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Renda Soylemez Wiener; Daniel C. Wiener; Robin J. Larson

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Benefits and Risks of Tight Glucose Control in Critically Ill Adults
A Meta-analysis

Renda Soylemez Wiener, MD, MPH
Daniel C. Wiener, MD
Robin J. Larson, MD, MPH

I N 2001 VAN DEN BERGHE ET AL[1] PUB-
lished a randomized controlled trial
of critically ill surgical patients
showing that tight glucose con-
trol reduced hospital mortality by one-
third. Since the greatest decrease in
deaths occurred in the subgroup of pa-
tients with sepsis and multisystem or-
gan failure, some speculated that the
benefits of tight glucose control might
extend to medical intensive care unit
(ICU) patients as well.[2]

Because few interventions in criti-
cally ill adult patients reduce mortality
to this extent, the results of this trial were
enthusiastically received and rapidly in-
corporated into guidelines. In 2004, the
Surviving Sepsis Campaign[3] recom-
mended glucose control for all patients
with sepsis and explicitly stated, "There
is no reason to think that these data are
not generalizable to all severely septic
patients." This recommendation per-
sists in the 2008 update, now endorsed
internationally by 16 professional soci-
eties.[4] In addition, the Institute for
Healthcare Improvement,[5] the Volun-
teer Hospital Association,[6] the Michi-
gan Health and Safety Coalition,[7] the
American Association of Clinical Endo-

Context The American Diabetes Association and Surviving Sepsis Campaign recom-
mend tight glucose control in critically ill patients based largely on 1 trial that shows
decreased mortality in a surgical intensive care unit. Because similar studies report con-
flicting results and tight glucose control can cause dangerous hypoglycemia, the data
underlying this recommendation should be critically evaluated.

Objective To evaluate benefits and risks of tight glucose control vs usual care in criti-
cally ill adult patients.

Data Sources MEDLINE (1950-2008), the Cochrane Library, clinical trial registries,
reference lists, and abstracts from conferences from both the American Thoracic So-
ciety (2001-2008) and the Society of Critical Care Medicine (2004-2008).

Study Selection We searched for studies in any language in which adult intensive
care patients were randomly assigned to tight vs usual glucose control. Of 1358 iden-
tified studies, 34 randomized trials (23 full publications, 9 abstracts, 2 unpublished stud-
ies) met inclusion criteria.

Data Extraction and Analysis Two reviewers independently extracted informa-
tion using a prespecified protocol and evaluated methodological quality with a stan-
dardized scale. Study investigators were contacted for missing details. We used both
random- and fixed-effects models to estimate relative risks (RRs).

Results Twenty-nine randomized controlled trials totaling 8432 patients contributed
data for this meta-analysis. Hospital mortality did not differ between tight glucose con-
trol and usual care overall (21.6% vs 23.3%; RR, 0.93; 95% confidence interval [CI],
0.85-1.03). There was also no significant difference in mortality when stratified by glu-
cose goal ([1] very tight: ≤110 mg/dL; 23% vs 25.2%; RR, 0.90; 95% CI, 0.77-1.04; or
[2] moderately tight: <150 mg/dL; 17.3% vs 18.0%; RR, 0.99; 95% CI, 0.83-1.18) or
intensive care unit setting ([1] surgical: 8.8% vs 10.8%; RR, 0.88; 95% CI, 0.63-1.22;
[2] medical: 26.9% vs 29.7%; RR, 0.92; 95% CI, 0.82-1.04; or [3] medical-surgical: 26.1%
vs 27.0%; RR, 0.95; 95% CI, 0.80-1.13). Tight glucose control was not associated with
significantly decreased risk for new need for dialysis (11.2% vs 12.1%; RR, 0.96; 95%
CI, 0.76-1.20), but was associated with significantly decreased risk of septicemia (10.9%
vs 13.4%; RR, 0.76; 95% CI, 0.59-0.97), and significantly increased risk of hypoglyce-
mia (glucose ≤40 mg/dL; 13.7% vs 2.5%; RR, 5.13; 95% CI, 4.09-6.43).

Conclusion In critically ill adult patients, tight glucose control is not associated with
significantly reduced hospital mortality but is associated with an increased risk of hy-
poglycemia.

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and questions on p 972.

Author Affiliations: VA Outcomes Group, Depart-
ment of Veterans Affairs Medical Center, White River
Junction, Vermont, and Dartmouth Institute for Health
Policy and Clinical Practice, Dartmouth Medical School,
Hanover, New Hampshire (Drs Soylemez Wiener and
Larson); and Dartmouth-Hitchcock Medical Center,
Lebanon, New Hampshire (Dr Wiener).

Corresponding Author: Renda Soylemez Wiener, MD,
MPH, VA Outcomes Group, 111 B, Department of Vet-
erans Affairs Medical Center, White River Junction,
VT 05009 (renda.s.wiener@dartmouth.edu).
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C. Angus, MD, MPH, Contributing Editor, *JAMA*
(angusdc@upmc.edu).

crinologists,[8] and the American Diabetes Association[9] now recommend tight glucose control in all critically ill adults. These recommendations have led to worldwide adoption of tight glucose control in a variety of ICU settings.[10-14]

Subsequent large randomized controlled trials of tight glucose control in medical and mixed medical-surgical ICU settings,[15-17] however, have failed to replicate this mortality benefit. Moreover, a recent cohort study[18] of more than 10 000 critically ill adults showed a trend toward increased mortality with increasing use of tight glucose control after adjustment for disease severity. In addition, many studies have reported high rates of hypoglycemia with tight glucose control—some as high as 30% to 40%, as compared with the 5% rate found in the initial trial by van den Berghe et al.[1] Hypoglycemia is not benign in critically ill patients; it has been linked to serious neurologic events ranging from seizures to coma.[19,20]

Consequently, considerable controversy has emerged as to whether tight glucose control is warranted in all critically ill adults. We report the findings of a meta-analysis of randomized controlled trials examining the risks and benefits of tight glucose control as compared with usual care in critically ill adults. In addition to the overall analysis, we conducted subgroup analyses on 2 variables that have been debated in the controversy over tight glucose control: glucose goal ($\leq$110 mg/dL or <150 mg/dL) and ICU setting (medical, surgical, or all critically ill patients).

METHODS
Search Strategy

We searched MEDLINE (1950-June 6, 2008) to identify studies in any language relevant to our research question. We used exploded Medical Subject Headings in the following search strategy: *intensive care units* or *critical care* or *critical illness* or *postoperative care* or *sepsis* or *myocardial infarction* or *stroke* or *cardiovascular surgical procedures*, or *wounds and injuries*; and *blood glucose* or *insulin* (*administration and dosage*, *adverse effects*, *therapeutic use*, *therapy*). We

combined the findings of this search with phases 1 and 2 of a highly sensitive search strategy[21] recommended by the Cochrane Collaboration for identifying all randomized controlled trials in MEDLINE. Using similar search terms, we also searched the Cochrane Library (issue 1, 2008) and multiple trial registries (all in August 2007) including clinicaltrials .gov (National Institutes of Health), the Current Controlled Trials registry (which has the capacity to search the International Standard Randomized Controlled Trial Number registry and 12 other trial registries), the Australian New Zealand Clinical Trials Registry, and Japan's University Hospital Medical Information Network Clinical Trial Registry. We manually searched abstracts from the conference proceedings of the American Thoracic Society (2001-2008) and the Society of Critical Care Medicine (2004-2008). In addition, we reviewed reference lists of relevant articles to identify any additional studies overlooked by our search.

Study Selection

Inclusion Criteria. We included randomized controlled trials that met each of the following criteria: (1) the setting was an adult ICU; (2) the intervention group received tight glucose control (glucose goal <150 mg/dL obtained using an insulin infusion during part or all of the ICU stay); (3) the comparison group received usual care (glucose goal and method of insulin administration could vary between studies); and (4) the primary or secondary end points included hospital or short-term mortality ($\leq$30-day), septicemia, new need for dialysis, or hypoglycemia. To convert glucose values to mmol/L, multiply by 0.0555.

Exclusion Criteria. Studies were excluded if the intervention was conducted primarily during the intraoperative period rather than during the ICU stay or if we were unable to obtain adequate details of study methodology or results from the article or study investigators.

Missing Data. We contacted the investigators of all unpublished studies as

well as any published studies in which data were missing to confirm eligibility and obtain additional study details.

Data Abstraction and Quality Assessment

Two unblinded reviewers (R.S.W. and D.C.W.) independently assessed and abstracted pertinent data from trials in duplicate using a standardized, predefined form (available from authors). Abstracted data included each study's methodology, setting, baseline patient characteristics, intervention, outcomes, and follow-up. We formally assessed the methodologic quality of each trial using the Jadad scale,[22] which incorporates randomization, blinding, and attrition to derive a score of 0 to 5, with higher scores indicating higher quality. Any discrepancies between the 2 reviewers were resolved through discussion. For 4 studies that were presented at meetings but not yet published, the authors provided either the unpublished data or manuscripts.[23-26] For 2 additional studies that were presented at meetings[17,27] and for 2 unpublished studies, the authors completed a standardized data abstraction form (J. R. A. Azevedo et al, January 2008, and R. P. C. Chan et al, July 2007).

Outcome Measures

Primary Outcome Measure: Hospital Mortality. We considered a reduction in hospital mortality to be the most important potential benefit of tight glucose control. Hospital mortality was defined as death occurring during the hospital stay or within 30 days following admission.

Secondary Outcome Measures: Septicemia, New Need for Dialysis, and Hypoglycemia. We compared the association of tight glucose control vs usual care with 2 additional potential benefits of tight control: rates of septicemia and new need for dialysis. These outcomes were chosen because they have biological plausibility, given the association of uncontrolled hyperglycemia with recurrent infection and chronic renal insufficiency in diabetic patients, and because they were shown

to be reduced in the initial trial by van den Berghe et al.[1] We defined septicemia to encompass the terms *sepsis*, *septicemia*, *bacteremia*, or a description of positive blood cultures; a general description of infection did not qualify. New need for dialysis referred specifically to patients without a preexisting dialysis requirement who subsequently developed acute renal failure that required dialysis. Specific criteria for determining the need for dialysis were not reported; however, those patients with an increase in serum creatinine without the need for dialysis were not included in this definition.

Hypoglycemia is the major potential harm of tight glucose control. We defined hypoglycemia to include patients with 1 or more blood glucose measurements of 40 mg/dL or lower and recorded whether any associated symptoms were reported. Of note, our definition is well below the glucose level that the American Diabetes Association considers to represent hypoglycemia (glucose <70 mg/dL).[9] We chose this strict definition to capture hypoglycemic events severe enough to have potential clinical relevance, whether or not concurrent symptoms occurred, and because a glucose level of 40 mg/dL or lower was the most common definition of hypoglycemia used in the included trials.

All outcome measures were calculated on a per-patient basis; for example, a patient with several episodes of hypoglycemia would only count as 1 occurrence for that outcome.

Subgroup Analyses

A priori we identified 2 variables for subgroup analysis based on the main controversies in the debate surrounding tight glucose control: glucose goal and ICU setting.

Glucose Goal in the Tight Control Group. Differing opinions exist about the optimal level of tight glucose control. Based on the 2008 recommendations for glucose control in critically ill patients from the American Diabetes Association[9] (as close to 110 mg/dL as pos-

sible) and the Surviving Sepsis Campaign[4] (<150 mg/dL), we stratified studies by glucose goal in the tight glucose control group into 2 categories: very tight control (upper limit of glucose goal ≤110 mg/dL); and moderately tight control (upper limit of glucose goal 111-150 mg/dL).

ICU Setting. Because of the concern that the pathophysiological effect of hyperglycemia may differ between surgical and medical critically ill patients, we stratified trials by ICU setting into 3 categories: (1) surgical (including general surgical, cardiothoracic, neurosurgical, and trauma ICUs); (2) medical (including general medical, cardiac, and neurologic ICUs); or (3) mixed medical-surgical ICUs. For those trials that did not specify the ICU setting,[28-31] we categorized the setting as medical-surgical.

Sensitivity Analyses

We performed sensitivity analyses based on 3 prespecified clinically relevant variables: proportion of diabetics, use of insulin-only infusions, and achieved mean glucose level in the study groups. Since individuals with diabetes vs those without diabetes may differ in whether hyperglycemia is a maladaptive response that should be treated, we restricted analysis to trials in which one-third or less individuals had diabetes (an arbitrary cut point based on a natural break in the distribution of proportion of those with diabetes in the included trials). We restricted analysis to trials using insulin-only infusions (as opposed to glucose-insulin-potassium infusions), because these interventions may have different effects. We restricted analysis to studies in which the mean glucose level achieved in the tight glucose control and usual care groups differed by at least 20 mg/dL (a difference that we specified a priori to be clinically meaningful), because studies that failed to achieve a clinically significant difference in glucose levels between study groups might have biased our results toward the null. In addition, for the subgroup analysis of

very tight vs moderately tight glucose control, we performed an analysis in which studies were categorized based on actual mean glucose level achieved rather than target glucose goal because in many studies, the target glucose goal and achieved glucose level in the tight control group were disparate.

Quantitative Data Synthesis

We used the analytic approach and software provided by the Cochrane Collaboration for all analyses (Review Manager [RevMan] version 4.2, Nordic Cochrane Centre, Copenhagen, Denmark). This software calculates relative risks (RRs) for studies with at least 1 occurrence in either study group for each outcome. Trials with missing outcome data or zero occurrences in both groups were excluded from the meta-analysis of that outcome. We calculated a pooled RR and 95% confidence interval (CI) for each outcome and considered findings to be statistically significant if the test for overall effect had a *P* value of less than .05.

For each outcome, we assessed for important variability among the trial results contributing to each summary estimate using 2 thresholds based on the χ^2 test. We considered a *P* value of less than .10 to indicate statistically significant heterogeneity. Because some heterogeneity is inevitable in meta-analysis, some argue that rather than assessing its statistical significance, investigators should assess its effect. One such method is to assess I^2, which quantifies the proportion of the variability in trial results that is due to heterogeneity rather than chance and uses a value greater than 50% to indicate meaningful heterogeneity. In our meta-analysis, if either threshold for variability was met, we identified each responsible trial and reviewed its clinical and methodological characteristics to determine whether an explanation for the outlying results existed. For each such case we report 2 summary estimates: (1) an estimate based on all studies with usable data, including the out-
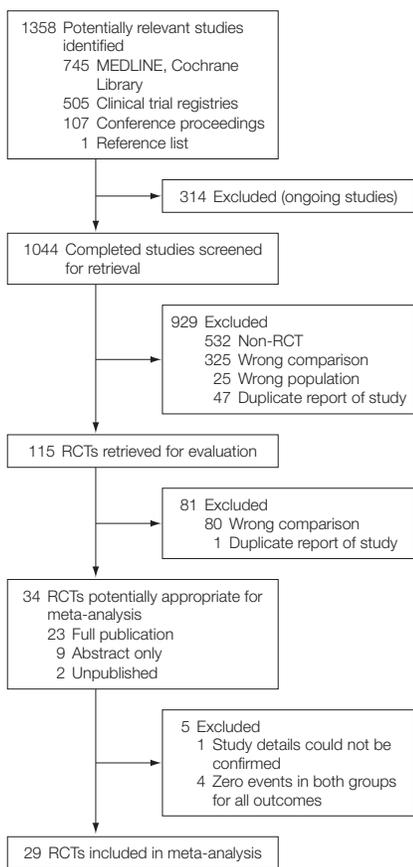
RCT indicates randomized controlled trial.

lying trial(s); and (2) an estimate based on the largest group of studies with usable data that passed both the *P* value and I^2 thresholds.

There is disagreement about whether fixed- or random-effects models are preferred when calculating summary estimates for meta-analyses (*Cochrane Handbook for Systematic Reviews of Interventions* version 5.0; available at http://www.cochrane-handbook.org). While fixed-effects models typically result in narrower CIs, the 2 models tend to provide similar results unless heterogeneity is present among the included studies. We believe the random-effects model is more appropriate for meta-analyses that evaluate the efficacy of an intervention, particularly for analyses with important downsides, be-

cause it reduces the risk of a type I error. Moreover, when heterogeneity is present, the random-effects model is recommended by the Cochrane Collaboration because its assumptions account for the presence of variability among included trials. Therefore, we report the results of the random-effects model for all outcomes. In addition, if no heterogeneity existed among studies, we have provided results of the fixed-effects model for situations in which the 2 models yielded substantially different findings.

We visually assessed a funnel plot of study size vs effect size for our primary outcome of hospital mortality to seek evidence of publication bias.

RESULTS

Search Results and Trial Flow

We initially identified 1358 potentially eligible studies (**FIGURE 1**), the majority of which were excluded because they were ongoing, were not randomized controlled trials, or tested an intervention other than tight glucose control. After detailed review of the remaining 115 randomized controlled trials, 34 (including the 2 unpublished studies) met all inclusion criteria and were considered as potentially appropriate for inclusion in our meta-analysis.[1,15-17,23-50] Subsequently, we excluded 1 trial[34] because we were unable to confirm full study details despite multiple attempts to contact the investigators, and another 4 trials[28,32,40,42] because they reported zero events in both study groups for all outcomes relevant to our analysis. This left 29 randomized controlled trials (19 full publications,* 8 published in abstract form only,[17,23-27,47,50] and 2 unpublished studies) including 8432 patients with usable data for our meta-analysis.

Study Characteristics

TABLE 1 provides the characteristics of the 34 randomized controlled trials that met our inclusion criteria. Trials were conducted in a diverse array of coun-

tries, most often at a single center. Study sizes ranged widely (10->1500 patients) with 21 trials enrolling fewer than 100 patients and 7 trials with more than 500 patients. The study participants encompass a broad distribution of adult ICU patients, as indicated by the variety of mean ages (46-75 years), distributions by sex (31%-95% men), proportions of patients with diabetes (0%-100%), and degree of disease severity as measured by mean Acute Physiology and Chronic Health Evaluation (APACHE II) score (9-32). Only 2 studies[29,46] had discrepant baseline patient characteristics in the intervention vs control groups. In both of these trials, disease severity was lower in the tight glucose control than usual care group (mean APACHE II score 14 vs 17 in the trial by Wang et al[29]; and 19 vs 22, *P* < .01 in the trial by Mitchell et al[46]). All trials had follow-up rates of 80% or greater. Because none of the trials attempted to double-blind study group assignment, no trial could receive a Jadad quality score higher than 3 out of 5. Target glucose goals, as well as mean achieved glucose levels, varied between trials in both the tight control and usual care groups (**TABLE 2**).

Primary Outcome: Hospital Mortality

Twenty-seven trials, including the 2 unpublished ones, provided usable data on hospital mortality.† Among these trials, there was no significant difference in hospital mortality between tight glucose control and usual care strategies (21.6% vs 23.3%; RR, 0.93; 95% CI, 0.85-1.03; **FIGURE 2**).

We also performed subgroup analyses stratifying trials by ICU setting and by glucose goal in the tight control group. There was no significant difference in hospital mortality when we stratified by surgical (8.8% vs 10.8%; RR, 0.88; 95% CI, 0.63-1.22), medical (26.9% vs 29.7%; RR, 0.92; 95% CI, 0.82-1.04), and medical-surgical ICU setting (26.1% vs 27.0%; RR, 0.95; 95% CI, 0.80-1.13; Figure 2). Similarly, there

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*References 1, 15, 16, 29-31, 33, 35-39, 41, 43-46, 48, 49.

†References 1, 15-17, 23-27, 29, 30, 35-39, 41, 43-50.

Table 1. Characteristics of Randomized Controlled Trials Comparing Tight Glucose Control vs Usual Care in Critically Ill Adults and Meeting All Inclusion Criteria

Source	Region/ Country	No. of Study Sites	No. of Patients	Admitting Diagnosis, %	Mean Age, y	Male Sex, %	Diabetic, %	Disease Severity Index Score, Mean[a]	Follow-up	Jadad Quality Score[b]
Surgical ICU										
Very tight control, glucose goal ≤110 mg/dL										
van den Berghe et al,[1] 2001	Belgium	1	1548	Cardiac surgery, 63	62.8	71	13	9.0	Hospital stay	3
Hoedemaekers et al,[32] 2005[c]	the Netherlands	1	20	CABG, 100	64.2	90	0	9.1	Hospital stay	2
van Wezel et al,[33] 2006[d]	the Netherlands	1	44	CABG, 100	63.0	80	0	2[e]	Hospital stay	2
He et al,[34] 2007[c,f]	China	1	188	Abdominal surgery, 40; neurosurgery, 20	65.5	68	18	17.2	Hospital stay	2
Stecher et al,[27] 2006[g]	Slovenia	1	117	Trauma, 37; abdominal surgery, 28	52.6	67	13	19.0	NA	NA
Moderately tight control, glucose goal <150 mg/dL										
Grey and Perdrizet,[35] 2004	United States	1	61	General surgery, 100	55.6	70	12	15.3	Hospital stay	2
Bilotta et al,[36] 2007	Italy	1	78	Aneurysm clipping following subarachnoid hemorrhage, 100	53.0	31	10	NA	6 mo	3
He et al,[34] 2007[b,e]	China	1	188	Abdominal surgery, 40; neurosurgery, 20	65.5	68	18	17.2	Hospital stay	2
Bilotta et al,[37] 2008	Italy	1	97	Traumatic brain injury requiring surgery, 100	52.5	55	12	60.8[e]	6 mo	3
Kia et al,[23] 2005[g]	United States	1	265	Abdominal surgery, 72	68.2	52	26	17.2	90 d	3
Chan[h]	Brazil	1	98	CABG, 46; valve surgery, 54	57.5	45	34	NA	Hospital stay	NA
Medical ICU										
Very tight control, glucose goal ≤110 mg/dL										
Bland et al,[38] 2005	United States	1	10	Acute respiratory failure, 70	56.7	70	40	NA	28 d	2
van den Berghe et al,[15] 2006	Belgium	1	1200	Respiratory, 43; gastrointestinal/ hepatic, 25	63.5	62	17	23	Hospital stay	3
Oksanen et al[39] 2007	Finland	2	90	Out-of-hospital ventricular fibrillation arrest, 100	64.0	77	79	24.9	30 d	2
Benito et al,[40] 2008 (INSUCOR)[c]	Spain	1	28	Acute myocardial infarction, 100	64.6	72	0	1.3[e]	Hospital stay	3
Fernandez et al,[24] 2005[g]	Puerto Rico	1	20	Sepsis, 80	71.9	95	85	14.5	Hospital stay	NA
Moderately tight control, glucose goal <150 mg/dL										
Davies et al,[41] 1991[c]	Scotland	4	69	Acute myocardial infarction, 100	62.0	NA	100	NA	Hospital stay	2
Stefanidis et al,[42] 2002[c]	Greece	1	51	Non–ST-elevation acute coronary syndrome, 100	66.0	61	100	NA	Hospital stay	2
Walters et al,[43] 2006	Great Britain	1	25	Acute cerebrovascular event, 100	75.1	40	52	8.0[e]	30 d	3
Gray et al,[44] 2007 (GIST-UK)[c]	Great Britain	21	933	Acute cerebrovascular event, 100	75.2	45	16	44.6[e]	90 d	3
Bruno et al,[45] 2008 (THIS)	United States	5	46	Acute cerebrovascular event, 100	59.1	57	91	9.3[e]	90 d	3

(continued)

Table 1. Characteristics of Randomized Controlled Trials Comparing Tight Glucose Control vs Usual Care in Critically Ill Adults and Meeting All Inclusion Criteria (cont)

Source	Region/ Country	No. of Study Sites	No. of Patients	Admitting Diagnosis, %	Mean Age, y	Male Sex, %	Diabetic, %	Disease Severity Index Score, Mean[a]	Follow-up	Jadad Quality Score[b]
Medical-surgical ICU Very tight control, glucose goal ≤110 mg/dL										
Yu et al[30] 2005	China	1	55	Sepsis, 100	46.0	56	NA	10.5	Hospital stay	2
Mitchell et al[46] 2006	Australia	1	70	Medical, 62; surgical, 38	65.5	60	14	20.5[i]	Hospital stay	3
Wang et al,[29] 2006	China	1	116	Medical, 85; surgical, 15	66.2	67	11	16.5[i]	Hospital stay	3
Brunkhorst et al,[16] 2008 (VISEP)	Germany	18	537	Sepsis (medical, 47; surgical, 53)	64.6	60	30	20.2	90 d	3
Iapichino et al,[31] 2008	Italy	3	72	Sepsis (medical, 64; surgical, 32)	62.3	65	17	41.8[e]	90 d	3
Mackenzie et al,[25] 2005 (GLYCOGENIC)[g]	Great Britain	2	240	Medical, 54; surgical, 46	64.5	83	83	21.9	Hospital stay	3
Arabi et al,[26] 2006[g]	Saudi Arabia	1	523	Medical, 83; surgical, 17	52.4	75	40	22.8	Hospital stay	3
De La Rosa et al[47] 2006[g]	Colombia	1	504	NA	NA	NA	NA	NA	28 d	2
Devos,[17] 2007 (GLUCONTROL)[g]	Europe	21	1101	Medical, 42; surgical, 58	64.8	63	19	15	Hospital stay	3
Moderately tight control, glucose goal <150 mg/dL										
Farah et al,[48] 2007	Israel	1	89	NA	73.1	52	59	22.1	28 d	2
McMullin et al,[49] 2007 (LOGIC)	Canada	1	20	Medical, 100	68.8	45	65	31.7	Hospital stay	2
Saberi et al,[28] 2004[c,g]	United States	1	60	NA	NA	NA	NA	NA	NA	NA
Henderson et al,[50] 2005 (SUGAR)[g]	Canada	1	67	NA	56.4	69	NA	21.1	28 d	NA
Azevedo[h]	Brazil	2	337	Medical, 60; surgical, 40	56.2	54	31	67.3[e]	Hospital stay	2

Abbreviations: CABG, coronary artery bypass graft; ICU, intensive care unit; NA, not available from manuscript or authors.
[a] Scores are Acute Physiology and Chronic Health Evaluation (APACHE II) unless otherwise noted (range, 0-71 with higher scores indicating a higher risk of death).
[b] Jadad scores range from 0 to 5 with higher scores indicating better methodologic quality. Adapted from Jadad et al.[22]
[c] Studies were excluded from final meta-analysis.
[d] Studies used glucose-insulin-potassium infusions in the intervention group; all other studies used insulin alone.
[e] Studies used alternate scoring indexes to indicate disease severity: van Wezel, Euroscore (<4 indicates low perioperative risk); Bilotta 2008, Simplified Acute Physiology Score II (range, 0-163 with higher scores indicating more severe illness); Benito, Killip Score (range, 1-4 with higher scores indicating higher risk of death); Walters, National Institutes of Health (NIH) Stroke Score (range, 0-31 with higher scores indicating higher risk of death); Gray, European Stroke Score (range, 0-100 with lower scores indicating higher risk of death); Bruno, NIH Stroke Score (range, 0-31 with higher scores indicating higher risk of death); Iapichino, Simplified Acute Physiology Score II (range, 0-163 with higher scores indicating more severe illness); Azevedo, APACHE III (range, 0-299 with higher scores indicating higher risk of death).
[f] Study has 3 groups comparing very tight glucose control, moderately tight glucose control, and usual care.
[g] Denotes abstract that was presented at a meeting but not yet published.
[h] Denotes unpublished data.
[i] In these 2 studies, baseline APACHE II scores differed between the study groups at baseline.

was no significant difference in hospital mortality between tight glucose control and usual care strategies when we stratified by glucose goal in the tight control group (very tight [23.2% vs 25.2%; RR, 0.90; 95% CI, 0.77-1.04]; and moderately tight [17.3% vs 18.0%; RR, 0.99; 95% CI, 0.83-1.18]; **FIGURE 3**). Tests for heterogeneity identified the trial by Wang et al[29] as having outlying results for both the subgroups of trials in the medical-surgical ICU ($P=.03$, $I^2=48\%$) and trials of very tight glucose control ($P=.02$, $I^2=49\%$), which appeared to be explained by the previously mentioned discrepancy in baseline disease severity. Exclusion of the outlying trial[29] resolved this heterogeneity but did not significantly change the findings of either subgroup analysis (medical-surgical ICU [RR, 1.00; 95% CI, 0.90-1.11], very tight control [RR, 0.94; 95% CI, 0.84-1.05]).

Secondary Outcomes: Septicemia, New Need for Dialysis, Hypoglycemia

The associations of tight glucose control on all of the secondary outcomes

analyzed and stratified by glucose goal in the tight control group are shown in Figure 3. The associations between tight glucose control and all outcomes, stratified by ICU setting are shown in **FIGURE 4** (data supporting these outcomes are available from the authors on request).

Rates of septicemia were reported in 9 trials.[1,15,23,26,30,35-37,48] Tight glucose control was associated with signifi-cantly reduced risk of septicemia as compared with usual care (10.9% vs 13.4%; RR, 0.76; 95% CI, 0.59-0.97). When stratified according to ICU set-ting, this reduction in septicemia was limited to surgical ICU patients[1,23,35-37] (4.6% vs 8.4%; RR, 0.54; 95% CI, 0.38-0.76) and was not observed in medi-cal[15] or medical-surgical ICU pa-tients[26,30,48] (Figure 4). When stratified by glucose goal in the tight control group (Figure 3), there was a nearly significant reduction in septicemia that was limited to studies using moder-ately tight glucose control (8.8% vs 14.6%; RR, 0.64; 95% CI, 0.41-1.00). The test for heterogeneity was signifi-cant only for the subset of trials using very tight glucose control ($P = .04$; $I^2 = 64\%$). We identified the surgical ICU trial by van den Berghe et al as the outlying study,[1] but could not find

Table 2. Glucose Goals and Mean Achieved Levels in Trials Included in the Final Meta-Analysis

Source	Tight Control		Usual Care	
	Glucose Goal, mg/dL	Glucose Achieved, Mean (SD), mg/dL	Glucose Goal, mg/dL	Glucose Achieved, Mean (SD), mg/dL
Surgical ICU				
Very tight control, glucose goal ≤110 mg/dL				
van den Berghe,[1] 2001	80-110	104 (19)	180-200	153 (33)
van Wezel,[33] 2006	72-99	95 (NA)[a]	<200	124 (NA)[a]
Stecher,[27] 2006[b]	80-110	NA	140-180	NA
Moderately tight control, glucose goal <150 mg/dL				
Grey,[35] 2004	80-120	125 (36)	180-220	179 (61)
Bilotta,[36] 2007	80-120	93 (16)	<220	147 (25)
Bilotta,[37] 2008	80-120	92 (16)	<220	147 (25)
Kia,[23] 2005[b]	75-115	109 (33)	180-200	144 (42)
Chan[c]	80-120	127 (NA)	<200	168 (NA)
Medical ICU				
Very tight control, glucose goal ≤110 mg/dL				
Bland,[38] 2005	80-110	105 (26)	180-200	177 (46)
van den Berghe,[15] 2006	80-110	111 (29)	180-200	153 (31)
Oksanen,[39] 2007	72-108	90 (23)[a]	108-144	115 (23)[a]
Fernandez,[24] 2005[b]	80-110	120	<150	205
Moderately tight control, glucose goal <150 mg/dL				
Davies,[41] 1991	72-144	185 (38)	<180	193 (65)
Walters,[43] 2006	90-144	124 (16)	<270	146 (14)
Gray,[44] 2007 (GIST-UK)	72-126	113 (NA)	<306	122 (NA)
Bruno,[45] 2008 (THIS)	90-130	133 (16)	<200	190 (64)
Medical-surgical ICU				
Very tight control, glucose goal ≤110 mg/dL				
Yu,[30] 2005	80-110	103 (22)	180-200	198 (29)
Mitchell,[46] 2006	80-110	97 (NA)[a]	180-200	142 (NA)[a]
Wang,[29] 2006	80-110	99 (68)	180-200	185 (25)
Brunkhorst,[16] 2008 (VISEP)	80-110	112 (NA)	180-200	151 (NA)
Iapichino,[31] 2008	80-110	110 (17)	180-200	163 (29)
Mackenzie,[25] 2005 (GLYCOGENIC)[b]	72-108	126 (43)	180-198	151 (43)
Arabi,[26] 2006[b]	80-110	115 (18)	180-200	171 (34)
De La Rosa,[47] 2006[b]	80-110	NA	180-200	NA
Devos,[17] 2006 (GLUCONTROL)[b]	80-110	119 (NA)	140-180	147 (NA)
Moderately tight control, glucose goal <150 mg/dL				
Farah,[48] 2007	110-140	142 (14)	140-200	174 (20)
McMullin,[49] 2007 (LOGIC)	90-126	128 (47)	144-180	169 (38)
Henderson,[50] 2005 (SUGAR)[b]	72-126	NA	162-200	NA
Azevedo[c]	80-120	134 (NA)	<180	144 (NA)

Abbreviations: ICU, intensive care unit; NA, not available from manuscript or authors.
SI conversion factor: To convert glucose to mmol/L, multiply values by 0.0555.
[a] Achieved score is approximate.
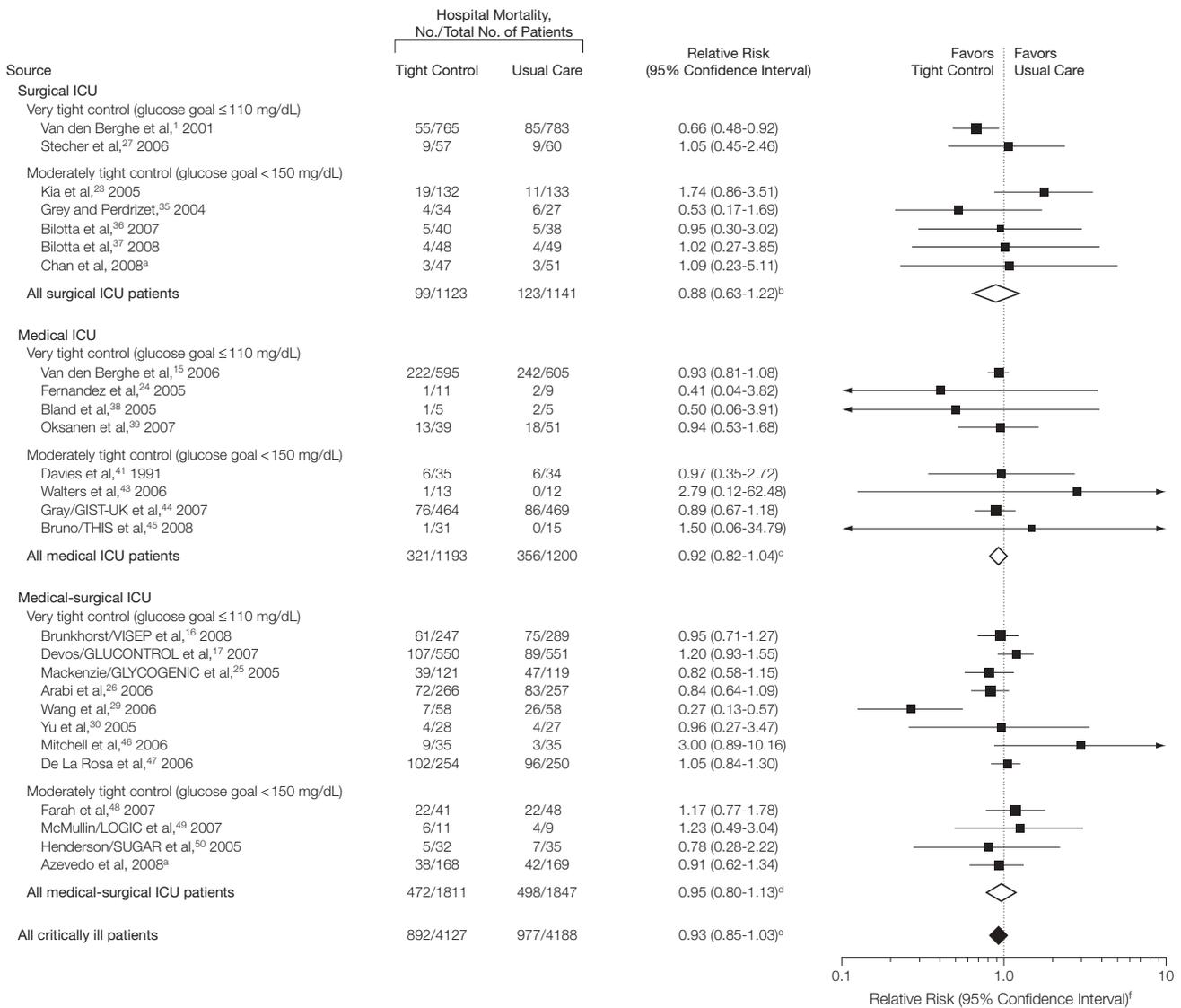[b] Denotes abstract that was presented at a meeting but not yet published.
[c] Denotes unpublished data.

an obvious reason for the outlying results. Analysis limited to the studies with homogeneous results did not change our finding of nonsignificant reduction in septicemia for the subset of trials on very tight glucose control.

New need for dialysis was reported in 8 published trials[1,16,23,25,26,30,35,50] and in 1 that was unpublished (Azevedo). There was no significant association between tight glucose control and a new need for dialysis overall (11.2% vs 12.1%; RR, 0.96; 95% CI, 0.76-1.20). Subgroup analyses stratifying by glucose goal (Figure 3) and ICU setting (Figure 4) also showed no significant association of tight glucose control with new need for dialysis. The test for hetero-

Figure 2. Association of Tight Glucose Control vs Usual Care With Hospital Mortality, Stratified by ICU Setting and Glucose Goal in Tight Control Group

Source	Hospital Mortality, No./Total No. of Patients		Relative Risk (95% Confidence Interval)
	Tight Control	Usual Care	
Surgical ICU			
Very tight control (glucose goal ≤110 mg/dL)			
Van den Berghe et al,[1] 2001	55/765	85/783	0.66 (0.48-0.92)
Stecher et al,[27] 2006	9/57	9/60	1.05 (0.45-2.46)
Moderately tight control (glucose goal <150 mg/dL)			
Kia et al,[23] 2005	19/132	11/133	1.74 (0.86-3.51)
Grey and Perdrizet,[35] 2004	4/34	6/27	0.53 (0.17-1.69)
Bilotta et al,[36] 2007	5/40	5/38	0.95 (0.30-3.02)
Bilotta et al,[37] 2008	4/48	4/49	1.02 (0.27-3.85)
Chan et al, 2008[a]	3/47	3/51	1.09 (0.23-5.11)
All surgical ICU patients	99/1123	123/1141	0.88 (0.63-1.22)[b]
Medical ICU			
Very tight control (glucose goal ≤110 mg/dL)			
Van den Berghe et al,[15] 2006	222/595	242/605	0.93 (0.81-1.08)
Fernandez et al,[24] 2005	1/11	2/9	0.41 (0.04-3.82)
Bland et al,[38] 2005	1/5	2/5	0.50 (0.06-3.91)
Oksanen et al,[39] 2007	13/39	18/51	0.94 (0.53-1.68)
Moderately tight control (glucose goal <150 mg/dL)			
Davies et al,[41] 1991	6/35	6/34	0.97 (0.35-2.72)
Walters et al,[43] 2006	1/13	0/12	2.79 (0.12-62.48)
Gray/GIST-UK et al,[44] 2007	76/464	86/469	0.89 (0.67-1.18)
Bruno/THIS et al,[45] 2008	1/31	0/15	1.50 (0.06-34.79)
All medical ICU patients	321/1193	356/1200	0.92 (0.82-1.04)[c]
Medical-surgical ICU			
Very tight control (glucose goal ≤110 mg/dL)			
Brunkhorst/VISEP et al,[16] 2008	61/247	75/289	0.95 (0.71-1.27)
Devos/GLUCONTROL et al,[17] 2007	107/550	89/551	1.20 (0.93-1.55)
Mackenzie/GLYCOGENIC et al,[25] 2005	39/121	47/119	0.82 (0.58-1.15)
Arabi et al,[26] 2006	72/266	83/257	0.84 (0.64-1.09)
Wang et al,[29] 2006	7/58	26/58	0.27 (0.13-0.57)
Yu et al,[30] 2005	4/28	4/27	0.96 (0.27-3.47)
Mitchell et al,[46] 2006	9/35	3/35	3.00 (0.89-10.16)
De La Rosa et al,[47] 2006	102/254	96/250	1.05 (0.84-1.30)
Moderately tight control (glucose goal <150 mg/dL)			
Farah et al,[48] 2007	22/41	22/48	1.17 (0.77-1.78)
McMullin/LOGIC et al,[49] 2007	6/11	4/9	1.23 (0.49-3.04)
Henderson/SUGAR et al,[50] 2005	5/32	7/35	0.78 (0.28-2.22)
Azevedo et al, 2008[a]	38/168	42/169	0.91 (0.62-1.34)
All medical-surgical ICU patients	472/1811	498/1847	0.95 (0.80-1.13)[d]
All critically ill patients	892/4127	977/4188	0.93 (0.85-1.03)[e]

ICU indicates intensive care unit.
[a] Data are from unpublished sources (see "Data Abstraction and Quality Assessment" section).
[b] Test for heterogeneity for surgical ICU patients, $I^2 = 17\%$; $P = .30$.
[c] Test for heterogeneity for medical ICU patients, $I^2 = 0\%$; $P = .98$.
[d] Test for heterogeneity for medical-surgical ICU patients, $I^2 = 48\%$; $P = .03$. If Wang et al,[29] with baseline discrepancy in disease severity, is excluded, pooled relative risk is 1.00 (95% confidence interval, 0.90-1.11), test for heterogeneity, $I^2 = 0\%$; $P = .47$.
[e] Test for heterogeneity for all critically ill patients, $I^2 = 18\%$; $P = .20$.
[f] Center of data marker denotes point estimate of relative risk; width of data marker is sized according to weight assigned to the study; and line length denotes 95% confidence interval.

geneity was significant (P=.06; I^2=55%) only for the subgroup of trials evaluating very tight glucose control; again, the van den Berghe surgical ICU trial[1] was the outlying study. Regardless of whether the outlying trial was excluded or not, the findings were not statistically significant (Figure 3). Conversely, while the subgroup of trials[1,23,35] conducted in the surgical ICU (Figure 4) exceeded both thresholds of heterogeneity, the summary estimates differed based on the model used. While the findings of the random-effects model were not significant (RR, 0.69; 95% CI, 0.38-1.26), using a fixed-effects model resulted in a significant reduction in new need for dialysis (RR, 0.64; 95% CI, 0.45-0.92).

Hypoglycemia was reported in 14 published trials‡ and in 1 that was unpub-

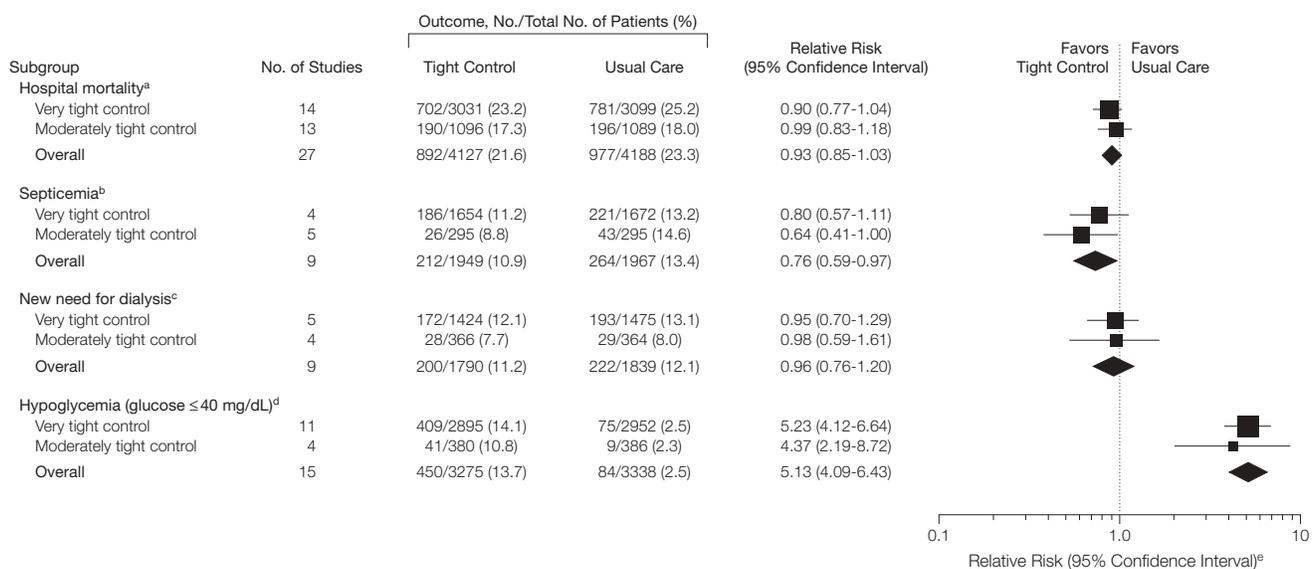‡References 1, 15-17, 23, 25, 26, 31, 33, 37, 38, 46, 47, 50.

lished (Azevedo). Tight glucose control was associated with an increased risk of hypoglycemia (13.7% vs 2.5%; RR, 5.13; 95% CI, 4.09-6.43). As would be expected, when compared with usual care, the risk of hypoglycemia was higher with patients receiving very tight glucose control than for those with moderately tight glucose control (Figure 3). The increased risk of hypoglycemia was fairly consistent across ICU settings (Figure 4). Trials that were conducted in the medical ICU indicated heterogeniety (I^2, 51%), but with only 2 trials[15,38] in this subgroup, we cannot determine which trial is the outlier. Nonetheless, we would judge the trial[38] of 8 patients reporting no increased risk of hypoglycemia to be less reliable than the larger study,[15] which found a significantly increased risk. While most trials reported that few or none of the hypoglycemic events were associated with overt symptoms, some studies found that patients who experi-

enced hypoglycemia had a higher risk of death.[15,16,26]

Sensitivity Analyses

For each of our sensitivity analyses (restricting to trials with 34% of patients with diabetes or fewer, trials using insulin-only infusions, trials that achieved mean glucose levels that differed by at least 20 mg/dL between study groups, and stratifying trials by actual glucose level achieved in the tight glucose control group), the point estimates for most outcomes changed minimally. Those point estimates with moderate changes remained within wide confidence intervals. Only 2 findings changed in statistical significance when stratified by actual glucose level achieved: the reduction in septicemia became statistically significant in the subgroup of trials of very tight glucose control (RR, 0.58; 95% CI, 0.42-0.80); whereas in trials of moderately tight glucose control, the reduc-

Figure 3. Association of Tight Glucose Control vs Usual Care With Outcomes Among Critically Ill Adults, Stratified by Glucose Goal in Tight Control Group

Subgroup	No. of Studies	Outcome, No./Total No. of Patients (%)		Relative Risk (95% Confidence Interval)
		Tight Control	Usual Care	
Hospital mortality[a]				
Very tight control	14	702/3031 (23.2)	781/3099 (25.2)	0.90 (0.77-1.04)
Moderately tight control	13	190/1096 (17.3)	196/1089 (18.0)	0.99 (0.83-1.18)
Overall	27	892/4127 (21.6)	977/4188 (23.3)	0.93 (0.85-1.03)
Septicemia[b]				
Very tight control	4	186/1654 (11.2)	221/1672 (13.2)	0.80 (0.57-1.11)
Moderately tight control	5	26/295 (8.8)	43/295 (14.6)	0.64 (0.41-1.00)
Overall	9	212/1949 (10.9)	264/1967 (13.4)	0.76 (0.59-0.97)
New need for dialysis[c]				
Very tight control	5	172/1424 (12.1)	193/1475 (13.1)	0.95 (0.70-1.29)
Moderately tight control	4	28/366 (7.7)	29/364 (8.0)	0.98 (0.59-1.61)
Overall	9	200/1790 (11.2)	222/1839 (12.1)	0.96 (0.76-1.20)
Hypoglycemia (glucose ≤40 mg/dL)[d]				
Very tight control	11	409/2895 (14.1)	75/2952 (2.5)	5.23 (4.12-6.64)
Moderately tight control	4	41/380 (10.8)	9/386 (2.3)	4.37 (2.19-8.72)
Overall	15	450/3275 (13.7)	84/3338 (2.5)	5.13 (4.09-6.43)

[a]Tests for heterogeneity for hospital mortality: very tight control, I^2=49%, P=.02; moderately tight control, I^2=0%, P=.92; overall, I^2=18%, P=.20. This excludes Wang et al[29]: very tight control relative risk, 0.94 (95% confidence interval, 0.84-1.05), test for heterogeneity: I^2=19%, P=.25.
[b]Tests for heterogeneity for septicemia: very tight control, I^2=64%, P=.04; moderately tight control, I^2=0%, P=.63; overall, I^2=35%, P=.14.This excludes van den Berghe[1]: very tight control relative risk, 0.92 (95% confidence interval, 0.71-1.20), test for heterogeneity: I^2=31%, P=.24.
[c]Tests for heterogeneity for new need for dialysis: very tight control, I^2=55%, P=.06; moderately tight control, I^2=0%, P=.64; overall, I^2=25%, P=.22. This excludes van den Berghe[1]: very tight control relative risk, 1.13 (95% confidence interval, 0.91-1.40), test for heterogeneity: I^2=0%, P=.86.
[d]Tests for heterogeneity for hypoglycemia: very tight control, I^2=0%, P=.48; moderately tight control, I^2=0%, P=.91; overall, I^2=0%, P=.74.
[e]Center of data marker denotes point estimate of relative risk; and line length denotes 95% confidence interval. Data markers are sized to reflect the weight of the studies.

tion in septicemia was no longer significant (RR, 0.87; 95% CI, 0.63-1.21).

Publication Bias
Upon visual inspection of the funnel plot for hospital mortality, we found no evidence of publication bias (data not shown).

COMMENT
In this meta-analysis of randomized controlled trials of tight glucose control vs usual care in critically ill adults, we found no significant difference in hospital mortality or new need for dialysis. Although tight glucose control was associated with a significant reduction in septicemia overall, subgroup analysis suggested this benefit was limited to surgical ICU patients. On the other hand, we found clear evidence of the main harm of tight glucose control: hypoglycemia increased roughly 5-fold, regardless of the ICU setting, and was more common with patients receiving very tight than moderately tight glucose control. In short, our meta-analysis does not support the benefits of tight glucose control reported in the initial trial by van den Berghe et al,[1] yet it suggests a much higher risk of hypoglycemia.

Our study has several limitations. Since we have pooled results from individual trials, our analysis is limited by any flaws in the methodology of these underlying trials. Although none of the included trials attempted to double-blind study group assignments, which could have introduced bias if patients were treated differently based on knowledge of their assignment, all trials achieved a good balance in the relevant baseline characteristics except as noted, and all had greater than 80% follow-up. The potential for differential treatment in these unblinded studies is most relevant for the outcome of new need for dialysis, which is likely to be determined at least in part subjectively, by the treating physicians.

Although several of the included studies were small, the main limitations of such trials (lack of power and narrow generalizability) would be attenuated by inclusion in a meta-analysis, and exclusion of such studies could introduce bias. Despite the increased power derived from pooling many studies, our meta-analysis may still be underpowered to detect small differences in outcomes between tight glucose control and usual care strategies. For example, for the primary outcome of hospital mortality, our meta-analysis is powered (assuming 2-sided alpha=.05 and power=0.8) to determine statistical significance of a

Figure 4. Association of Tight Glucose Control vs Usual Care With Outcomes Among Critically Adults, Stratified by ICU Setting

Subgroup	No. of Studies	Outcome, No./Total No. of Patients (%)		Relative Risk (95% Confidence Interval)
		Tight Control	Usual Care	
Hospital mortality[a]				
Surgical ICU	7	99/1123 (8.8)	123/1141 (10.8)	0.88 (0.63-1.22)
Medical ICU	8	321/1193 (26.9)	356/1200 (29.7)	0.92 (0.82-1.04)
Medical-surgical ICU	12	472/1811 (26.1)	498/1847 (27.0)	0.95 (0.80-1.13)
Overall	27	892/4127 (21.6)	977/4188 (23.3)	0.93 (0.85-1.03)
Septicemia[b]				
Surgical ICU	5	47/1019 (4.6)	87/1030 (8.4)	0.54 (0.38-0.76)
Medical ICU	1	48/595 (8.1)	42/605 (6.9)	1.16 (0.78-1.73)
Medical-surgical ICU	3	117/335 (34.9)	135/332 (40.7)	0.86 (0.71-1.04)
Overall	9	212/1949 (10.9)	264/1967 (13.4)	0.76 (0.59-0.97)
New need for dialysis[c]				
Surgical ICU	3	47/931 (5.0)	74/943 (7.8)	0.69 (0.38-1.26)
Medical ICU	0			
Medical-surgical ICU	6	153/859 (17.8)	148/896 (16.5)	1.11 (0.91-1.36)
Overall	9	200/1790 (11.2)	222/1839 (12.1)	0.96 (0.76-1.20)
Hypoglycemia (glucose ≤40 mg/dL)[d]				
Surgical ICU	4	48/967 (5.0)	8/987 (0.8)	5.37 (2.64-10.93)
Medical ICU	2	112/599 (18.7)	20/609 (3.3)	3.65 (0.76-17.37)
Medical-surgical ICU	9	290/1709 (17.0)	56/1742 (3.2)	4.95 (3.75-6.54)
Overall	15	450/3275 (13.7)	84/3338 (2.5)	5.13 (4.09-6.43)

ICU indicates intensive care unit.
[a]Tests for heterogeneity for hospital mortality: surgical, I^2=17%, P=.30; medical, I^2=0%, P=.98; medical-surgical, I^2=48%, P=.03; overall, I^2=18%, P=.20. This excludes Wang et al[29]: medical-surgical relative risk, 1.00 (95% confidence interval, 0.90-1.11), test for heterogeneity: I^2=0%, P=.47.
[b]Tests for heterogeneity for septicemia: surgical, I^2=0%, P=.73; medical not applicable; medical-surgical, I^2=0%, P=.49; overall, I^2=35%, P=.14.
[c]Tests for heterogeneity for new need for dialysis: surgical, I^2=30%, P=.24; medical not applicable; medical-surgical, I^2=0%, P=.96; overall, I^2=25%, P=.22. Using a fixed-effects model for surgical: relative risk, 0.64 (95% confidence interval, 0.45-0.92).
[d]Tests for heterogeneity for hypoglycemia: surgical, I^2=0%, P=.83; medical, I^2=51%, P=.15; medical-surgical, I^2=0%, P=.51; overall, I^2=0%, P=.74.
[e]Center of data marker denotes point estimate of relative risk; and line length denotes 95% confidence interval. Data markers are sized to reflect the weight of the studies.

2.6% absolute difference in mortality (20.7% vs 23.3%) but not the 1.7% difference in mortality that we actually identified (21.6% vs 23.3%). To be powered to establish statistical significance of a 1.7% difference between groups would require an estimated 19 146 patients.

Trials that were included in our meta-analysis varied widely with regard to baseline patient characteristics and insulin infusion protocols. However, this diversity, which did not appear to influence tests for heterogeneity except as noted, allowed us to capture the full scope of critically ill adults and ICU processes of care. Furthermore, we did not find major changes in our results when we performed sensitivity analysis based on variables of potential clinical relevance, which suggests further support for combining the broadly representative studies. Nonetheless, because it remains reasonable to expect that our overall negative findings might contain important subgroups that would benefit from tight glucose control, we present the findings stratified by the most widely debated variables—glucose goal in the tight control group and ICU setting.

Our meta-analysis shows that subsequent trials have not borne out the impressive results of tight glucose control promised by the initial trial by van den Berghe et al.[1] Tests of heterogeneity identified this trial as having outlying results when compared with subsequent randomized controlled trials reporting outcomes of septicemia and new need for dialysis. There are at least 3 reasons the results of this trial may differ from subsequent studies: bias, chance, and atypical clinical practices. Although this trial was not blinded, which could lead to bias, none of the other trials were blinded and we doubt this explains the discrepancy between study results. The initial trial by van den Berghe et al,[1] reported unusually high mortality in the usual care group based on the disease severity, a finding which may be due to chance. Moreover, several aspects of this trial have been criticized[51-53] for using atypi-

cal clinical practices. Specifically, the use of early glucose infusion and parenteral nutrition, both of which may artificially induce hyperglycemia, may have contributed to the outlying results seen in this trial.

The surgical population or even more specifically cardiac surgery patients who comprised the bulk of the patients in the initial trial by van den Berghe et al,[1] may represent the group most likely to benefit from tight glucose control. However, our meta-analysis demonstrates that subsequent randomized controlled trials of this intervention in surgical patients have not confirmed a significant reduction in mortality, a finding supported by a subgroup analysis of surgical patients (n=6431) in a recent large cohort study.[18] Furthermore, subsequent randomized controlled trials of tight glucose control during[54] or after (unpublished data from Chan et al) cardiac surgery have also failed to confirm a reduction in mortality with tight glucose control.

Practical problems implementing tight glucose control have occurred both inside and outside of clinical trial settings. Actually achieving the target glucose goal can be difficult; even under the close supervision of a clinical trial, 4 published and 2 unpublished of the 29 studies (21%) in our meta-analysis did not achieve a mean glucose level within 5 mg/dL of the stated goal in the tight control group[17,24,25,41] (and unpublished data from Chan et al and Azevedo et al). In practice, there has been substantial resistance to full adherence with tight glucose control by nursing staff, due both to the increased workload stemming from the need for frequent glucose monitoring and changes in infusion rate and to concerns about risk of hypoglycemia.[53,55,56] These concerns of hypoglycemia appear to be warranted, as indicated by the significant increase in risk of hypoglycemia in our meta-analysis. Whether these hypoglycemic events are a causal factor in these patients' deaths or simply a marker of disease severity is unknown.

Overall, we believe the 29 trials included in our meta-analysis allow us to draw conclusions about the benefits and risks of tight glucose control in the broad spectrum of critically ill adults. We found that tight glucose control was not associated with a significant reduction in hospital mortality or in new need for dialysis, but was associated with a markedly increased risk of hypoglycemia. Although we found a statistically significant association with reduction in septicemia, the reduction may have been in less severe episodes of septicemia, given the lack of an associated reduction in hospital mortality. Moreover, when stratified by ICU setting, the significant association with reduced risk of septicemia was limited to trials conducted in the surgical ICU. Given the overall findings of this meta-analysis, it seems appropriate that the guidelines recommending tight glucose control in all critically ill patients should be reevaluated until the results of larger, more definitive clinical trials are available.

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likely to benefit from intervention such as surgery would be highly desirable.

Valvular calcification was not described in the study by Tzemos et al, although the extent of such calcification has been found to be a strong independent predictor of outcome of aortic stenosis,[2] congruent with how the disease process at the tissue level is understood. In addition, valvular calcification increases leaflet stiffness and reduces systolic opening, eventually leading to a reduction in the area of the valve, so calcification could be present before aortic stenosis. If valvular calcification was independently associated with primary cardiac events, it may be a better predictor of outcome that could help in the selection of patients who are likely to benefit from intervention.

Ze-Zhou Song, MS
zezhou_song@126.com
Department of Ultrasound
The First Affiliated Hospital
Zhejiang University
Hangzhou, China

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In Reply: We are unable to address Mr Song's question about the extent of aortic valve calcification and whether it was predictive of primary cardiac events because valvular calcification was not examined in our study. However, a recent study of patients with a normal or minimally dysfunctional bicuspid valve was apparently the first to report the prognostic role of an index of aortic valve degeneration that incorporated the extent of valve thickening, calcification, and mobility.[1] While the extent of valvular calcification has been shown to independently predict outcomes in asymptomatic older adults with severe aortic stenosis,[2] valve calcification may be only one of several factors that predict outcomes in younger patients with bicuspid aortic valve.

Samuel Siu, MD
samuel.siu@lhsc.on.ca
University of Western Ontario
London, Ontario, Canada

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CORRECTION

Incorrect Data: In the Caring for the Critically Ill Patient article entitled "Benefits and Risks of Tight Glucose Control in Critically Ill Adults: A Meta-analysis," published in the August 27, 2008, issue of *JAMA* (2008;300[8]:933-944), an incorrect percentage was reported in Table 1 on page 938. In the row "Mackenzie et al,[25] 2005 (GLYCOGENIC)[g]," the percentage of patients reported in the column "Diabetic,%" should have been "17."