Insulin in acute coronary syndrome: a narrative review with contemporary perspectives

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Abstract

The role of insulin in the treatment of acute coronary syndrome (ACS) has been widely studied over the **past 100** years. The current indication for its use in this context is the treatment of **hyperglycemia, irrespective of diabetes**, which is associated with adverse outcome. Initial theories proposed that **glucose was beneficial in the context of myocardial ischemia and insulin was required to enable glucose cell uptake**. However, studies testing this hypothesis with routine insulin administration during ACS have produced disappointing results and research interest has therefore declined. We propose that the less well known but important vasodilator effect of insulin has been overlooked by some of these studies and warrants further consideration. Previous reports have shown that hyperinsulinemic euglycaemia improves myocardial blood flow reserve. With this in mind, this review considers the role of insulin in the context of ACS from the perspective of a vasodilator rather than a metabolic modulator. We discuss the importance of time to treatment, dosage of insulin administered, problems with hypoglycaemia and insulin resistance, and how they may have affected the outcomes of the major trials. Finally, we propose new **study designs that allow determination of the optimal vasodilator conditions for the use of insulin as adjunctive pharmacotherapy during myocardial ischaemia.**

Keywords: insulin; myocardial blood flow reserve; acute coronary syndrome; coronary artery disease.

Abbreviations:

ACS	Acute Coronary Syndrome
GIK	Glucose-Insulin-Potassium
AMI	Acute Myocardial Infarction
IIT	Intense Insulin Therapy
MBFR	Myocardial Blood Flow Reserve
MBF	Myocardial Blood Flow
HUVEC	Human Umbilical Vein Endothelial Cells
STEMI	ST Elevation Myocardial Infarction
PET	Positron Emission Tomography
CAD	Coronary Artery Disease
T2DM	Type 2 Diabetes Mellitus

ECG Electrocardiogram

Conflicts of Interest

The authors report no relationships that could be construed as a conflict of interest

Introduction

Hypo- and hyperglycemia (dysglycaemia) are common in acute coronary syndrome (ACS), and as such, improvement in blood glucose has been extensively studied as a potential therapeutic target. The current role of insulin therapy at the time of ACS is the **regulation of blood glucose**. This was consequent to the publication of the DIGAMI trial in 1997 which **concluded** that **maintaining euglycaemia** improved outcome [1]. However the majority of subsequent large-scale multi-centre trials employing strategies with much tighter blood glucose control and have involved over 25,000 patients in total, have generally failed to demonstrate any clinical benefit. The reasons for this are unclear but several theories, including the occurrence of hypoglycemia **and hyperglycemia**, have been suggested [2-5].

Trials utilising insulin in ACS have their basis centred around two beneficial mechanisms. Firstly, the addition of glucose, insulin, and potassium (GIK) therapy is believed to optimise fuel conditions for the heart and prevent arrhythmia during myocardial ischaemia [6]. Secondly, the regulation of blood glucose during myocardial ischemia in the form of intense insulin therapy (IIT) could prevent the detrimental effects of dysglycaemia. Our group demonstrated that an intravenous insulin infusion increases peak myocardial blood flow (MBF) by up to 30% [7]. Intuitively, in the setting of ACS, the vasodilator aspect of insulin should be beneficial as a form of adjunctive reperfusion therapy **particularly in the immediate time period following primary angioplasty for STEMI. Insulin may also be helpful in mitigating the effects of the 'no-reflow' phenomenon which occurs in up to 50% of patients undergoing primary percutaneous coronary intervention (PCI) [8]. In the setting of NSTEMI, insulin's vasodilator effect may reduce ischemia by either increasing flow down the partially obstructed culprit vessel or by enhancing collateral flow.** We therefore suggest consideration be given as to whether insulin's vasodilator rather than metabolic action has an important role to play in the context of myocardial ischemia **[9,10].** The potent vasodilator effect of insulin on the myocardial vasculature is well described in the literature, yet this action is rarely credited as being of potential mechanistic benefit in the setting of ACS-related GIK and IIT studies **[11-13].** Previous IIT and GIK trials were purposefully designed to exploit the metabolic benefits of insulin rather than its effect on microvascular function. This biochemically orientated approach could explain the negative outcomes in previous insulin-based ACS studies. If we accept the premise that insulin has a role as adjunctive reperfusion therapy then several aspects in trial design such as time to treatment and dosage, could have important mitigating effects.

This review considers the role of insulin in the context of acute coronary syndromes from the perspective of a vasodilator rather than metabolic action.

Methodology

We performed a systematic search (using PUBMED, EMBASE, Cochrane Central Register of Controlled Trials CENTRAL, and Google Scholar) for randomised trials and review articles from 1960 to November 2015 of the English literature **regarding the** use of insulin in ACS, and insulin's effect on myocardial blood flow. In order to identify and retrieve all potentially relevant articles regarding this topic, the search was performed utilizing the terms ‘insulin’, ‘myocardial blood flow’, 'myocardial infarction', 'coronary flow reserve' and ‘acute coronary syndrome’. **Articles perceived to be relevant to insulin use in ACS were selected for review. References of the studies could also be included in the analysis.**

Glucose-insulin-potassium infusions during acute coronary syndromes

Metabolic modulation of acute myocardial infarction with glucose-insulin-potassium (GIK) infusion was originally proposed in the 1960’s [14]. The concept is attractive because the therapy is simple, low cost and easily implemented. GIK infusions were thought to be potentially beneficial through several different mechanisms. Free fatty acids are normally the primary fuel source for the heart but are toxic to the myocardium in the ischemic setting causing sarcolemmal and mitochondrial membrane disruption [15]. Exogenous insulin was known to suppress circulating levels of free fatty acids and also prevent their uptake by the myocardium [16,17,15]. Provision of high-dose glucose was thought to improve the efficiency of myocardial energy production during acute ischemia by becoming the preferred fuel source for the heart. **Intracellular levels of potassium are depleted during ischemia and therefore the provision of exogenous potassium to increase levels within the myocyte were believed to raise the threshold for ventricular arrhythmias [18,19]. An overview by Fath-Ordoubadi in 1997 resulted in a revival of interest in GIK administration for treating acute myocardial infarction (AMI) [20].** The first study in the post-thrombolytic era to investigate this concept was the ECLA-GIK pilot trial in 1998 [21]. This study randomised patients with suspected AMI to low or high dose GIK following admission. They found that there was a significant 66% reduction in mortality in those patients who received both **high-dose** GIK and reperfusion strategies **compared to reperfusion alone**. **Importantly, this was driven by an unexpectedly high mortality rate in the control arm**

(15%) which the authors attributed to the small cohort. Nonetheless this re-stimulated great interest in GIK therapy in ACS and a further 10 trials have taken place since, one of which did not reach completion, and another was an analysis of two studies combined **(see tables 1 and 2). Study design varied considerably with regards insulin infusion dosage and regulation of blood glucose parameters.** Overall, a total of 26,855 patients have been recruited with studies ranging from the small (120 patients) to the very large (over 20,000). The results have been disappointingly conflicting. Two studies have shown a benefit in primary end-point with evidence in favour of GIK (total 525 patients)[21,22], seven showed no difference (25,496 patients)[23-29], and one showed increased harm (954 patients) [30].

Intensive insulin therapy during acute coronary syndromes

Several studies have demonstrated that in-patient hyperglycemia is associated with a significant increase in mortality in ACS. It was therefore thought that improved glycemic control in ACS would relate to improved outcomes. The Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) was the first study to investigate this hypothesis [1]. This study randomised patients with DM presenting with an AMI to receive either intensive insulin therapy (IIT) or conventional treatment for hyperglycemia. After 1-year, a significant 29% relative risk reduction in all-cause mortality was observed with IIT. As a result of this landmark study, national guidelines were changed recommending that IIT should be used to control elevated blood glucose in those patients presenting with ACS and hyperglycemia. Insulin-based glycemic control for patients following ACS is now widespread and common practice in the Western world [31]. In line with this thinking, subsequent studies were undertaken to examine whether a narrower range of glucose control would translate into lower mortality rates. Three separate studies involving almost a total of 1800 patients have since been undertaken **(tables 1 and 2)** [32-34]. **The method of IIT differed significantly between studies: HI-5 regulated blood glucose between 4 - 10mmol, DIGAMI-2 opted for ongoing glucose regulation using subcutaneous insulin following intravenous infusion, and RECREATE targeted lower blood glucose during intravenous insulin infusion.** However all have failed to show any significant benefit with regard to improved blood glucose control and primary endpoints.

Intensive insulin therapy and glucose-insulin-potassium infusions lack efficacy in acute coronary syndromes

Since DIGAMI there have been thirteen clinical trials investigating the effect of GIK infusions and IIT in ACS (Tables 1 and 2). Apart from three, all have failed to show any convincing significant benefit and two actual harm. The reasons for the failure of these studies to demonstrate clinical benefit is unclear but several theories have been postulated. The foremost is that hypoglycaemia in the insulin-treated groups may be having an adverse effect. Several studies have associated hypoglycaemia (plasma glucose ≤3.9mmol/l) with an increase in cardiovascular mortality, including those following an ACS [35,36]. Hypoglycemia, either symptomatic or biochemical, is a frequent occurrence in the insulin arm, ranging from 10-22% **(see tables 1 and 2 for hypoglycemia occurence in studies)**. Hypoglycemia has been demonstrated to have a number of adverse physiological effects, including the induction of a hypercoagulant state, an inflammatory response, QT prolongation and a detrimental effect on cardiac metabolism because of the inability of the heart to use glucose [37,38].

The effect of insulin on myocardial blood flow

Myocardial blood flow reserve (MBFR) is the ratio of MBF at peak hyperaemia to that at rest, and, in the context of unobstructed coronary arteries, is a measure of microcirculatory function. Peak hyperaemia is usually achieved by the administration of a vasodilator drug such as adenosine or dipyridamole. Values of MBFR in healthy individuals is usually >2.0 [39]. Our group (see fig.1) demonstrated that insulin-induced hypoglycaemia was associated with a 14% reduction in MBFR with respect to baseline values in both type 1 diabetics and healthy controls [2]. We suggested that the reduction in blood flow occurring during hypoglycaemia might be detrimental in the context of ACS. Importantly, we also noted that hyperinsulinemic euglycemia (insulin infused at 1.5mU/Kg/min) was associated with a 22% increase in MBFR above baseline. This increase in myocardial blood flow by hyperinsulinemia had also been observed in other previous human studies. In 1997, Rogers et al reported a 12% increase in coronary sinus blood flow in patients with suspected ischaemic heart disease who received a GIK infusion [11]. A further study found that local intracoronary insulin infusion increased coronary sinus blood flow, suggesting a direct insulin-mediated effect [12]. Sundell et al observed that higher blood insulin levels resulted in greater increases in myocardial blood flow [40]. Despite the potent vasodilator effect of insulin on the myocardial vasculature being well described in the

literature, this action is rarely credited as being of potential mechanistic benefit in the setting of ACS-related GIK and IIT studies. Furthermore, the mechanism by which insulin induces vasodilation is not fully understood but is thought to be mediated through nitric oxide release [12]. Sobrevia performed the first in vitro study to examine this association by monitoring L-arginine transport – a precursor for nitric oxide production - into human umbilical vein endothelial cells (HUVECs) [41]. When HUVECs were incubated with insulin under conditions of euglycaemia (5mmol/L) there was a 2.5-fold increase in the transport of the amino acid L-arginine (a precursor for nitric oxide production via nitric oxide synthase) into the HUVECs. They also noted a 3-fold increase in intracellular cyclic guanosine monophospate (cGMP) concentrations - an index of nitric oxide synthesis. This data demonstrated that insulin led to an endothelium-dependent release of nitric oxide and this was suggested to be the mechanism behind insulin-induced vasodilatation.

Insulin: vasodilator and metabolic actions in acute coronary syndromes

Intuitively, in the setting of ACS, the vasodilator aspect of insulin should be beneficial as a form of adjunctive reperfusion therapy. We must therefore consider whether insulin's vasodilator action also has an important role to play in the context of myocardial ischemia. Previous IIT and GIK trials were designed to exploit the metabolic benefits of insulin rather than its effect on microvascular function. Thus it is worth re-examining from a reperfusion stand-point, how the biochemically adopted approach in trial design, could have affected outcomes with previous insulin-based ACS studies. Thus, if insulin's vasodilator action is important as adjunctive reperfusion therapy then the following aspects in trial design could have a significant effect:

1. Time delay to initiation of insulin therapy following acute myocardial ischemia.
2. Optimum treatment dose with insulin therapy to achieve maximum vasodilator effect.
3. Prevalence of hypoglycaemia.
4. The role of insulin resistance.

Time delay to initiation of insulin therapy in IIT and GIK ACS studies

It is well established that the mortality following AMI is directly related to infarct size. Infarct size is directly related to the area of ischemic myocardium at risk and the duration of ischemia. For the past 40 years, clinical research in reperfusion therapy has been directed towards the development of agents that improve MBF in the

most rapid and complete manner possible. This has been achieved with great success using biological clot dissolution (thrombolysis) and, has been superseded by mechanical means (primary angioplasty). It is well established that any delay in reperfusion therapy is directly related to an adverse outcome and that 'time is muscle' [42].

Out of the 14 reports on IIT and GIK, the times from onset of chest pain to administration of IIT and GIK ranged from 55 minutes to 19hrs. In the DIGAMI study, insulin was given 'within 24hrs' [1]. Furthermore, because either median or mean values are consistently quoted this means that a significant percentage of patients received insulin therapy beyond that time frame. For example, in the largest study (CREATE-ECLA) of 20,000 patients with **ST-elevation myocardial infarction (**STEMI**)**, the median time to randomisation was 4.7hrs resulting in 20% of patients receiving GIK 8-12hrs after symptom onset [25]. In the REVIVAL study, 25% of patients received insulin therapy more than 18hrs after symptom onset [24]. **The IMMEDIATE trial administered fixed-dose GIK infusions out-of-hospital and achieved a median treatment initiation time of 1.3 hours after symptom onset [29]. However only 50% of enrolled patients resulted in a final diagnosis of ACS suggesting that many patients had alternate diagnoses, and this may have inadvertently affected outcome. Nevertheless, in sub-group analysis of the STEMI population, there was a significant reduction in composite outcome of cardiac arrest and 1-year mortality.**

Clearly if insulin therapy is to be successful as an adjunctive reperfusion therapy, treatment needs to be given as quickly as possible and within a minimum timeframe. The wide range of times to treatment in all of the above trials may have had an important confounding effect.

Suboptimal treatment dose with insulin therapy to achieve maximum vasodilator effect

The doses of insulin therapy in the GIK and IIT trials varied considerably, with some protocols containing high and low dose arms, and others titrating insulin infusion rates according to blood glucose. Where data was available, the mean insulin infusion rate (in mU/kg/min) for each major trial was calculated and presented in tables 1 and 2. Our group demonstrated that 1.5mU/kg/min insulin is able to increase peak MBF by 30% compared to without [7]. This dose compares favourably with the findings of Sundell [40]. He showed that an insulin infusion of 1.0mU/kg/min and 5mU/kg/min produced a 19% and 44% increase in adenosine-induced peak hyperemic MBF respectively. In the post-DIGAMI GIK and IIT studies the doses infused ranged between 0.2mU/kg/min up to a maximum of 1.25mU/kg/min. Seven of these studies had infusion rates of <1mU/kg/min

[1,30,22,28,21,33,34], and two did not report their infusion rates [23,43]. Clearly, it is possible that the hyperemic effect of insulin in myocardial ischemia may have to be above a certain value to be effective and that, for example, doses lower than 1mU/kg/min may not be sufficient.

High prevalence of hypoglycemia during IIT and GIK studies

Hypoglycaemia, which reduces MBF, occurred frequently in the treatment arms of the GIK and IIT studies **and ranged from 0 to 23% (see tables 1 and 2).** However, in 5 studies the rates were not mentioned at all [28,26,27,29,21]. Some studies recorded symptomatic hypoglycaemia only (not biochemical) and this would significantly underestimate true biochemical hypoglycemia [22,25].

Furthermore, the frequency of glucose measurements varied widely, with three studies only measuring blood glucose three times within a 24-hour period and are therefore likely to have missed episodes of hypoglycemia [22,25,26].

The role of insulin resistance

Insulin resistance is present in patients with type 2 diabetes (T2DM) and also those patients with metabolic syndrome. The prevalence of T2DM within the ACS-related GIK and IIT trials ranged from 6-39%, and was pre-requisite for all patients participating in the DIGAMI-2 trial [32]. Central abdominal obesity (BMI >30 kg/m^2) which forms a major parameter of the 'pre-diabetes' metabolic syndrome is associated with insulin resistance [44]. Obesity was prevalent in over 23% of patients in insulin-related ACS trials, implying that metabolic syndrome and therefore insulin resistance was also present [22,32,23]. **In fact, a recent study identified that insulin resistance in non-diabetics was diagnosed in 60-70% of their STEMI cohort [45].** The results of studies investigating the effect of insulin resistance on MBF have been conflicting. Quantitative assessment of MBF using PET in 167 angina patients found IR to be an independent predictor of reduced hyperaemic MBF [46]. Another study demonstrated a diminished MBF response to exogenous insulin administration in obese subjects using both physiological and supra-physiological hyperinsulinemia regimens [47]. In contrast however, Sondergaard using PET, reported no difference in hyperemic MBF between T2DM and non-diabetics with coronary artery disease, in response to hyperinsulinemia [48]. If we consider that insulin resistance does indeed impair insulin's vasodilatory effect on MBF, then this may explain at least in part the disappointing

results in some of the GIK and IIT ACS studies which contained a significant number of patients with metabolic syndrome and T2DM.

The effects of insulin infusion on myocardial ischemia - what has gone before and what is not known

Human studies investigating whether an infusion of insulin (whilst maintaining normoglycemia) can improve MBF within ischemic myocardium, have been limited and inconclusive. Marano examined the effect of a GIK infusion on peak MBF but this was 24 hours after a completed infarct [49]. The group showed that although there was improvement in flow, this was confined to the segments adjacent to the infarcted area. **Bucciarelli-Ducci et al administered 24-hour GIK infusions on STEMI patients initiated prior to undergoing primary PCI. GIK infusion was found to be associated with improved myocardial blush grade which is used as an angiographic marker of myocardial reperfusion after PCI [50]. These two studies add further argument that timely administration of such therapies predict myocardial salvage.** There have also been studies undertaken during the 1970's in patients with ischemic heart disease but these produced conflicting and unreliable results [51,52]. In general, they used small numbers, were observational and had little or no statistical power. Furthermore, the assessment of ischemia was indirect, using symptoms, ECG and end-diastolic pressure changes. Large bolus doses of both insulin and glucose were also given which often caused transient and severe hyperglycemia (>30mmol). **This may be important because in STEMI patients, hyperglycemia is a strong predictor of impaired coronary flow prior to primary PCI [53].**

Specifically, there have been two studies, both in 2006, looking at the effects of hyperinsulinemic euglycemia on MBF in patients with ischemic heart disease [54,48]. All subjects had stable angina with documented significant CAD, rather than ACS. Each study produced conflicting results to the other. Using the vasodilator (adenosine) PET to assess MBF, Lautamaki investigated the effects of hyperinsulinemic euglycemia in 47 patients with significant CAD and T2DM [54]. Insulin was infused at 1mU/kg/min **for 60 minutes** with the result that MBF to the ischemic regions was improved by 20% compared to without insulin. However, the vasodilator flow assessments (with and without insulin) were performed within a single session and always in this set order: placebo infusion followed by insulin infusion. This methodological strategy could have inadvertently induced a pre-conditioning effect and reduced ischemic burden in the insulin-based arm [55].

Sondergaard examined 27 patients with CAD, of whom 12 had T2DM [48]. She reported that hyperinsulinemic euglycemia (1mU/kg/min **infused for 2 hours**) had no effect on hyperaemic MBF in the ischemic regions.

However they did not show increased flow in the healthy regions either, which is surprising as this feature has been consistently demonstrated in other studies.

Importantly, neither study found an increase in area of myocardial ischemia. This 'coronary steal phenomenon' can theoretically occur when maximal vasodilatation of resistance vessels occurs in non-ischemic regions with diversion of blood away from underperfused regions where the vasodilator reserve has been exhausted [56]. **This phenomenon could potentially worsen myocardial ischaemia, but it should be pointed out that insulin has not been demonstrated to elicit this response in either animal or human studies.** In summary therefore, the effect of hyperinsulinemic euglycemia on patients with myocardial ischemia is not known.

Future Research

The potential confounding factors that may offset the beneficial therapeutic effects of hyperinsulinaemia during ischaemia are summarised in figure 2. We recommend that any future studies should initially address these before any further large trials examining the vasodilatory effects of hyperinsulinaemia in myocardial ischemia are undertaken. Larger randomised control trials could then be designed to assess the effects of acute insulin therapy in ACS from the perspective of adjunctive reperfusion therapy.

Conclusion

Exploration of the potential benefits of insulin therapy in the context of acute coronary syndrome has been extensively studied over the last 50 years. Although the initial studies showed promise, later studies have been surprisingly disappointing in terms of clinical outcome. This may be because previous trials have been designed around the metabolic modulatory aspects of insulin, and have overlooked its potent vasodilator effect. As a result, delay in initiation of therapy, insufficient insulin dose, insulin resistance and hypoglycemia may all have had important mitigating effects in terms of outcome. We recommend detailed studies determining the optimum conditions for insulin's vasodilator effect on myocardial blood flow before any further large-scale ACS trials involving insulin are undertaken.

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Table 1: Studies that showed benefit of insulin in ACS

Study	Treatment strategy	Design	Outcomes	Occurence of hypoglycaemia (%)	Type 2 diabetes (%)	Insulin dose (mU/kg/min)[†]	Time from symptom onset to treatment (hrs)
DIGAMI 1997 [1]	**GR**	620 patients (mean age 68) with ACS and blood glucose > 11mmol/l randomised IIT for ≥24 hours followed by long-term subcutaneous insulin vs usual care.	1-year mortality significantly lower in the IIT arm (19 vs 26%, relative reduction 30%, p=0.027). In patients not previously on insulin and low cardiovascular risk, in-hospital mortality was significantly lower (5% vs 12%, relative reduction 58%, p<0.05).	15	82	1.2 first hour then titrated to glucose	Mean (SD) 13 (7)
ECLA-GIK Pilot 1998 [21]	**GIK**	405 patients with ACS (mean age 58) randomised to 24-hours high vs low dose GIK infusion vs usual care.	62% received reperfusion therapy (95% thrombolysis, 5% PCI). No significant difference in in-hospital mortality between groups. In subgroup analysis GIK plus reperfusion group had lower mortality (5 vs 15% p=0.01). Composite endpoint of death, non-fatal ventricular fibrillation, and heart	Not mentioned	15[‡]	High dose 1.3. Low dose 0.5.	Mean (SD) 11 (0.56)

[†] Estimated based on 70kg subject
[‡] Includes type 1 diabetes as proportion not given

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			failure was lower in GIK group (12 vs 20% p=0.03).				
GIPS-1 2003 [23]	**GIK and GR**	940 patients (mean age 60) presenting with STEMI eligible for reperfusion therapy were randomised to GIK infusion vs usual care prior to revascularisation.	No significant difference in 30-day mortality, but patients who received GIK without clinical heart failure had lower 30-day mortality (1.2 vs 4.2% p=0.01).	0	11‡	Dose titrated glucose 7-11mmol/L.	Median (IQR) 3(2, 4).
Krlijanac 2005 [22]	**GIK**	120 patients with STEMI received thrombolytic therapy and randomised to GIK infusion vs usual care.	Major adverse cardiac events (MACE), defined as a composite of cardiac death, reinfarction, malignant arrhythmias, and severe heart failure at 1-month and 1-year, was lower in GIK group at 1-month (10% vs 33% p=0.004) and 1-year (13% vs 40%, p=0.001).	2	17‡	0.8	Mean (SD) 3(2)

Table 2: Studies that showed no benefit from insulin in ACS

Study (Year)	Treatment strategy	Design	Outcomes	Hypoglycaemia (%)	Type 2 Diabetes (%)	Insulin dose (mU/kg/min)[§]	Time from symptom onset to treatment (hrs)
POL-GIK (1999) [30]	**GIK**	954 patients with chest pain and 'ischaemic ECG' within 24-hours were randomised to GIK vs saline for 24-hours plus usual care.	ACS confirmed in 88%. 60% received fibrinolysis. Non-cardiac mortality was higher in GIK group (11.1 vs 6.5% p=0.01). Causes of non-cardiac mortality were stroke, GI bleeding, and neoplastic disease. Cardiac death, resuscitated cardiac arrest, congestive heart failure, reinfarction, arrhythmia, and angiography at 35 days were no different between groups.	7.6	6.5	0.3	Median (IQR) 5 (3,10)
REVIVAL (2004) [24]	**GIK**	312 patients with ACS (80% STEMI) within 48 hours randomised to 24-hour infusion of GIK vs control. Myocardial perfusion scintigraphy was performed at baseline and 2 weeks to compare myocardial salvage in infarct territory-matched	98% received reperfusion therapy (89% PCI and 11% thrombolysis). 15% did not complete GIK infusion due to adverse events. Myocardial salvage was not improved by insulin overall, but subgroup analysis showed diabetics had improved myocardial salvage index. There was no difference in 6-month mortality.	Not mentioned	23**	1.2	Median (IQR) 9 (3,18)

[§] Estimated based on 70kg subject
[**] Includes type 1 diabetes as proportion not given

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		patients.					
DIGAMI-2 (2005) [32]	**GR (target 7-10 mmol/l)**	1253 patients with type-2 diabetes or glucose >11mmol/l with suspected ACS were randomised to 24-hour infusion of insulin-glucose followed by subcutaneous insulin or standard glucose control vs usual care.	84% had confirmed myocardial infarction (44% had STEMI). Mortality at 2 years was no different between groups. Secondary endpoints of stroke and reinfarction were also no different.	11	100	1.2 first hour then titrated to blood glucose	Mean (SD) 13(7)
CREATE-ECLA (2005) [25]	**GIK**	20201 patients with STEMI randomised to 24-hour infusion of GIK vs usual care.	9% received PCI. 74% received thrombolysis. No significant difference between groups in 30-day mortality. No difference in cardiac arrest, cardiogenic shock, composite death/nonfatal cardiac arrest. Insulin group displayed no benefit in pre-specified subgroups, including strata of time from symptom to randomisation, killip class, type of reperfusion therapy, diabetes status, and baseline glucose.	0.4	18	1.3	Median (IQR) 5 (3,7)
GIPS-II (2006) [28]	**GIK and GR**	889 patients with STEMI eligible for reperfusion therapy without heart failure randomised to GIK infusion for 12hrs vs nil plus usual care.	94% received reperfusion therapy (88% primary PCI). There was no significant 30-day mortality benefit in the insulin group.	Not mentioned	6	Titrated but mean 2.3(SD 1.8) in first hour	Not mentioned
Hi-5 (2006) [33]	**GR (target 4-10 mmol/l)**	240 patients with acute myocardial infarction within 24hrs and either	72% had STEMI. 68% received reperfusion therapy. In-hospital, 3-month, and 6-month mortality	10	39	0.5 first hour then titrated	Mean (SD) 13(8)

		known diabetes or glucose > 7.8mmol/l randomised to insulin infusion ≥24hrs vs conventional treatment.	were not significantly different between groups. The insulin group had lower incidence of in-hospital cardiac failure (13% vs 23%, p=0.04) and reinfarction within 3 months (2% vs 6%, p=0.05)				
OASIS-6 (2007) [26]	**GIK**	2748 patients with STEMI randomised to 24-hour GIK infusion vs usual care.	42% received thrombolysis, and 32% received PCI. No significant difference between groups in 30-day outcomes of death, heart failure, or composite death/heart failure. No difference in 6-month heart failure, composite heart failure/death, myocardial infarction, stroke, cardiogenic shock, and cardiac arrest.	Not mentioned	15	1.3	Not mentioned
Combined OASIS-6 + CREATE ECLA analysis (2007) [27]	**GIK**	n=22943	No significant difference between groups in 30-day mortality, heart failure, or composite death/heart failure. In subanalysis days 0-3, mortality and composite death/heart failure was increased in the insulin treated group (6.2% vs 5.5% p=0.03, and 15.8% vs 14.5% p=0.02, respectively). Hyperglycaemia, hyperkalaemia, and high Kilip class predicted adverse outcome.	Not mentioned	17	1.3	Not mentioned

IMMEDIATE (2012) [29] ††	**GIK**	871 pre-hospital patients with suspected ACS randomised to GIK infusion vs 5%-dextrose placebo.	50% progressed to myocardial infarction. 41% with STEMI and 47% undergoing primary PCI. Progression to MI and 30-day mortality was no different between groups. Composite endpoint of cardiac arrest and in-hospital mortality was lower in insulin group (4.4% vs 8.7%, p=0.01).	Not mentioned	29**	1.3	Median (IQR) 1.5(1,3)
RECREATE (2012) [34]	**GR (target 5-6.5 mmol/l)**	287 patients with STEMI within 24 hours onset and blood glucose>8mmol/l randomised to IIT vs usual care.	77% received thrombolysis, and 14% received PCI. 30-day all cause mortality were similar in both groups(~9%). Reinfarction, stroke, congestive heart failure, and rehospitalisation were no different between groups.	23	30**	Titrated to blood glucose. Mean 0.5mU/kg/min(SD 0.3) in 24hrs	Median (IQR) 10(6,18)

** Includes type 1 diabetes as proportion not given

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Figure Legends

Figure 1. Myocardial blood flow reserve (MBFR) at baseline and during hyperinsulinemic euglycemia (HE) and hyperinsulinemic hypoglycemia (HH). In healthy controls HE increases MBFR 22% above baseline, whereas HH reduces MBFR 14% below baseline (both $p<0.0001$). There was a similar effect in diabetics. Solid circles, healthy control subjects; solid squares, type 1 diabetes mellitus patients (mean±SD)[7].

Figure 2. Diagram illustrating the effects of insulin on myocardial ischaemia and potential confounding factors.

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