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## Insulin therapy in acute coronary syndromes: an appraisal of completed and ongoing randomised trials with important clinical end points

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### Abstract

Insulin therapy was first proposed as an adjunctive therapy in patients with acute coronary syndromes (ACS) in the 1960s. Since then, numerous randomised clinical trials have been conducted to determine the efficacy and to define the role of insulin therapy in ACS. This review will discuss: 1) completed trials of insulin therapy in ACS, including both glucose-insulin-potassium (GIK) approaches and non-GIK approaches; 2) trials of insulin therapy in critically ill non-ACS patients and the lessons from these trials that can be applied to trials of insulin in ACS patients; and 3) a summary of ongoing and planned trials of insulin in ACS patients.

### Keywords

acute coronary syndromes; clinical trials; diabetes mellitus; glucose; insulin; review

### Introduction

Clinical trials in acute coronary syndromes (ACS) have largely focused on interventions that restore coronary blood flow through regions that are compromised by total or near-total atherothrombotic occlusions. Since the advent of reperfusion therapy, however, the

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#### Conflicts of interest statement

AG and KN are on the steering committee for the RECREATE pilot study. HG is the principal investigator of the RECREATE pilot study and holds the Population Health Institute Chair in Diabetes Research. GU is on the steering committee of the INTENSIVE trial. PFW has no disclosures.

discovery of additional agents that inhibit platelets, coagulation factors or thrombosis has yielded diminishing incremental clinical benefit. Accordingly, attention has shifted to discovering adjunctive therapies that operate through mechanisms other than the optimisation of coronary flow. One such approach, broadly designated as metabolic modulation therapy, involves administration of insulin to patients in the early stages of ACS. This review will summarise the most important advances in the use of insulin therapy and the control of circulating blood glucose concentrations in ACS, and we emphasise data from trials in which important clinical end points have been reported.

## Completed studies of glucose-insulin-potassium (GIK) therapy in acute coronary syndromes

The potential benefit of insulin in ACS patients was first proposed in the 1960s.<sup>1–3</sup> These early reports postulated that administering a solution containing glucose, insulin and potassium (GIK) would benefit the ischaemic myocardium in that: a) insulin would shift the primary metabolic substrate of the ischaemic myocardium from free fatty acids (the primary fuel source for the healthy heart but toxic in the setting of ischaemia)<sup>4,5</sup> to glucose; b) glucose would provide metabolic substrate for anaerobic glycolysis; and c) potassium would prevent insulin-mediated hypokalaemia while optimising intramyocellular potassium levels.<sup>3</sup> The hypothesised net effect of GIK therapy was enhanced myocardial performance, decreased arrhythmogenicity and decreased myocardial damage. Several clinical trials have tested this hypothesis in ACS patients, with varying GIK formulations, routes of administration and duration of therapy. The most notable of these studies are summarised in table 1 and are discussed below.

### Meta-analysis of GIK trials

In 1997, Fath-Ordoubadi and Beatt published an overview of nine randomised controlled trials of GIK therapy versus no GIK therapy in acute myocardial infarction (MI) (conducted from 1965–1995), in which a total of 1,932 patients were included.<sup>6</sup> Only trials that described proper randomisation procedures and documented in-hospital mortality were included. The authors reported that 154 of 956 GIK patients (16.1%) died, compared with 205 of 972 (21%) control patients (odds ratio 0.72, 95% confidence intervals [CI] 0.57–0.90). An important limitation of this meta-analysis was that eight of the nine included studies were conducted in the pre-reperfusion era, in which the observed mortality rate in the control group exceeded 20%. Nevertheless, this meta-analysis provided significant enthusiasm for the GIK hypothesis, since prior GIK studies had been underpowered to determine the effect of GIK on significant clinical outcomes.

### The ECLA-GIK Pilot trial

The Estudios Cardiológicos Latinoamérica (ECLA) investigators based in six Latin American countries conducted a pilot trial<sup>7</sup> of GIK therapy in which 405 patients with acute MI were randomised to one of three arms: high-dose GIK (25% glucose, 50 IU/L of insulin and 40 mmol/L of KCl infused at 1.0 mL/kg/hour), low-dose GIK (10% glucose, 20 IU/L of insulin and 80 mmol/L of KCl infused at 1.5 mL/kg/hour), and control (no GIK infusion). In a comparison combining both GIK groups versus control, there was a lower rate of in-hospital mortality that favoured GIK therapy (6.7% vs. 11.5%, relative risk [RR] 0.58, 95% CI 0.30–1.10, *p*=NS). The difference in glucose at 24 hours was approximately 10 mg/dL (0.55 mmol/L) (145 mg/dL [7.98 mmol/L] in the GIK groups and 135 mg/dL [7.43 mmol/L] in the control group). In an analysis of one-year mortality in which the high-dose GIK, low-dose GIK and control groups were analysed separately, mortality was similar (16%) in the low-dose GIK and the control groups, but one-year mortality was lower in the high-dose GIK group (7%; log-rank *p* value 0.046). The authors also reported a mortality benefit with

GIK therapy in the subgroup of patients who underwent reperfusion therapy (62% of the total trial population). Based on the ECLA pilot study, the authors concluded that subsequent GIK trials should use the high-dose GIK formulation, and that GIK therapy might have an optimal effect in patients who undergo reperfusion therapy.

### **The Glucose Insulin Potassium Study (GIPS) and GIPS 2**

As data were limited on the effects of GIK therapy in acute MI patients undergoing reperfusion therapy with primary percutaneous coronary intervention (PCI), the Glucose Insulin Potassium Study (GIPS) investigators randomised 940 patients with acute ST-segment elevation MI (STEMI) to open-label GIK infusion versus no infusion.<sup>8</sup> A glucose-potassium solution was infused through a peripheral line at a rapid rate of 3 mL/kg/hour for 8–12 hours, and a separate insulin drip was titrated to achieve blood glucose levels of 126–198 mg/dL (6.93–10.89 mmol/L). The primary end point, death at 30 days, did not differ between the GIK group (23 deaths in 476 patients [4.8%]) and the control group (27 deaths in 464 patients [5.8%]), RR 0.82, 95% CI 0.46–1.46. In a pre-specified subgroup analysis of the 856 (91%) patients with no signs of heart failure (Killip class I), mortality was lower among patients who received GIK therapy (1.2%) compared with no GIK (4.2%). Therefore, the GIPS investigators conducted a second trial, the GIPS-2 study,<sup>9–11</sup> in which GIK versus no GIK was compared in 889 acute STEMI patients who had no clinical heart failure on admission, of whom 88% underwent reperfusion primary PCI. However, in contrast to the subgroup analysis results from the first GIPS study, GIPS-2 found no difference in 30-day death between the GIK group (2.9%) and the control group (1.8%) (odds ratio [OR] 1.6; 95% CI 0.7 to 4.0,  $p=0.27$ ).<sup>10</sup> There was also no difference in mortality at one year.<sup>9</sup> The GIPS-2 investigators speculated that their findings may have been due to the delayed initiation of GIK therapy after reperfusion therapy in many patients.<sup>10</sup>

### **The CREATE-ECLA trial**

The Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation-Estudios Clínicos Latino América (CREATE-ECLA) trial is the largest clinical trial to investigate GIK. It included 20,201 people from 470 centres around the world, and participants were randomised to either a 24-hour infusion of fixed dose intravenous GIK therapy (equivalent to the high-dose GIK solution from the ECLA pilot study) in addition to standard care, or to standard care alone.<sup>12,13</sup> The primary end point was all-cause mortality at 30 days, which did not differ between the GIK and control groups (10.0% vs. 9.7%,  $p=0.45$ ). No benefit for GIK therapy was demonstrated in any pre-specified subgroups, including strata of time from symptom onset to randomisation, different Killip classes, presence or absence or type of reperfusion therapy, the presence or absence of diabetes mellitus, and strata of baseline glucose. GIK provided no clinical benefit in any of these subgroups. Thus, CREATE-ECLA established that administering fixed-dose GIK therapy for acute STEMI provided no benefit. Of note, the CREATE-ECLA trial did not test the efficacy of dosing insulin to achieve glucose lowering,<sup>14</sup> and the mean glucose level at 24 hours was actually higher in the GIK arm (155 mg/dL, 8.53 mmol/L) compared with the control arm (135 mg/dL, 7.43 mmol/L).

### **The OASIS-6 GIK trial**

The OASIS-6 study was a two-by-two factorial trial that evaluated the efficacy of fondaparinux versus placebo in 12,000 patients with acute STEMI,<sup>15,16</sup> of whom 8,000 were also to be randomised to GIK versus no GIK. However, the GIK component of the trial was terminated early after 2,748 patients had been enrolled, at the time of announcement of the CREATE-ECLA trial results.<sup>15</sup> Despite its early termination, the OASIS-6 GIK trial represents the second largest trial of insulin therapy in acute MI to date. The OASIS-6 GIK trial showed no difference between the GIK and control arms in the rate of death at either 30

days (7.6% for GIK vs. 6.7% for control, hazard ratio [HR] 1.14 [95% CI 0.86–1.51],  $p=0.36$ ) or at 180 days (10.8% for GIK vs. 10.4% for control, HR 1.04 [95% CI 0.83–1.31],  $p=0.72$ ).

### Combined OASIS-6 GIK and CREATE-ECLA GIK trial analysis

Prior to the unblinding of the CREATE-ECLA or the OASIS-6 trials, an analysis was pre-specified in which data from patients from both GIK trials would be combined to determine the effect of GIK versus no GIK on early (0–3 days) and late (4–30 days) periods following presentation for acute MI. It was hypothesised on the basis of animal and human translational studies that the greatest benefit for GIK would occur at 0–3 days (during and soon after the infusion period), with no further benefit at 4–30 days.<sup>15</sup> In this combined trial analysis of 22,943 patients, GIK therapy was actually associated with a higher mortality rate from 0–3 days compared with control (6.2% vs. 5.5%, HR 1.13 [95% CI 1.02–1.26],  $p=0.03$ ), as well as a higher rate of the composite of death or heart failure from 0–3 days (12.9% vs. 12.0%, HR 1.09 [95% CI 1.02–1.18],  $p=0.02$ ). This surprising result prompted the CREATE-ECLA and OASIS-6 GIK investigators to conduct a post-hoc analysis to explore the reasons for possible early harm in the GIK group. Patients in the GIK arm experienced higher levels of glucose than control arm patients at six hours (186 mg/dL [10.23 mmol/L] vs. 148 mg/dL [8.14 mmol/L]) and at 24 hours (153 mg/dL [8.42 mmol/L] vs. 135 mg/dL [7.43 mmol/L]), and it has been shown in numerous epidemiological studies that elevated in-hospital glucose levels are associated with higher rates of short- and long-term mortality in acute MI patients.<sup>17–28</sup> GIK also caused greater elevations in in-hospital potassium levels (24-hour potassium was 4.4 mEq/L in the GIK arm versus 4.0 mEq/L in the control arm), and greater fluid gain (total volume infused, including all therapies, in the first 24 hours was 3,000 mL in the GIK group versus 1,700 mL in the control group). After adjusting for each of these post-randomisation factors (glucose, potassium and net fluid gain), GIK was no longer associated with harm at three days. This finding strongly suggested that any putative benefit of insulin therapy in acute MI may have been undermined by the hyperglycaemia, hyperkalaemia and/or the volume overload induced by the high-dose GIK formulation.

Further analyses of the data refuted the possibility that GIK would only benefit patients when initiated early and/or before reperfusion therapy<sup>29–31</sup> These analyses showed that: a) GIK was of no benefit in the 9,388 patients who presented within four hours of symptom onset;<sup>15</sup> and b) mortality did not differ among the 2,278 patients in whom GIK was started before reperfusion therapy (8.3% dead at 30 days), the 6,689 patients who received GIK after reperfusion (8.1% dead at 30 days), or the 9,369 patients who were in the control arm and underwent reperfusion therapy (8.4% dead at 30 days) ( $\chi^2$  for the difference among groups=0.66;  $p=0.72$ ).<sup>31</sup> Thus, high-dose GIK did not benefit any patient subgroup, regardless of the timings between symptom onset, GIK infusion initiation, and the administration of reperfusion therapy.

### Other studies of insulin therapy in acute coronary syndromes using non-GIK approaches

The majority of insulin trials in ACS patients used the GIK approach, in which insulin was administered at a fixed dose or concentration without the objective of lowering glucose levels. A few studies, however, have been conducted in which insulin was dosed to achieve a lower glucose level in the insulin arm than in the control arm.

## DIGAMI and DIGAMI 2

The Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial randomised 620 patients with diabetes and acute MI to one of two strategies: usual care in which no study insulin was administered; or standard care plus insulin in the form of an intravenous glucose-insulin infusion (without potassium) for at least 24 hours, immediately followed by subcutaneous insulin therapy four times a day for at least three months.<sup>32,33</sup> The primary end point in DIGAMI was all-cause mortality at three months. The admission glucose level in this population was similar in each group (283 mg/dL [15.6 mmol/L] in the control arm and 277 mg/dL [15.2 mmol/L] in the insulin arm). After 24 hours of the glucose-insulin infusion, the glucose level was 211 mg/dL (11.6 mmol/L) in the control group and 173 mg/dL (9.5 mmol/L) in the insulin group, for a mean difference of 38 mg/dL (2.1 mmol/L). However, this glucose difference narrowed to only 14 mg/dL (0.77 mmol/L) at hospital discharge (162 mg/dL [8.9 mmol/L] in the control and 148 mg/dL [8.1 mmol/L] in the insulin group).

Mortality was lower in the insulin versus control arm at one year (18.6% vs. 26.1%,  $p=0.0273$ )<sup>32</sup> and at 3.4 years (33% vs. 44%,  $p=0.011$ ).<sup>33</sup> However, there was no statistically significant difference in the trial's pre-specified primary end point of mortality at three months (12.4% insulin vs. 15.6% control,  $p=NS$ ) or in in-hospital mortality (9.1% vs. 11.1%,  $p=NS$ ).<sup>32</sup> These results led to speculation that the multidose subcutaneous insulin regimen (and not the 24-hour in-hospital glucose-insulin infusion) was primarily responsible for the difference in long-term mortality.

To test this hypothesis, the DIGAMI investigators conducted a second study (DIGAMI-2) in which 1,850 patients with type 2 diabetes and acute MI were to be randomised to one of three arms: glucose-insulin infusion followed by long-term subcutaneous insulin (the same as the treatment arm in the first DIGAMI trial); glucose-insulin infusion alone with no subsequent subcutaneous insulin; and standard care with no study insulin. The primary end point was all-cause mortality at two years. The study was terminated early by the steering committee after 1,253 patients had been enrolled. In contrast to the first DIGAMI trial which achieved a fasting glucose contrast between groups of 38 mg/dL (2.1 mmol/L), this study only achieved a glucose contrast of 16 mg/dL (0.9 mmol/L), with 164 mg/dL (9.0 mmol/L) and 180 mg/dL (9.9 mmol/L) in the insulin and control arms, respectively). Moreover, there was no difference in two-year mortality among groups (23.4% for glucose-insulin infusion plus subcutaneous insulin; 21.2% for glucose-insulin infusion only; and 17.9% for no study insulin at all;  $p>0.15$  for all pairwise comparisons).<sup>34</sup>

## Hi-5 study

The Hyperglycemia Intensive Insulin Infusion In Infarction (HI-5) study tested whether an insulin infusion titrated to achieve a target glucose range would be beneficial in acute MI with or without ST-segment elevation.<sup>35</sup> In Hi-5, patients with admission blood glucose 140 mg/dL (7.7 mmol/L) were randomised to intensive insulin therapy (target glucose 72–180 mg/dL [4.0–9.9 mmol/L]) compared with control arm patients (no insulin treatment unless glucose exceeded 288 mg/dL [15.8 mmol/L]). A total of 244 patients (48% with and 52% without known diabetes) were randomised; their mean baseline glucose level was 198 mg/dL (10.9 mmol/L). There was no difference between the insulin and control groups in the primary end point of mortality during hospitalisation (4.8% insulin vs. 3.5% control,  $p=0.75$ ), at three months (7.1% insulin vs. 4.4% control,  $p=0.42$ ), or at six months (7.9% vs. 6.1%,  $p=0.62$ ). In the insulin group, there was a lower incidence of cardiac failure during the inpatient period (12.7% vs. 22.8%,  $p=0.04$ ) and of reinfarction at three months (2.4% vs. 6.1%,  $p=0.05$ ). There was also no difference in the achieved glucose levels at 24 hours (149 mg/dL [8.2 mmol/L] insulin and 162 mg/dL [8.9 mmol/L] control,  $p=NS$ ).



## **Trials of insulin therapy in critically ill patients with conditions other than acute coronary syndromes**

### **Insulin in critically ill patients meta-analysis**

A meta-analysis of 35 randomised trials of insulin therapy in a total of 8,478 subjects was published in 2004.<sup>36</sup> Critically ill hospitalised patients with a variety of conditions (not only ACS) were included. Using a random-effects model, insulin therapy was associated with a lower risk of short-term mortality (RR 0.85, 95% CI 0.75–0.97). Interestingly, the benefit of insulin therapy was observed when the meta-analysis was restricted to trials in which a specific glucose range was targeted (RR 0.71, 95% CI 0.54–0.93), but not when a glucose goal was unspecified (RR 0.87, 95% CI 0.73–1.04). These findings are consistent with the majority of GIK trials in ACS in which insulin was administered in a fixed dose with a formulation that did not target glucose lowering (and often raised glucose levels), and in which no clinical benefit was observed.

### **Leuven surgical intensive care unit (ICU) insulin study**

In the single-centre Leuven surgical intensive care unit (ICU) study published in 2001,<sup>37</sup> 1,548 patients in the surgical ICU (63% of whom had undergone cardiac surgery and 13% of whom had diabetes) were randomised to intensive intravenous insulin therapy (target blood glucose 80–110 mg/dL [4.4–6.1 mmol/L]) versus conventional glycaemic control (insulin administered only if glucose exceeded 215 mg/dL [11.8 mmol/L] to achieve a target of 180–200 mg/dL [9.9–11.0 mmol/L]). The average morning blood glucose level achieved in the insulin and control arms was 103 mg/dL (5.7 mmol/L) and 153 mg/dL (8.4 mmol/L), respectively. Although the trial was designed to enrol 2,500 patients, the trial was terminated early due to the superiority of insulin therapy. The primary end point was death in the ICU from any cause, which occurred in 35 of 765 (4.6%) insulin patients and 63 of 783 (8.0%) control patients (unadjusted  $p=0.005$ ;  $p$  value corrected for repeated interim analyses  $<0.04$ ). This mortality difference was sustained until hospital discharge (in-hospital mortality 7.2% vs. 10.9%,  $p=0.01$ ). Several measures of morbidity, including the duration of mechanical ventilation, the incidence of renal failure, occurrence of septicaemia and development of critical-illness polyneuropathy, were all lower in the insulin arm than in the conventional arm. Based on this one study, intensive glycaemic control rapidly became the standard of care in many ICUs all over the world,<sup>38</sup> and professional medical societies extrapolated these results beyond the surgical ICU to recommend tight glycaemic control in essentially all critically ill hospitalised patients.<sup>39,40</sup>

### **Leuven medical ICU insulin study**

The Leuven investigators conducted a second trial to determine whether the same strategy of intensive glycaemic control would improve outcomes in medical ICU patients.<sup>41</sup> A total of 1,200 patients admitted to the medical ICU were randomised to intensive insulin therapy (target blood glucose 80–110 mg/dL [4.4–6.1 mmol/L]) or to conventional care (target glucose 180–200 mg/dL [9.9–11.0 mmol/L]). The average morning blood glucose level achieved in the insulin arm was 111 mg/dL (6.1 mmol/L), compared with 153 mg/dL (8.4 mmol/L) in the control group. In contrast to the surgical ICU study, insulin therapy did not reduce in-hospital mortality (37.3% in the insulin arm vs. 40.0% in the control arm,  $p=0.33$ ). However, in an exploratory analysis, patients who received ICU care for more than three days experienced lower mortality if they were in the insulin-treated group (43.0%) compared to the control group (52.5%,  $p=0.009$ ); clearly, this subgroup could only be identified after the study was completed. The Leuven investigators also reported that insulin therapy reduced the occurrence of acute kidney injury and shortened the duration of mechanical ventilation, length of stay in the ICU, and length of hospitalisation. Nevertheless, the

primary results were in contrast to the prior Leuven surgical ICU study and highlighted the uncertainty regarding the role of insulin therapy in critically ill patients.<sup>38,42</sup>

### **Glucontrol trial**

The Glucontrol trial was designed to compare two strategies of glycaemic control (blood glucose target of 80–110 mg/dL [4.4–6.1 mmol/L] vs. 140–180 mg/dL [7.7–9.9 mmol/L]) in 3,500 patients in medical or surgical ICUs in Europe.<sup>43,44</sup> However, the trial was terminated after only 1,101 patients had been enrolled due to a higher rate of hypoglycaemia in the intensive target arm compared with the control arm (9.8% vs. 2.7%,  $p < 0.0001$ ).<sup>43</sup> The mean post-admission glucose levels in the intensive and control arms were 119 mg/dL and 147 mg/dL (6.5 mmol/L and 8.1 mmol/L) respectively, and the proportions of time spent in the assigned glucose ranges were only 40.8% and 38.2%, respectively. There was no difference in mortality between the glucose control arms (16.7% in the more intensive control vs. 15.2% in the less intensive control arm,  $p = \text{NS}$ ).

### **WISEP trial**

The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (WISEP) trial<sup>45</sup> enrolled 537 patients with septic shock in 18 centres across Germany. This trial achieved mean morning blood glucose levels of 112 mg/dL (6.2 mmol/L) and 151 mg/dL (8.3 mmol/L) in the insulin and control arm, respectively. However, it was also terminated early due to excess hypoglycaemia (defined as a blood glucose  $< 40$  mg/dL [2.2 mmol/L]) in the insulin arm compared to control (17.0% vs. 4.1%;  $p < 0.001$ ). Mortality at 28 days (24.7% insulin vs. 26.0% control,  $p = 0.74$ ) and at 90 days (39.7% vs. 35.4%,  $p = 0.31$ ) did not differ between groups.

## **What can trials of insulin in non-ACS patients teach us about the design and conduct of insulin in ACS trials?**

The medical ICU trials discussed above enrolled very few patients with ACS. The Leuven medical ICU study included only 50 patients (4%) in whom the primary reason for ICU admission was a cardiovascular diagnosis,<sup>41</sup> and the WISEP trial was restricted to septic shock patients. Nevertheless, important insights from the above trials of intensive glucose control in non-ACS patients can be used to inform the design of insulin trials in ACS patients. First, caution must be exercised so that positive results of isolated studies are not implemented prematurely into clinical practice before they can be externally validated (as was done following publication of the results of the Leuven surgical ICU study). Moreover, positive results should not be extrapolated beyond the population in which they were studied (i.e. results of insulin therapy in acute STEMI patients who undergo reperfusion therapy should not be extrapolated to non-ST-elevation ACS settings, in which early management differs greatly).

Second, stopping rules for trials of insulin therapy in ACS should be rigorous and based on clinically important end points (such as death, cardiogenic shock, coma, seizure or cardiac arrest), and not on biochemical end points such as hypoglycaemia if these are unaccompanied by obvious deleterious effects in the study subjects. The reported association of biochemical hypoglycaemia with worse outcomes in epidemiological analyses of both non-ACS<sup>37,41,43,45</sup> and ACS<sup>20,46,47</sup> patients probably reflects the fact that critically ill individuals who develop hypoglycaemia are more severely ill than those who do not. Clearly, hypoglycaemia is expected to occur more frequently in patients in whom tighter glycaemic control is targeted, just as bleeding occurs more frequently in ACS patients treated with antiplatelet, anticoagulant and fibrinolytic agents. However, the absence of any negative effect of insulin on mortality in several trials in which the insulin group had clearly

greater rates of hypoglycaemia<sup>37,41,43,45</sup> provides reassurance regarding the safety of insulin infusion. Therefore, clinical trials should monitor insulin-treated patients carefully for symptomatic hypoglycaemia, but trials should not be stopped because of more frequent hypoglycaemic episodes that do not translate into increased rates of important clinical end points.

Finally, steering committees and data safety monitoring boards of future glucose control trials should refrain from terminating trials early due to “overwhelming” benefit of insulin therapy. The Leuven surgical ICU study was terminated early after 1,548 of 2,500 planned patients had been enrolled, but interim analyses were conducted by the data safety monitoring very frequently (every three months). Even though the analysis of the primary outcome was adjusted for these frequent interim analyses, a benefit for insulin therapy might still have been detected by chance alone.<sup>48</sup> Thus, as in other trials, intensive insulin therapy trials in ACS patients should only be stopped early if clear and sustained evidence of benefit or harm is detected during limited numbers of pre-planned interim analyses that preserve study power and that are based on predetermined thresholds.

## Ongoing trials of insulin therapy in acute coronary syndromes and other critically ill patients

Insulin therapy in critically ill patients continues to be an active area of clinical investigation. This section discusses one ongoing medical ICU trial of insulin-mediating glucose lowering, one ACS trial of GIK therapy, and three other ACS trials of insulin dosed to achieve tight glucose control (table 1).

### NICE-SUGAR trial

The Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) Study<sup>49</sup> will enrol a total of 6,100 medical ICU patients from 35 ICU sites in Australia, New Zealand, Canada and the US. Subjects will be randomised in an open-label fashion to one of two glucose target ranges: 81–108 mg/dL (4.5–5.9 mmol/L) or 144–180 mg/dL (7.9–9.9 mmol/L). The primary end point will be 90-day mortality.<sup>50</sup> As of May 31, 2008, more than 5,600 subjects have been enrolled, and after two interim analyses the data safety monitoring committee of the trial has made no recommendation to stop the trial, unblind the results or change the study plan.<sup>51</sup> Enrolment is expected to be completed in September 2008, with results available in the first half of 2009.<sup>51</sup>

### IMMEDIATE trial

The Immediate Metabolic Myocardial Enhancement During Initial Assessment and Treatment in Emergency Care (IMMEDIATE) trial is an ongoing randomised, double-blind, placebo-controlled trial that will randomise 15,450 ACS patients to GIK infusion (30% dextrose mixed with 80 mEq/L of potassium chloride, and 50 units/L of regular insulin) or to a placebo 5% dextrose infusion at a rate of 1.5 ml/kg/hour for a total of 12 hours.<sup>52–54</sup> The primary hypothesis is that GIK infusion will reduce all-cause mortality at 30 days and at one year compared with the placebo solution. Secondary hypotheses are that GIK will reduce the incidence of pre-hospital and in-hospital cardiac arrest, as well as the composite of death or heart failure at 30 days and at one year. The two major differences from prior GIK trials are that in IMMEDIATE: 1) enrolment will not be restricted to only those with acute STEMI but will also include patients with unstable angina and non-ST-segment elevation myocardial infarction; and 2) GIK infusion will be initiated by the paramedics in the pre-hospital setting to ensure that GIK is given well in advance of reperfusion therapy in patients who are eligible for emergency reperfusion. Patient enrolment began in 2006, and completion is not expected until 2012. Given the possibility of early harm with GIK therapy



suggested by the CREATE-ECLA and OASIS-6 GIK trial analyses,<sup>15</sup> hyperglycaemia, hyperkalaemia and hypervolaemia will need to be carefully monitored.

### **SWEET-ACS trial**

The Intensified Multifactorial Intervention on Hyperglycemic Patients with Acute Coronary Syndromes (SWEET-ACS) trial<sup>55</sup> will randomise 1,500 patients with troponin-positive ACS (with or without diabetes) with an admission blood glucose between 140–200 mg/dL (7.7–11.0 mmol/L) to an intensified multifactorial intervention strategy versus conventional care. The conventional care arm will receive in-hospital glycaemic control targeting a blood glucose of < 140 mg/dL (7.7 mmol/L). Following hospital discharge, this group will receive a multifactorial intervention that aims to achieve the levels of glycosylated haemoglobin (HbA<sub>1c</sub>), fasting plasma glucose, blood pressure, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides that are recommended by the 2005 American Diabetes Association guidelines.<sup>56</sup> In comparison, patients in the intensified intervention arm will receive more aggressive in-hospital glucose control (target blood glucose 80–110 mg/dL [4.4–6.1 mmol/L]) and, upon hospital discharge, they will receive a more intensified intervention aimed at achieving even more aggressive risk factor control than that recommended by the American Diabetes Association. The primary end point will be a composite of cardiovascular mortality, non-fatal infarction, non-fatal stroke or hospitalisation for heart failure at two years' follow-up. Although the intervention will be multifactorial and will include both inpatient and outpatient risk factor reduction with long-term follow-up, clinical events will be documented at 30 days also to provide insight regarding the efficacy of the in-hospital phase of glucose control. Recruitment is still in its early stages and results are not anticipated for several years.

### **INTENSIVE trial**

The Intensive Insulin Therapy and Size of Infarct as a Visual End-point by cardiac magnetic resonance imaging (INTENSIVE) trial<sup>54,57</sup> plans to randomise up to 700 patients with acute anterior STEMI, symptom onset within six hours of presentation and admission glucose 140 mg/dL (7.7 mmol/L) to one of two arms: intensive insulin therapy or no insulin. In the insulin arm, an insulin infusion will be administered to maintain glucose in the range of 90–130 mg/dL (4.9–7.2 mmol/L). The comparison group will have standard care with sliding scale insulin if glucose exceeds 180 mg/dL (9.9 mmol/L). The primary end point of this mechanistic trial will be infarct size as determined by cardiac magnetic resonance imaging (MRI); secondary end points will include the change in markers of inflammation and oxidative stress in the insulin compared with control groups. Although clinical end points will be documented, the trial will not be powered to detect a difference in meaningful clinical end points.

### **RECREATE pilot study**

The REsearching Coronary REDuction by Appropriately Targeting Euglycemia (RECREATE) pilot trial<sup>58</sup> is designed to test the safety of an insulin algorithm to lower glucose levels in hyperglycaemic acute MI patients when implemented in multiple centres around the world. Five hundred patients from more than 20 sites in North America, Argentina and India with acute STEMI and with admission glucose 144 mg/dL (8.0 mmol/L) will be randomised to one of two arms: intensive insulin therapy for 30 days or standard care with insulin administered only if deemed necessary. Patients without diabetes and those with diabetes who were not previously taking insulin will be included. In the intensive insulin therapy group, patients will receive an intravenous insulin infusion that is titrated to maintain plasma glucose in the range of 90–120 mg/dL (4.9–6.6 mmol/L), followed by subcutaneous glargine insulin on the ward that aims to maintain a morning plasma glucose level under 100 mg/dL (5.5 mmol/L). Insulin arm patients will be instructed to continue to

self-administer glargine insulin upon discharge until 30 days after randomisation. The primary end point will be the difference between groups in glucose level achieved at 24 hours; key secondary end points will include the difference in glucose levels at seven and 30 days. Safety end points will include the frequency of symptomatic and severe hypoglycaemic episodes. Clinical end points, including mortality, reinfarction, stroke and rehospitalisation for congestive heart failure, will also be documented. If successful, the pilot study will then be scaled up to a larger trial powered to determine whether intensive insulin therapy when compared with standard care reduces short-term mortality in acute MI.

## Conclusions

After almost 50 years, the role of insulin therapy in ACS continues to be actively investigated. Trials of fixed-dose GIK therapy in ACS have largely shown no clinical benefit, and the focus has shifted to conducting trials in which insulin is dosed to achieve and maintain glucose levels in the near-normal range. This strategy has already been tested with mixed results in critically ill populations without ACS, and the lessons learned from these trials can be used to inform the conduct of trials of insulin therapy in ACS. The efficacy of insulin-mediated glucose control in ACS patients is uncertain at present, and several questions remain unanswered (such as the ideal glucose target, significance of hypoglycaemia and optimal duration of insulin treatment). Evidence suggests that infusion-related hyperglycaemia, hyperkalaemia and hypervolemia should be avoided, as should delays in reperfusion therapy when initiating insulin therapy immediately upon hospital presentation. Until results from ongoing insulin trials in ACS patients are available, conservative recommendations for glucose control<sup>18</sup> (e.g. consider insulin treatment if glucose exceeds 180 mg/dL [9.9 mmol/L]) would appear to be appropriate.

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Table 1

Important trials of insulin therapy in ACS and non-ACS patients

Trial and year published	Population	Percent with diabetes	Intervention	Total N	1° clinical outcome	Rate of outcome in intervention arm	Rate of outcome in control arm	p-value
ECLA-GIK pilot trial <sup>7</sup> (1998)	Acute MI with or without ST elevation	16%	3 arms: high-dose GIK, low-dose GIK and control (no GIK)	407	All-cause in-hospital mortality	18 of 268 (6.7%) (both GIK arms combined)	16 of 139 (11.5%)	NS
GIPS <sup>8</sup> (2003)	Acute ST elevation MI	11%	GIK infusion × 8–12 hours versus no GIK infusion	940	All-cause death at 30 days	23 of 476 (4.8%)	27 of 464 (5.8%)	0.50
GIPS-2 <sup>9-11</sup> (2006)	Acute ST elevation MI, Killip class I only	10%	GIK infusion × 8–12 hours versus no GIK infusion	889	All-cause death at 30 days	13 of 444 (2.9%)	8 of 445 (1.8%)	0.27
CREATE-ECLA <sup>12,13</sup> (2005)	Acute ST elevation MI	18%	GIK infusion × 24 hours versus no GIK infusion	20,201	All-cause death at 30 days	1,004 of 10,088 (10.0%)	976 of 10,107 (9.7%)	0.45
OASIS-6 GIK trial <sup>15</sup> (2007)	Acute ST elevation MI	14%	GIK infusion × 24 hours versus no GIK infusion	2,748	All-cause death at 30 days	104 of 1,374 (7.6%)	92 of 1,374 (6.7%)	0.36
DIGAMI <sup>32,33</sup> (1995)	Acute MI with or without ST elevation	100%	IV glucose-insulin (GI) × 24 hours followed by SC insulin × three months, versus no insulin	620	All-cause death at three months	38 of 306 (12.4%)	49 of 314 (15.6%)	NS
DIGAMI-2 <sup>34</sup> (2005)	Acute MI with or without ST elevation	100%	3 arms: IV GI × 24 hours plus SC insulin × 3 mos; IV GI infusion × 24 hours only; or no insulin	1,253	All-cause death during follow-up (mean two years)	111 of 474 (23.4%) and 107 of 473 (22.6%)	59 of 306 (19.1%)	0.157
Hi-5 study <sup>35</sup> (2006)	Acute MI with or without ST elevation, admission glucose > 140 mg/dL	48% <sup>e</sup>	Insulin drip for 24 hours to maintain glucose 72–180 mg/dL (4.0–9.9 mmol/L), versus standard care	240	All-cause in-hospital death	4.8%	3.5%	0.75
Leuven surgical ICU <sup>37</sup> (2001)	Surgical ICU on ventilator	13%	Insulin infusion to maintain blood glucose 80–110 mg/dL (4.4–6.1 mmol/L) while in ICU, versus	1,548	All-cause death in the ICU	35 of 765 (4.6%)	63 of 783 (8.0%)	<0.04*

Trial and year published	Population	Percent with diabetes	Intervention	Total N	1° clinical outcome	Rate of outcome in intervention arm	Rate of outcome in control arm	p-value
Leuven medical ICU <sup>41</sup> (2006)	Medical ICU	17%	no insulin infusion Insulin infusion to maintain blood glucose 80–110 mg/dL (4.4–6.1 mmol/L) while in ICU, versus no insulin infusion	1,200	All-cause death in-hospital	222 of 595 (37.3%)	242 of 605 (40.0%)	0.33
Glucotrial <sup>45</sup> 2007, (abstract only)	Medical-surgical ICUs	Not published	Insulin infusion to achieve blood glucose 80–110 mg/dL (4.4–6.1 mmol/L), versus control 140–180 mg/dL (7.7–9.9 mmol/L)	1,101	All-cause death in the ICU	16.7%	15.2%	NS
WISEP study <sup>45</sup> (2008)	ICU patients with severe sepsis or septic shock	30%	Insulin infusion to maintain blood glucose 80–110 mg/dL (4.4–6.1 mmol/L) while in ICU, versus control (treat only if glucose > 200 mg/dL [11.0 mmol/L])	537	All-cause death at 28 days	61 of 247 (24.7%)	75 of 289 (26.0%)	0.74
NICE-SUGAR <sup>49-51</sup> (ongoing)	Medical ICU patients with Various conditions	N/A	Intensive glucose control (81–108 mg/dL, 4.5–5.9 mmol/L) while in ICU, versus less intense glucose control (144–180 mg/dL, 7.9–9.9 mmol/L)	Planned 6,100; over 5,600 already enrolled	All-cause death at 90 days	N/A	N/A	N/A
IMMEDIATE trial <sup>52-54</sup> (ongoing)	Acute MI with or without ST elevation and unstable angina	N/A	GIK therapy initiated in the pre-hospital setting versus no GIK	Planned 15,450 patients	All-cause death at 30 days and one year	N/A	N/A	N/A
SWEET-ACS trial <sup>55</sup> (ongoing)	Acute MI with or without ST elevation, admission glucose between 140–200 mg/dL (7.7–11.0 mmol/L)	N/A	Intensified multifactorial risk factor control (including tight glucose control in-hospital) versus less intense risk factor control	Planned 1,500 patients	Composite of CV death, non-fatal MI, non-fatal stroke, heart failure at two years	N/A	N/A	N/A
INTENSIVE trial <sup>54,57</sup> (ongoing)	Acute anterior ST elevation MI with admission glucose 140 mg/dL (7.7 mmol/L)	N/A	Insulin-glucose infusion to maintain glucose at 90–130 mg/dL (4.9–7.2 mmol/L), versus standard	Planned 700 patients	Will document clinical end points, but primary end point is infarct size	N/A	N/A	N/A

Trial and year published	Population	Percent with diabetes	Intervention	Total N	1° clinical outcome	Rate of outcome in intervention arm	Rate of outcome in control arm	p-value
RECREATE pilot study <sup>58</sup> (ongoing)	Acute ST elevation MI with admission glucose > 144 mg/dL (8.0 mmol/L)	NA	care (treat only if glucose > 180 mg/dL, 9.9 mmol/L) Insulin infusion to maintain plasma glucose in the range of 90–120 mg/dL (4.9–6.6 mmol/L), versus standard care	Planned 500 patients	by cardiac MRI Difference in glucose levels achieved at 24 hours, and seven and 30 days	N/A	N/A	N/A

\* p-value adjusted for multiple interim analyses of the primary outcome

**Key:** ACS = acute coronary syndrome; GI = glucose-insulin; GIK = glucose-insulin-potassium; ICU = intensive care unit; MI = myocardial infarction; N/A = not applicable; SC = subcutaneous; CV = cardiovascular; MRI = magnetic resonance imaging