

# Insulin Therapy for Critically Ill Hospitalized Patients

## A Meta-analysis of Randomized Controlled Trials

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**Background:** Hyperglycemia is common in critically ill hospitalized patients, and it is associated with adverse outcomes, including increased mortality. The objective of this meta-analysis was to determine the effect of insulin therapy initiated during hospitalization on mortality in adult patients with a critical illness.

**Methods:** An electronic search in the English-language articles of MEDLINE and the Cochrane Controlled Clinical Trials Register and a hand search of key journals and relevant review articles were performed. Randomized controlled trials that reported mortality data on critically ill hospitalized adult patients who were treated with insulin were selected. Data on patient demographics, hospital setting, intervention (formulation and dosage of insulin, delivery method, and duration of therapy), mortality outcomes, adverse events, and methodological quality were extracted.

**Results:** Thirty-five trials met the inclusion criteria.

Combining data from all trials using a random-effects model showed that insulin therapy decreases short-term mortality by 15% (relative risk [RR], 0.85; 95% confidence interval [CI], 0.75-0.97). In subgroup analyses, insulin therapy decreased mortality in the surgical intensive care unit (RR, 0.58; 95% CI, 0.22-0.62), when the aim of therapy was glucose control (RR, 0.71; 95% CI, 0.54-0.93), and in patients with diabetes mellitus (RR, 0.73; 95% CI, 0.58-0.90). A near-significant trend toward decreasing mortality was seen in patients with acute myocardial infarction who did not receive reperfusion therapy (RR, 0.84; 95% CI, 0.71-1.00). No randomized trials of insulin in the medical intensive care unit were identified.

**Conclusion:** Insulin therapy initiated in the hospital in critically ill patients has a beneficial effect on short-term mortality in different clinical settings.

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**H**YPERGLYCEMIA IS COMMON in hospitalized patients and is associated with adverse outcomes, including an increased risk of in-hospital mortality.<sup>1,2</sup> Hyperglycemia is most often seen in patients with diabetes mellitus who display a worse prognosis when hospitalized compared with those without diabetes mellitus.<sup>3,4</sup> However, even without diagnosed diabetes mellitus, in-hospital hyperglycemia of new onset is common in the general hospital wards<sup>5,6</sup> and in intensive care units,<sup>7,8</sup> and it carries a higher risk for increased in-hospital morbidity and mortality.<sup>2,9-13</sup>

Insulin administration has been used in patients hospitalized with critical illnesses, other than hyperglycemic crises, to improve clinical outcomes. A meta-analysis of trials that used insulin as a glucose-insulin-potassium (GIK) infusion showed that GIK may have an important role in reducing the in-hospital mortality

after acute myocardial infarction.<sup>14</sup> Since the publication of this meta-analysis, there have been additional trials examining the effect of insulin therapy in treating critically ill patients with and without acute myocardial infarction.

The objective of our meta-analysis was to examine the effect of insulin therapy initiated during hospitalization on mortality in adult patients hospitalized for a critical illness, defined as acute myocardial infarction, stroke, coronary artery bypass grafting, or an illness requiring admission to the intensive care unit.

## METHODS

### DATA SOURCES

We searched MEDLINE (from January 1, 1966, to April 24, 2003) and the Cochrane Controlled Clinical Trials Register (second quarter, 2003) for randomized controlled trials of insulin in critically ill hospitalized adult pa-

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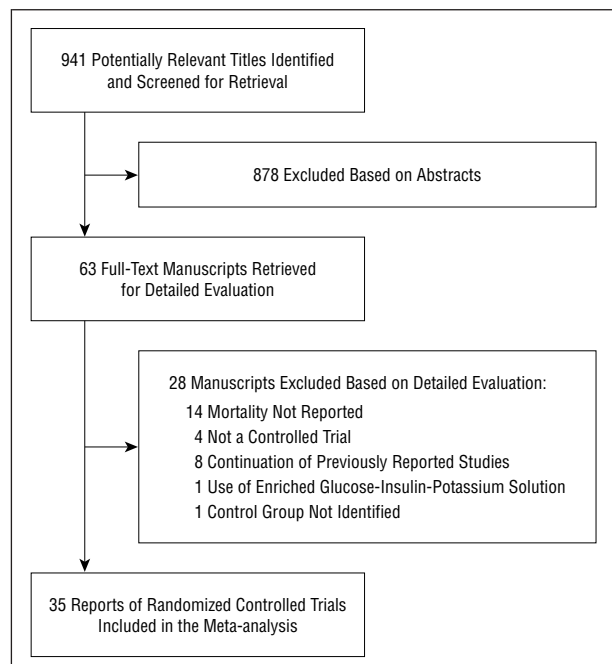


Figure 1. Search results.

tients. The following terms were used: *insulin, glucose-insulin-potassium, GIK, hospital, intensive care unit, hyperglycemia, coronary artery bypass, CABG, myocardial infarction, stroke, mortality, human, and clinical trial*. Studies in pregnant women and children were excluded. We limited our search to articles published in the English language. Bibliographies of all relevant retrieved articles from the search were examined manually for additional articles. Relevant review articles,<sup>14-19</sup> monographs,<sup>20</sup> and personal reference lists were also searched manually for additional articles. To minimize the effect of publication bias, we also searched for and reviewed abstracts published in meeting proceedings.

#### STUDY SELECTION CRITERIA

Two reviewers (A.G.P. and R.D.S.) independently screened abstracts according to the inclusion criteria. An abstract was judged relevant if it included original clinical trial data of critically ill hospitalized adult patients who were treated with insulin (regardless of type and form) while hospitalized in which mortality outcomes were reported in relation to insulin therapy. Full-text articles were retrieved and reviewed if a decision on inclusion could not be made based on the abstract. Patients with acute myocardial infarction or stroke, those undergoing coronary artery bypass grafting, and those in intensive care units were defined as having a critical illness. The full text of relevant reports was reviewed, and studies that were randomized and controlled were included in the analysis. We used the following features to assess the quality of the included reports: allocation generation (proper randomization), allocation concealment, placebo-controlled status, blinding, and intention-to-treat analysis.

#### DATA EXTRACTION

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 mellitus and glucose threshold for initiating insulin therapy in the control group), baseline characteris-

tics of the study population (sample size for intervention and control groups, age, and percentage male), intervention (formulation and dosage 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 and causes), adverse events (eg, hypoglycemia), and methodological quality. For trials with duplicate publications, the most complete or updated one was eligible for consideration.

Controlled trials that reported short-term mortality (in hospital or within 30 days after discharge) in relation to insulin therapy as an outcome were included in the meta-analysis. When reported in the article, adverse events of insulin therapy such as hypoglycemia were noted and recorded. The total number of subjects with reported outcomes in each intervention or control arm was abstracted.

#### DATA SYNTHESIS

Each study contributed one 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 that weighted studies by the inverse of the within-study and between-studies variances.<sup>21</sup> We performed subgroup analyses in studies that differed in the following variables: methodological quality, maintenance of euglycemia as the target of insulin therapy, inclusion of patients with diabetes mellitus, clinical condition or hospital setting, method of insulin administration (GIK vs non-GIK), and use of reperfusion therapy in studies of acute myocardial infarction.

### RESULTS

#### SEARCH RESULTS

Our search results are summarized in **Figure 1**. The initial search identified 941 potentially relevant reports. Sixty-three reports were thought to be relevant, and the full text of these reports was retrieved for detailed review. We excluded 28 for reasons shown in Figure 1. The characteristics of the remaining 35 trials<sup>22-56</sup> that were included in the meta-analysis are summarized in **Table 1**.

In-hospital mortality among the studies ranged from 0% to 32% (median, 8%). Cardiac-related causes (arrhythmias and heart failure) were most common in patients admitted with myocardial infarction, while multiple organ failure with sepsis was the main cause of death in the surgical intensive care unit. A statistically significant reduction of overall mortality was seen in only 2 studies.<sup>23,52</sup> The rest of the studies showed a beneficial trend or no benefit from insulin therapy, except for the study by Ceremuzynski et al<sup>47</sup> in which mortality was higher in the insulin (administered as GIK) than the control group. A higher incidence of noncardiac causes of death in the GIK group (2.4% vs 0.2% in controls) accounted for much of the increased mortality in the GIK group in this study.

#### METHODOLOGICAL QUALITY

The reported methods quality of the included studies varied widely. Method of allocation generation, allocation concealment, blinding status, and intention-to-treat analy-

**Table 1. Characteristics of Studies Included in the Meta-analysis**

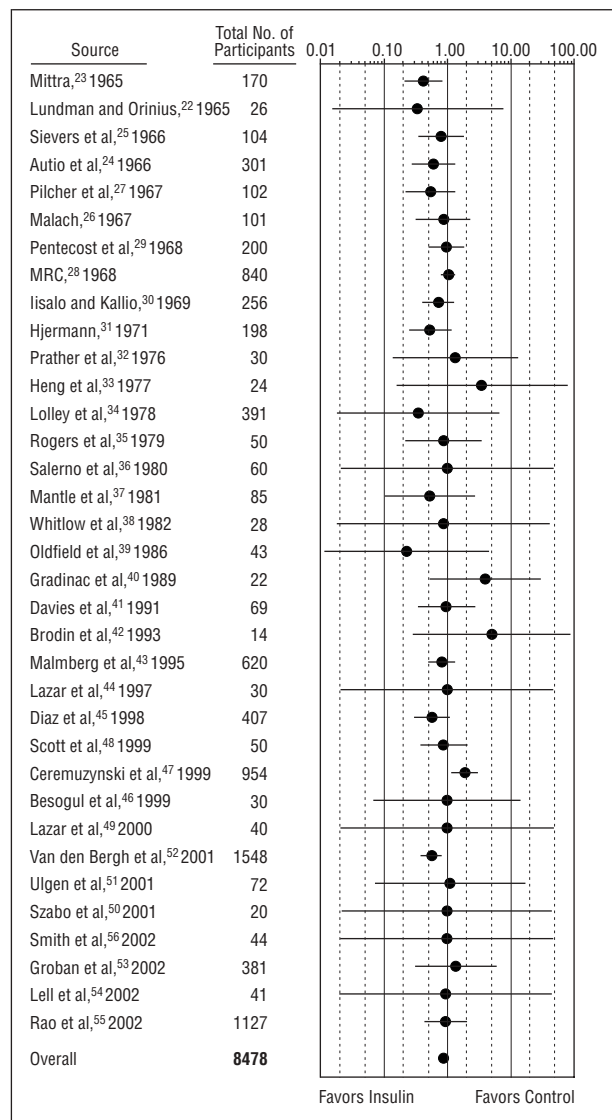
Source	Total No. of Participants	Properly Randomized	Hospital Setting	Reason for Admission	Event Rate in Controls, %	Intervention		Glucose Goal?	Reperfusion Therapy (Thrombolysis or PTCA)	Diabetics Excluded?
						Type	Duration			
Mitra, <sup>23</sup> 1965	170	Yes	Ward	AMI	28.2	GIK	14 d	No	No	IDDM only
Lundman and Orinius, <sup>22</sup> 1965	26	No	Ward	AMI	7.7	GIK	72 h	No	No	Yes
Sievers et al, <sup>25</sup> 1966	104	No	Ward	AMI	20.4	GIK	72 h	No	No	No
Autio et al, <sup>24</sup> 1966	301	No	Ward	AMI	10.3	GIK	72 h	No	No	No
Pilcher et al, <sup>27</sup> 1967	102	NR	Ward	AMI	22.6	GIK	14 d	No	No	Yes
Malach, <sup>26</sup> 1967	101	No	Ward	AMI	14.8	GIK	72 h	No	No	No
Pentecost et al, <sup>29</sup> 1968	200	Yes	CCU	AMI	16.0	GIK	48 h	No	No	IDDM only
MRC, <sup>28</sup> 1968	840	Yes	Ward	AMI	24.4	GIK	14 d	No	No	Yes
Isalo and Kallio, <sup>30</sup> 1969	256	No	Ward	AMI	18.2	GIK	14 d	No	No	Yes
Hjermann, <sup>31</sup> 1971	198	Yes	Ward	AMI	16.7	GIK	10 d	No	No	Yes
Prather et al, <sup>32</sup> 1976	30	No	CCU	AMI	8.3	GIK	48 h	No	No	No
Heng et al, <sup>33</sup> 1977	24	NR	CCU	AMI	0.0	GIK	12 h	No	No	Yes
Lolley et al, <sup>34</sup> 1978	391	NR	OR	CABG	1.1	GIK	44 mo	No	NA	Yes
Rogers et al, <sup>35</sup> 1979	50	NR	CCU	AMI	14.8	GIK	2 d	No	No	IDDM only
Salerno et al, <sup>36</sup> 1980	60	NR	OR	CABG	0.0	GIK	8 h	No	NA	Yes
Mantle et al, <sup>37</sup> 1981	85	NR	CCU	AMI	9.1	GIK	48 h	No	No	IDDM only
Whitlow et al, <sup>38</sup> 1982	28	Yes	CCU	AMI	0.0	GIK	48 h	No	No	IDDM only
Oldfield et al, <sup>39</sup> 1986	43	Yes	OR	MVR	8.7	GIK	12 h	NO	NA	No
Gradinac et al, <sup>40</sup> 1989	22	No	SICU	CABG	9.1	GIK	48 h	No	NA	No
Davies et al, <sup>41</sup> 1991	69	NR	CCU	AMI	17.6	Insulin IV	24 h	Yes	NR	No
Brodin et al, <sup>42</sup> 1993	14	NR	OR	CABG	0.0	GIK	NR	No	NA	No
Malmberg et al, <sup>43</sup> 1995	620	NR	CCU	AMI Diabetes mellitus	11.1	Insulin IV or SQ	10 d	Yes	Thrombolysis	No
Lazar et al, <sup>44</sup> 1997	30	No	OR	CABG	0.0	GIK	>12 h	No	NA	Yes
Diaz et al, <sup>45</sup> 1998	407	Yes	CCU	AMI	11.5	GIK	24 h	No	Thrombolysis or PTCA	No
Scott et al, <sup>48</sup> 1999	50	Yes	Ward	Stroke	32.0	GIK	24 h	Yes	NA	IDDM only
Ceremuzyński et al, <sup>47</sup> 1999	954	Yes	CCU	AMI	4.8	GIK	24 h	No	Thrombolysis	IDDM only
Besogul et al, <sup>46</sup> 1999	30	NR	OR	MVR	6.7	GIK	12 h	No	NA	No
Lazar et al, <sup>49</sup> 2000	40	No	OR	CABG Diabetes mellitus	0.0	GIK	12 h	Yes	NA	No
Van den Berghe et al, <sup>52</sup> 2001	1548	Yes	SICU	Mechanical ventilation	8.0	Insulin IV	3 d	Yes	NA	No
Ulgen et al, <sup>51</sup> 2001	72	NR	CCU	AMI	2.6	GIK	24 h	No	Thrombolysis	No
Szabo et al, <sup>50</sup> 2001	20	NR	OR	CABG	0.0	GIK	6 h	Yes	NA	No
Smith et al, <sup>56</sup> 2002	44	Yes	OR	CABG	0.0	GIK	10 h	Yes	NA	IDDM only
Groban et al, <sup>53</sup> 2002	381	NR	OR	CABG	1.6	Insulin IV	2 h	Yes	NA	Yes
Lell et al, <sup>54</sup> 2002	41	Yes	OR	CABG	0.0	GIK	12 h	No	NA	No
Rao et al, <sup>55</sup> 2002	1127	Yes	OR	CABG	2.3	Insulin IV	1 h	No	NA	No

Abbreviations: AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CCU, coronary care unit; GIK, glucose-insulin-potassium solution; ICU, intensive care unit; IDDM, insulin-dependent diabetes mellitus (includes type 1 or type 2); IV, intravenous; OR, operating room; MRC, Medical Research Council; MVR, mitral valve replacement; NA, not applicable; NR, not reported; PTCA, percutaneous transluminal coronary angioplasty; SICU, surgical intensive care unit; SQ, subcutaneous.

sis were fully described in few manuscripts. The method of allocation generation was clearly reported in 22 studies, and it was appropriate by current standards in 13 of them. Blinding status was clearly reported in 10 studies, and only 5 were double blinded.<sup>31,38,39,52,55</sup> If we applied strict criteria for inclusion such as appropriate randomization, double-blind status, and statistical methods that were clearly stated in the manuscripts, only 2 studies<sup>47,52</sup> would satisfy these criteria.

### META-ANALYSIS AND SUBGROUP ANALYSIS

When the data from all trials were combined using a random-effects model, insulin therapy in critically ill hospitalized adult patients was associated with a statistically significant 15% reduction in death relative to controls (relative risk [RR], 0.85; 95% confidence interval [CI], 0.75-0.97) (**Figure 2**). The trials included in this review shared the use of insulin in critically ill hospital-



**Figure 2.** Relative risk and 95% confidence interval of individual studies. MRC indicates Medical Research Council.

ized patients. However, they differed in various factors, as shown in Table 1. We performed subgroup analyses (**Table 2**) to determine the effect of changing baseline variables on mortality and to gain insight into the appropriate use of insulin in critically ill patients.

### Control of Glycemia

We compared trials in which the goal of insulin therapy was to achieve glucose control vs trials that administered insulin without aiming for a glucose goal. In the trials that targeted glucose, a 29% reduction in mortality was seen in patients randomized to insulin compared with controls (RR, 0.71; 95% CI, 0.54-0.93). The 2 largest trials included the DIGAMI study<sup>43</sup> in 620 patients with diabetes mellitus and myocardial infarction admitted to the coronary care unit, where the glucose goal was 126 to 196 mg/dL (7.0-10.9 mmol/L), and the study by Van den Bergh et al<sup>52</sup> in 1548 patients admitted to the surgical intensive care unit, where the glucose goal was 80 to 110 mg/dL (4.4-

6.1 mmol/L). No benefit was seen when insulin was administered without regard to glucose levels. Most of the trials that did not target euglycemia administered insulin in the form of a GIK solution.

### Inclusion of Patients With Diabetes Mellitus

Next, we looked at whether inclusion of patients with diabetes mellitus affected mortality. All studies excluded patients with severe or unstable hyperglycemia on admission in whom therapy with insulin would be clearly indicated. Combining data from studies that included patients with diabetes mellitus regardless of whether they were treated with insulin before hospitalization showed a significant benefit of insulin therapy on mortality (RR, 0.73; 95% CI, 0.58-0.90). There was also a benefit of insulin therapy in studies that excluded patients with insulin-requiring diabetes mellitus, but this effect was attenuated. In contrast, there was no benefit of insulin therapy in trials that excluded all patients with a history of diabetes mellitus.

### Clinical Condition or Hospital Setting

When we examined the clinical setting in which insulin therapy was administered, we found that in patients admitted for acute myocardial infarction there was a trend toward benefit with insulin therapy (RR, 0.84; 95% CI, 0.69-1.01). In the trials that administered insulin perioperatively for cardiac surgery, no benefit of insulin administration was appreciated. There was 1 large trial<sup>52</sup> in the surgical intensive care unit that showed a significant benefit of 42% reduction in mortality with insulin therapy. We found no randomized trials of insulin therapy in the medical intensive care unit.

### GIK vs Non-GIK Method of Insulin Administration

In most studies, insulin was administered as a GIK solution. When the data from all GIK trials were combined, there was a trend for GIK to reduce mortality that did not reach statistical significance (RR, 0.90; 95% CI, 0.77-1.04). In contrast, when we combined the data from the 5 trials that administered insulin by a method other than GIK, there was a statistically significant relative risk mortality reduction of 27% (RR, 0.73; 95% CI, 0.56-0.95) with insulin therapy.

### Insulin Therapy in Acute Myocardial Infarction

Among the 30 GIK trials, 18 were performed in the setting of an acute myocardial infarction. Therapy with GIK was initiated as soon as the diagnosis of suspected myocardial infarction was made, which was within 24 hours of hospital admission. Duration of therapy with GIK varied from 24 hours to 14 days, with most interventions lasting between 24 and 72 hours. In these 18 trials, insulin in the form of GIK showed a near-significant trend toward decreased mortality (RR, 0.82; 95% CI, 0.65-1.02).

In 2 additional trials,<sup>41,43</sup> an insulin-glucose infusion was given with the goal of maintaining glucose within a narrow range. When we combined the data from all 20 trials

**Table 2. Subgroup Analyses of the Effect of Insulin Therapy on Mortality in Critically Ill Hospitalized Patients**

Variable	No. of Trials	No. of Patients Analyzed	Mortality Rate of Control Group, %*	Mortality Relative Risk (95% Confidence Interval)
All studies				
Random effects	35	8478	9.7	0.85 (0.75-0.97)
Fixed effects	35	8478	9.7	0.85 (0.74-0.97)
Glucose goal				
Yes <sup>41,43,48-50,52,53,56</sup>	8	2772	8.4	0.71 (0.54-0.93)
No <sup>22-40,42,44-47,51,54,55</sup>	27	5706	9.8	0.87 (0.73-1.04)
Inclusion of patients with diabetes mellitus†				
All patients with diabetes mellitus included <sup>24-26,32,39-43,45,46,49-52,54,55</sup>	17	4589	9.0	0.73 (0.58-0.90)
Patients with diabetes mellitus included except IDDM <sup>23,29,35,37,38,47,48,56</sup>	25	6170	8.3	0.81 (0.68-0.98)
Patients with diabetes mellitus excluded <sup>22,27,28,30,31,33,34,36,44,53</sup>	10	2308	13.1	0.91 (0.75-1.11)
Clinical condition or hospital setting				
Acute myocardial infarction <sup>22-33,35,37,38,41,43,45,47,51</sup>	20	4637	13.9	0.84 (0.69-1.01)
Cardiac surgery <sup>34,36,39,40,42,44,46,49,50,53-56</sup>	13	2248	1.9	1.09 (0.63-1.90)
Surgical intensive care unit <sup>52</sup>	1	1548	8.0	0.58 (0.22-0.62)
Stroke <sup>48</sup>	1	53	32.0	‡
Medical intensive care unit	0	...	...	...
Method of insulin administration				
Non-GIK <sup>41,43,52,53,55</sup>	5	3745	6.4	0.73 (0.56-0.95)
GIK (all medical conditions) <sup>22-40,42,44-51,54,56</sup>	30	4733	12.4	0.90 (0.77-1.04)
GIK in acute myocardial infarction <sup>22-33,35,37,38,45,47,51</sup>	18	3948	13.9	0.82 (0.65-1.02)
GIK in cardiac surgery <sup>34,36,39,40,42,44,46,49,50,54,56</sup>	11	735	1.6	1.24 (0.48-3.17)
GIK in stroke <sup>48</sup>	1	53	32.0	‡
Reperfusion therapy used?§				
Yes <sup>43,45,47,51</sup>	4	2053	7.9	0.90 (0.54-1.820)
No <sup>22-33,35,37,38,41</sup>	16	2584	17.5	0.84 (0.71-1.00)

Abbreviations: GIK, glucose-insulin-potassium solution; IDDM, insulin-dependent diabetes mellitus (includes type 1 or type 2).

\*Overall weighted control rate.

†Patients with severe or unstable hyperglycemia on admission in whom insulin therapy was indicated were excluded.

‡Too few patients for a meaningful calculation for relative risk.

§Only studies with acute myocardial infarction as an entry criterion are included.

that administered insulin in the setting of acute myocardial infarction, the notable trend toward benefit with insulin remained (RR, 0.84; 95% CI, 0.69-1.01). In the trials of myocardial infarction, a benefit was seen in studies that did not exclude patients with diabetes mellitus (RR, 0.75; 95% CI, 0.57-1.00), but the benefit was lessened and became nonsignificant in those studies that excluded patients with diabetes mellitus (RR, 0.82; 95% CI, 0.61-1.11).

To gain further insight into the relationship between the use of insulin in the setting of myocardial infarction, we compared studies that used reperfusion therapy (thrombolytics or primary angioplasty) vs those that did not. In studies done without reperfusion, there was a marginally significant reduction in mortality (RR, 0.84; 95% CI, 0.71-1.00), while no benefit was seen in the 4 studies in which patients received reperfusion therapy.

### Hypoglycemia

Incidence of hypoglycemia, measured biochemically, was reported in only 10 studies.\* When data from these studies were combined, we found that patients receiving insulin therapy were about 3 times as likely to develop hypoglycemia as controls (RR, 3.4; 95% CI, 1.9-6.3). No adverse clinical outcomes associated with hypoglycemia were observed in any of these studies. Hypoglyce-

mia was more common in studies that used a protocol aiming at maintaining euglycemia. The effect of GIK on glucose levels was variable, with some studies reporting hypoglycemia, while others reported hyperglycemia.

### COMMENT

Therapy with insulin in adult patients hospitalized for a critical illness, other than hyperglycemic crises, may have beneficial effects in different clinical settings. Our analysis showed that therapy with insulin decreased mortality in the surgical intensive care unit when the aim of therapy was glucose control and in patients with diabetes mellitus. A nearly significant benefit was seen in patients with acute myocardial infarction who did not receive reperfusion therapy.

In-hospital hyperglycemia, especially of new onset, is often seen as an adaptive response, caused by increased insulin resistance during periods of stress.<sup>57</sup> It is often referred to as “stress” hyperglycemia, and it is considered a marker of illness severity rather than a real medical entity that needs to be managed. Recent evidence, however, challenges that notion.<sup>1,6,9-11</sup> In these studies, in-hospital hyperglycemia was shown to be independently associated with adverse outcomes, including mortality.

Various mechanisms have been proposed in an effort to explain the adverse effects of hyperglycemia on patient outcomes and the potential benefit of insulin therapy:

\*References 22, 23, 42-44, 47, 49, 52, 53, 55.

(1) Hyperglycemia is associated with altered immune function and susceptibility to infection.<sup>58,59</sup> (2) Insulin and glucose administration may provide myocardial protection during ischemia by suppressing free fatty acids and increasing availability of glucose as a myocardial substrate.<sup>60</sup> (3) Hyperglycemia per se may not be an independent risk factor for mortality, but it may be a marker of insulin resistance and associated conditions such as impaired fibrinolysis and platelet function, which lead to hypercoagulability and increased risk for thrombotic events.<sup>61</sup>

Our subgroup analysis showed that the beneficial effect of insulin on decreasing mortality in critically ill patients was apparent in studies that aimed at normalization of serum glucose. However, in the trials described in this meta-analysis, it is difficult to distinguish the effects of improved glycemia from other potential effects of insulin. In a post hoc analysis of the study by Van den Berghe et al,<sup>62</sup> hyperglycemia and insulin dosage were independent predictors of death.

Our analysis also showed that in-hospital therapy with insulin is more beneficial in patients with diabetes mellitus. This is not surprising as in-hospital hyperglycemia is most often seen in patients with a history of diabetes mellitus, who exhibit a higher rate of in-hospital complications compared with nondiabetic patients,<sup>3,4</sup> and, therefore, are positioned to benefit the most from insulin therapy. As many as 40% of patients without a history of diabetes mellitus and with stress hyperglycemia on hospital admission have unrecognized diabetes mellitus.<sup>7,63</sup> If insulin therapy benefits patients with diabetes mellitus during critical illnesses, many of these patients would be deprived of this benefit if their stress hyperglycemia is not adequately recognized and properly managed during hospitalization.

Our results showed a near-significant trend toward a benefit with GIK administration in patients with acute myocardial infarction. A previous meta-analysis by Fath-Ordoubadi and Beatt<sup>14</sup> that examined the use of GIK for myocardial infarction found a statistically significant reduction in mortality of 28% associated with the use of GIK solution. Most of the GIK studies included in that meta-analysis were done in the era before reperfusion therapy (thrombolytics or angioplasty), and their relevance in today's practice is unclear. In contrast, our analysis included the DIGAMI study<sup>43</sup> and other recent large studies<sup>45,47,51</sup> that administered reperfusion therapies as part of the routine care for acute myocardial infarction. In subgroup analysis, we found that the use of insulin during myocardial infarction in the pre-reperfusion era provided a marginally significant benefit, similar to the meta-analysis findings by Fath-Ordoubadi and Beatt, but we did not appreciate any benefit of insulin use when we combined data from studies that used thrombolytics or angioplasty. Therefore, it appears that the potential benefit of GIK for myocardial infarction is attenuated with concomitant use of reperfusion therapy. However, GIK may still have an important role in the period before reperfusion, such as in the prehospital emergency medical care or on presentation to the emergency department.

The inconsistent results seen in studies with GIK may, at least in part, be due to the inflexibility of this regimen. Standard GIK solutions cannot be adapted to maintain euglycemia, and their effect on glycemia is unpre-

dictable. Therefore, although GIK solutions may have cardioprotective properties, their propensity to increase glucose levels may negate any beneficial direct metabolic effects on cardiac tissue.

In contrast to GIK, when insulin was administered alone, a statistically significant reduction in mortality was seen. This group included the 2 largest trials<sup>43,52</sup> that targeted euglycemia with the use of an insulin infusion.

Our results do not support the use of insulin, as administered in the trials we examined, for decreasing mortality in the perioperative setting for open heart surgery. The observed lack of efficacy in this setting may be due to (1) the wide range of ways in which insulin was administered in the perioperative setting or (2) the relative low baseline mortality risk associated with modern cardiac surgery.<sup>64</sup>

In the studies we reviewed, insulin therapy was well tolerated. Hypoglycemia was common but was also well tolerated, and few patients had to stop the intervention because of hypoglycemia.

A potential limitation of our study is that most of the trials we analyzed did not report their methods based on the rigorous CONSORT criteria.<sup>65</sup> As most of these trials were reported before the CONSORT criteria became available, we believe our inclusion of these studies is appropriate and our analysis is valid.

Our review combined studies with varying methods of insulin administration in diverse clinical settings. We considered combining these studies to be appropriate because the mechanisms by which hyperglycemia exerts its adverse effects on mortality and morbidity may be shared among these clinical settings.

## CONCLUSIONS

In conclusion, we found that insulin therapy initiated in the hospital in critically ill patients has a beneficial effect on short-term mortality in the surgical intensive care unit, in patients with diabetes mellitus, and in patients with myocardial infarction who were not treated with reperfusion therapy. We found that targeting euglycemia, with a flexible regimen of insulin and glucose as required, appears to be the main determinant of the benefit of insulin therapy. Whether the beneficial effect of insulin therapy applies to additional clinical settings (such as stroke) or patient groups (such as the medical intensive care unit or general surgical or medical ward) remains to be determined.

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