the various factors involved in insulin protocol implementation, experts have suggested that each institution should individualize its approach to protocol implementation on the basis of institutional and provider resources and its patient population (118). For example, patients in the MICU seem to have the highest risk for hypoglycemia (119–122).

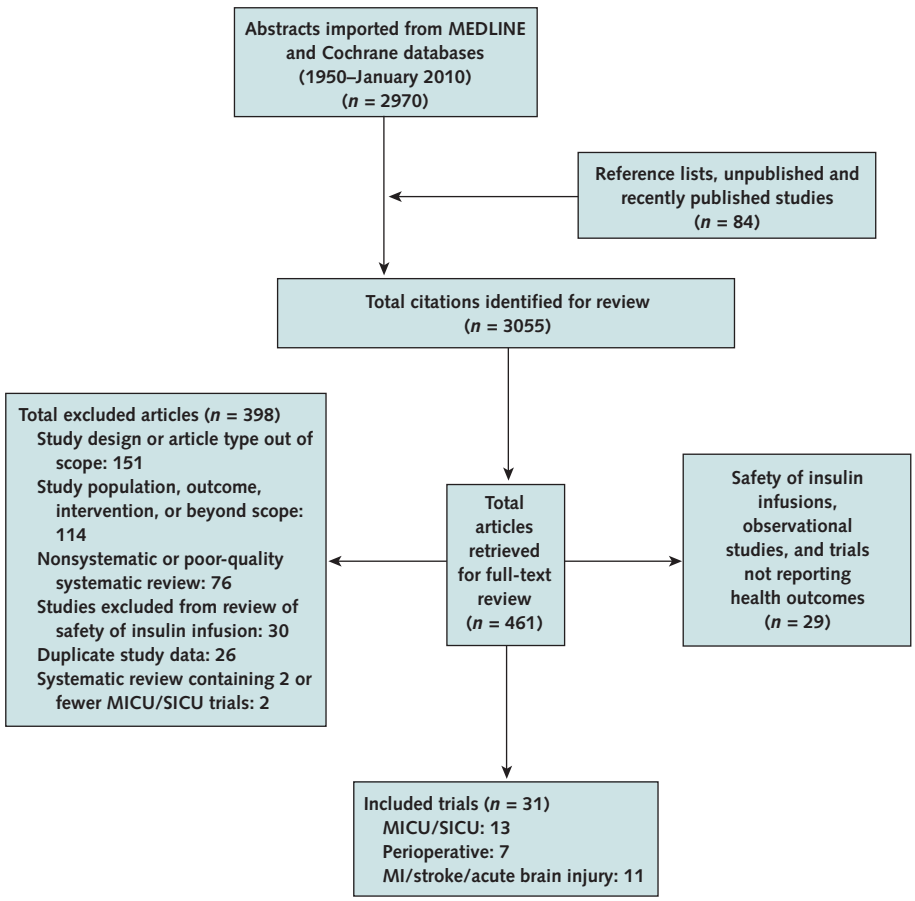
Three recent fair-quality systematic reviews (64–66) have attempted to clarify characteristics of insulin infusion protocols that are able to decrease blood glucose levels without increasing rates of hypoglycemia, but no completed studies directly compared insulin infusion protocols. The reviews stressed that, given these various factors, each institution should individualize its approach to protocol implementation on the basis of its patient population and its institutional and provider resources (64).

Limitations

Several factors limit this body of evidence. Most of these trials were small, single-center studies conducted in ICU or surgical settings. This fact may limit the generalizability of findings, especially to general medical ward settings. Patient selection criteria were not always clear. Researchers conducting the included studies consecutively enrolled patients in the insulin protocol being investigated, but the method for choosing patients for the protocol were unclear (104, 106, 123). Studies also varied greatly in populations studied, glycemic targets, definitions of hypoglycemia, and the actual IIT protocols. However, no studies have directly compared differing insulin infusion approaches.

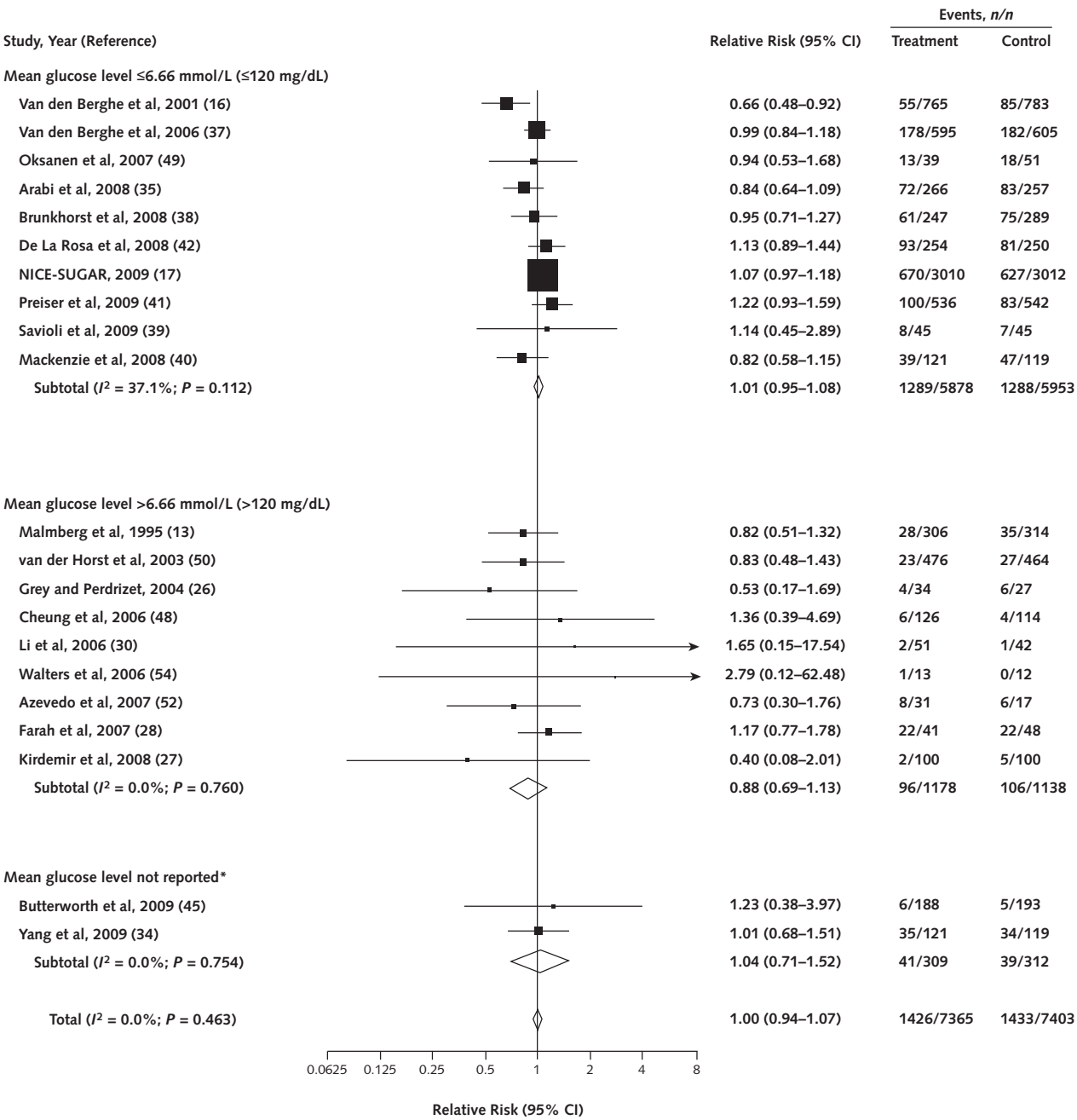
Finally, we reviewed the safety of subcutaneous SSI. The very limited body of evidence on this factor suggests that SSI and more complex basal-bolus regimens have similar safety profiles, although SSI may be less effective in controlling blood glucose levels.

Appendix Figure 1. **Literature search and selection.**



MI = myocardial infarction; MICU = medical intensive care unit; SICU = surgical intensive care unit.

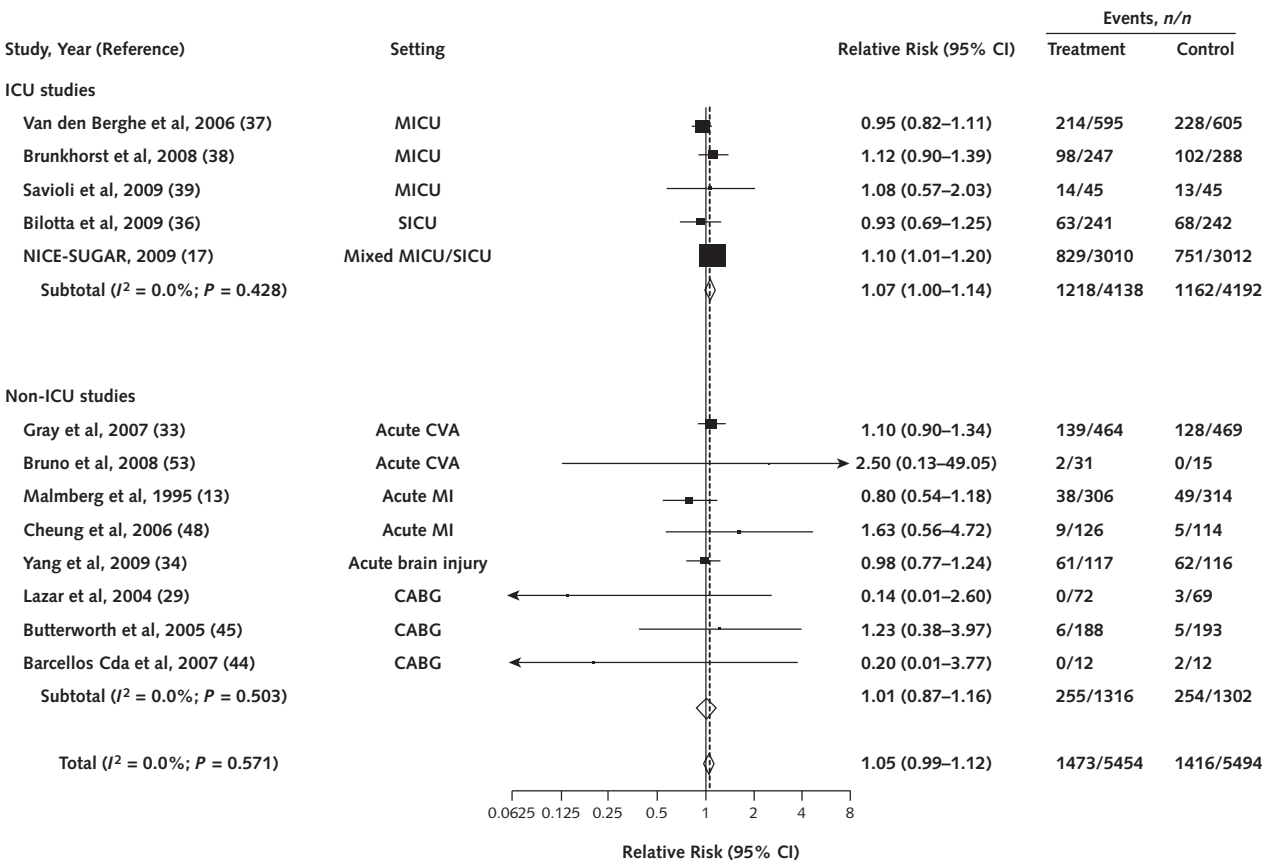
Appendix Figure 2. **Short-term mortality in studies of intensive insulin therapy, by the mean glucose level achieved in the intervention group.**



Short-term mortality includes death occurring within 28 d of or during the ICU or hospital stay; we used 28-d mortality in the meta-analysis when a study reported >1 outcome. *Events* is the number of deaths among participants in the treatment and control groups. NICE-SUGAR = Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation study.

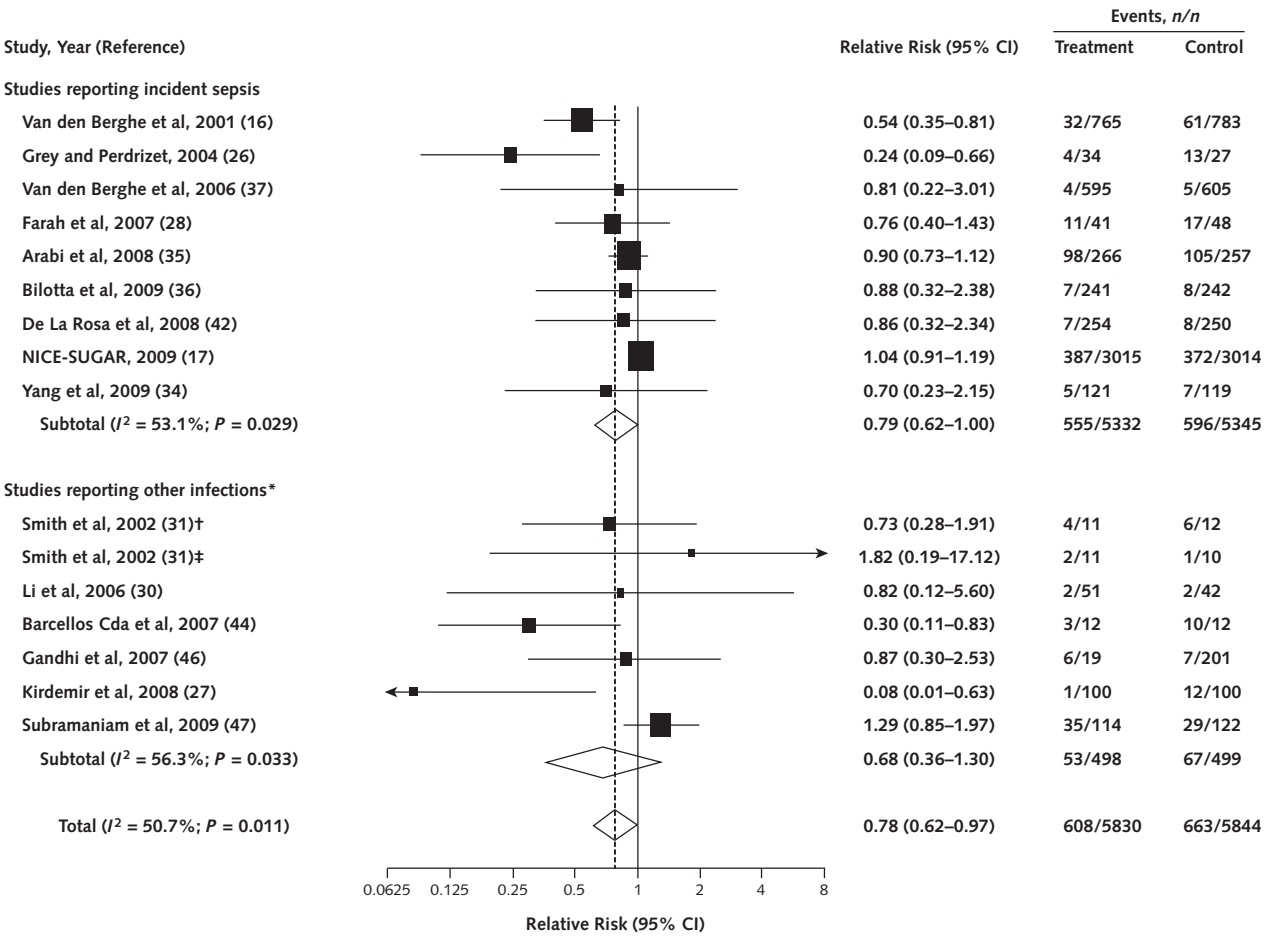
* During the intraoperative period in Butterworth and colleagues' study (45), the treatment group achieved mean blood glucose levels of approximately 6.1 to 10.2 mmol/L (110 to 185 mg/dL). Glucose levels were not reported in Yang and colleagues' study (34).

Appendix Figure 3. **Mortality at 90 or 180 d in studies of intensive insulin therapy, by inpatient setting.**



Events is the number of deaths among participants in the treatment and control groups. CABG = coronary artery bypass graft; CVA = cerebrovascular accident; ICU = intensive care unit; MI = myocardial infarction; MICU = medical intensive care unit; NICE-SUGAR = Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation study; SICU = surgical intensive care unit.

Appendix Figure 4. **Effects of intensive insulin therapy on rates of infection in various inpatient settings.**



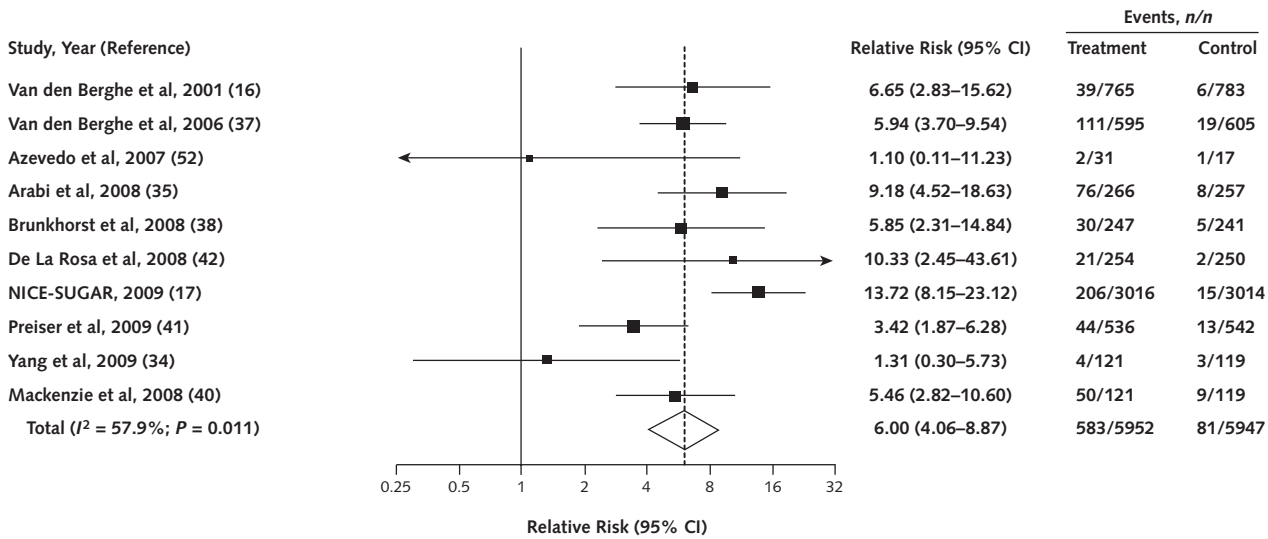
We included inpatients in the MICU, SICU, and perioperative settings as well as patients with stroke or acute brain injury. *Events* is the number of participants with 1 or more infections in the treatment and control groups. MICU = medical intensive care unit; NICE-SUGAR = Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation study; SICU = surgical intensive care unit.

* Includes wound infections, urinary tract infections, pneumonia, or a combination of these conditions.

† Data include only cardiopulmonary bypass subgroup.

‡ Data include only off-pump cardiopulmonary bypass subgroup.

Appendix Figure 5. **Risk for hypoglycemia in studies of intensive insulin therapy in various inpatient settings.**



We included inpatients in the MICU, SICU, and perioperative settings as well as patients with traumatic brain injury. We defined hypoglycemia as a blood glucose level less than 2.2 mmol/L (<40 mg/dL). *Events* is the number of participants with 1 or more hypoglycemic episodes in the treatment and control groups. MICU = medical intensive care unit; NICE-SUGAR = Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation study; SICU = surgical intensive care unit.

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