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Insulin Therapy and In-Hospital Mortality in Critically Ill Patients: Systematic Review and Meta-analysis of Randomized Controlled Trials

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ABSTRACT. *Background:* Hyperglycemia is common in critically ill hospitalized patients and has been associated with adverse outcomes, including increased mortality. In this review, we examine the effect of insulin therapy on mortality in critically ill patients. *Methods:* We updated our previous systematic review and meta-analysis to include recently published trials that report data on the effect of insulin therapy initiated during hospitalization on mortality in adult patients with a critical illness. We also include a short primer on the methods of systematic reviews and meta-analyses, outlining the specific steps and challenges of this methodology. We performed an electronic search in the English language of MEDLINE and the Cochrane Controlled Clinical Trials Register and a hand search of key journals and relevant review articles for randomized controlled trials that reported mortality data on critically ill hospitalized adult patients treated with insulin (regardless of method of administration). *Results:* We identified 38 relevant studies that entered the analysis. We found that therapy with insulin in adult patients hospitalized for a critical illness, other than hyperglycemic crises, may decrease mortality in certain groups of patients. The beneficial effect of insulin was evident in the surgical intensive care unit (relative risk [RR], 0.58; confidence interval [CI], 0.22–0.62) and in patients with diabetes (RR, 0.76; CI, 0.62–0.92). There was a trend toward benefit in patients with acute myocardial infarction (RR, 0.89; CI, 0.76–1.03). Targeting euglycemia appears to be the main determinant of the benefit of insulin therapy (RR, 0.73; CI, 0.57–0.94). *Conclusions:* Insulin therapy in adult patients hospitalized for a critical illness, other than hyperglycemic crises, may decrease mortality in certain groups of patients. (*Journal of Parenteral and Enteral Nutrition* **30:**164–172, 2006)

Hyperglycemia is common in critically ill hospitalized patients, and it is associated with adverse outcomes, including an increased risk of in-hospital mortality.[1,2] Insulin administration has been used in patients hospitalized with critical illnesses, other than hyperglycemic crises, to improve clinical outcomes. Therapy with insulin has been studied extensively in the setting surrounding an acute myocardial infarction (AMI).[3] In the majority of these trials, insulin has been administered as a glucose-insulin-potassium (GIK) infusion, with conflicting results. The frequently cited study by van den Berghe et al,[4] a randomized clinical trial in the surgical intensive care unit (ICU) that showed a marked decrease in mortality in patients randomized to tight glycemic control with insulin, has generated remarkable interest in the topic of insulin therapy in critically ill patients. Over the last few years, professional organizations have called for insulin therapy aiming at tight glycemic control in all hospitalized patients, and multiple articles have been published describing a variety of protocols aiming at achieving tight glycemic control in the ICU.[5] However, the role of insulin therapy in critically ill patients remains unclear. The clinical setting and patient population where insulin therapy may be of benefit, the optimal method, dosing, and timing of insulin administration are issues that remain unsettled.

We recently published a systematic review and meta-analysis examining the effect of insulin therapy initiated during hospitalization on mortality in adult patients hospitalized for a critical illness.[6] The details of the methodologies of this meta-analysis can be found in that publication. In this review, we have updated our previous systematic review to include additional randomized trials that have been recently published. We also include a short primer on the methods of systematic reviews and meta-analyses. For the remainder of this article, unless where it is specified, we will use the term *systematic review* to include meta-analysis.

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METHODOLOGY OF SYSTEMATIC REVIEWS

The fundamental premise of evidence-based medicine is that a comprehensive, unbiased assessment and synthesis of relevant evidence will yield the most reliable information to inform health care practices. Sys-

TABLE I
Steps/challenges of systematic reviews and meta-analyses and how these are addressed in this review

Step/Challenge	Solution
Developing a protocol	The review included experts in diabetes (Pittas, Siegel) and the methodology of evidence-based medicine (Lau, Pittas).
Formulating a research question	Formulated a specific research question that is answerable and clinically important: What is the effect of insulin therapy on short-term (in-hospital or 30-day) mortality in critically ill hospitalized adult nonpregnant patients?
Systematic review of the literature (minimize publication, author and other biases)	We searched in MEDLINE and Cochrane for articles published in the English language.
Quality assessment of the included studies	We collected data on allocation generation, allocation concealment, placebo-controlled status, blinding, and intention-to-treat analysis.
Statistical method for combining data to provide an overall estimate and confidence intervals for the treatment effect	To combine data, we used the random effects model, which considers both the between-study variance and the within-study variance of the included studies.
Sensitivity analysis	We performed clinically relevant subgroup analyses.

tematic review and meta-analysis are essential tools of evidence-based medicine. These methods follow precise steps, and each step has its own challenges. These challenges are summarized in Table I, and below we discuss how we addressed these issues in our present review.

Developing a Protocol

Conducting systematic reviews and meta-analyses requires specific methodological knowledge. Collaborative efforts between clinical and methodological experts enhance the quality and usefulness of the review. Most meta-analyses are retrospective analyses of published data; a prospectively formulated protocol that is carefully followed will minimize bias. A protocol should include the specific research question(s), literature search strategy, selection criteria, approach to critical appraisal of the studies, method of statistical analyses, and interpretation of the results.

Formulating Research Question(s)

Formulating an answerable and clinically important research question is the most critical step in any systematic review. For systematic reviews of interventions, the PICO (Population, Intervention, Comparator, Outcome) approach has been found to be very useful to define research questions.[7] The research question thus formulated will guide every phase of the review process, from searching the literature to interpreting the results. An example of a well-formulated question is: What is the effect of insulin therapy on short-term (in-hospital or 30-day) mortality in critically ill hospitalized adult nonpregnant patients?

Literature Search

A systematic review should be comprehensive. However, the literature search and selection of articles are often constrained by available resources. Literature search strategy and selection of inclusion language for the review should be guided by careful forethought. A literature search generally begins with a search of the MEDLINE database because it is free and readily available. Many authors also search the Cochrane Library's Controlled Clinical Trials Registry. For most mainstream medical topics, the incremental yield of searching additional databases such as EMBASE is minor and seldom affects the overall conclusion. The usefulness of including non–English-language articles is also topic dependent. For certain topics, using all languages may actually result in a biased assessment of the overall effect if certain countries publish only positive results.

For our review, we extended our previous search of MEDLINE (to June of 2005) and the Cochrane Library's Controlled Clinical Trials Register (to third quarter of 2005) for randomized controlled trials of insulin in critically ill hospitalized adult patients. Critically ill patients were defined as those admitted to any ICU or any patients with AMI or stroke. The following key search terms were used: *insulin*, *glucose-insulin-potassium*, *GIK*, *hospital*, *intensive care unit*, *hyperglycemia*, *coronary artery bypass*, *CABG*, *acute myocardial infarction*, *stroke*, *mortality*, *human*, *clinical trial*. Our search did not specifically include studies with "sepsis" or "other infection" as an inclusion criterion. However, given that many studies we included had patients in ICUs, sepsis was likely a medical condition. We excluded studies with pregnant women and children, and we limited our search to articles published in the English language. Bibliographies of all relevant retrieved articles, relevant recent review articles, personal reference lists and abstracts published in proceedings were also searched manually for additional articles. Articles identified from the search were judged relevant if they reported original data from randomized controlled clinical trials of critically ill hospitalized adult patients that were treated with insulin (regardless of type and form) while hospitalized in which mortality outcomes were reported in relation to insulin therapy. Patients with AMI, those undergoing coronary artery bypass grafting, and those in ICUs were defined as having a critical illness.

The following data were collected from each report: year published, source of publication, country of origin, clinical condition or hospital setting, subject eligibility criteria (presence of diabetes), baseline characteristics of study population (sample size for intervention and control, age, % male), intervention (formulation and dose of insulin, delivery method, duration of therapy and whether a glucose goal for insulin therapy was defined), duration of follow-up, mortality outcome

(number of deaths in each arm and causes), adverse events (eg, hypoglycemia), and methodological quality (allocation generation, allocation concealment, placebo-controlled status, blinding, and intention-to-treat analysis). For trials with duplicate publications, data from the most recent one were used.

Assessing the Quality of Studies

It is important to ensure that conclusions drawn from systematic reviews are based on good-quality studies. However, the evaluation of study quality is not straightforward. Quality scores based on design and conduct of studies have been found to yield inconsistent results.[8,9] Another problem is that the assessment of study quality is based on author-supplied information in the article. However, the absence of information in the paper does not mean that a specific feature of the trial was not performed.

Combining Data

Meta-analysis is a systematic review in which the authors have decided that sufficient data are available from individual studies to address a specific question and have combined them to provide an overall answer. The most common form of meta-analysis is using a fixed or random-effects model to calculate an overall estimate. Both continuous data (eg, hemoglobin A1c) and dichotomous data (eg, odds ratio, risk ratio, or risk difference of being dead or alive) could be used in a meta-analysis.[10] A fixed-effect model weighs studies by their size and the number of events. A random-effects method weighs studies by a combination of size and events and across studies differences. The random-effects model tends to give more conservative results (ie, wider confidence interval) when there is heterogeneity across studies and is generally recommended.

For the present meta-analysis, the main outcome was short-term mortality (in-hospital or within 30 days after discharge) in relation to insulin therapy. Total number of subjects with reported outcomes in each intervention or control arm was abstracted and entered in the meta-analysis. Each study contributed 1 result to the meta-analysis. Relative risk of mortality reduction was the primary measure of treatment effect. Relative risks from each included trial were combined using a random-effects model.

Exploring Heterogeneity and Performing Sensitivity Analysis

Differences of results across several studies in a meta-analysis are to be expected, and efforts should be made in the analyses to explore these differences. A number of methods have been developed, including subgroup analysis and meta-regression.[11] In a subgroup analysis, studies are segregated according to clinically plausible reasons (eg, patients' characteristics, study design or protocol differences) that may give rise to different study results.

Meta-analyses are then performed on these subgroups and their results compared. A meta-regression describes the relationship between a variable of interest (eg, mean level of cholesterol reduction in a trial) with the outcomes (eg, mortality) across several studies. The unit of analysis is the study. Subgroup meta-analyses should be interpreted carefully because these comparisons are not being made within the same study. Results from meta-regression may also be biased because of selective reporting of covariates.

In the present review, we performed subgroup analyses in studies that differed in the following parameters: method of insulin administration (GIK *vs* non-GIK), maintenance of euglycemia as the target of insulin therapy, clinical condition or hospital setting, and inclusion of patients with diabetes.

We did not rate the quality of individual studies in the meta-analysis, because quality-rating systems that have been proposed to rate the quality of individual studies has not been found to be reliable.[9] Furthermore, individual factors used to assess quality also have not been found to be consistently related to the magnitude of effects size.[8]

Publication Bias

Unpublished studies with negative results threaten the validity of a meta-analysis.[12] Methods have been proposed to detect or to adjust for unpublished studies. However, these methods are based on certain assumptions that may not be true. Funnel plot is a popular method used by many authors to detect publication bias. However, the validity of this method has been challenged.[13] The only foolproof method to reduce the risk of publication bias is the registration of all human clinical trials before their conduct, which is now a requirement for publication in major medical journals.[14]

RESULTS

Since our last systematic review,[6] we identified 5 additional trials that met our search criteria.[15–19] One study[20] provided updated information to a previously reported study,[21] which we removed from this review. For the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction-2 (DIGAMI-2), a large trial on glucose-insulin infusion in patients with diabetes admitted for AMI,[18] we were unable to obtain 30-day mortality data, even after contacting the investigators; therefore, that study did not enter our meta-analyses. Thus, 4 new studies[15–17,19] were added to our previously identified trials,[4,22–54](Table II) and all data were incorporated in the present meta-analysis.

In-hospital mortality among the studies ranged from 0% to 32% (median 9.6%). In approximately one-third of the studies that reported cause of death, cardiac-related causes (arrhythmias, heart failure) were most common in patients admitted with myocardial infarction. In the surgical ICU, multiple-organ failure with sepsis was the main cause of death. A statistically significant reduction in overall mortality compared with the control group was seen in only 2 studies.[4,22] The remaining studies showed a beneficial trend or no

TABLE II
Characteristics of included studies

Study (First Author)	Year	Total # Participants	Properly Randomized	Hospital Setting	Reason for Admission	Mortality Rate in Controls (%)	Intervention		Glucose Goal?	Reperfusion Therapy (Thrombolysis or PTCA)	Diabetics Excluded?
							Type	Duration			
1. Mittra	1965	170	Yes	Ward	AMI	28.2	GIK	14 d	No	No	IDDM only
2. Lundman	1965	26	No	Ward	AMI	7.7	GIK	72 h	No	No	Yes
3. Sievers	1966	104	No	Ward	AMI	20.4	GIK	72 h	No	No	No
4. Autio	1966	301	No	Ward	AMI	10.3	GIK	72 h	No	No	No
5. Pilcher	1967	102	NR	Ward	AMI	22.6	GIK	14 d	No	No	Yes
6. Malach	1967	101	No	Ward	AMI	14.8	GIK	72 h	No	No	No
7. Pentecost	1968	200	Yes	CCU	AMI	16.0	GIK	48 h	No	No	IDDM only
8. MRC	1968	840	Yes	Ward	AMI	24.4	GIK	14 d	No	No	Yes
9. Iisalo	1969	256	No	Ward	AMI	18.2	GIK	14 d	No	No	Yes
10. Hjermann	1971	198	Yes	Ward	AMI	16.7	GIK	10 d	No	No	Yes
11. Prather	1976	30	No	CCU	AMI	8.3	GIK	48 h	No	No	No
12. Heng	1977	24	NR	CCU	AMI	0.0	GIK	12 h	No	No	Yes
13. Lolley	1978	391	NR	OR	CABG	1.1	GIK	44 mo	No	NA	Yes
14. Rogers	1979	50	NR	CCU	AMI	14.8	GIK	2 d	No	No	IDDM only
15. Salerno	1980	60	NR	OR	CABG	0.0	GIK	8 h	No	NA	Yes
16. Mantle	1981	85	NR	CCU	AMI	9.1	GIK	48 h	No	No	IDDM only
17. Whitlow	1982	28	Yes	CCU	AMI	0.0	GIK	48 h	No	No	IDDM only
18. Oldfield	1986	43	Yes	OR	MVR	8.7	GIK	12 h	No	NA	No
19. Gradinac	1989	22	No	SICU	CABG	9.1	GIK	48 h	No	NA	No
20. Davies	1991	69	NR	CCU	AMI	17.6	Insulin IV	24 h	Yes	NR	No
21. Brodin	1993	14	NR	OR	CABG	0.0	GIK	NR	No	NA	No
22. Malmberg	1995	620	NR	CCU	AMI; diabetes	11.1	Insulin IV/SQ	10 d	Yes	Thrombolysis	No
23. Lazar	1997	30	No	OR	CABG	0.0	GIK	>12 h	No	NA	Yes
24. Diaz	1998	407	Yes	CCU	AMI	11.5	GIK	24 h	No	Thrombolysis or PTCA	No
25. Ceremuzynski	1999	954	Yes	CCU	AMI	4.8	GIK	24 h	No	Thrombolysis	IDDM only
26. Besogul	1999	30	NR	OR	MVR	6.7	GIK	12 h	No	NA	No
27. van den Berghe	2001	1548	Yes	SICU	Mechanical ventilation 60% cardiac surgery patients	8.0	Insulin IV	3 d	Yes	NA	No
28. Ulgen	2001	72	NR	CCU	AMI	2.6	GIK	24 h	No	Thrombolysis	No
29. Szabo	2001	20	NR	OR	CABG	0.0	GIK	6 h	Yes	NA	No
30. Smith	2002	44	Yes	OR	CABG	0.0	GIK	10 h	Yes	NA	IDDM only
31. Groban	2002	381	NR	OR	CABG	1.6	Insulin IV	2 h	Yes	NA	Yes
32. Lell	2002	41	Yes	OR	CABG	0.0	GIK	12 h	No	NA	No
33. Rao	2002	1127	Yes	OR	CABG	2.3	Insulin IV	1 h	No	NA	No
34. Van der Horst	2003	940	Yes	CCU	AMI	5.8	GIK	12 h	Yes	PTCA	No
35. Pache	2004	312	Yes	CCU	AMI	3.2	GIK	24	No	Thrombolysis or PTCA	No
36. Lazar	2004	141	Yes	OR	CABG	0	GIK	12 h	Yes	NA	No
37. Mehta	2005	20,201	Yes	CCU	AMI	9.7	GIK	24 h	No	Thrombolysis or PTCA	IDDM only
38. Malmberg*	2005	1253	Yes	CCU	AMI, diabetes	NR	Insulin IV/SQ	24 h	Yes	Thrombolysis or PTCA	No

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CCU, coronary care unit; GIK: glucose-insulin-potassium solution; IDDM, insulin requiring diabetes mellitus (includes type 1 or type 2); MVR, mitral valve replacement; NA, not applicable; NR, not reported; OR, operating room; PTCA, percutaneous transluminal coronary angioplasty; SICU, surgical intensive care unit; SQ, subcutaneous.
*Data on 30-day mortality were not available from the study by Malmberg et al (2005), and data from this study were not included in the meta-analyses.

TABLE III
Subgroup analyses of the effect of insulin therapy on mortality in critically ill hospitalized patients

	No. of Trials	No. Patients Analyzed	Mortality Rate Control Group (%)*	Relative Risk (95% CI) for Mortality
Method of insulin administration				
Non-GIK[4,18,41,43,52,54]†	6	3745	6.4	0.73 (0.56–0.95)
GIK (all medical conditions)[15,17,19,20,22–40,42,44–47,49–51,53]	32	26234	9.98	0.96 (0.89–1.03)
GIK in AMI[15,17,19,22–33,35,37,38,45,46,50]	21	25401	12.1	0.89 (0.77–1.03)
GIK in cardiac surgery[20,34,36,39,40,42,44,47,49,51,53]	11	833	3.0	1.24 (0.48–3.17)
Glucose goal				
Yes[4,15,18,20,41,43,49,53,54]	8	3760	7	0.73 (0.57–0.94)
No[17,19,22–40,42,44–47,50–52]	29	26219	9.8	0.94 (0.85–1.04)
Clinical condition or hospital setting				
AMI[15,17–19,22–33,35,37,38,41,43,45,46,50]	24	26090	10.4	0.89 (0.76–1.03)
Cardiac surgery[20,34,36,39,40,42,44,47,49,51–54]	13	2341	1.8	1.09 (0.61–1.93)
Surgical intensive care unit[4]	1	1548	8.0	0.58 (0.22–0.62)
Inclusion of patients with diabetes‡				
All patients with diabetes included[4,15,17,20,24–26,32,39–43,45,47,49–52]	19	5939	7.0	0.76 (0.62–0.92)
Patients with diabetes included except IDDM[4,15,17,19,20,22,24–26,29,32,35,37–43,45–47,49–53]	27	6170	9.3	0.86 (0.73–1.02)
Patients with diabetes excluded[23,27,28,30,31,33,34,36,44,54]	10	2308	13.1	0.91 (0.75–1.11)

AMI, acute myocardial infarction; CI, confidence interval; GIK, glucose-insulin-potassium solution; IDDM, insulin requiring diabetes mellitus (included type 1 or type 2).
*Overall weighted control rate.
‡Patients with severe or unstable hyperglycemia on admission where insulin therapy was indicated were excluded.
†Data on 30-day mortality were not available from the study by Malmberg et al (2005), and data from this study were not included in the meta-analyses.

benefit from insulin therapy, with the exception of the study by Ceremuzynski et al[46] where total mortality was higher in the insulin (administered as GIK) than the control group, primarily due to noncardiac causes.

The reported methodological quality of the studies included in the analysis varied widely. Method of allocation generation, allocation concealment, blinding status, and intention-to-treat analysis were fully described in very few manuscripts. If we applied strict criteria for inclusion that included appropriate randomization (sequence generation, allocation concealment, and implementation), double-blind status, and statistical methods that were clearly stated in the manuscripts, only 2 studies would satisfy these criteria.[4,46]

SUBGROUP ANALYSES

Although all trials included in this review shared the use of insulin in critically ill hospitalized patients, they used varying methods of insulin administration in diverse clinical settings (Table II). Therefore, we performed clinically relevant subgroup analyses to determine the effect of changing baseline parameters on mortality and to gain insight into the appropriate use of insulin in subsets of critically ill patients.

Method of Insulin Administration, GIK vs *Non-GIK*

GIK. In the majority of the trials we identified and included in this review, insulin was administered as a GIK solution in patients with AMI or in the perioperative cardiac surgery setting. The concept of altering the metabolic milieu during myocardial ischemia with a GIK solution was developed more than 4 decades ago and has been studied extensively mostly in centers outside the United States. In our prior meta-analysis, when the data from all GIK trials (in patients with myocardial infarction or those undergoing cardiac surgery) were combined, there was a trend for GIK to reduce mortality, but that did not reach statistical significance (relative risk [RR], 0.90; 95% confidence interval [CI], 0.77–1.04).[6] Among 18 trials of GIK in patients with AMI, we previously found a near-significant trend in favor of GIK administration (RR, 0.82; 95% CI, 0.65–1.02).[6] In the last 2 years, 3 randomized clinical trials of GIK in patients with AMI have been published, with neutral results.[15,17,19] When the data from these trials were included in the present meta-analysis, GIK administration had a neutral effect on mortality in patients admitted with myocardial infarction (Table III). Similarly, when we combined the data from the 11 trials of GIK in patients undergoing cardiac surgery, GIK administration provided no mortality benefit.

There are various explanations for the neutral effect seen with insulin therapy as part of a GIK solution. First, the initial promising GIK studies were small and were done in the era before reperfusion therapy (thrombolytics or angioplasty) and other modern therapies for myocardial infarction, and their relevance in today's practice is unclear. Indeed, in further subgroup analysis, we found that the use of GIK during myocardial infarction in the prereperfusion era[22–33,35,37,38,41] provided a marginally significant benefit (RR, 0.84; 95% CI, 0.71–1.00), but we did not appreciate any benefit of insulin use when we combined data from studies that used thrombolytics or angioplasty (RR, 1.02; 95% CI, 0.75–1.39).[15,17,19,45,46,50] Therefore, it appears that the potential benefit of GIK infusion for myocardial infarction is attenuated with concomitant use of reperfusion therapy. However, GIK infusion may still have in important role in the period before reper-

fusion, such as in the prehospital emergency medical service or immediately upon presentation to the emergency room. This hypothesis is currently tested in the IMMEDIATE trial (Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care), an ongoing, large NHLBI (National Heart, Lung, and Blood Institute)-funded clinical trial.[55] Second, the neutral results seen in studies with GIK may be due to the inflexibility of this regimen. By definition, standard GIK solutions cannot be adapted to maintain euglycemia. As a result, the effect of the GIK solution on glycemia is unpredictable, which limits its usefulness, especially in patients with or at risk for glucose intolerance. Indeed, in the most recent and largest clinical trial of GIK, both hyperglycemia and hypoglycemia were more frequent in the GIK infusion group.[19] Therefore, although GIK solutions may in theory have cardioprotective properties, their propensity to increase glucose levels may negate any beneficial direct metabolic effects on cardiac tissue. A modified regimen of GIK that aims at lowering glucose concentration may be of benefit.

Non-GIK. We identified only 6 randomized trials in critically ill patients with insulin therapy that was not administered as a GIK solution.[4,18,41,43,52,54] In contrast to our results with studies that used insulin in the form of GIK, when we combined the data from these trials, there was a statistically significant relative risk mortality reduction of 27% (RR, 0.73; 95% CI, 0.56–0.95) with insulin therapy (Table III).

Control of Glycemia vs *Insulin Administration*

An area of debate in this area is whether glycemic improvement *vs* administration of insulin is the primary contributor to outcomes seen in clinical trials of critically ill patients. We compared trials where the goal of insulin therapy was to maintain glucose control *vs* trials that administered insulin without aiming for a glucose goal. No benefit was seen when insulin was administered without regard to glucose levels (Table III). Nearly all trials that did not target euglycemia (28 of 29) administered insulin in the form of a GIK solution. In the trials that targeted glucose, a 27% reduction in mortality was seen in patients randomized to insulin compared with controls (RR, 0.73; 95% CI, 0.57–0.94). The 2 largest trials include the DIGAMI study[43] in 620 patients with diabetes mellitus and myocardial infarction admitted to the coronary care unit where the glucose goal in the intervention arm was 126–196 mg/dL (7–10.9 mmol/L), and the study by van den Berghe et al[4] in 1548 patients admitted to the surgical ICU, where the glucose goal was 80–110 mg/dL (4.4–6.1 mmol/L). In the trial by van den Berghe et al, there was a statistically significant relative risk reduction of 42% in the intensive-treatment group (mean glucose, 103 mg/dL) compared with the conventional-treatment group (mean glucose, 153 mg/dL). In the DIGAMI study, the in-hospital mortality was lower in the intensive-treatment group (9.1%; mean glucose, 8.2 mmol/L) compared with the conventional-treatment group (11.1%; mean glucose, 9 mmol/L), but the difference was not statistically significant. The recently completed DIGAMI-2[18] did not provide in-hospital or 30-day mortality data, which would allow us to evaluate the short-term effect of in-hospital insulin therapy. At the end of follow-up (median study duration, 2.1 years), there was no difference in mortality between the 3 arms (acute insulin-glucose therapy followed by insulin-based long-term glucose control *vs* acute insulin-glucose therapy followed by standard glucose control *vs* routine metabolic management). In DIGAMI-2, all 3 arms had equivalent glycemic control during the study. The results from DIGAMI-2 and our subgroup analysis suggest an important role of targeting euglycemia in relation to mortality.

Clinical Condition or Hospital Setting

AMI/Cardiac Care Unit. The majority (24 of 38) of trials included in this review were performed in the setting of an AMI, and in nearly all of them (21 of 24), insulin was administered as a GIK solution (see above and Table III). When we combined the data from all trials that administered insulin (irrespective of form and type of insulin) in the setting of AMI, a trend toward a small benefit with insulin therapy was seen (RR, 0.89; CI, 0.76–1.03). As mentioned previously, insulin administration as a GIK infusion without a glucose goal has disadvantages that may neutralize any beneficial effects of insulin therapy. Three trials administered insulin in the setting of AMI, but not in the form of a GIK solution.[18,41,43] In these 3 studies, an insulin-glucose infusion was given with the goal of maintaining glucose within a narrow range (72–144 mg/dL [4–8 mmol/L] in the study by Davies et al[41] and 126–180 mg/dL [7–10 mmol/L] in the DIGAMI and DIGAMI-2 studies). Because only 2 of these 3 trials had available 30-day mortality data, we were unable to estimate a meaningful RR.

Cardiac Surgery. Extrapolating from the clinical setting of myocardial infarction, insulin (administered as a GIK solution in 11 of 13 trials) has been used in the perioperative setting for open-heart surgery. After combining data from all 13 trials that administered insulin (irrespective of form and type of insulin) perioperatively for cardiac surgery, no benefit of insulin administration was appreciated (Table III). The observed lack of efficacy in this setting may be due to (1) the wide range of ways that insulin was administered in the perioperative setting, including problems with GIK infusion discussed earlier, and (2) the relative low baseline mortality risk associated with modern cardiac surgery, which would require a large number of participants to show a mortality difference between groups. Our findings are in contrast with the oftencited but uncontrolled and retrospective study by Furnary et al,[56] which showed that implementation of an insulin infusion protocol aiming at lowering glucose in the cardiothoracic ICU was associated with reduced mortality. However, it is interesting to note that in the study by van den Berghe et al[4] where postoperative glucose control was targeted, cardiac surgery was the reason for admission to the surgical ICU in 63% of participants.

Surgical ICU. The best-designed and one of the largest studies with insulin therapy in critically ill patients has been conducted in the surgical ICU in Belgium and showed a significant benefit of 42% reduction in mortality in participants treated with intensive insulin therapy.[4]

Medical ICU. We found no published randomized trials of insulin therapy in the medical ICU. However, a study by van den Berghe and colleagues[4] in patients admitted to the medical ICU has been completed and results are forthcoming.

Inclusion of Patients With Diabetes

All studies excluded patients with severe or unstable hyperglycemia on admission when therapy with insulin would be clearly indicated. Combining data from the 19 studies that included patients with diabetes regardless of whether they were treated with insulin or not before hospitalization showed a significant benefit of insulin therapy on mortality (RR, 0.76; 95% CI, 0.62–0.92). There was a trend toward a benefit of insulin therapy in studies that excluded only patients with insulin-requiring diabetes. In contrast, in trials that excluded all patients with a history of diabetes, there was no benefit seen with insulin therapy. Our finding that in-hospital therapy with insulin is more beneficial in critically ill patients with diabetes is not surprising as in-hospital hyperglycemia is most often seen in patients with a history of diabetes who also exhibit a higher rate of in-hospital complications compared with nondiabetic patients.[57,58] However, it is also important to note that as many as 40% of patients without a history of diabetes but with "stress" hyperglycemia on hospital admission have unrecognized diabetes.[59,60] Therefore, any potential benefits of insulin therapy probably extend to all critically ill patients with hyperglycemia regardless of their prior history of diabetes.

Hypoglycemia

Aggressive treatment of hyperglycemia with insulin is often limited by the development of hypoglycemia, which may have adverse effects in the critically ill patient. Hypoglycemia was common in the studies we reviewed, seen in as many as 15% of patients in one study,[43] and it was more prevalent in studies aiming at euglycemia. As expected, the effect of GIK on glucose levels was variable, with studies reporting both hypoglycemia and hyperglycemia. Incidence of hypoglycemia, measured biochemically, was reported in only 11 studies.[4,19,20,22,23,42–44,46,52,54] In these studies, patients receiving insulin therapy were nearly 3 times as likely to develop hypoglycemia as controls (RR, 3.0; 95% CI, 1.4–6.6). However, no adverse clinical outcomes associated with hypoglycemia were reported, and very few patients had to stop the intervention because of hypoglycemia. However, in contrast to clinical trials, detection and appropriate management of hypoglycemia may be more challenging in the everyday care of critically ill patients.

Potential Limitations

Our review and meta-analysis has certain limitations. First, the care of the critically ill patient has changed significantly in the last 40 years; therefore, trials conducted decades ago may not be currently clinically relevant. Next, we examined only the effect of insulin therapy on mortality. Insulin therapy may have additional benefits that that may not always translate in appreciable mortality benefits that can only be measured in large trials.

CONCLUSIONS

Our present systematic review of the available literature on randomized trials extends the findings of our previous analyses that therapy with insulin therapy in adult patients hospitalized for a critical illness, other than hyperglycemic crises, may decrease mortality in certain groups of patients. The beneficial effect of insulin was evident in the surgical ICU and in patients with diabetes, whereas findings were conflicting in patients with AMI. Targeting euglycemia appears to be the main determinant of the benefit of insulin therapy. Results from a randomized trial in the medical ICU are awaiting publication.

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REFERENCES

1. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet.* 2000;355:773–778.
2. Bolk J, van der Ploeg T, Cornel JH, Arnold AE, Sepers J, Umans VA. Impaired glucose metabolism predicts mortality after a myocardial infarction. *Int J Cardiol.* 2001;79:207–214.
3. Fath-Ordoubadi F, Beatt KJ. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: an overview of randomized placebo-controlled trials. *Circulation.* 1997;96:1152–1156.
4. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med.* 2001;345:1359–1367.
5. Garber AJ, Moghissi ES, Bransome ED Jr, et al. American College of Endocrinology position statement on inpatient diabetes and metabolic control. *Endocr Pract.* 2004;10(suppl 2):4–9.
6. Pittas AG, Siegel RD, Lau J. Insulin therapy for critically ill hospitalized patients: a meta-analysis of randomized controlled trials. *Arch Intern Med.* 2004;164:2005–2011.
7. Counsell C. Formulating questions and locating primary studies for inclusion in systematic reviews. *Ann Intern Med.* 1997;127:380–387.
8. Balk EM, Bonis PA, Moskowitz H, et al. Correlation of quality measures with estimates of treatment effect in meta-analyses of randomized controlled trials. *JAMA.* 2002;287:2973–2982.
9. Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA.* 1999;282:1054–1060.
10. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med.* 1997;127:820–826.
11. Lau J, Ioannidis JP, Schmid CH. Summing up evidence: one answer is not always enough. *Lancet.* 1998;351:123–127.
12. Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. *J Clin Epidemiol.* 2000;53:207–216.

13. Tang JL, Liu JL. Misleading funnel plot for detection of bias in meta-analysis. *J Clin Epidemiol.* 2000;53:477–484.
14. DeAngelis CD, Drazen JM, Frizelle FA, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *JAMA.* 2004;292:1363–1364.
15. van der Horst IC, Zijlstra F, van't Hof AW, et al. Glucose-insulin-potassium infusion inpatients treated with primary angioplasty for acute myocardial infarction: the glucose-insulin-potassium study: a randomized trial. *J Am Coll Cardiol.* 2003;42:784–791.
16. Grey NJ, Perdrizet GA. Reduction of nosocomial infections in the surgical intensive-care unit by strict glycemic control. *Endocr Pract.* 2004;10(suppl 2):46–52.
17. Pache J, Kastrati A, Mehilli J, et al. A randomized evaluation of the effects of glucose-insulin-potassium infusion on myocardial salvage in patients with acute myocardial infarction treated with reperfusion therapy. *Am Heart J.* 2004;148:e3.
18. Malmberg K, Ryden L, Wedel H, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J.* 2005;26:650–661.
19. Mehta SR, Yusuf S, Diaz R, et al. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. *JAMA.* 2005;293:437–446.
20. Lazar HL, Chipkin SR, Fitzgerald CA, Bao Y, Cabral H, Apstein CS. Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. *Circulation.* 2004;109:1497–1502.
21. Lazar HL, Chipkin S, Philippides G, Bao Y, Apstein C. Glucose-insulin-potassium solutions improve outcomes in diabetics who have coronary artery operations. *Ann Thorac Surg.* 2000;70:145–150.
22. Mittra B. Potassium, glucose, and insulin in treatment of myocardial infarction. *Lancet.* 1965;2:607–609.
23. Lundman T, Orinius E. Insulin-glucose-potassium infusion in acute myocardial infarction. *Acta Med Scand.* 1965;178:525–528.
24. Autio L, Hakkila J, Hartel G, Ikkala E. Anticoagulants and Sodi-Pallares infusion in acute myocardial infarction. *Acta Med Scand.* 1966;179:355–360.
25. Sievers J, Lindh J, Johansson BW, Karnell J. Acute myocardial infarction treated by glucose-insulin-potassium (GIK) infusion. *Cardiology.* 1966;49:239–247.
26. Malach M. Polarizing solution in acute myocardial infarction. *Am J Cardiol.* 1967;20:363–366.
27. Pilcher J, Etishamuding M, Exon P, Moore J. Potassium, glucose and insulin in myocardial infarction. *Lancet.* 1967;1:1109.
28. Potassium, glucose, and insulin treatment for acute myocardial infarction. *Lancet.* 1968;2:1355–1360.
29. Pentecost BL, Mayne NM, Lamb P. Controlled trial of intravenous glucose, potassium, and insulin in acute myocardial infarction. *Lancet.* 1968;1:946–948.
30. Iisalo E, Kallio V. Potassium, glucose and insulin in the treatment of acute myocardial infarction. *Curr Ther Res Clin Exp.* 1969;11:209–215.
31. Hjermann I. A controlled study of peroral glucose, insulin and potassium treatment in myocardial infarction. *Acta Med Scand.* 1971;190:213–218.
32. Prather JW, Russell RO Jr, Mantle JA, McDaniel HG, Rackley CE. Metabolic consequences of glucose-insulin-potassium infusion in treatment of acute myocardial infarction. *Am J Cardiol.* 1976;38:95–99.
33. Heng MK, Norris RM, Singh BN, Barratt-Boyes C. Effects of glucose and glucose-insulin-potassium on haemodynamics and enzyme release after acute myocardial infarction. *Br Heart J.* 1977;39:748–757.
34. Lolley DM, Ray JF 3rd, Myers WO, Sheldon G, Sautter RD. Reduction of intraoperative myocardial infarction by means of exogenous anaerobic substrate enhancement: prospective randomized study. *Ann Thorac Surg.* 1978;26:515–524.
35. Rogers WJ, Segall PH, McDaniel HG, Mantle JA, Russell RO Jr, Rackley CE. Prospective randomized trial of glucose-insulin-potassium in acute myocardial infarction: effects on myocardial hemodynamics, substrates and rhythm. *Am J Cardiol.* 1979;43:801–809.
36. Salerno TA, Wasan SM, Charrette EJ. Glucose substrate in myocardial protection. *J Thorac Cardiovasc Surg.* 1980;79:59–62.
37. Mantle JA, Rogers WJ, Smith LR, et al. Clinical effects of glucose-insulin-potassium on left ventricular function in acute myocardial infarction: results from a randomized clinical trial. *Am Heart J.* 1981;102(3 pt 1):313–324.
38. Whitlow PL, Rogers WJ, Smith LR, et al. Enhancement of left ventricular function by glucose-insulin-potassium infusion in acute myocardial infarction. *Am J Cardiol.* 1982;49:811–820.
39. Oldfield GS, Commerford PJ, Opie LH. Effects of preoperative glucose-insulin-potassium on myocardial glycogen levels and on complications of mitral valve replacement. *J Thorac Cardiovasc Surg.* 1986;91:874–878.
40. Gradinac S, Coleman GM, Taegtmeyer H, Sweeney MS, Frazier OH. Improved cardiac function with glucose-insulin-potassium after aortocoronary bypass grafting. *Ann Thorac Surg.* 1989;48:484–489.
41. Davies RR, Newton RW, McNeill GP, Fisher BM, Kesson CM, Pearson D. Metabolic control in diabetic subjects following myocardial infarction: difficulties in improving blood glucose levels by intravenous insulin infusion. *Scott Med J.* 1991;36:74–76.
42. Brodin LA, Dahlgren G, Ekestrom S, Settergren G, Ohqvist G. Influence of glucose-insulin-potassium on left ventricular function during coronary artery bypass grafting. *Scand J Thorac Cardiovasc Surg.* 1993;27:27–34.
43. Malmberg K, Ryden L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol.* 1995;26:57–65.
44. Lazar HL, Philippides G, Fitzgerald C, Lancaster D, Shemin RJ, Apstein C. Glucose-insulin-potassium solutions enhance recovery after urgent coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 1997;113:354–360.
45. Diaz R, Paolasso EA, Piegas LS, et al. Metabolic modulation of acute myocardial infarction: the ECLA (Estudios Cardiologicos Latinoamerica) Collaborative Group. *Circulation.* 1998;98:2227–2234.
46. Ceremuzynski L, Budaj A, Czepiel A, et al. Low-dose glucose-insulin-potassium is ineffective in acute myocardial infarction: results of a randomized multicenter Pol-GIK trial. *Cardiovasc Drugs Ther.* 1999;13:191–200.
47. Besogul Y, Tunerir B, Aslan R, Isiksoy S, Colak O, Kural T. Clinical, biochemical and histochemical assessment of pretreatment with glucose-insulin-potassium for patients undergoing mitral valve replacement in the third and fourth functional groups of the New York Heart Association. *Cardiovasc Surg.* 1999;7:645–650.
48. Scott JF, Robinson GM, French JM, O'Connell JE, Alberti KG, Gray CS. Glucose potassium insulin infusions in the treatment of acute stroke patients with mild to moderate hyperglycemia: the Glucose Insulin in Stroke Trial (GIST). *Stroke.* 1999;30:793–799.
49. Szabo Z, Arnqvist H, Hakanson E, Jorfeldt L, Svedjeholm R. Effects of high-dose glucose-insulin-potassium on myocardial metabolism after coronary surgery in patients with type II diabetes. *Clin Sci (Lond).* 2001;101:37–43.
50. Ulgen MS, Alan S, Akdemir O, Toprak N. The effect of glucose-insulin-potassium solution on ventricular late potentials and heart rate variability in acute myocardial infarction. *Coronary Artery Dis.* 2001;12:507–512.
51. Lell WA, Nielsen VG, McGiffin DC, Schmidt FE Jr, Kirklin JK, Stanley AW Jr. Glucose-insulin-potassium infusion for myocardial protection during off-pump coronary artery surgery. *Ann Thorac Surg.* 2002;73:1246–1251.
52. Rao V, Christakis GT, Weisel RD, Ivanov J, Borger MA, Cohen G. The insulin cardioplegia trial: myocardial protection for urgent coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 2002;123:928–935.
53. Smith A, Grattan A, Harper M, Royston D, Riedel BJ. Coronary revascularization: a procedure in transition from on-pump to off-pump? The role of glucose-insulin-potassium revisited in a randomized, placebo-controlled study. *J Cardiothorac Vasc Anesth.* 2002;16:413–420.
54. Groban L, Butterworth J, Legault C, Rogers AT, Kon ND, Hammon JW. Intraoperative insulin therapy does not reduce the

need for inotropic or antiarrhythmic therapy after cardiopulmonary bypass. *J Cardiothorac Vasc Anesth.* 2002;16:405–412.
55. The IMMEDIATE trial. Available at: http://www.clinicaltrials.gov/ct/gui/show/NCT00091507. Accessed July 1, 2005.
56. Furnary AP, Gao G, Grunkemeier GL, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 2003;125:1007–1021.
57. Guvener M, Pasaoglu I, Demircin M, Oc M. Perioperative hyperglycemia is a strong correlate of postoperative infection in type II diabetic patients after coronary artery bypass grafting. *Endocr J.* 2002;49:531–537.
58. Zuanetti G, Latini R, Maggioni AP, Santoro L, Franzosi MG. Influence of diabetes on mortality in acute myocardial infarction: data from the GISSI-2 study. *J Am Coll Cardiol.* 1993;22:1788–1794.
59. Norhammar A, Tenerz A, Nilsson G, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet.* 2002;359:2140–2144.
60. Krebs JD, Robinson GM, Smith RB, Toomath RJ. Follow up testing of hyperglycaemia during hospital admission: combined use of fasting plasma glucose and HbA1c. *N Z Med J.* 2000;113:379–381.