VA HSR&D

Management of Inpatient Hyperglycemia: A Systematic Review

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PREFACE

VA's Health Services Research and Development Service (HSR&D) works to improve the cost, quality, and outcomes of health care for our nation's veterans. Collaborating with VA leaders, managers, and policy makers, HSR&D focuses on important health care topics that are likely to have significant impact on quality improvement efforts. One significant collaborative effort is HSR&D's Evidence-based Synthesis Program (ESP). Through this program, HSR&D provides timely and accurate evidence syntheses on targeted health care topics. These products will be disseminated broadly throughout VA and will: inform VA clinical policy, develop clinical practice guidelines, set directions for future research to address gaps in knowledge, identify the evidence to support VA performance measures, and rationalize drug formulary decisions.

HSR&D provided funding for the two Evidence Based Practice Centers (EPCs) supported by the Agency for Healthcare Research and Quality (AHRQ) that also had an active and publicly acknowledged VA affiliation – Southern California EPC and Portland, OR EPC – so they could develop evidence syntheses on requested topics for dissemination to VA policymakers. A planning committee with representation from HSR&D, Patient Care Services, Office of Quality and Performance, and the VISN Clinical Management Officers, has been established to identify priority topics and to insure the quality of final reports.

Comments on this evidence report are welcome and can be sent to Susan Schiffner, ESP Program Manager, at Susan.Schiffner@va.gov.

TABLE OF CONTENTS

BACKGROUND

Hyperglycemia is a common finding among medical and surgical inpatients with and without known diabetes,(2, 3) and is associated with poor outcomes across a variety of inpatient subpopulations.(2, 4-8) The relationship between hyperglycemia and inpatient outcomes may be weaker in patients with diabetes than in patients without diabetes.(9, 10)

Hyperglycemia may be a marker of severe, acute illness, one of many physiological derangements associated with an abundance of counter-regulatory hormones, insulin resistance, and suppression of anabolic pathways.(11) On the other hand, many investigators believe that hyperglycemia itself may worsen outcomes by contributing to inflammation, oxidative stress, poor immune function, and endothelial dysfunction.(12)

Interventions to control hyperglycemia in inpatients have largely centered on the use of adjustable insulin infusions to lower blood glucose. An early trial in myocardial infarction patients found that lowering blood glucose using intensive insulin therapy (IIT) reduced long-term mortality, though it remains unclear whether the inpatient or outpatient components of the intervention were responsible for the benefit.(13) An influential single-center observational study of cardiac surgery patients reported reduced wound infection and mortality rates after the introduction of an intensive care unit IIT protocol.(14, 15) Subsequently a single-center trial in critically ill surgical patients suggested a mortality benefit from IIT used to achieve normoglycemia.(16)

These findings have fueled widespread interest in inpatient glycemic control strategies,(17, 18) and organizations have called for strict glycemic control strategies to be implemented in a variety of intensive care unit settings.(12, 19) More recently, new trials have been completed that may help clarify the balance of benefits and harms of widespread IIT implementation in intensive care units. We conducted a systematic review of trials and a critical appraisal of frequently cited observational studies to identify strengths of—and gaps in—the evidence supporting broad use of IIT to achieve glycemic control in inpatients.

METHODS

Topic Development

The review was commissioned by the Department of Veterans Affairs' Evidence-based Synthesis Program. We conferred with VA and non-VA experts to select the patients and subgroups, interventions, outcomes, and setting addressed in the review.

The objectives of this review are to address the following questions:

1. Does the use of intensive insulin therapy (IIT) to achieve tight glycemic control compared to less tight glycemic control improve final health outcomes in the following patients?

- patients in the surgical intensive care unit
- patients in the medical intensive care unit
- patients in the perioperative setting
- acute myocardial infarction patients
- acute stroke patients
- general surgical ward patients
- general medicine ward patients

2. What are the harms of strict glycemic control in the above subpopulations?

3. What are the most effective and safest means of lowering blood glucose in the above subpopulations?

Figure 1 illustrates the analytic framework that guided our review and synthesis.

Figure 1. Analytic Framework
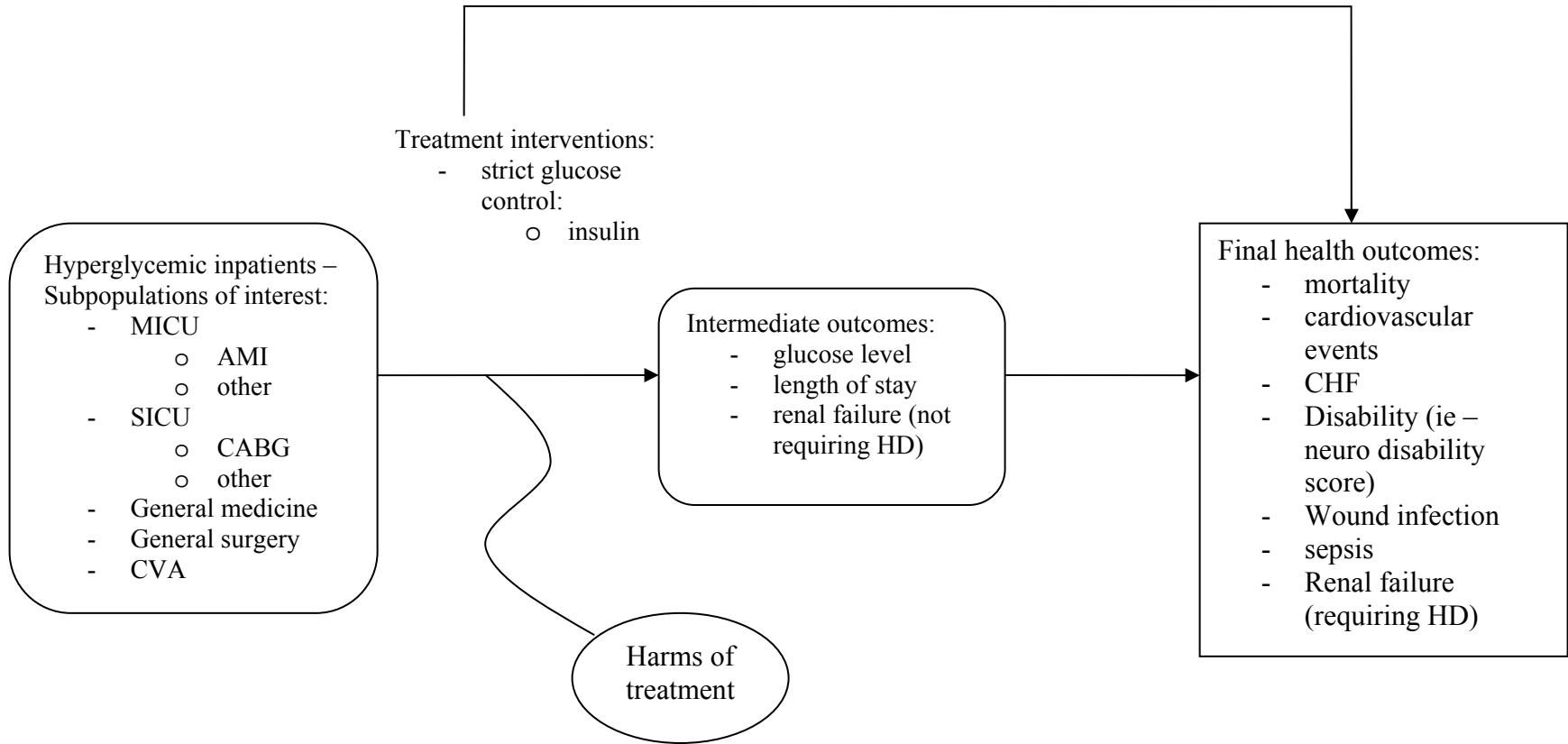
Search Strategy

We conducted a search in Medline and the Cochrane database of systematic reviews of literature published from 1950 through May 2008. Appendix A provides the search strategy in detail. We obtained additional articles from systematic reviews, reference lists of pertinent studies, reviews, 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 X1).

Study Selection

Three reviewers assessed for relevance the abstracts of citations identified from literatures searches. Full-text articles of potentially relevant abstracts were retrieved for further review. Each article retrieved was reviewed using the eligibility criteria shown in Appendix B.

Eligible articles had English-language abstracts and provided primary data relevant to the key questions. Eligibility criteria varied depending on the question of interest, as described below.

To evaluate the efficacy of intensive insulin therapy (IIT) in hospitalized patients, we considered prospective, controlled clinical trials of insulin-based protocols targeted to strict glycemic targets compared to those targeted to less strict glycemic targets. We also considered clinical trials of fixed-dose insulin-based treatment regimens in myocardial infarction patients. The studies had to report at least one prespecified final health outcome (Appendix B). Unpublished studies were included if the authors could provide enough information about the methodology and results to fully evaluate the study's quality. We excluded insulin-based studies conducted in myocardial infarction patients prior to widespread availability of thrombolytics (i.e., enrolling patients prior to 1990).(20) We categorized perioperative trials as those in which IIT was begun pre-, intra-, or immediately post-operatively, and was continued for less than 24 hours post-operatively. We considered patients in neurologic, neurosurgical, and coronary intensive care units separately from patients in general medical and surgical ICUs. Though observational studies using historic control groups were initially excluded from our review, after consultation with experts we decided to include a discussion and critique of frequently cited observational studies.

To assess the risk of hypoglycemia associated with IIT, we included controlled trials and uncontrolled series that reported rates of hypoglycemia in ICU patients treated with IIT, even if they did not report health outcomes. In order to avoid studies with substantial selection bias, we included only interventional prospective cohort studies in which patients were consecutively enrolled and in which there was minimal loss to follow-up. Because tight glycemic control strategies require some personnel training and institutional acceptance, we included only studies in which the intervention was evaluated over a prolonged period of time (defined as 6 months for the purposes of this review) as we felt these studies were most likely to provide externally valid results.

To assess the effectiveness of specific inpatient blood glucose control strategies in lowering blood glucose, we evaluated fair to good quality systematic reviews of insulin infusion protocols. Because of the relative dearth of information guiding insulin management in general medical or surgical ward patients, we also included primary data from controlled clinical trials evaluating subcutaneous insulin management strategies in general medical or surgical ward patients (e.g., those that compared sliding scale insulin to scheduled insulin).

Data abstraction

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

Rating the body of evidence

We assessed the overall quality of evidence for outcomes using a method developed by the Grade Working Group.(1) The Grade method considers the consistency, coherence, and applicability of a body of evidence, as well as the internal validity of individual studies to classify the grade of evidence across outcomes as follows:

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 quality of each study was rated as good, fair, or poor based on the following criteria: the comparability of treatment groups; the adequacy of randomization; whether treatment allocation was concealed; whether eligibility criteria were specified; the use of blinding among patients, care providers, and outcome assessors; whether the analysis was intention-to-treat, or conducted with post-randomization exclusions, or with extensive or differential loss to follow-up; clearly defined interventions and reliable outcome measurement (Appendix C).(21)   When reviewers disagreed, consensus was reached through discussion with all authors.

Data synthesis

Because all ICU trials except one (22) were either small (n < 100) (23-25) or did not reach recruitment goals (16, 26-29), we performed a meta-analysis of trials conducted in critical care settings to estimate with greater power the effects of achieving normoglycemia using IIT on short-term mortality and hypoglycemia. The clinical heterogeneity of insulin interventions, glucose targets, and population characteristics precluded quantitative analysis within the perioperative, myocardial infarction, and stroke subgroups. We abstracted the number of events and total subjects from each treatment arm, and obtained a pooled estimate of relative risk (RR) using a random effects model.(30) Trials reporting hospital or 28-day mortality were included in the short-term mortality analysis. We performed sensitivity analyses to assess the effects of short-term mortality definition (i.e. hospital or 28 day mortality), as well as the effects of excluding trials using higher intervention glucose targets.

Statistical heterogeneity was assessed by Cochran's Q test and I^2 statistic.(31) Because of the small number of trials that could be combined, we did not perform assessments for publication bias.(32) All analyses were performed using Stata 10.0 (StataCorp, College Station, TX, 2007).

Peer review

A draft version of this report was sent to the technical advisory panel and additional peer reviewers. Their comments and our responses are shown in Appendix D.

RESULTS

Literature Flow

We reviewed 2313 titles and abstracts from the electronic search, and identified an additional 44 from reference mining and recently published studies. We also identified 9 unpublished or ongoing studies.(26-28, 33-38) Three of these studies have been completed and the authors provided enough information for us to quality rate and formally include the studies.(26-28)

After applying inclusion/exclusion criteria at the abstract level, 356 full-text articles were reviewed, as shown in Figure 2. Of the full-text articles, we rejected 288 that did not meet our inclusion criteria.

Figure 2. Management of Inpatient Hyperglycemia Literature Flow

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                    ┌─────────────────────────────────┐
                    │  Abstracts imported from MEDLINE │
                    │        (1950-May 2008)           │
                    │           N = 2313               │
                    └─────────────────────────────────┘
                                    │
┌──────────────────────────┐       │       ┌──────────────────────────────┐
│ Unpublished or ongoing    │       │       │ Reference mining and recently │
│ studies                   │       │       │ published studies             │
│ N = 9                     │       │       │ N = 44                        │
└──────────────────────────┘       │       └──────────────────────────────┘
           │                        │                      │
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        ┌─────────────────────────────────────────────────────┐
        │    Total number of citations identified for review   │
        │                   N = 2366                           │
        └─────────────────────────────────────────────────────┘
                                    │
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                    ┌─────────────────────────────────┐
                    │  Total number of articles retrieved │
                    │           N = 356               │
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Total excluded articles = 288
Study design or article type out of scope = 125
Non-systematic or poor-quality systematic review = 67
Study outcome not within scope = 30
Duplicate data = 25
GIK study pre-thrombolytic era = 16
Intervention not within scope = 17
Topic not within scope = 7
Study population not within scope = 1

KQ1 MICU/SICU
N=9
— 1 SR
— 8 RCTs

KQ1 MI/Stroke
N=13
— 1 SR
— 12 RCTs

KQ1 Perioperative
N=6
— 1 SR
— 5 RCTs

KQ3 Hyperglycemia management protocols
N=15
— 2 RCTs
— 10 observational studies & trials without health outcomes
— 3 SRs

KQ2 Hypoglycemia
N=35
— 2 SRs
— 23 RCTs
— 10 observational studies & trials without health outcomes

Note: Some studies applied to multiple KQs

7

KEY QUESTION #1. Does strict glycemic control compared to less strict glycemic control improve final health outcomes in the following patients?

Patients in Medical and Surgical Intensive Care Units

Eight unblinded randomized, controlled trials evaluated tight glycemic control using intensive insulin therapy (IIT) in critically ill patients (Table 1).(16, 22-24, 26-29) Two trials included critically ill surgical patients (SICU)(16, 24), two trials included critically ill medical patients (MICU),(22, 23) and four trials included a mixed SICU/MICU population.(26-29) All of the trials except for one(23) investigated the relative benefits of glucose targets in the normoglycemic range (80 – 110 mg/dL) compared to moderate glucose targets (140 – 200 mg/dL). Our combined analysis of all seven ICU studies(16, 22, 24, 26-29) evaluating the use of intensive insulin therapy to achieve normoglycemia found the intervention had a neutral effect on short-term mortality (RR 0.90; 95% CI 0.78 – 1.03, I^2 40.7%; Figure 3), and substantially increased the risk of hypoglycemia (RR 5.32; 95% CI 4.21 – 6.73, I^2 2.28%; Figure 4).(GRADE: Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate).

SICU

In one influential trial, Van den Berghe et al randomized 1548 SICU patients to either a simple IIT protocol (Leuven protocol) targeted to normal blood glucose (80 – 110 mg/dL by morning blood glucose), or conventional therapy designed to keep blood glucose 180 – 200 mg/dL. This study was terminated early after finding all-cause ICU mortality was significantly lower in the intensive insulin group (4.6% v. 8%, relative risk 0.58, 95% CI 0.38-0.78)(Table 1).(16) The short-term mortality benefit was limited to the subgroup of patients requiring 5 or more days of ICU care (10.6 vs 20.2%, p = 0.005), and long-term mortality did not differ between the two groups.(39) The intervention group experienced a higher cumulative incidence of hypoglycemia (5% v. 0.76%; RR 6.65, 95 % CI 2.83 – 15.62).

This trial was conducted in a SICU that used intravenous glucose and TPN routinely, and monitored all patients with arterial blood sampling, a more accurate method than capillary blood sampling. These practices are not standard in most SICUs. These characteristics may limit the applicability of these results to nonsurgical patients, patients not receiving parenteral nutrition, and centers mainly relying on capillary blood samples.(40-42) Given the nature of the intervention and need for frequent monitoring, blinding of care providers was not possible in this or any of the other studies considered. Though outcomes assessors were blinded, it is possible that patients assigned to IIT received better overall management as a result of the intensive monitoring required for IIT.

A poor quality trial conducted among 61 SICU patients found that establishing normal blood glucose levels (80 – 120 mg/dL) compared to a moderate glucose target (180 – 220

mg/dL) in surgical ICU patients using IIT similar to the Leuven protocol was associated with a 4-fold decrease in intravascular device and bloodstream infections (p<0.05), but not a decrease in mortality (Table 1).(24) The study had numerous methodologic flaws including lack of blinding of outcome assessors, poorly defined exclusion criteria, and failure to report numbers of patients excluded and reasons for exclusion.

MICU

The mortality benefits seen in Van den Berghe et al's SICU trial have not been replicated in MICU populations.(16) A fair-quality trial by Van den Berghe et al included 1200 adult patients admitted to a single medical ICU.(22) As with the other included trials, blinding of care providers was not feasible and could potentially have resulted in treatment bias. Those who were assumed to require less than three days of intensive care, specifically those who were able to receive oral nutrition, were excluded. The methods, insulin regimens and glucose targets were similar to Van den Berghe's 2001 surgical ICU study, but both arterial and capillary blood samples were used in this study for glucose monitoring. Patients received just over 1200 kcal/day of nutritional support in both groups and the vast majority received most nutrition parenterally. Neither in-hospital nor ICU mortality was reduced in the overall intention to treat population, but in-hospital mortality was reduced from 52.5% to 43% (relative risk 0.82, 95% CI not given, p=0.009) in the prespecified subgroup of patients staying in the ICU for at least a third day. There was a nonsignificant mortality increase associated with intensive therapy (relative risk 1.09, 95% CI 0.9-1.32) amongst the 433 patients requiring less than 3 days of ICU care. The incidence of hypoglycemia was significantly higher in the intervention group (Table 4) and mortality was non-significantly higher among those who experienced at least one episode of hypoglycemia (66.7% v. 46.4%, p = 0.1).

A small, poor quality trial in a single MICU examined the efficacy of targeting more moderate glucose goals: 110-140 mg/dl in the intensive group and 140-200 in the control group.(23) Neither ICU nor one month mortality were reduced, but the intervention group did have a reduced incidence of a combined outcome of cerebro- and cardiovascular events (12.2% v. 39.6%, p = 0.004). Methodologic details, including blinding of outcomes assessors and numbers of patients excluded, were not described.

Mixed ICU populations
Four recently completed trials including mixed MICU/SICU populations also consistently failed to demonstrate an overall mortality benefit of achieving normoglycemia using IIT. A recently published fair quality trial used a two-by-two factorial design to assess IIT as well as two different types of volume resuscitation in MICU patients with severe sepsis.(29) This multi-center study used the Leuven protocol and was stopped early because of an excess risk of severe hypoglycemia in the intervention group (17.0% v. 4.1%; RR 4.11, 95% CI 2.21 – 7.63), with many of the hypoglycemic events classified as life-threatening (Table 4). Hypoglycemia was independently associated with mortality (HR 3.31, 95% CI 2.23 – 4.90). There was no significant difference between the groups for the primary outcomes of death at 28 days and multi-organ failure.

Three of the trials have not yet been published, but each of the authors shared methodologic and outcome details complete enough to allow quality rating and inclusion in our quantitative and qualitative analyses.(26-28) GLUCONTROL is a recently completed fair quality randomized, multi-center trial that has been submitted for publication.(28) Using a insulin infusion protocol similar to the Leuven protocol, the IIT group was targeted to 80-110 mg/dl, and the comparator group was targeted to a more moderate range of 140-180 mg/dl. The trial was stopped after enrolling 1101 of a planned 3500 patients because of an excess risk of hypoglycemia in the intervention group (14.5 v. 3.9%; RR 3.64, 95% CI 2.30 – 5.75).(28)   Of note, the median blood glucose achieved in the control group (134 mg/dL) was lower than that achieved in the control groups in any of the other trials, further reducing the power to detect a significant difference in outcome between the two groups.. The ICU mortality rate – the primary outcome – did not differ between the two groups, but one month mortality was nonsignificantly higher in the intervention group (24.5 v. 20.7%; RR 1.19, 95% CI 0.95 – 1.48). There was no difference in patient-days on renal replacement therapy between the two groups (521 v. 526, p = NS).
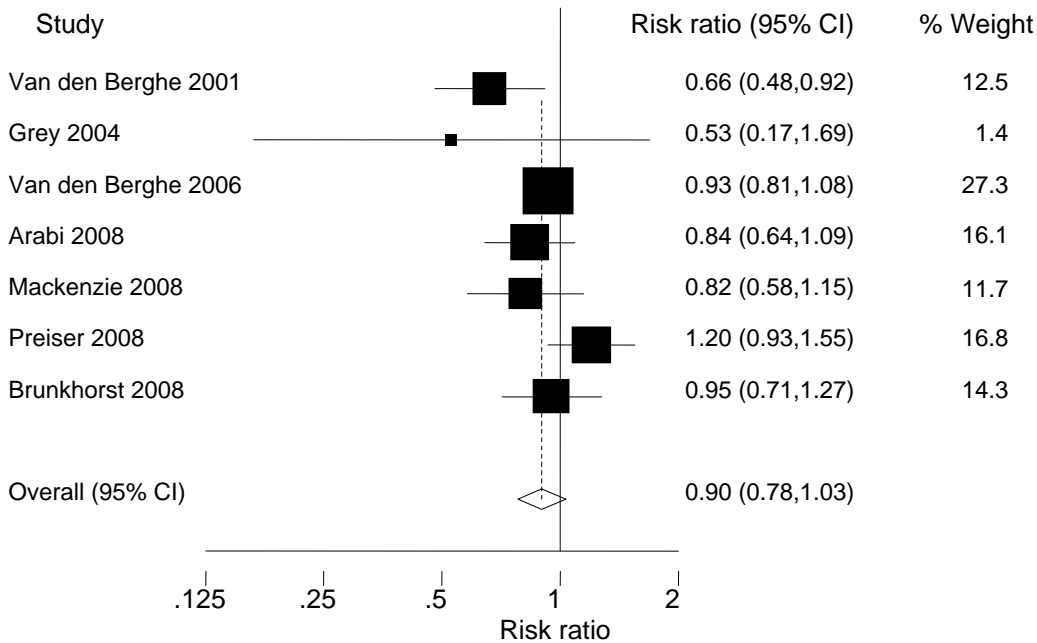
Another fair-quality MICU/SICU trial also found no significant difference in hospital mortality after adjusting for differences in baseline characteristics, notably a significantly smaller proportion of diabetic patients in the IIT group (Hospital mortality: 27.1% versus 32.3%, p=0.19).(26) Hypoglycemia occurred more often in the intensive group (9.1/100 treatment days versus 0.9/100 treatment days, p<0.0001). There was no difference between groups in any of the secondary outcomes, including hospital mortality, ICU or hospital length of stay, duration of mechanical ventilation, need for renal replacement therapy or PRBC transfusion.

Finally, a poor quality trial found in-hospital mortality was similar between the two groups (I v. C, 32.3 v. 39.5%, p = 0.28).(27) Nearly 75% of patients admitted to the two ICUs were excluded, most because the length of stay was projected to be < 48 hours. The incidence of hypoglycemia was higher in the intensive group: 6.7% versus 0.8%, p=0.02 by morning whole blood glucose measures, and 41.3% v. 7.6%, p < .0001 by bedside glucometer measures. There were significantly more patients with liver disease in the control group which may have contributed to the higher hypoglycemia rates.

Meta-analysis

Our combined analysis of all seven ICU studies(16, 22, 24, 26-29) evaluating the use of intensive insulin therapy targeted to normoglycemia found the intervention had a neutral effect on short-term mortality (Figure 3, RR 0.90; 95% CI 0.78 – 1.03, I^2 40.7%). A sensitivity analysis including the study that evaluated a more moderate glucose target (110 – 140 mg/dL compared to 140 – 200 mg/dL) produced similar short-term mortality results (RR 0.92; 95% CI 0.80 – 1.05, I^2 38.7%).

Figure 3. Individual and combined estimates of mortality in MICU/SICU studies comparing intensive insulin with conventional therapy

Study	Risk ratio (95% CI)	% Weight
Van den Berghe 2001	0.66 (0.48,0.92)	12.5
Grey 2004	0.53 (0.17,1.69)	1.4
Van den Berghe 2006	0.93 (0.81,1.08)	27.3
Arabi 2008	0.84 (0.64,1.09)	16.1
Mackenzie 2008	0.82 (0.58,1.15)	11.7
Preiser 2008	1.20 (0.93,1.55)	16.8
Brunkhorst 2008	0.95 (0.71,1.27)	14.3
Overall (95% CI)	0.90 (0.78,1.03)	

One good-quality meta-analysis of 29 trials evaluating tight glycemic control in critically ill patients was just published and similarly found no hospital mortality advantage (21.6 vs 23.3%; RR 0.93, 95% CI 0.85 – 1.03, I^2 18%) or decrease in need for renal replacement therapy (11.2 vs 12.1%; RR 0.96, 95% CI 0.76 – 1.20, I^2 25%) from IIT compared to usual care, but did find a reduced incidence of septicemia in the IIT group (10.9 vs 13.4%; RR 0.76, 95% CI 0.59 – 0.97, I^2 35%).(43) The authors included studies from a variety of settings which we considered separately, including neurologic, neurosurgical, and cardiac intensive care units. They also combined trials which used different intervention group glucose targets: a sensitivity analysis limited to trials achieving normoglycemia in the intervention groups found similar results.

In-progress trials

Several trials investigating the efficacy of achieving normoglycemia with IIT in critically ill patients are in progress.(33, 36, 37) Of note, the NICE-SUGAR multi-center trial will be the largest to date and has randomized nearly 6000 medical and surgical ICU patients with results expected in early 2009.(33, 44)

11

Table 1. Trials in patients in medical and surgical intensive care units

Study	Population, Setting, N, % DM	Glucose target, T v. C (mg/dL)	Glucose monitoring method	Inpatient BG achieved, T v. C (mg/dL)	Mortality, T v. C (RR, 95% CI)	Concomittant therapy/nutrition	Quality¶
(16)	SICU n=1548 13% DM	80-110 v. 180-200	Arterial blood samples	103 v. 153* (p<0.001)	ICU mortality 4.6 v. 8% (p=0.005 unadjusted) RR 0.42 (95% CI 0.22-0.62); Hospital mortality: 7.2 v. 10.9% (p = 0.01) RR 0.66; 95% CI 0.48 – 0.92; New renal replacement: 4.8 v. 8.2% (p = 0.007) Sepsis: 4.2 vs 7.8% (p = 0.003)	On adm, all pts fed with IV glc; next day TPN, TPN and enteral, or enteral initiated; no sig diff between groups. 85.2 % received majority of calories through parenteral nutrition‖	Fair
(24)	SICU n=61 15% DM	80-120 v. 180-220	Not reported	125 v. 179† (p<0.001)	Hospital mortality: 11 v. 21% (p=0.50) RR 0.53; 95% CI 0.17 – 1.69 Sepsis: 4 fold increased risk of bloodstream infections in control group, numbers not provided	---	Poor
(22)	MICU n=1200 16% DM	80-110 180-200	Arterial and capillary blood samples	111 v. 153* (p<0.001)	ICU mortality: 24.2 v. 26.8% (p=0.31) Hospital mortality: 37.3 v. 40.0% (p = 0.33) RR 0.93; 95% CI 0.81 – 1.08 90 d mortality: 35.9 v. 37.7% (p=0.53) New renal replacement: 20.8 vs 22.7% (p = 0.5)	Mean kcal/d: Conv: 1238, Int 1202. 85.2 % received majority of calories through parenteral nutrition‖	Fair
(23)	MICU, n=89 DM: 48.8% T, 68.8% C (p = NS)	110-140 v. 140-200	Not reported	142 v. 174† (p<0.001)	ICU mortality: 39 v. 31.3% (NS) 28d mortality: 53.6 v. 45.8% (NS) RR 1.17; 95% CI 0.77 – 1.78 Sepsis: 26.8 vs 35.4% (p = NS)	---	Poor

Study	Population, Setting, N, % DM	Glucose target, T v. C (mg/dL)	Glucose monitoring method	Inpatient BG achieved, T v. C (mg/dL)	Mortality, T v. C (RR, 95% CI)	Concomittant therapy/nutrition	Quality¶
(29)	Septic patients in 18 MICUs, n=537 30% DM	80-110 v. 180-200	Arterial and capillary blood samples	112 v. 151* (p<0.001)	28 d mortality: 24.7 v. 26% (p=0.74) RR 0.95, 95% CI 0.70-1.28 90 day mortality: 39.7 v. 35.4% (p = 0.31) New renal replacement: 27.5 vs 22.5% (p = 0.19)	Mean daily caloric intake kcal/d 1236+/-534, p=0.47	Fair
(28)	MICU/SICU n=1101 DM: 16.5% T, 21.8% C (p=0.031)	80-110 v. 140-180	Arterial and capillary blood samples	108 v. 134* (p=nr)	ICU mortality: 16.7 v. 15.2% 28-day mortality: 24.5 v. 20.7%; RR 1.19; 95% CI 0.95 – 1.48 Days on renal replacement: 521 vs 526 (p = NS)	Percentage of days on parenteral nutrition: 26 +/- 44 % (T), 27 +/- 44% (C)	Fair
(26)	MICU/SICU N=523 DM: 32.0% T, 47.9% C (p = 0.0002)	80-110 v. 180-200	Arterial and capillary blood samples	115 v. 171† (p<0.0001)	ICU mortality: 13.5 v. 17.1% (p=0.70) RR 1.09, 95% CI 0.70-1.72§ Hospital mortality: 27.1 v. 32.3% (p=0.19) RR 0.84; 95% CI 0.64 – 1.09§ New renal replacement: 11.7 v. 12.1% (p=0.89)§	Mean daily caloric intake kcal/d 916+/-500 v. 830+/- 509 >75% enteral	Fair
(27)	MICU/SICU - two centers n=240 14-19% DM	72-108 180-198	Whole blood monitoring	126 v. 151* 113 v. 144‡ (p<0.0001)	ICU mortality: 19 v. 22.7% (p=0.53) Hospital mortality: 32.2 v. 39.5% (p=0.28) RR 0.82; 95% CI 0.58 – 1.15	---	Poor

* Morning blood glucose

† Average of blood glucose measurements, not otherwise specified

‡ Time-weighted mean blood glucose

§ Adjusted for chronic liver disease, traumatic brain injury, APACHE II and INR.

||Data from combined analysis of Van den Berghe SICU and MICU trials(45), data not reported in individual trials

¶The full quality rating for each study is provided in Appendix E.

Acute Myocardial Infarction Patients

Adjustable dose insulin infusions

Six unblinded trials have examined tight glycemic control using adjustable dose insulin-based regimens (Table 2).(13, 46-50) As a body of evidence, these studies lacked coherence and did not consistently demonstrate a benefit of adjustable dose insulin-based regimens in acute myocardial infarction patients. Variation in trial design, achievement of recruitment goals, glucose level achieved, and concomitant therapy for myocardial infarction limit the strength of this conclusion. (GRADE: Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate.)

Three trials of insulin-glucose infusions in patients with acute myocardial infarction had conflicting findings.(13, 46, 47) The DIGAMI study was a fair quality trial,(13) in which intervention patients were maintained on an insulin infusion with the target plasma glucose 126 – 198 mg/dL for at least 24 hours and were subsequently transitioned to a multi-dose outpatient insulin regimen. The control group did not routinely receive insulin. Both groups were markedly hyperglycemic on admission (intervention mean 277 mg/dL, control mean 282 mg/dL, p = NS), but the intervention group achieved better in-hospital glucose control (172.8 mg/dL v. 210.6 mg/dL, p < .001) and maintained better glycemic control at one year of follow-up. The three-month mortality rate did not differ significantly between groups, but the intervention group had lower mortality by one year (18.6% v. 26.1%, RR 0.69, 95% CI 0.49 – 0.96, p = .027). It is unclear whether the benefit was related to the acute intervention or the longer-term insulin therapy. Applicability of the study results to current MI populations may be limited: only 50% of patients received revascularization therapy, the trial predates widespread statin use, and a large proportion (42 %) of eligible patients were excluded because of lack of willingness or ability to comply with a complex insulin regimen.

The DIGAMI II trial was a poor quality trial designed to determine whether the mortality benefit seen in the earlier trial was related to use of a tight glycemic control strategy during the acute hospital setting or the outpatient follow-up period.(47) There were two intervention groups: one received an insulin-glucose infusion and was transitioned to an insulin-based outpatient regimen, and the other received only the insulin-glucose infusion with subsequent diabetes care left to the discretion of the physician. The trial was stopped early due to slow enrollment and the difference in blood glucose achieved at 24 hours between groups was smaller than anticipated (163.8 v. 180 mg/dL, p < .001). Adjusted long-term mortality (mean follow-up 2.1 years) did not differ among the groups, though one analysis did suggest those treated with outpatient insulin during follow-up had a significantly higher risk of non-fatal myocardial infarction or stroke compared to those on oral glucose-lowering treatments (adjusted HR 1.71; 95% CI 1.25 – 2.35).(51)

A third fair quality trial investigated intensive insulin therapy given only during the acute post-infarct period with a moderate glucose target (72 – 180 mg/dL).(46) The difference

in blood glucose achieved during hospitalization between the two groups did not achieve significance (149.2 v. 162 mg/dL). There was no difference in inpatient, 3 month, or 6 month mortality between the intervention and control groups. Though there was a suggestion of reduced cardiac events and CHF in the intervention group, these reductions were not consistent across the follow-up period.

One small fair quality trial compared a normoglycemic to a moderate glucose target in survivors of ventricular fibrillation cardiac arrest.(48) Insulin infusion dosing was left to the discretion of the nurse without a strict protocol. The trial was stopped early after an interim analysis failed to provide any evidence of benefit. The authors found no difference in 30 day mortality, but the group randomized to a normoglycemic target did experience a higher incidence of moderate hypoglycemia (blood glucose < 54 mg/dL; 18% v. 2 %, p < .0001).

Two trials investigated the use of adjustable dose insulin as part of a glucose-insulin-potassium (GIK) infusion (Table 2).(49, 50) Van der Horst et al investigated a high-dose GIK infusion with a broad glucose target range in 940 patients with acute ST elevation myocardial infarction, approximately ten percent of whom had known diabetes.(49) There was no significant difference in blood glucose achieved between the two groups. There was no reduction in 30 day mortality in the overall group. The large prespecified subgroup of patients without signs of heart failure did experience a mortality benefit from GIK infusion (RR 0.28, 95% CI 0.1 - 0.75, ARR 3.0), but there were a large number of prespecified subgroups. A poor quality trial included a similar number of patients, with a similar proportion of diabetics, and found no difference in 30 day or one-year mortality rates between the two groups.(50, 52) The insulin infusion was targeted to a moderate glucose range, but the authors did not report blood glucose achieved or hypoglycemia rates in the two groups.

Fixed dose insulin infusions

We found good evidence that insulin used as part of a fixed-dose glucose-insulin-potassium infusion does not consistently improve final health outcomes in acute myocardial infarction patients, and may increase short-term mortality (not shown in table).(GRADE: High = Further research is unlikely to change out confidence on the estimate of effect.) An analysis combining results from two large fair-quality multi-center trials included nearly 23,000 patients and found no difference at 30 days in mortality (HR 1.04; 95% CI, 0.96 – 1.13; p = .33), development of congestive heart failure (HR 0.99; 95% CI, 0.93 – 1.06; p = .82), or reinfarction (HR 0.99; 95% CI, 0.84 – 1.17; p = .93).(53-55) Of note, in both trials the post-randomization glucose was higher in the GIK group, and the combined analysis showed an increase in 3 day mortality in the GIK group (HR 1.13; 95% CI, 1.02 - 1.26).

Three small trials of fixed high-dose GIK infusions reported clinical outcomes. One study of poor quality reported found no difference in mortality at 6 months.(56) Another fair-quality trial found a reduction in a composite outcome of short- (10.0 vs 32.5%, RR 0.24; 95% CI 0.09 – 0.63) and long-term (13.0 vs 40.0%, RR 0.22; 95% CI 0.09 – 0.55)

cardiac events.(57) One small, poor quality study, hampered by poor reporting of follow-up, randomization, and allocation concealment, showed a reduction in congestive heart failure incidence.(58)   Additionally, one fair-quality trial examined a fixed low-dose GIK infusion and found an excess in 35 day and 6 month mortality in the intervention group, with many of the excess deaths occurring within the first three days of the trial.(59)

One good-quality meta-analysis included 24 studies of insulin use in acute myocardial infarction patients.(60) The vast majority (n = 21) of these trials examined insulin in the form of fixed-dose GIK infusions, and 15 of these were conducted during the pre-thrombolytic era (pre-1990). When all studies, regardless of the form of insulin used or study date, were combined, there was a non-significant reduction in mortality (RR 0.89, 95% CI, 0.76 – 1.03). The pre-thrombolytic era studies seemed to account for most of this borderline benefit: when the 15 pre-thrombolytic era GIK studies were combined, there was a similar mortality reduction of borderline significance (RR 0.84, 95% CI, 0.71 – 1.00) while the six post-thrombolytic era trials found a neutral effect of GIK infusion on mortality (RR 1.02, 95% CI, 0.75 – 1.39). Three non-GIK trials included the two DIGAMI trials detailed above and a third smaller trial conducted prior to widespread thrombolytic use.(20) The authors could not pool these results because DIGAMI II did not report 30 day mortality outcomes.

Acute Stroke Patients

There is very little fair or good-quality evidence investigating tight glycemic control in patients who have suffered a cerebrovascular accident (Table 2). (GRADE: Low – Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate.) The largest trial to date was poor quality and reported largely negative results.(61)   The intervention group's glycemic target was very strict (72 – 126 mg/dL) while the control group only received insulin if blood glucose ranged above 300 mg/dL. The intervention group did achieve a lower 24 hour mean blood glucose (mean glucose difference 10.3 mg/dL; 95% CI 4.9 - 15.5), though this data was only available in half the population. The intervention did not reduce mortality or severe disability at 90 days. The trial was stopped early because of low participation rates.

A second much smaller fair-quality trial in patients with subarachnoid hemorrhage failed to find a long-term clinical benefit from tight glycemic control, but did find a reduced infection rate in the short-term (27% v. 42%, p < .001).(62) A small poor quality study included a subgroup of acute brain injury patients from a larger ICU trial.(63) Intervention patients received an insulin infusion but failed to achieve normoglycemic targets, and control patients received little insulin but received low glucose enteral feeds and intravenous fluids. There was no difference in ICU mortality or rates of neurologic recovery.

Table 2. Trials in patients with acute MI or stroke

Study	Population n % DM	Glucose target, T v. C (mg/dL)	Glucose monitoring method	Inpatient blood glucose achieved mean (SD), T v. C (mg/dL)	Mortality, T v. C (RR, 95% CI)	Concomittant therapy/nutririon, T v. C (%)	Quality*
Insulin-glucose infusions							
(46)	acute MI n = 240 DM 49%	T: 72 - 180 C: < 288	capillary blood glucose	T: 149.4 (39.6) C: 162 (50.4) p = NS	Inpatient mortality: 4.8% v. 3.5%, p = .75 3 month mortality: 7.1% v. 4.4%, p = .42	percutaneous coronary intervention: 32 v. 39; thrombolysis: 32 v. 32 most patient received aspirin, beta-blockers and statins (numbers NR)	Fair
(13)	acute MI n = 620 DM 39%	T: 126 - 198 C: NR	whole blood samples, bedside reflectance meter monitoring	24 hours: T: 172.8 (59.4) C: 210.6 (73.8) p < .001	3 month mortality: 12.4% v. 15.6%, p = NS 1 year mortality: 18.6% v. 26.1 %, RR 0.69; 95% CI 0.49 – 0.96	thrombolytics - 50%, heparin - 17%, aspirin at d/c - 80%, beta blockers at d/c - 70%, insulin treatment at one year: 72% v. 49% (p < .0001)	Fair
(47)	acute MI, n = 1253 DM 77%* (with established DM, 23% had "newly diagnosed DM <1y)	group 1 and 2: 126 - 180 group 3: NR	NR	24 hours: group 1: 163.8 (54.0), group 2: 163.8 (50.4), group 3: 180.0 (64.8) p = .0001	Adjusted 2-year morality HR (95% CI): Group 1 v. group 3 = 1.19 (0.86 - 1.64) Group 2 v. group 3 = 1.23 (0.89 - 1.69)	percutaneous coronary intervention: 44 (gr 1) v. 40 (gr 2) v. 45 (gr 3) thrombolysis: 36 v. 34 v. 38 Aspirin at d/c: 89 v. 90 v. 84 Beta-blocker at d/c: 83 v. 84 v. 81 Lipid lowering at d/c: 67 v. 69 v. 57	Poor
(48)	Ventricular fibrillation survivors n = 90 DM 11%	T: 72 – 108 C: 108 – 144	arterial blood glucose	I = 90 (81 - 104.4) C = 115.2 (99 - 133.2), p < .0001	30 day mortality: 33% v. 35%, p = 0.85	Therapeutic hypothermia	Fair
(63)	Acute brain injury N = 48 DM % NR 64.5% with CVA	T: 80 – 120 C: < 180	Capillary blood glucose	Mean (inter-quartile range: T: 138.9 (125.6 - 174), C: 148.4 (131.5 - 188.6), p = .16	ICU mortality: 25.8 v. 35.2, p = 0.5	Enteral nutrition; control group enteral formula had lower % carbohydrates	Poor

Study	Population n % DM	Glucose target, T v. C (mg/dL)	Glucose monitoring method	Inpatient blood glucose achieved mean (SD), T v. C (mg/dL)	Mortality, T v. C (RR, 95% CI)	Concomittant therapy/nutrition, T v. C (%)	Quality
Insulin-glucose infusions, continued							
(61)	acute CVA n = 933 DM 17%	T: 72 - 126 C: < 306	capillary blood glucose	24 hour mean difference I v. C (95% CI): 10.3 (4.9 - 15.5), p < .0001	90 day mortality: 30.0% v. 27.3%, OR (95% CI) = 1.14 (0.86 - 1.51) 90 day severe disability: 35.1% v. 36.0%, OR (95% CI) = 0.96 (0.70 - 1.32)	NR	Poor
(62)	subarachnoid hemorrhage n = 78 DM 10%	T: 80 - 120 C: 80-220	arterial blood glucose	NR	6 month mortality: 15.0% v. 18.4%, p = NS Total infection rate: 27% v. 42%, p < .001	Intracranial aneurysm clipping, intravenous calcium antagonists	Fair
Adjustable GIK infusions							
(49)	acute MI undergoing PTCA n = 940 DM 11%	T: 126 - 198 C: NR	whole blood samples	16 hours: T: 138.6 C: 145.8 p = NS	30 day mortality: 4.8 v. 5.8, RR 0.82; 95% CI 0.46 - 1.46	Percutaneous coronary intervention: 91.6 v. 91.4 CABG: 4.0 v. 4.1	Fair
(50)	acute MI n = 864 DM 10%	T: 108 - 180 C: NR	NR	NR	One year mortality: 5.3% v. 3.9%, p = .33 Recurrent MI: 4.6% v. 4.6%, p = .99	Percutaneous coronary intervention: 94 v. 93 Thrombolysis: 1 v. 3 Aspirin at d/c: 95 v. 93 Beta-blocker at d/c: 91 v. 86 Statin at d/c: 88 v. 87	Poor-fair

*The full quality rating for each study is provided in Appendix E.

Perioperative Patients

Overall, the evidence, including five RCTs conducted in patients undergoing cardiac surgery,(64-68) is methodologically limited, evaluates heterogenous treatment approaches, and does not provide clear, consistent evidence of benefit from tight glycemic control strategies in the perioperative setting (Table 3). (GRADE: low = Further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.)

Two fair-quality trials were designed to evaluate the efficacy of achieving intraoperative normoglycemia using IIT during cardiopulmonary bypass.(65, 66) One trial which excluded diabetic patients found no significant differences between groups in rates of neurologic morbidity or mortality, but did find a trend toward increased hypoglycemia in the intervention group (11.7% v. 6.2%, p = 0.07).(65) In the second trial only the intervention group was targeted to normoglycemia during surgery, but both groups received insulin infusions with normoglycemic targets during the post-operative period.(66) More patients in the intensive insulin group than the control group died (2% v. 0%, p=0.06) or suffered a stroke (4% v. 1%, p=0.02) within 30 days after surgery.

Two RCTs examined the effect of GIK infusion administered just before surgery and maintained for 6-12 hours after surgery, using an adjustable-dose GIK infusion with a moderate glucose target range.(67, 68) One was a fair-quality trial (n=141) that found no significant differences in short-term mortality or MI, although GIK-treated patients had significantly higher cardiac indices (2.9 v. 2.4 L/min/m^2 after GIK infusion was discontinued at 18 h), less need for pacing (14% v. 39%, p=0.001), a lower incidence of infections (0 v. 13%, p=0.01), and shorter postoperative hospital stays (6.5 v. 9.2 days, p=0.003).(67) Survival at 2 years was marginally better among GIK patients in this study (p=0.04). The other study was a poor-quality pilot trial in 44 patients without diabetes, and found no differences between groups in wound infection, length of stay, or 30-day mortality.(68)

A poor-quality trial including CABG patients with diabetes (n=93) compared use of an insulin infusion to subcutaneous sliding scale insulin in order to achieve a moderate glucose target (150-200 mg/dL) in the immediate post-operative period.(64) The insulin infusion group achieved a lower post-operative mean blood glucose level (195 v. 288 mg/dL, p<0.001). There were no between-group differences in mortality, length of ICU stay, or frequency of sternal wound infections.

One good quality systematic review and meta-analysis included a large number of trials with patients receiving some form of insulin intraoperatively, perioperatively, and/or postoperatively.(69) The majority of trials included patients undergoing CABG, although a handful of trials examined other surgical populations. The authors included studies of GIK and insulin-alone infusions, and studies with and without a glucose target. Most trials were of poor to fair quality. We had excluded a number of these trials from our own review that did not examine prespecified health outcomes,(70-83) or that examined an insulin-based intervention without a glucose target.(70, 71, 73-76, 83, 84) When all

14 trials reporting mortality outcomes were combined, there was a 31% reduction in mortality (RR 0.69, 95% CI, 0.51 – 0.94). However, when the Van den Berghe SICU trial(22) was excluded from the meta-analysis, the authors found no mortality difference between the two groups (RR 0.92, 95% CI, 0.57 – 1.48). The Van den Berghe trial examined a qualitatively different intervention (ie – tight glycemic control throughout the ICU stay) and is extensively discussed along with the other trials examining glucose control in critically ill patients.

Table 3. Trials in patients undergoing cardiac surgery

Study	Population Setting, N, % DM	Intervention and comparator	Glucose monitoring method	Glucose target, T v. C (mg/dL)	Inpatient BG achieved, T v. C (mg/dL)	Mortality, T v. C (% per group)	Concomittant therapy/nutrition	Quality *
(65)	CABG with CPB 0% DM n = 188 intensive IT; 193 saline placebo	T: Insulin infusion during surgery, if glucose > 100. C: saline placebo infusion. BG was measured for analysis.	Arterial blood samples	T: 70-100 C: not specified	T v. C levels were significantly lower (p<0.01), values not reported	In-hospital 2.1 v. 1.6% (p=ns) 6-month 3.2% v. 2.6% (p=ns)	100-200 mL of dextrose 55 was administered when BG decreased to <70 mg/dl.	Fair
(66)	48% CABG 52% other cardiac surgery 20% DM n = 188 intensive IT; 191 conventional IT	T: Insulin infusion during surgery, if glucose > 100. C: IV bolus of insulin if glucose >200; infusion if >250. Both groups received insulin infusion on arrival in ICU.	Arterial blood samples	T: 80 -100 C: <200	After CPB, T v. C (mg/dL): 123 v. 148 (p=<.001) At arrival in ICU: 114 v. 157 (p<0.001) In ICU, both groups received IIT. After 24 hrs in ICU: 103 v. 104 mg/dL (p=0.72)	30 days after surgery: 2 v. 0% (p=0.06)	During first 24 hr after surgery, pts were not given SQI or oral diabetic meds and received only clear liquids by mouth.	Fair
(67)	CABG 100% DM n = 72 GIK; 69 no-GIK	T: GIK infusion started just before surgery; continued 12h after arrival in ICU. C: SQ sliding scale insulin	Not reported	T: 126 - 200 C: <250	12 hours post surgery mean (SD) in mg/dL: T = 134.3 (3.7) C = 266.8 (6.3)	30 days: 0 v. 0% 2 yrs: 0 v. 10% (p=0.04)	None. Pts resumed preop diabetic regimens (oral agents or insulin) after the 18-hr study period	Fair
(68)	CABG 0%DM n= 22 GIK; 22 D5W	T: GIK infusion started just before surgery; continued until 6h after reperfusion C: D5W placebo infusion, with no glucose monitoring	Serum	T: 89-179 C: not specified	NR	No deaths occurred within 30 days in either group	---	Poor

Study	Population Setting, N, % DM	Intervention and comparator	Glucose monitoring method	Glucose target, T v. C (mg/dL)	Inpatient BG achieved, T v. C (mg/dL)	Mortality, T v. C (% per group)	Concomittant therapy/nutrition	Comments
(64)	CABG 100% DM n = 51 CII; 42 SQI	CII v. SQI.	Not reported	T: 150 - 200 C: 150 - 200	Post-op day 1 mean in mg/dL (SD NR): I = 195.0, C = 229.1, p <.001	Mortality: 3.9 v. 2.4% (p = ns)	Most patients returned to oral feeding during the 1st or 2nd postoperative day. Intermittent insulin injections were given instead of a continuous infusion once patients began eating.	Poor

*The full quality rating for each study is provided in Appendix E.

Abbreviations: CII = Continuous insulin infusion; C = Comparator; DM = Diabetes mellitus; SQI = subcutaneous insulin; T = Treatment

General Medicine Ward Patients

There were no studies evaluating a tight glycemic control strategy to less tight glycemic control in general medical ward patients.

Observational Studies

The following observational studies did not meet our initial inclusion criteria but we discuss them in further detail because they report health outcomes, have been cited frequently, and have informed clinical practice.

The Portland Diabetic Project was a single-center observational study of diabetic cardiac surgery patients treated between 1987 and 2005.(14, 15) The control group consisted of patients treated between 1987-1991 during which time subcutaneous insulin was used to maintain blood glucose at or below 200 mg/dL. An insulin infusion protocol was subsequently introduced in a graded fashion with glucose targets gradually lowered over time in an effort to improve staff/institutional acceptance and lower the risk of hypoglycemia.   Compared with the historic control group, the first intervention cohort, which was maintained on a peri- and postoperative insulin infusion with a moderate glucose target (150-200 mg/dL), had a significantly lower risk of deep sternal wound infections (DSWI) (0.8% v. 2.0%, p = .01) even after controlling for patient level and surgical confounding variables.(17) A subsequent analysis reported a lower cardiac mortality in the over 4500 patients enrolled during the insulin infusion era compared with historic controls (1.1% v. 4.4%, p < .001). The overall incidence of hypoglycemia was not reported.

In 2007 D'Alessandro et al used the EuroSCORE risk stratification algorithm to compare expected and observed mortality rates in diabetic patients undergoing cardiac surgery.(85-88) Between 2003 and 2004 patients were treated with an intra- and post-operative insulin infusion protocol similar to that of Furnary et al with target blood glucose 150-200mg/dL and a post-operative target of < 140 mg/dL.   Observed and expected mortalities in the historical controls were similar, while patients treated during the protocol era had a lower observed mortality than expected (OR 0.28; 95% CI, 0.09 – 0.82). Morbidity rates, including DSWI, did not differ between the two groups. The hypoglycemia rate was not reported.

Another observational study included mixed medical and surgical ICU patients admitted between 1999 and 2006 (89). Mortality was compared before and after a protocol to maintain glucose between 80 and 140mg/dl was instituted in 2003. The protocol prompted subcutaneous insulin use when blood glucose ranged 140-199 mg/dL and an insulin infusion when blood glucose exceeded 200mg/dL (the thresholds were lowered during the last year of the study). The mean (SD) blood glucose was 124.4 mg/dL (51.3) and 154.0 mg/dL (87.5) in the post- and pre-protocol eras, respectively. The authors found a lower mortality rate during the tight glycemic protocol era (OR 0.68; 95% CI 0.57-0.80, p<0.001) and most of this benefit was seen in nondiabetic patients. The rate of
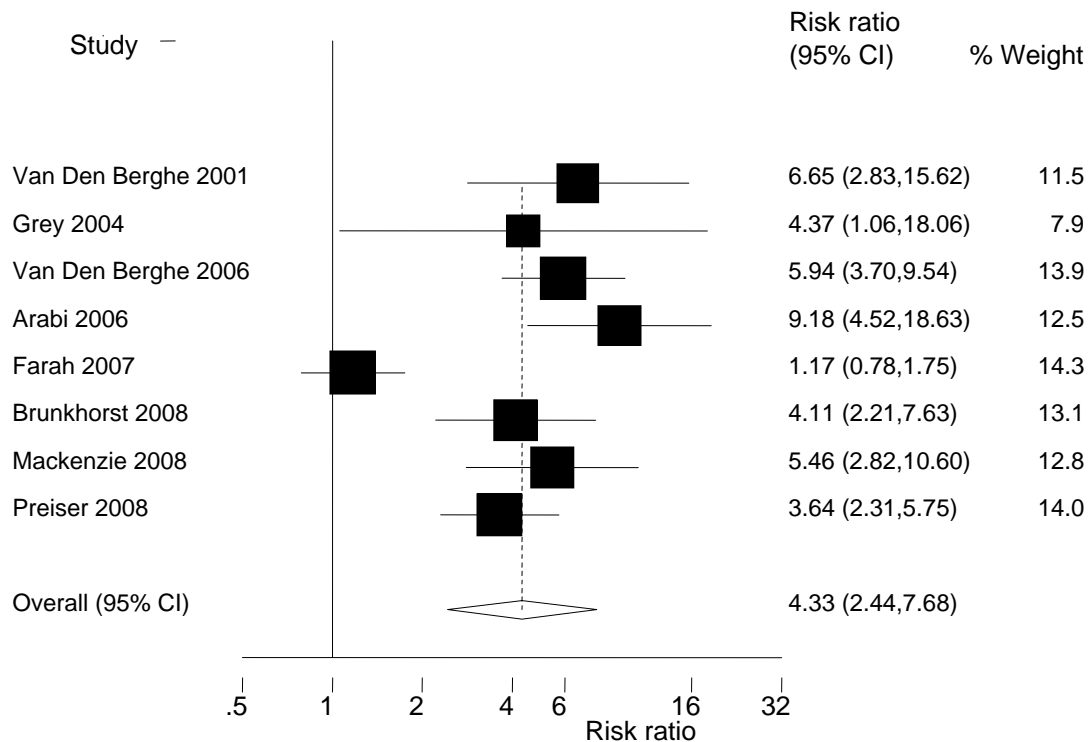
severe hypoglycemia was relatively low overall, but increased during the protocol era (1.50 v. 2.26%, p = .051).

These studies have several important strengths: large size, consecutive enrollment, thorough follow-up, and an attempt to control for severity of illness and other confounding factors. They also provide important insights into the feasibility of establishing various glycemic control strategies in "real-world" settings. However, these studies also have several important weaknesses which temper their use in drawing conclusions about the efficacy of tight glycemic control in improving health outcomes and the use of specific glucose targets. Observational studies may overestimate magnitude of treatment effect when compared to randomized studies.(90) Because of the use of historic controls, it is difficult to ascertain the proportion of the health outcome improvement that was attributable to the insulin-based glycemic control strategies. For example, one study found a 25% drop in mortality within the subset of patients with the poorest glycemic control.(89) A number of interventions and quality improvement initiatives may contribute to improved outcomes in surgical and critically ill patients.(91, 92) The change efforts heralded by a glycemic control strategy may also improve provider and institutional acceptance of other quality improvement intitiatives and may reduce variation in practice around efforts such as infection control.(93) Also, as in the reviewed randomized trials, these single-center studies were necessarily unblinded and some improvement attributable to increased vigilance, more intensive training of staff, and more intensive data registry use is certainly possible. Finally, two of the studies did not report overall hypoglycemia rates, making it more difficult to draw conclusions about protocol safety.

KEY QUESTION #2. What are the harms of strict blood glucose control in the above subpopulations?

The highest occurrence of hypoglycemia appeared among critically ill patients receiving IIT aimed at achieving normoglycemia (Figure 4, RR 5.32; 95% CI 4.21 – 6.73, I^2 2.28%; Table 4), especially those in the MICU, of whom a large proportion had risk factors for hypoglycemia such as sepsis, malnutrition, liver disease, congestive heart failure, and renal insufficiency.(94-97)

Figure 4. Individual and combined estimates of hypoglycemia in MICU/SICU studies comparing intensive insulin with conventional therapy

Study	Risk ratio (95% CI)	% Weight
Van Den Berghe 2001	6.65 (2.83,15.62)	11.5
Grey 2004	4.37 (1.06,18.06)	7.9
Van Den Berghe 2006	5.94 (3.70,9.54)	13.9
Arabi 2006	9.18 (4.52,18.63)	12.5
Farah 2007	1.17 (0.78,1.75)	14.3
Brunkhorst 2008	4.11 (2.21,7.63)	13.1
Mackenzie 2008	5.46 (2.82,10.60)	12.8
Preiser 2008	3.64 (2.31,5.75)	14.0
Overall (95% CI)	4.33 (2.44,7.68)	

Risk ratio: .5 1 2 4 6 16 32

A recent fair quality meta-analysis included several of the same ICU trials(16, 22, 29) as well as several that did not prespecify health outcomes(98-101) and found a similar risk of hypoglycemia (RR 4.97; 95% CI, 3.65 – 6.76, p < .001).(102) Another recent good quality meta-analysis examined perioperative insulin infusions, many of which used higher glucose targets in the intervention groups: 20/34 included studies reporting hypoglycemia rates found that insulin-infusion was associated with a two-fold increased risk of hypoglycemia (RR 2.07, 95% CI, 1.29 – 3.32).(69)

The consequences of hypoglycemia in hospitalized patients are unclear. There were few reported in-hospital adverse effects of hypoglycemia during intensive insulin therapy in the reported RCTs (Table 4), though many critically ill patients included in these studies were sedated thus limiting the completeness of neurologic assessment. One study

reported a case of cardiac asystole related to treatment-induced hypoglycemia.(103) Several MICU studies found an excess mortality risk or extended length of stay among patients experiencing one or more episodes of severe hypoglycemia, though it is unclear if hypoglycemia was a causative factor or simply a marker for more severe disease.(10, 26, 28, 29)

Most of the observational studies and trials without health outcomes that we examined used more conservative blood glucose targets and found far lower rates of hypoglycemia (Table 5). There was little information about hypoglycemia rates in general medical/surgical ward patients where staffing ratios, patient heterogeneity and diet may vary substantially.

Few studies have examined the long-term consequences of hypoglycemia. Svensson et al investigated the association between in-hospital hypoglycemia and 2 year all-cause mortality in a cohort of over 700 diabetic patients admitted with acute coronary syndrome. Hypoglycemia, defined as blood glucose < 55 mg/dL, occurred in 6.4% of patients and was associated with an almost 2-fold risk of 2 year all cause mortality (HR 1.93, 95% CI 1.18 – 3.17). Though comorbidities and other prognostic factors were controlled for, the study was observational and cannot explain whether hypoglycemia was simply a marker of more severe disease, or whether treatment-induced hypoglycemia itself can lead to adverse consequences. Several small studies(104-106) have suggested that hypoglycemia may induce transient ischemia and catecholamine surges, but these effects have not been well-studied in large groups of inpatients with the power to investigate downstream clinical consequences.

Table 4. Frequency of hypoglycemia in randomized controlled trials

Study	Population	Intervention (T: treatment, C: control)	Glucose target (mg/dL)	Hypogly-cemia definition (mg/dL)	Frequency of hypoglycemia (% with one or more episode/persons studied) T v. C; Adverse events due to hypoglycemia
(22)	MICU	Insulin infusion in both groups*‡	T: 80-110mg/dl C: 180-200mg/dl	<40	18.7% v. 3.1%; AEs NR
(23)	MICU	Insulin infusion in both groups*‡	T: 110-140 C: 140-200	< 40	Total # of hypoglycemic episodes per group: 23 v. 23; AEs none
(29)	MICU	Insulin infusion in both groups*‡	T: 80-110 C: 180-200	<60	17% v. 4.1%, RR 4.11; 95% CI 2.21 – 7.63; More episodes (T v. C) described as life-threatening (5.3 v. 2.1%, p = 0.05) and requiring prolonged hospitalization (2.4 v. 0.3%, p = 0.05)
(16)	SICU	Insulin infusion in both groups*‡	T: 80-110mg/dl C: 180-200mg/dl	<40	5% v. 0.76%, RR 6.65; 95% CI 2.83 – 15.62; AEs NR
(24)	SICU	Insulin infusion in both groups*‡	T: 80-120mg/dl C: 180-220mg/dl	<60	32% v. 7.4%, RR 4.37; 95% CI 1.06 – 18.06; AEs none
(26)	Mixed MICU/SICU	Insulin infusion in both groups*‡	T: 80-110 C: 180-200	< 40	28.6 v. 3.1, p < 0.0001; ICU mortality in patients with hypoglycemia: 23.8% v.. 13.7%, P=0.02. Among pts with hypoglycemia, higher mortality in IIT v. control group (25.0 v. 12.5%)
(27)	Mixed MICU/SICU	Insulin infusion in both groups*‡	T: 72 – 108 C: < 198	< 40	41.3 v. 7.6%, p < 0.0001; One case of cardiac asystole associated with rescue dextrose infusion in hypoglycemic patient
(28)	Mixed MICU/SICU	Insulin infusion in both groups*‡	T: 80 – 110 C: 140 – 180	< 40	14.5 v. 3.9%; ICU mortality in patients with hypoglycemia: 32.2 v. 13.6% (p<.01)
(13)	Acute MI	T: Insulin infusion*† for 24 hours then multidose insulin regimen for at least 3 months. C: usual care	T: 126 - 198 mg/dL C: not specified	<54	15.0 v. 0%, p < .001; AEs NR
(46)	Acute MI	T: insulin infusion* for 24 h. C: usual care, supplemental insulin if glucose > 288 mg/dL	T: 72 - 180 mg/dL C: not specified	< 63	10.3 v. 1.8%, p = .02; AEs NR

Study	Population	Intervention (T: treatment, C: control)	Glucose target (mg/dL)	Hypogly-cemia definition (mg/dL)	Frequency of hypoglycemia (% with one or more episode/persons studied) T v. C; Adverse events due to hypoglycemia
(47)	Acute MI	T: Int 1 - insulin infusion*† and outpatient multidose insulin, Int 2 - insulin infusion only. C: usual care	T: 126 - 180 mg/dL C: not specified	< 54	Gr 1 v. Gr2 v. Gr3: 12.7 v 9.6 v 1.0; 1/3 of patients with hypoglycemia were symptomatic, no reported adverse clinical events
(50, 107)	Acute MI	T: adjustable high-dose GIK* C: usual care	T: 108 - 180 mg/dL C: not specified	NR	NR; AEs NR
(49)	Acute MI	T: adjustable high-dose GIK*† C: usual care	T: 128 - 198 mg/dL C: not specified	NR	0 v. 0; AEs NR
(48)	Ventricular fibrillation survivors	Insulin infusion in both groups, no protocol	T: 72 – 108 C: 108 – 144	< 54	18 vs 2; AEs NR
(61)	Stroke	T: Adjustable GIK infusion* C: saline infusion, insulin allowed if glucose > 306 mg/dL	T: 72 - 126 C: < 306	< 72 for > 30 mins	15.7, control group rate NR; AE s none
(63)	Acute brain injury	T: Insulin infusion‡ C: regular insulin if glucose >180 mg/dL; lower carbohydrate enteral formula	T: 80 – 120 C: < 180	< 40	6.4 vs 5.8; AEs NR
(62)	Neurosurgical ICU, subarachnoid hemorrhage	Insulin infusion in both groups	T: 80- 120 C: 80-220	NR	NR; AEs NR
(64)	Perioperative, CABG	T: Insulin infusion*† C: subcutaneous insulin	T: 150 - 200 C: 150 - 200	NR	NR
(65)	Perioperative, CABG	T: Intra-operative insulin infusion* C: saline infusion.	T: 70-100 C: not specified	<70	11.7% v. 6.2% (p=0.07); AEs NR

Study	Population	Intervention (T: treatment, C: control)	Glucose target (mg/dL)	Hypogly-cemia definition (mg/dL)	Frequency of hypoglycemia (% with one or more episode/persons studied) T v. C; Adverse events due to hypoglycemia
(66)	Perioperative, cardiac surgery	T: Intra-operative insulin infusion* C: IV bolus of insulin if BG >200; infusion if >250. Both groups received 24h postop insulin infusion in ICU	T: 80 -100 C: <200	< 60	1% v. 1% (p=1.0); AEs NR
(67)	Perioperative, CABG	T: Intra- and 12h postoperative GIK infusion* C: SQ sliding scale insulin	T: 126 - 200 C: <250	NR	NR; AEs NR
(68)	Perioperative, CABG	T: Intra- and 6h postoperative GIK infusion* C: D5W placebo infusion, with no glucose monitoring	T: 89-179 C: not specified	NR	NR; AEs NR

*Insulin infusion rate was based on current blood glucose

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

‡Factors included in insulin infusion rate calculations not reported, or protocol allows for dosing based on provder discretion

§Excess risk of severe hyperglycemia (BG>350 mg/dL) occurred in intervention group

Abbreviations: AEs = adverse events; NR = not reported

Table 5. Frequency of hypoglycemia in observational studies and trials not reporting health outcomes

CT, HC, or Obs. Study	Population	Factors included in insulin infusion rate calculations	Glucose target (mg/dL)	Mean glucose achieved mg/dL (SD)	Hypogly- cemia definition (mg/dL)	Frequency of hypoglycemia (% with 1+ episode/ persons studied)	Comments
Obs. (108)	MICU/SICU (no cardiothoracic surgery) 49.5% DM n = 90	Current glucose Rate of change in glucose Current insulin rate	75-120	133.5 (43.9)	<40 <60	0.09* 1.0*	All patients received continuous 10% dextrose solution. Mean BG achieved was higher than intended (133.6 mg/dL). All consecutive patients on protocol were included, but it is unclear how patients were chosen for protocol.
Obs. (109)	SICU (47% cardiothoracic surgery) 35.5% DM n = 276	Current glucose Rate of change in glucose	80 – 110	135.3 (49.9)	<60	1.5*	Included only glucose management service consult patients. Protocol did not achieve goal (mean capillary glucose 135.3 (49.9) mg/dL).
Obs. (110)	CTICU (2 centers) 34.0% DM N = 118	Current glucose Rate of change in glucose Current insulin rate	100 – 139	Non-DM patients: 120.0 (14.0) DM patients: 122.0 (9.0)	< 60	0.2*	Overall mean glucose achieved not reported. 73% within 80 – 139 mg/dL range.
Obs. (89)	ICU (66% med, 28% surg, 6% trauma) 21.4% DM n=2699	Current glucose	80-140	124.4 (51.3)	<40 <70	0.58* 1.78*	---
Obs. (111)	Burn-Trauma ICU 33% DM N = 30	Current glucose	< 120	115.9 – 119.5	< 60	5.0	All consecutive patients on protocol were included, but it is unclear how patients were chosen for protocol.
Obs. (112)	Trauma ICU % DM NR n = 24	Current glucose Rate of change in glucose Current insulin rate Estimated insulin sensitivity	< 110	118.9 (27.3)	<50 <70	0 2.0*	All consecutive patients on protocol were included, but it is unclear how patients were chosen for protocol.

CT, HC, or Obs. Study	Population	Factors included in insulin infusion rate calculations	Glucose target (mg/dL)	Mean glucose achieved mg/dL (SD)	Hypogly-cemia definition (mg/dL)	Frequency of hypoglycemia (% with 1+ episode/ persons studied)	Comments
CT (113)	Trauma ICU 8.6% DM N=243	Computerized algorithm Current glucose Current insulin rate	80-110	116.0 (37.0)	<40	7.8	Computer algorithm was compared to paper-based protocol with which hypoglycemia rate was nonsignificantly higher (11%, p = 0.25)
HC (114)	MICU/SICU (5 ICUs across 2 centers) % DM NR n = 2398	Computerized algorithm; current glucose; rate of change in glucose; Estimated insulin sensitivity	80 – 110	106.5 (39.1)	< 50 < 70	0.4* 5.0*	Treating physicians referred patients for infusion protocol. Each patient's estimated insulin sensitivity was part of the titration algorithm.
HC (98)	MICU/SICU 32.0 % DM n = 44	Current glucose Rate of change in glucose	90-144	128.0 (32.0)	<40 <72	0.2* 3.8*	All consecutive patients on protocol were included, but it is unclear how patients were chosen for protocol.
HC (115)	CTICU 32.0 % DM N = 168	Current glucose Current insulin rate Presence of diabetes or steroids	80 - 150	NR % glucose within range: 61	< 40 < 65	7.1 16.7	Patients received no enteral or parenteral nutrition for first 24 hours post-operatively

*rate reported as # hypoglycemic occurences/# total glucose measurements
Abbreviations: CT = Controlled trial; HC = study using historical control; Obs = Observational study

KEY QUESTION #3. What are the most effective and safest means of lowering blood glucose in hospitalized patients?

Insulin infusions

We evaluated three recent fair-quality systematic reviews,(116-118) of studies evaluating the effects of different insulin infusion protocols (IIPs) on glycemic control. There were no completed studies directly comparing these protocols, though we found two in-progress comparative effectiveness trials.(34, 35) The protocols differed in terms of patient characteristics, target glucose ranges, the time required to achieve the target glucose, the incidence and definition of hypoglycemia, the rationale or algorithm used for adjusting the insulin rates, the methods used to assess effectiveness and the methods of glucose monitoring. One review stressed that, given this variety of factors, each institution should individualize its approach to protocol implementation based on its patient population as well as its institutional and provider resources.(116) Another review focusing on ICU protocols used computer simulations to model patterns of insulin administration and similarly concluded that the variability amongst protocols precludes dissemination of a single protocol.(118) The authors suggest the better protocols incorporate bolus insulin doses, account for the direction and rate of glucose change, and make allowances for "off-protocol" adjustments. A third review concludes protocols that incorporate factors such as the rate of glucose change, the current blood glucose and insulin rate may be more effective than simple sliding scale infusion protocols in lowering blood glucose while maintaining relatively low rates of hypoglycemia, though this conclusion is not based on direct comparisons of protocols.(117)

Protocols used in observational studies and trials not examining health outcomes that we assessed are summarized in Table 5.(89, 98, 108-111, 113-115, 119, 120) Protocols used in the efficacy trials varied across subpopulations as detailed in Tables 1, 2, and 3. In general, protocols that were successful in targeting normoglycemia were also associated with a substantially elevated risk of hypoglycemia (Table 4). One observational study found a computerized insulin infusion protocol which incorporated factors such as insulin sensitivity achieved its normoglycemic target with relatively low rates of hypoglycemia.(114)

Subcutaneous insulin

Subcutaneous sliding scale insulin (SSI) regimens have a number of theoretical disadvantages when used as the sole method for inpatient glycemic control and authors have called for a reduction in the widespread use of sliding scale subcutaneous insulin.(121) A limited body of small, mainly single-center controlled trials suggest subcutaneous sliding scale insulin regimens may be relatively ineffective in targeting lower blood glucose. A prospective, multi-center trial compared a basal bolus regimen with SSI in general medical ward patients with type 2 diabetes and found the basal-bolus regimen led to longer duration of time within the target glucose range, from 38% to 66%, with no differences in the incidence of hypoglycemia.(122) A trial in patients with a glucose of more than 144 mg/dl after Roux-en-Y gastric bypass randomized the subjects

(n=81) to SSI or insulin glargine.(123)   Mean glucose was 154 versus 134 mg/dl in the SSRI and glargine groups, respectively, p<0.01. Hypoglycemia defined as glucose <60mg/dl occurred in only 3 of the 926 readings (2 in glargine and 1 in SSI). A randomized controlled trial of 153 diabetic patients admitted to a family medicine service found that the addition of a subcutaneous sliding scale insulin regimen to routine diabetes medications (oral agents or scheduled insulin) led to no difference in the time spent in the hyper- or hypoglycemic range (124). A second trial randomized 93 post-operative cardiac surgery patients to either an insulin infusion or to a subcutaneous sliding scale regimen. Mean blood glucoses of less than 200mg/dl occurred in more often in the infusion group (28.6 to 64.7%, p<0.001). (64).

SUMMARY AND DISCUSSION

Observational and biologic plausibility studies suggest an association between hyperglycemia and worsening health outcomes in hospitalized patients. However, trial evidence of the efficacy of tight, compared to less tight, glycemic control strategies using IIT in various inpatient subpopulations is limited. Current evidence does not conclusively support existing guideline recommendations to routinely maintain a blood glucose ≤ 110 mg/dL in ICU patients, and there is very little data on the health outcome benefits of achieving more moderate blood glucose control (eg – 110 – 180 mg/dL) compared to less strict targets in various inpatient subpopulations.(125)

Single-center evidence from one group of investigators had shown a mortality and morbidity benefit from IIT in subgroups of patients requiring prolonged ICU stays, (16, 22) while our meta-analysis of seven ICU studies showed that achieving normoglycemia using a relatively simple insulin infusion protocol had no effect on short-term mortality but did substantially increase the risk of hypoglycemia.

Several factors may account for the discrepancy in results between the Van den Berghe trials and data from other centers. The aggressive use of parenteral nutrition, especially in the SICU study showing benefit,(16) differs from practice in many centers.(126) Parenteral nutrition has been associated with hypertriglyceridemia, insulin resistance, increased infection rates and mortality, leading to speculation that the observed benefits of intensive insulin in this population actually reflect a reduction in harm from aggressive nutrition practices.(127-131) It is unclear whether the control group mortality rate in this study was higher than expected. The authors of the study have reported mortality rates lower than expected based on the EuroSCORE of the cardiac surgery patients, though a review of EuroSCORE performance characteristics found that scores in the range reported in the trial may underestimate mortality by almost 3 %.(85, 132) On the other hand, a post-hoc analysis using combined data from both the Van den Berghe SICU and MICU studies found a mortality benefit in subgroups receiving the highest and lowest amounts of parenteral glucose.(45)

The exclusive use of arterial blood sampling in the Van den Berghe SICU study also has implications for the applicability of results across diverse ICU settings since very few medical centers use arterial blood sampling to monitor glucose control. Capillary blood sampling is more commonly used and is less dependable in critically ill patients, due to a number of factors including vasopressor therapy, perfusion pressure, pH, and others.(133-135) There is a very low rate of agreement between capillary and whole blood glucose samples, particularly in the hypoglycemic range.(99, 136)

Finally, this SICU study had a relatively low event rate and was stopped early for benefit with less than half the projected number of participants recruited, raising the possibility that the reported treatment effect was larger than the "true" treatment effect.(137) Indeed, the effect size decreased substantially, though remained significant, after the authors adjusted for the repeated interim analyses which had prompted the early recruitment discontinuation.(138)

Three of the trials that failed to show a mortality benefit from achieving normoglycemia in critically ill patients were stopped early due to an excess risk of hypoglycemia in the intervention groups, thus raising the possibility that the lack of observed benefit may actually reflect inadequate power to detect a health benefit.(26, 28, 29) However, the trials did not demonstrate a consistent trend towards benefit and combining these studies in our meta-analysis should increase the power to detect a health benefit if one were present. Furthermore, the inability to implement the insulin infusion protocol in various settings without high rates of hypoglycemia may underscore problems with feasibility and generalizability across institutions. It is unclear whether the high hypoglycemia rates are due to insulin infusion protocol characteristics, staffing characteristics, patient comorbidities, or the very tight glucose target itself. Since the health consequences of insulin-induced hypoglycemia in hospitalized patients are as yet unclear, interventions associated with high rates of hypoglycemia should demonstrate compelling benefit across a variety of institutions before being widely implemented.

The current body of trial evidence in perioperative patients is heterogenous and inconclusive. The most dramatic evidence of health outcome benefits from tight glycemic control in the perioperative setting comes from retrospectively controlled observational studies with methodologic flaws.(14, 15, 88) Well-designed controlled clinical trials in this population would add substantially to our body of knowledge.

Evidence supporting the efficacy of tight glycemic control in myocardial infarction populations is similarly limited and inconsistent. One trial showed a mortality reduction from moderate inpatient and outpatient glucose control in severely hyperglycemic myocardial infarction patients, but this older trial was conducted prior to the widespread use of cholesterol lowering therapies and mechanical revascularization techniques.(13) More recent studies have been negative, but methodologic considerations limit the strength of conclusions drawn from these trials.(46, 47) There is very little fair-good quality empiric data in general surgical or medical ward settings, or in stroke patients.

The ability to achieve glucose targets safely is likely to depend on multiple factors including the titration characteristics of the protocol, patient characteristics, as well as staffing ratios and provider acceptance. A number of mainly single-center observational studies and trials that did not examine health outcomes found relatively low rates of hypoglycemia. Characteristics of these studies suggest there may be several variables responsible for the lower rates of hypoglycemia: modest glucose targets (approximately 100 – 180 mg/dL), an iterative, institution-based protocol development and deployment process, and insulin protocol titration innvovations. There is relatively little information on insulin protocols that have achieved normoglycemic targets with low rates of hypoglycemia.

Limitations

Our review has several potential limitations. We did not exclude individual trials based on quality rating alone. Thus the strength of our conclusions is inherently limited by the quality variation among included studies. We did make an effort to note particular methodologic limitations, and each study was closely reviewed for overall quality using a rigorously developed approach. The studies included in our quantitative synthesis differed in some important respects: population studied and the attendant differences in event rates (ie – SICU v. MICU), interval of outcome reporting, and glucose monitoring method. The applicability of results from the included studies is limited by a variety of factors: patient characteristics, event rates, concomitant therapy, institution characteristics, and monitoring methodology. Most of these were single-center studies, yet the relative success or failure of an insulin-based intervention is likely to depend, to a significant extent, on systems characteristics which are unique to a given institution or health system. Finally, the included trials relied on glucose measurements from a defined reference time, rather than 24 hour glucose levels achieved, thus potentially obscuring the inherent variability in glucose control through the course of intensive care.(139)

Future research recommendations

The bulk of efficacy evidence comes from studies in critically ill populations. Even amongst these studies, the patient characteristics, underlying event rates, and risk of hypoglycemia varied substantially. There is almost no empiric data available to guide glucose management practice in non-ICU settings. Future trials should enroll general medical and surgical ward patients.

The current body of evidence has not defined a glucose threshold that should prompt more aggressive intervention in various subpopulations. Given the observed risk of hypoglycemia in patients exposed to insulin therapy designed to normalize blood glucose, and the relatively low hypoglycemia rates in observational studies using less strict targets, the efficacy of higher glucose targets should be examined prospectively in various subpopulations.

As discussed, there are a variety of insulin titration protocols. Those that take into account a patient's insulin sensitivity and rate of glucose change are theoretically attractive, but future studies should rigorously evaluate these protocols and compare them to simpler protocols.

Individual institutions describing their experience implementing intensive insulin protocols suggest that the increase in nursing workload and fear of hypoglycemia were significant, but surmountable, barriers to implementation.(140, 141) The cost of attaining normal blood glucose in critically ill patients is unclear. Van der Berghe et al found that IIT targeted to normoglycemia was cost-saving using data from their SICU study.(142) Cost analyses using more recent data have not yet been conducted. Since insulin therapy can be resource intensive, future studies should examine the real cost and the

opportunity cost of such treatment, as well as patient and staff acceptance across a variety of settings.

Transitions of care (e.g., ICU to ward, hospital to home) are fraught with uncertainty and there is likely a high rate of adverse events during these transitions, including an increased risk of post-discharge hypoglycemia.(143, 144) Studies should examine the safest and most effective ways to adapt insulin management in patients transitioning from one level of care to another.

There is a relative dearth of evidence evaluating the safety and efficacy of non-infusion based insulin protocols. Trials evaluating subcutaneous insulin protocols with moderate glucose targets in the medical ward setting would be of great use to clinicians.

Finally, newer technologies may enhance the safety and efficacy of inpatient glycemic management. Innovations such as continuous blood glucose monitoring systems and computer-based algorithms should be evaluated in various inpatient subpopulations.

CONCLUSIONS

The use of intensive insulin therapy to achieve normoglycemia in critically ill patients does not clearly result in health outcome benefits and is associated with high rates of hypoglycemia. More moderate blood glucose control to targets above the normoglycemic range can likely be safely achieved, though the health outcome benefit of this practice has not been well studied. Tables 6 and 7 summarize the findings of this systematic review for each key question.

Table 6. Summary of Systematic Evidence Review, Key Question 1: Does strict glycemic control compared to less strict glycemic control improve final health outcomes in the following patients?

Patient subgroup	Type of Evidence	Quality (GRADE) of Evidence	Comments	Net effect*
Acute myocardial infarction patients	2 systematic reviews; 10 RCTs	High = Further research is unlikely to change our confidence on the estimate of effect.	We found good quality evidence that insulin used as part of a fixed-dose glucose-insulin-potassium infusion does not consistently improve final health outcomes in acute myocardial infarction patients, and may increase short-term mortality.	(–)
		Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	Several trials examined tight glycemic control using adjustable dose insulin-based regimens, and failed to demonstrate consistent evidence of benefit in acute myocardial infarction patients. Variation in trial design, achievement of recruitment goals, glucose level achieved, and concomitant therapy for myocardial infarction limit the strength of this conclusion.	(÷)
Acute stroke patients	3 RCTs	Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate	There is very little good-quality evidence investigating tight glycemic control in patients who have suffered a cerebrovascular accident.	(÷)
Patients in medical and/or surgical intensive care units	8 RCTs	Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	Single-center evidence had initially shown a mortality and morbidity benefit from IIT in subgroups of patients requiring prolonged ICU stays, but the applicability of these data to other ICUs may be limited and subsequent trials have not confirmed this benefit. Our meta-analysis found the use of intensive insulin therapy to achieve normoglycemia had a neutral effect on short-term mortality, but increased the risk of hypoglycemia more than five-fold.	(÷)

Patient subgroup	Type of Evidence	Quality (GRADE) of Evidence	Comments	Net effect*
Perioperative patients	1 systematic review; 5 RCTs	Low = Further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	Overall, there is no clear evidence showing a benefit of tight glycemic control strategies in the perioperative setting, but the trial evidence is methodologically limited. The studies varied widely in design, blood glucose levels attained, and in the inclusion of patients with diabetes, limiting the comparability of results across studies. Several studies were underpowered to evaluate health outcomes. The best quality evidence of benefit comes from the single-center SICU study discussed in the ICU section.	(÷)
General medicine ward patients	None	Very Low = Any estimate of effect is very uncertain.	There were no studies evaluating a tight glycemic control strategy to less tight glycemic control in general medical ward patients.	(0)

* (+) benefit; (–) harm; (÷) mixed findings/no effect; (0) no evidence

Table 7. Summary of Systematic Evidence Review, Key Questions 2 and 3.

KQ#	Key question	Type of Evidence	Grade of Evidence	Comments
2	What are the harms of strict glycemic control in the above subpopulations?	1 systematic review; 15 RCTs; 12 observational studies	Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	There is a considerable risk of hypoglycemia in medical ICU patients treated with intensive insulin protocols designed to normalize blood glucose. This risk was lower in surgical ICU patients receiving similar therapy, and in myocardial infarction, stroke, and perioperative patients in whom the target glucose level was generally not aimed at strict euglycemia. Observational studies suggest a moderate glycemic control can be safely achieved with modest glucose targets and variations in protocol design. Some studies suggest hypoglycemia in critically ill patients may be associated with excess mortality risk. The short-term and long-term consequences of hypoglycemia have not been well-studied.
3	What are the most effective and safest means of lowering blood glucose in the above subpopulations?	2 systematic reviews; 2 RCTs	Low = Further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	A number of insulin infusion protocols (IIPs) have been evaluated, but comparative effectiveness data are lacking. Protocols with moderate glucose targets appeared most feasible and were associated with the lowest hypoglycemia risk. Dynamic protocols that take into consideration the patient's insulin sensitivity and that have guidelines built into them to help prevent hypoglycemia may be preferred. The safe and effective introduction of insulin infusion protocols in a given institution is likely an iterative and multi-disciplinary endeavor. Basal bolus subcutaneous insulin regimens may be more effective than, and at least as safe as, sliding scale regimens, though there is very limited evidence comparing methods of blood glucose control in ward patients.

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