INTRODUCTION
Different types of hyperglycaemia like pre-existing diabetes, IFG, IGT, stress hyperglycaemia and new onset of diabetes are usually common with Acute Myocardial Infarction (AMI). In present day, Diabetes Mellitus (DM) is actually considered as a disease of heart, diagnosed by estimation of blood sugar. This over jealous statement has developed from the fact that, majority of Type 2 diabetes (T2DM) has cardiovascular complications either before or after diagnosis, and definitely in the long run.

UKPDS has proved beyond doubt that, tight glycaemic control can lower the macro vascular complications like Coronary Artery Disease (CAD), Peripheral Vascular Disease (PVD), and Cerebro Vascular Accidents (CVA) etc. In our country proper assessment of the existence and subsequent management of diabetes during diagnosis of AMI and the vice versa are rarely practiced. Care of the diabetic problem is considered as like the care of a ‘neglected step child’ compared to the care of the cardiac status. But without successful control of DM, effective results in AMI treatment is impossible, both during the acute state and also in follow up.

Our knowledge gaps include in defining the detrimental blood sugar values, optimal ways and timing of blood sugar examination during hospitalization due to AMI. Gaps are also there, to understand whether hyperglycaemia is a cause or simple effect of AMI in terms of mortality or morbidity. We also do not properly understand the physiological and pathological effects of blood sugar level on the cardiovascular states. As we will have to wait for the firm guidelines from large evidence based controlled studies on the ‘glycaemic care in AMI’ to be published, till then we must translate the present knowledge into the practice.

DM AND AMI: EPIDEMIOLOGY
Patients with T2DM, without previous MI have a risk of MI similar to a nondiabetic with one past history of MI, which practically means one T2DM when diagnosed had already an attack of MI and one case of evident MI subsequently is equivalent to a second attack of MI.1 Mortality from AMI in patients with DM is double than the risk as seen with non diabetics.2 Five year mortality in AMI with hospitalized diabetic patients is 75% higher than patients with malignant diseases3. Regardless of improved approaches, the mortality and morbidity in AMI remains very high in diabetes, compared to persons without diabetes.

Bartnik M et al analyzed the blood glucose pattern amongst hospital cases of acute coronary artery disease from 110 centers of 25 nations in Euro Heart Survey on Diabetes and the Heart. They found 71% of cases had abnormal blood glucose in any form. Out of them 31% had pre-existing DM, 15% newly diagnosed DM during the attack of AMI, 22% had IGT and 3% had IFG.4 This practically means that only a minor group (29%) of patients developing AMI is normoglycaemic.

EUROASPIRE II Study documented that 28% of cases of AMI had diabetes, either preexisting or newly diagnosed during AMI.5 The prevalence of pre-existing DM in patients with Acute Coronary Syndrome (ACS) varies between 19 to 23% in different studies like GRACE, OASIS and Euro Heart Survey.6
Insulin in Acute Myocardial Infarction with Diabetes

Peripheral glucose disposal. The glycaemic response to these “stress” hormones is exaggerated when superimposed on insulin resistance manifest as obesity in these patients.

Nicolau et al found that the hyperglycaemia in patients with AMI is a better predictor for mortality in younger patients than in the elderly population. Since advanced age is a strong independent risk factor for mortality in patients with AMI, hyperglycaemia may have a relatively greater importance in younger populations and a weaker impact in the elderly population.

Effect of Hyperglycaemia on AMI

Acute hyperglycaemia leads to many adverse effects that contribute to a poor outcome in STEMI as shown in Table 1. Hyperglycaemia is a result of relative insulinopenia, which lead to increased lipolysis and free fatty acid generation, as well as diminished myocardial glucose uptake and a decrease in glycolytic substrate for myocardial energy requirement. Myocardial ischemia results in an increased rate of glycogenolysis and glucose uptake via translocation of GLUT-4 receptors to the sarcolemma. Because glucose oxidation requires less oxygen than free fatty acid oxidation per molecule of ATP produced, myocardial energetics are more efficient during the increased dependence on glucose oxidation with ischaemia. With relative insulinopenia, however, the ischaemic myocardium is forced to use free fatty acids instead of glucose as an energy source because myocardial glucose uptake is acutely impaired. Thus, a metabolic crisis may arise as the hypoxic myocardium becomes less energy efficient in the setting of hyperglycaemia and insulin resistance.

The treatment of hyperglycaemia improves the metabolic crisis of myocardium. Treatment with insulin exerts also extra benefits as shown in Table 2.

Table 1: Acute Cardiovascular Effects of Hyperglycaemia

<table>
<thead>
<tr>
<th>Effect</th>
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<tbody>
<tr>
<td>Endothelial dysfunction</td>
</tr>
<tr>
<td>Platelet hyper-reactivity</td>
</tr>
<tr>
<td>Increased cytokine activation</td>
</tr>
<tr>
<td>Increased lipolysis and free fatty acid levels</td>
</tr>
<tr>
<td>Reduced glycolysis and glucose oxidation</td>
</tr>
<tr>
<td>Increased oxidative stress (?) Increased myocardial apoptosis</td>
</tr>
<tr>
<td>Impaired microcirculatory function (“no-reflow” phenomenon)</td>
</tr>
<tr>
<td>Impaired ischemic preconditioning</td>
</tr>
<tr>
<td>Impaired insulin secretion and insulin stimulated glucose uptake</td>
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</tbody>
</table>

Table 2: Potential Acute Cardiovascular Benefits of Insulin

<table>
<thead>
<tr>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary vasodilatation</td>
</tr>
<tr>
<td>Improved endothelial function</td>
</tr>
<tr>
<td>Improved platelet function</td>
</tr>
<tr>
<td>Antiapoptotic effect</td>
</tr>
<tr>
<td>Antioxidant effect</td>
</tr>
<tr>
<td>Anti-inflammatory effect</td>
</tr>
<tr>
<td>Antithrombotic effect</td>
</tr>
<tr>
<td>Decreased thromboxane AII levels</td>
</tr>
<tr>
<td>Increased prostacyclin release</td>
</tr>
<tr>
<td>Diminished plasminogen activator inhibitor-1 levels</td>
</tr>
</tbody>
</table>

Acute hyperglycaemia is common in patients with STEMI even in the absence of a history of type 2 DM. Hyperglycaemia is seen in up to 50% of all STEMI patients, whereas previously diagnosed DM is present in only 20% to 25% of STEMI patients. The prevalence of type 2 DM or impaired glucose tolerance are as high as 65% in AMI patients without prior DM when oral glucose tolerance testing is performed.

With every 18-mg/dL increase in glucose level, there is a 4% increase in mortality in nondiabetic subjects. When admission glucose level exceeds 200 mg/dL, mortality is similar in non-DM and DM subjects with MI. Admission glucose has been identified as a major independent predictor of both in-hospital congestive heart failure and mortality in STEMI. Fasting glucose the day after admission appears to be a better predictor of early mortality than glucose level on admission. Patients with both elevated admission glucose and an elevated fasting glucose the next day have a 3-fold increase in mortality. Similarly, failure of an elevated glucose level to fall within 24 hours of admission is associated with excess mortality in STEMI patients without DM.

The presence and degree of hyperglycaemia may not correlate with infarct size, as is commonly thought. Counter regulatory hormones (catecholamine’s, growth hormone, glucagon, and cortisol) are released in proportion to the degree of cardiovascular stress and may cause hyperglycaemia and an elevation of free fatty acids, both of which lead to an increase in hepatic gluconeogenesis and a decrease in insulin-mediated peripheral glucose disposal. The glycaemic response to these “stress” hormones is exaggerated when superimposed on insulin resistance manifest as obesity in these patients.

Nicolau et al found that the hyperglycaemia in patients with AMI is a better predictor for mortality in younger patients than in the elderly population. Since advanced age is a strong independent risk factor for mortality in patients with AMI, hyperglycaemia may have a relatively greater importance in younger populations and a weaker impact in the elderly population.

EFFECT OF HYPERGLYCAEMIA ON AMI

The treatment of hyperglycaemia improves the metabolic crisis of myocardium. Treatment with insulin exerts also extra benefits as shown in Table 2.

Table 3: Treatment targets after ACS & DM

<table>
<thead>
<tr>
<th>Target</th>
</tr>
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<tbody>
<tr>
<td>Revascularization</td>
</tr>
<tr>
<td>Anti-ischaemic drugs</td>
</tr>
<tr>
<td>Anti-platelet and anti-thrombin drugs</td>
</tr>
<tr>
<td>Secondary prevention by</td>
</tr>
<tr>
<td>Modulation of lifestyle including smoking</td>
</tr>
<tr>
<td>Blood pressure, sugar, lipid control</td>
</tr>
<tr>
<td>Renin – Angiotensin blockers</td>
</tr>
<tr>
<td>Beta blockers</td>
</tr>
</tbody>
</table>

The management target after ACS in DM is to prevent death, recurrent MI, heart failure, arrhythmias and progression of coronary atherosclerosis controlling myocardial function, abnormal platelet & coagulation function, stabilization of plaques, glucose and lipid control as shown in Table 3.
Success rate, in presence of DM are poorer to treat or save one life or to prevent one defined end point, since they have worser background and till now neglected approach are being maintained towards diabetic control. However the guideline for important treatment aims in DM as per European Guidelines by Third Joint Task Force (2003) is shown in Table 4.

**LIFESTYLE MODIFICATION**

As both the diseases, CAD and DM are the diseases of lifestyle, modification in terms of diet; exercises and smoking are highly helpful. Personal involvement and regular counseling are the key factors in its success.

**GLYCAEMIC CONTROL IN ACS**

Hyperglycaemia during acute attack of ACS is very common. This is regardless of whether there is pre-existing diabetes, event related new onset diabetes or stress hyperglycaemia (usually disappearing after the acute episode). In this entire situation, glycaemic control is a powerful predictor of survival and in- hospital complications as evidenced in prior studies. But many lacunae exist in our understanding of the situation, particularly the inter-dependency of hyperglycaemia and acute coronary events in terms of treatment outcome.

These gaps are –

1. Currently there is no consensus about the precise glucose value that should be considered abnormal on admission.
2. No consensus about the most ideal method of measuring the initial and subsequent blood glucose levels in the acute episode of ACS exists.
3. Benefits of treating hyperglycaemia and its suitable target values are not proved definitely.
4. It is not also clear, whether the admission blood glucose values or subsequent in-hospital values are more related to mortality and morbidity.
5. Finally the patho-physiological effect of hyperglycaemia in ACS outcome and the vice versa is not also well defined.

In 2008, American Heart Association Diabetes Committee reviewed the problem and published the opinion in Circulation15 as follows.

**ADMISSION BLOOD GLUCOSE AND ACS OUTCOME**

Several studies have tried to correlate that, higher admission blood glucose level determines the rate of hospital complications and chances of death. But till now no consensus exists regarding safe outcome level of admission blood glucose value. The incidence of this situation during ACS is noted in 25 to 50% cases in different studies.16 Capes et al in a meta-analysis of 15 studies observed that the relative risk of death with admission glucose >110mg / dl is 3.9 times higher than normal admission glucose in cases of ACS without diabetes16. In diabetic patients 70% higher risk in hospital death was reported, where admission glucose was >180mg/dl than with normal admission glucose.16 Foo et al studied 2127 patients with ACS and observed near – linear relationship between higher admission glucose level and higher rate of left ventricular failure and cardiac death17. Large infarct size amongst patients with or without diabetes was seen is hyperglycaemic AMI patients 18. Wahaab et al found the mortality risk of admission glucose is highest in hyperglycaemic AMI patients who had no history of previous diabetes 19. In the Cooperative Cardiovascular Project, a largest study of 141680 elderly AMI patients, significant 13% to 77% relative increase in 30day mortality and 7% to 46% in one year mortality were observed with higher admission glucose values. The risk of 30-day mortality was higher in new onset hyperglycaemia than known diabetes and risk started once blood glucose was higher than 110mg/dl but with higher threshold with known diabetics.20 Similarly in CREATE-ECLA Study, 30 day mortality was 14% in higher glucose group than control group of 6.6% 21 and in HI-5 study 6 month mortality was higher with near 24 hours glucose ≥144mg/dl.22

**Table 4 : Treatment goals by European Guidelines for Cardiovascular Diseases Prevention**

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Without proteinuria</th>
<th>130/80mm of Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>With proteinuria</td>
<td>&gt;1G/day</td>
<td>125/75 mm of Hg</td>
</tr>
</tbody>
</table>

2. **Self monitored blood glucose**
   - (mg/dl)
   - Fasting / Pre-prandial: 136-160
   - Postprandial (peak): 110-135
   - Before bed (night)

3. **HbA1C (%)**
   - 6.2 – 7.5

4. **Lipid profile**
   - LDL Cholesterol: <100
   - Total Cholesterol (TC): <175
   - HDL Cholesterol: >40 for men, >46 for woman
   - Non HDL Cholesterol: <150
   - Triglycerides: <150
   - TC : HDL: <3

5. **Smoking cessation**

6. **Regular physical activity** at least 30-45min /day, 5days / week

7. **BMI ≤25 kg/m²**, 10% reduction of weight for over weight

8. **Waist circumference** (ethnicity men <94cm, woman <80cm wise)

9. **Diet**
   - Salt intake: <6g/day
   - Fat intake: Saturated <10%, Trans fat <2% of total calories
   - PUFA n=6=4-8%, n=3=2G/day
   - Alcohol: Upto 30G in men, 20G in woman

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PERSISTENT HYPERGLYCAEMIA DURING HOSPITALIZATION

Hyperglycaemia during hospitalization is probably carrying more or at least some risks like admission glucose levels. Svensson et al observed a 46% increase in mortality in patients with ACS, where in-hospital blood glucose value was above 119mg/dl regardless of the values of admission glucose. Goyal et al also observed an increase in 30 and 180 day mortality with increase in blood glucose values during the first 24 hours of admission and the reverse. But till now, there is no definite study which has evaluated multiple blood sugar values in 24 hours and hence the real value of persistent hyperglycaemia can not be interpreted.

LINK BETWEEN HYPERGLYCAEMIA AND OUTCOME IN ACS

Whether hyperglycaemia is a cause of adverse outcome in ACS or a simple marker is not yet settled. The possible explanations for hyperglycaemia worsening the condition of ACS are as follows. 15

1. Decreased collateral circulation and increased infarct size
2. Abolition of ischaemic preconditioning and promotion of myocardial apoptosis
3. Higher circulatory catecholamine level
4. Elevation of blood pressures and prolongation of Q-T interval
5. Microvascular dysfunction and resultant perfusion defect
6. Endothelial dysfunction
7. No reflow phenomenon after reperfusion
8. Higher prothrombotic and pro-coagulant activity
9. Raised inflammatory markers
10. Oxidative stress related tissue injury, where acute fluctuation of blood glucose is more deleterious than persistent chronic one
11. Impaired myocardial glucose utilization due to higher free fatty acids, leading to worsening of ischemia and malignant arrhythmias
12. Impaired immune response
13. Impaired myocardial tissue repair due to inflammation, apoptosis etc.

PHARMACOTHERAPY OF HYPERGLYCAEMIA

Though it has been proved beyond doubt that, hyperglycaemia is deleterious in ACS but the therapeutic means to control it is not yet settled. Insulin has got salutary effects on the majority of the factors as discussed above.

They are:

1. Anti-inflammatory action (reduces c-reactive protein) during AMI and CABG
2. Inhibits oxidative stress, apoptosis and stimulates fibrinolysis
3. May improve myocardial flow

Achievement of normoglycaemia with insulin, show improved outcome. But insulin alone without achieving normo glycaemia is not rewarding. Thus question is raised whether the benefit is from insulin or normo glycaemia. Several trials have shown more adverse outcome with new onset DM, than preexisting DM in ACS. Possible explanations may be as follows:

1. Insulin treatment and achievement of normoglycaemia are much earlier in pre-existing DM
2. Higher degree of stress or illness is required to produce hyperglycaemia in nondiabetics than diabetics.

GLUCOMETRICS AND CONTROL OF HYPERGLYCAEMIA

HbA1C or fructosamine though is a useful measure of glycaemic status for prior 3 months and 2 weeks respectively; they can not help to assess the glycaemic state during one week or so during hospital stay of ACS. Several blood sugar values fasting, postprandial and random are done by finger prick examination to determine the insulin dose. Other measurements are mean glucose level, time averaged glucose level hyperglycaemia index and patient day glucose level. But no systematic evaluation of these measures has yet been available. New technologies like continuous glucose monitoring system (CGMS) might show some advantage in future day.

INTENSIVE INSULIN THERAPY, GLUCOSE CONTROL AND OUTCOME IN ACS

For the first time the most acceptable randomized trial on glucose control in DM are the two DIGAMI (Diabetes Mellitus, Insulin Glucose infusion in Acute Myocardial Infarction) studies. The DIGAMI -1 trial of 1995, analyzed 620 AMI patients with known DM and/or admission glucose >200mg/dl, treated with intensive insulin therapy (insulin glucose infusion for at least 24 hours). This was followed by multidose subcutaneous insulin therapy more than 3 months and compared with the control of conventional less aggressive therapy. Better glucose control (mean 24 hour post treatment glucose of 173mg/dl compared to 210mg/dl in the control) was achieved in the intensive treatment group. In the follow up study, significant mortality benefit was seen with intensive arm at both 1 year and 3.4 year follow up points. But like DIGAMI-1, DIGAMI-2 study could not establish
the substantial effect of intensive insulin therapy. They compared 3 different regimens: acute insulin glucose infusion followed by standard therapy on discharge and routine metabolic management in both impatient and outpatient set up in a total number of 1253 randomized AMI patients. There were no differences in outcomes out of these 3 groups, probably because of similar short term and long term control of glycaemic state.

Question was raised whether glycaemic control is the determining factor achieved by insulin or specific effects of insulin really relates. But in DIGAMI-2 study. But to utter surprise in this study, long term fasting glucose of 90 to 120mg/dl was not reached in the intensive arm. Thus DIGAMI-2 actually compared different insulin regimen not different intensities of glucose control. Further more, they did not include high risk cases of new onset DM.

The HI-5 (Hyperglycaemia: Intensive Insulin Infusion in Infarction) Study included 244 cases of AMI with known diabetes or admission glucose >140mg/dl. Patients subgrouped for intensive insulin infusion therapy received standard insulin and dextrose infusion and adjusted to maintain random blood glucose level between 72 and 180mg/dl. Patients in conventional groups received their baseline antidiabetics (including subcutaneous insulin) and additional subcutaneous insulin was given if blood glucose was above 288mg/dl. Results revealed no difference in mortality among the groups during hospital stay or at 3rd and 6th months. But statistical significant reduction was seen in post AMI heart failure during hospitalization and in re-infarct at 3 months in intensive treatment group. Similar to DIGAMI-2, HI-5 study also compared 2 different insulin strategies not 2 different intensities of glucose control. Additionally, no provision of tight glucose control was made after 24hours and number of patients recruited was far less than the intended number of 850 patients (based on power calculation).

CREATE – ECLA study is another multinational-randomized trial comparing the impact of glucose – insulin –potassium (GIK) and placebo on mortality in 2020 AMI patients. Patients with both normal and elevated blood glucose level on admission were selected and unlike the two DIGAMI trials, glucose control was not primary target without any pre-specified target of blood glucose. In fact in the GIK group, glucose level was higher than control. There was no difference is the rates of 30 day mortality, cardiac arrest, cardiogenic shock or re-infarction between the 2 groups.

Before 2001, practically there was no guideline about how to treat hyperglycaemia in diabetic and nondiabetic range during acute illness in intensive care unit (ICU), till van den Berghe et al demonstrated that lowering of blood glucose by intensive Insulin therapy upto 80 to 110mg/dl reduces the ICU mortality from 8% to 4.6% in surgical patients and as a whole from 10.9% to 7.2% . The improvement was seen significantly in patients with ICU stay >5days. ICU complications like septicemia, renal failure and transfusion requirements also were reduced by 41 to 50%. But off course this tight control was achieved with incidences of hypoglycaemia.

Later on in 2006 the same group analyzed the data on medical ICU patients only and demonstrated that intensive glucose control reduced the morbidity not mortality. However the mortality was lower amongst those persons who required ICU stay >3days. Patients who attained blood glucose below 110mg/dl had the lowest mortality and complication but higher hypoglycaemia rate (10.7%). This benefit was not seen in medical cases of ICU stay <3days and also not in patients with prior DM.

Because of definite difference in patient population of ACS who has higher chances of coronary spasm, arrhythmia, cerebro-vascular accidents, and the observational data of van den Berghe et al can not simply extrapolated to cases of ACS.

Myocardial protection with insulin administration at the time of reperfusion appears to be independent of the effects of insulin on glucose metabolism. Probably insulin leads to the cell survival signalling pathways in experimental models.

In humans, insulin infusion at the time of reperfusion has a profound anti-inflammatory effect and reduces infarct size.

We need multi centric well randomized clinical trials to settle this issue because till now the awareness of glycaemic control amongst physicians are very poor because a report published in 2005 showed that 78% of patients without known diabetes and 27% of patients with known diabetes were not given insulin therapy in spite of hyperglycaemia.

ACS OUTCOME AND HYPOGLYCAEMIA

One important finding against tight glycaemic control is that, single blood glucose below <54mg/dl during hospitalization was associated with 93% increase in relative risk of long term mortality. Other studies have shown hypoglycaemia on admission increases the risk of death or MI at 30days. So targeting tight control of blood glucose should also target to avoid hypoglycaemia to improve the outcome.

METHODS FOR GLYCAEMIC CONTROL

There is no dispute that during acute admission, Insulin is the only drug of choice. In view of the rapidly developing data demonstrating anti-inflammatory effects of insulin and a pro-inflammatory effect of glucose and FFAs, as well as the relation of clinical outcomes with indices of inflammation, maintenance of euglycaemia with the help of insulin infusion is a potentially important strategy for MI and CABG.

Insulin used is intravenous, diluted with normal saline or mixed with glucose and potassium solution as GIK solution. In controlled state subcutaneous insulin can also be used. In
A meta-analysis by Fath et al. of GIK trials done in the 1960s showed that GIK did not show any beneficial effects in recent clinical trials and thus this concept has been abandoned. A different concept of insulin treatment in ACS was tested in the form of a glucose–insulin–potassium infusion (GIK). This treatment was developed as a "polarising solution" to prevent arrhythmias and avoid further ischaemic damage in unselected patients with acute myocardial infarction.

From 1960 onwards, different (randomised) trials have been done, utilising GIK infusion and later insulin therapy in ACS patients. The most recent NICE-SUGAR trial even reported a higher incidence of death, similar to DIGAMI-2. Since hypoglycaemic episodes occurred more frequently in the Intensive Glucose Lowering (IGL) group, this resulted in a modification in the ACC/AHA guidelines. A report of the American College of Cardiology Foundation/American Heart Association Task Force recommend to use 10 mmol/l as a threshold for initiating treatment in STEMI patients.

The ESC guidelines still mention a target range of 5 to 7.8 mmol/l; however, these were established before the NICE-SUGAR results appeared. The fear for hypoglycaemia in certain IGL protocols seems grounded, and prevention requires frequent measurement or a wider glucose target range.

Meijering et al. evaluated insulin protocols in 24 studies (including six with AMI patients). The best results were found using a dynamic scale protocol for continuous intravenous insulin infusion, combined with frequent blood glucose measurement and taking into account changes in glucose levels rather than single values.

A meta-analysis by Fath et al. of GIK trials done in the pre-reperfusion therapy era (before 1988) showed a lower mortality in the GIK-treated group than in controls (16% vs. 21%; P=0.004). However, in later trials that included patients receiving reperfusion therapy (either by thrombolysis or mechanical), GIK did not show beneficial effects. Two studies showed a trend in cardiac and all-cause (GIPS) mortality in favour of GIK, though these did not reach statistical significance. Because in GIPS a subgroup of patients without heart failure had a lower 30-day mortality in the GIK-treated group (1.2% vs. 4.2%, P=0.01), GIPS-2 was set up excluding patients with symptoms of heart failure, but this study did not show any beneficial effect of GIK. The differences in effect of GIK between the earlier and more recent studies can be explained by improvements in treatment (including reperfusion, antiplatelet and β-blocker therapy), which is reflected in the lower mortality rates of the studies performed after 1987. In the more recent studies all 30–40 day mortality rates were below 16%, which is the mortality rate of GIK-treated patients in the meta-analysis of trials from 1965 to 1987.

Yun-Tao Zhao et al. in a meta-analysis, based on eight RCTs with GIK regimens showed that the insulin focus strategy is not effective in reducing the mortality of AMI by inhibiting FFA and reperfusion injury. Limited evidence, based on three RCTs, suggests that the glycaemia focus strategy is also not effective in reducing mortality in the absence of tight glycaemia control in AMI. It is evident that, despite a glycaemia focus, strict control of glycaemia in patients with AMI is difficult to attain. Furthermore, the advent of rapid angioplasty/stent and widespread use of aspirin, b blockers and statins have dramatically reduced mortality, over shadowing much of the effect of glycaemic control.

The results of this meta-analysis suggest that treatment with an insulin focus strategy only do where the aim is to deliver large doses of insulin without regard to the glucose level does not improve mortality when other modern therapies for AMI are used in the reperfusion era. Nevertheless, it remains possible that control of hyperglycaemia by insulin infusion with a glycaemia focus improves mortality in patients with AMI. Current evidence suggests that GIK with insulin does not reduce mortality in patients with AMI. However, studies of glycaemia are inconclusive and it remains possible that glycaemic control is beneficial. Comparison of glucose-insulin-potassium and insulin-glucose as adjunctive therapy in acute myocardial infarction: a contemporary meta-analysis of randomised controlled trials.

Recommended treatment targets in the management of patients with type 2 diabetes after acute coronary syndromes adapted mainly from the European Guidelines for Cardiovascular Disease Prevention, is as given in Table 5.

### Table 5: Targets of Glycaemic control in ACS

<table>
<thead>
<tr>
<th>Self-monitored blood glucose (in mg/dl)</th>
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<tbody>
<tr>
<td>• Fasting/pre-prandial</td>
</tr>
<tr>
<td>• Post-prandial (peak)</td>
</tr>
<tr>
<td>• Before bed/night</td>
</tr>
<tr>
<td>• HbA1C (%)</td>
</tr>
</tbody>
</table>

**Preparation of IV Insulin**

- 250 u of regular insulin is added to 250 ml of normal saline (or 125 u in 250 ml) and the drip connected to IV line and controlled by infusion pump at minimal rate of 40 ml/h.
- For glucose potassium insulin infusion (GIK) 500ml of 5% dextrose + 80 u of regular insulin + 40mEq of KCL are infused at 30ml/h
- Long acting insulin concurrently
- Improvement in insulin sensitivity after some time lower dosage
The schedule of dose titration for insulin is shown in Table 6.

**TYPE OF INSULIN**

For all probability short acting human or analog insulin is to be used as IV infusion. Intermediate or long acting insulins including analogs cannot be given IV and is not presently used in ICCU as a routine practice. But opinion is developing that if glargine or detemir SC is combined with short acting IV insulin from the ICCU, results are promisingly better. After the phase of ICCU selection of insulin depend upon the demand of the situation. Though short acting analogs like Aspart, Glulisine, and Lispro produce better control and less hypoglycaemia, there is no large scale data to recommend them routinely in AMI.

**FOLLOW UP THERAPY**

After discharge whether insulin is of extra benefit than oral antidiabetics is not proved beyond doubt. Oral agents if used should preferably include insulin sensitizers like metformin and glitazones. Beyond glycaemic control, they exert pleotropic effect endothelium, lipids, pro-coagulant and anti-platelet activity which is all required in ACS. Glitazones also prevents re-stenosis after stenting and coronary bypass surgery by inhibiting vascular endothelial neogenesis.

**POINTS TO BE FURTHER CLASSIFIED**

Till now researches and trials have enough deficiency to conclude a strong recommendations because of the following knowledge gaps.\textsuperscript{15}

1. Admission glucose or persistent glucose level, which one strongly influences the outcome?
2. Whether hyperglycaemia associated risk is dependent on particular time of the event?
3. Which one is optimum and safest target glucose level for patients with known and unknown DM?
4. What actual benefit in future can be obtained from intensive glycaemic control?
5. Current pattern of management of blood glucose and safety, feasibility and effectiveness of tight blood glucose control in ACS?
6. Reasons for poor outcome in ACS with newly diagnosed DM Admission glucose or persistent glucose level, which one strongly influence the outcome?
7. Whether hyperglycaemia associated risk is dependent on particular time of the event?
8. Which one is optimum and safest target glucose level for patients with known and unknown DM?
9. What actual benefit in future can be obtained from intensive glycaemic control?

To settle the above issues more large trials are required which should

1. Include patients with admission glucose >140mg/dl
2. Use safe glucose lowering protocol avoiding hypoglycaemia
3. Utilize sufficient statistical calculations for primary outcome.

The present recommendation of American Heart Association is as follows:\textsuperscript{15}

1. Glucose estimation should be a part of routine investigations in all case of ACS
2. Intensive glucose control for plasma glucose >180mg/dl and also for milder hyperglycaemia with suggested range of 90-140mg/dl avoiding hypoglycaemia
3. Insulin to be administered as intravenous infusion
4. Treatment should be started as early as possible
5. In non-ICU administer insulin as subcutaneously maintaining plasma glucose below 180mg/dl
6. For cases of new diabetes, do HbA1c and post discharge OGTT

In the most current recommendation by American Association of Clinical Endocrinologists and ADA the following guideline has been formulated:\textsuperscript{41}

1. Insulin should be started in persistent hyperglycaemia above 180mg/dl
2. Blood glucose range of 140-180mg/dl is recommended for majority of critically ill patients
3. IV insulin is the preferred method
4. Validated insulin protocol to be followed
5. Frequent glucose monitoring to achieve the goal and to avoid hypoglycaemia

**CONCLUSIONS**
For more than 50 years, the role of insulin therapy in ACS is being 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 in critically ill populations without ACS, and the lessons learned from these trials can be used to conduct the 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). As per evidence, infusion-related hyperglycaemia, hyperkalaemia and hypervolaemia should be avoided. Also avoid delays in reperfusion therapy when initiating insulin therapy immediately upon hospital admission. Until results from ongoing insulin trials in ACS patients are available, conservative recommendations for glucose control (e.g. consider insulin treatment if glucose exceeds 180 mg/dL [9.9 mmol/L]) would appear to be appropriate.

Multiple gaps still exist in our understanding of the relationship between elevated glucose and adverse outcomes, most importantly, whether hyperglycemia is a marker or a mediator of higher mortality and whether treatment of hyperglycemia improves outcomes.

Though convincing trials are lacking, till now insulin is best. Practically there is no option other than insulin during acute stage. Oral antidiabetic drugs in ICCU setup are not feasible most of the times. After discharge how long insulin is to be continued is not settled, but insulin sensitizers particularly thiazolidines should be must for prevention of further ACS or revascularization procedures. Targets Hba1C of 7% should always be achieved. Addressing these existing knowledge gaps, future studies may provide an opportunity to improve care and outcomes in patients with ACS.

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