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COMMENTARY

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Digami too?

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Do you Digami too? Few acronymic studies enter the everyday lexicon of medicine, but the prospective study linking better glucose control to improved survival after acute myocardial infarction, otherwise known as Digami, has certainly done so [1]. The Diabetes Insulin-Glucose in Acute Myocardial Infarction (Digami) study changed attitudes to diabetes in the coronary care unit in the same way that the Scandinavian simvastatin study changed attitudes to the importance of lipids in ischaemic heart disease [2]. Digami established that good control of diabetes following myocardial infarction decreased one year mortality by 30%. This is a comparable survival advantage to the administration of streptokinase (25% decrease in 5 week mortality [3]). All good films demand a sequel, and the same can be true of research studies.

Digami 2

Digami 2 was designed to test whether 'intense metabolic control by means of insulin' was able to reduce mortality following acute myocardial infarction [4]. The power calculation indicated that 3,000 patients would be required, but despite intense efforts at recruitment only 1,253 patients had been randomised after 5 years, and the steering committee stopped the trial. Competition for study recruitment with commercially funded studies may partially explain the difficulty. Worse still, the target blood glucose of 5 to 7 mmol/l was not achieved, and no clinically relevant metabolic difference was achieved between the active and control groups. The patients had been randomised between three groups: (1) acute insulin+long-term insulin treatment; (2) acute insulin+standard long-term treatment; (3) routine management. Blood glucose levels at 24 h were 9.1±3.0 and 9.1±2.8 vs 10.0± 3.6 mmol/l, respectively. Equally, there was no clinically or statistically significant difference in fasting blood glucose between the groups over 36 months of follow-up.

It would have been reasonable to conclude that the study had failed to achieve the conditions it set out to test; and that no improvement in blood glucose control leads to no improvement in outcome. Remarkably, the authors concluded that Digami 2 did not 'support the fact that an acutely introduced, long-term insulin treatment improves survival in type 2 diabetic patients following myocardial infarction'. The potential for confusion is clear.

Magic potion or metabolic control?

Improved survival following acute myocardial infarction in Digami 1 could have been due to (1) an effect on blood glucose, (2) an effect on lipid metabolism or (3) some undefined direct effect upon the myocardium. The surprising conclusion drawn by the authors appears to reflect the view that insulin is some sort of magic potion, use of which will be beneficial irrespective of the degree of glucose control achieved. There is, on the other hand, considerable evidence for a glucose-mediated effect. The effect of high glucose levels on thrombosis and endothelial function in vivo and in vitro has been well described. High glucose promotes platelet activation, which can be reversed by glucose lowering [5, 6]. Vascular endothelial dysfunction and inhibition of the fibrinolytic system are brought about by persistent high glucose levels, and circulating levels of the adhesion molecules intracellular adhesion molecule 1 (ICAM-I) and E-selectin are downregulated by normalisation of blood glucose [7, 8]. Wound healing is also slowed by high glucose levels [9]. The possibility of a mechanistic effect upon lipid metabolism must be considered, and it is certainly the case that plasma fatty acid levels and atherogenic small dense LDL particles can be decreased by insulin infusion [10], even if blood glucose is maintained. These changes will, however, always follow restoration of normal blood glucose levels. The alternative

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concept that a special effect on ischaemic myocardium might be achieved by simultaneous infusion of glucose and insulin can be traced back four decades [11]. Even though the idea was popularised [12], it remained an electrocardiographic observation. Overall, there are clear reasons for accepting an effect upon blood glucose as the determining factor in decreased morbidity and mortality. Even Digami 2 showed achieved glucose level to be a strong independent predictor of long-term mortality.

Several clinical studies have corroborated the practical impact of lowering blood glucose, and none more dramatically than the Leuven study. In this landmark study, van den Berghe and colleagues showed that very good control of blood glucose markedly improved survival of acutely unwell patients, and that the level of blood glucose achieved correlated with survival irrespective of treatment group [13]. In a follow-up study, the same group reported that intensive blood glucose control decreased morbidity and length of stay in a medical intensive care unit, even though the presenting blood glucose of the group was not particularly high at 9.0 mmol/l [14]. Blood glucose control matters during acute illness, especially if the illness is thrombotic or infective in nature. If glucose control is not achieved, management can be considered ineffective, regardless of whether therapy has been with diet, tablets or insulin. This point is particularly relevant to management of diabetes after the acute phase of myocardial infarction.

Long-term glucose management following myocardial infarction

The original Digami study spawned a belief amongst cardiologists that all patients with diabetes must be treated by insulin in the long term following myocardial infarction. This reflects the strict application of 'evidence-based' thought, given that control had been achieved in the study by use of insulin. However, it has long been established that insulin therapy in type 2 diabetes does not necessarily achieve better control than diet, exercise and tablets. For this reason many diabetologists interpreted the original Digami findings as indicating the need for acute control of blood glucose (always using insulin) followed by good control in the longer term (by the best means for the individual). This interpretation was supported in type 2 diabetes by UKPDS data showing that macrovascular disease progression was related to control of blood glucose but was unrelated to use of either sulfonylurea or insulin [15]. Further support for the benefit of good control comes from the Epidemiology of Diabetes Interventions and Complications (EDIC) study, which demonstrated that

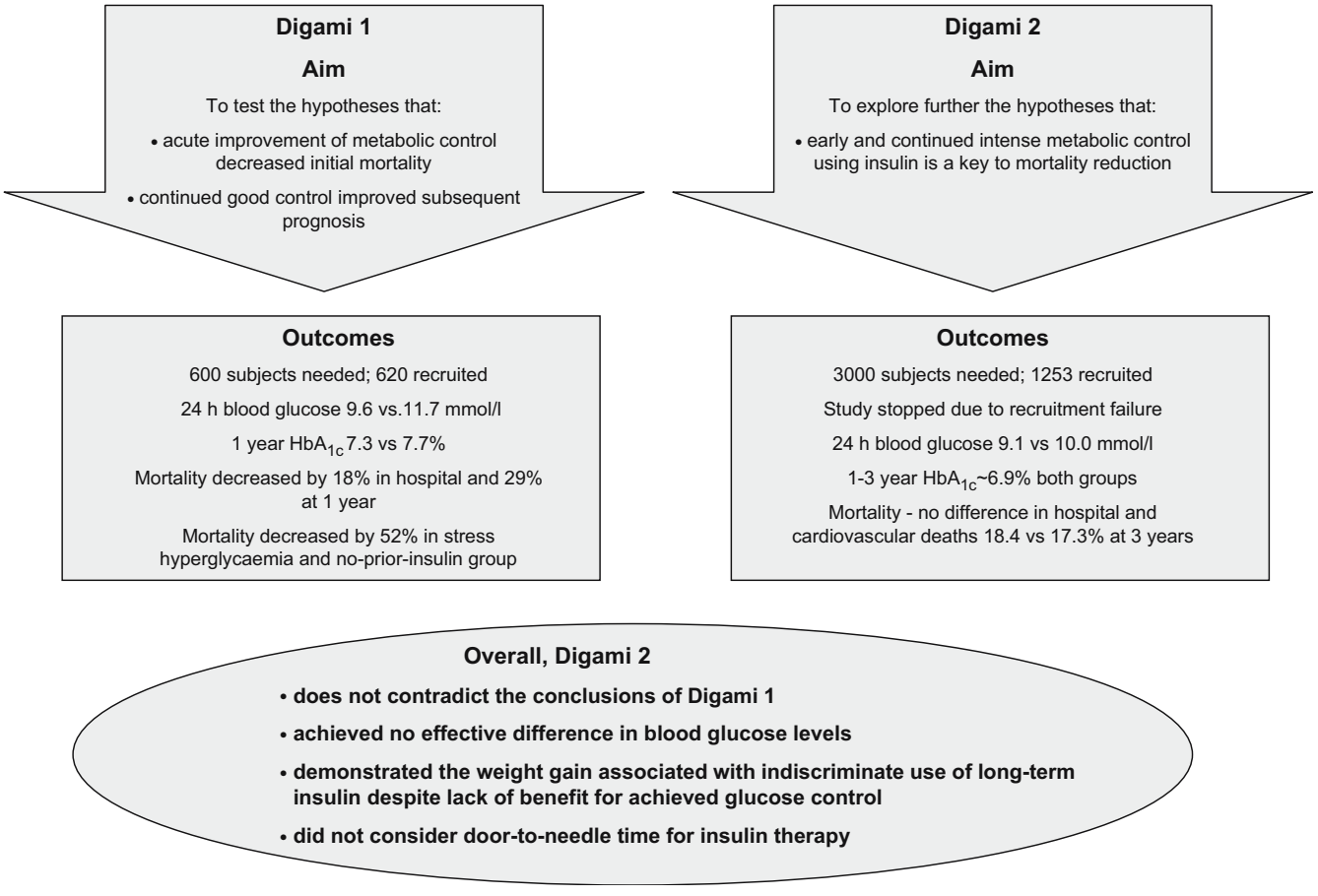

Fig. 1 Comparative summary of Digami 1 and Digami 2

long-term good glucose control is associated with a 57% decrease in major cardiovascular events [16].

The indiscriminate use of insulin for people with type 2 diabetes is associated with hazards. In Digami 2, inclusion in the long-term insulin group led to weight gain of 4.7 kg, compared with 0.4 kg in the standard treatment group despite identical blood glucose control. If oral agents can achieve glycaemic targets over the weeks and months following a coronary heart attack, this is more satisfactory than the protocol-driven use of insulin with its attendant risk of excessive weight gain. The likely benefits of metformin therapy also have to be borne in mind [17]. Good blood glucose control matters after myocardial infarction, and the best means of achieving it has to be individually determined. It is clear that a well designed study comparing diet and metformin therapy with long-term insulin therapy could provide direct trial data to test this concept.

Back to the future

The curious conclusions of Digami 2 raise a sobering question. Was the original Digami study solid? It set out to test the hypothesis that good metabolic control improved the prognosis of diabetic patients following myocardial infarction (Fig. 1) [1]. The power calculation indicated a need for 600 patients randomised to insulin treatment or standard management, and 620 patients were randomised. Blood glucose levels were identical at randomisation (15.4 mmol/l) and treatment achieved a reasonable difference at 24 h (9.6±3.3 vs 11.7±4.1 mmol/l; $p<0.0001$). HbA_{1c} decreased more in the insulin-treated group over 12 months (1.1±1.6 vs 0.4±1.8%; $p<0.05$). Mortality was improved by 18% in hospital (NS), 21% at 3 months (NS) and 29% at 1 year ($p<0.03$). There was clearly an effect on mortality as a consequence of prospective randomisation to the insulin-treated group, but the effect became manifest mainly during the acute episode (18%), increasing to 29% thereafter. Overall, the original Digami study provided clear information to guide clinical practice.

An important clinical pointer in the original Digami data has, however, received relatively little attention. Patients had been randomised in a stratified manner into four groups depending upon pre-infarct therapy with insulin and extent of adverse coronary risk factors as follows: (1) no insulin, low risk; (2) no insulin, high risk; (3) insulin, low risk; (4) insulin, high risk. Almost half of the entire cohort fell into the no prior insulin, low coronary risk group, and the reduction in mortality in this group both at 3 months and at 1 year was a staggering 52% ($p<0.05$). Hence, the largest effect on mortality in the original Digami study was seen in patients with stress hyperglycaemia and in patients with non-insulin-treated type 2 diabetes. These groups are also at high risk of further acute events, with high 6 month mortality [18]. This brings up a further paradox, given that doctors are least likely to prescribe insulin in the acute situation if diabetes has not been diagnosed prior to hospitalisation [19]. Communicating this message is likely to prove an uphill task.

Door-to-needle time

The need to bring blood glucose levels down effectively in the acute situation received scant attention in either of the Digami studies, both of which merely reported blood glucose levels 24 h after start of therapy. We know from data on use of fibrinolytics that early intervention in the thrombotic process saves lives, and door-to-needle time for streptokinase is an important concept. We also know that control of blood glucose normalises the thrombotic pathways [5–8, 10]. Is there not some urgency in achieving near-normoglycaemia after acute myocardial infarction? There was no mention of door-to-needle time for start of insulin therapy in either Digami study. Consideration of blood glucose control in the critical first few hours must surely be a relevant factor in infarct size and early mortality.

The principles of managing high blood glucose levels in the ill patient are two-fold. First, bring down blood glucose to target levels. Second, maintain steady blood glucose levels. The first principle must be fulfilled by use of insulin with frequent checks of blood glucose. The second may involve combined glucose and insulin infusion. But the regimen used in the Digami studies does not conform to these principles. It specifies use of both glucose and insulin from the start. The initial fall in blood glucose will be slowed by simultaneous infusion of glucose. In other words, it is targeted less at achievement of tight blood glucose control than at provision of extra insulin. Several simple means of achieving rapid control of blood glucose in acutely unwell patients have been published [13, 19], and the regimen adopted must be simple in order to perform robustly in everyday clinical practice. Using a fixed dose insulin regimen to achieve initial control [19], blood glucose levels of 8.0±0.7 mmol/l were observed 4 h after initiation of treatment, rather than 14.5± 1.3 mmol/l in the group not managed according to guideline (Roomallah B, unpublished audit). Given that rapid restoration of near-normal blood glucose levels will act to enhance fibrinolysis and decrease further thrombosis, it is highly likely that door-to-needle time is just as important for commencement of insulin infusion as for commencement of streptokinase.

Conclusions

Digami 2 does not contradict Digami 1. If good blood glucose control is not achieved, mortality cannot be expected to fall in those who are hyperglycaemic at presentation with acute myocardial infarction. There is a sound pathophysiological explanation for the potent effect of high glucose concentration upon impaired fibrinolysis and enhanced thrombogenesis, and this is supported by in vivo studies. The urgency for correction of abnormal blood glucose levels in the critical first few hours after acute

myocardial infarction was not considered by either Digami study.

The $64,000 question now comes into view. What is the effect of rapid, effective restoration of near-normoglycaemia upon early complications and mortality after acute myocardial infarction? Given the observations of van den Berghe and colleagues [13], a prospective study to answer this question may now be unethical and we may have to rely upon retrospective comparisons to be certain that this policy is as effective as expected. For the moment, best practice must consist of insulin infusion to bring down blood glucose to near-normal levels within a few hours and to maintain this during the acute phase of myocardial infarction. In the weeks and months after acute myocardial infarction best possible control must be sought, not necessarily using insulin therapy.

Let's try a new acronym. If Digami stands for 'Definitive, Immediate Gluco-control in Acute Myocardial Infarction' the title question can be repeated. Do you Digami? Your future patients may hope so.

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