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DO YOU SEE A ROLE FOR INSULIN INFUSION THERAPY DURING ACUTE MYOCARDIAL INFARCTION?

Several studies have evaluated the effects of achieving glycemic control with insulin following acute cardiovascular events. In the original Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study, a glucose/insulin infusion was started in patients with type 2 diabetes (T2DM) within 24 hours of acute myocardial infarction (MI). Glycemic control improved, and the relative risk for long-term mortality decreased by 38% overall and by 51% in lower-risk patients who had not previously received insulin treatment. The control group, on the other hand, experienced a 44% overall mortality rate over several years.

The DIGAMI 2 study was an international study designed to confirm whether in-hospital insulin administration and/or in-hospital insulin administration plus follow-up subcutaneous insulin therapy reduced mortality rates compared with standardized treatment. Unfortunately, the trial encountered numerous problems. DIGAMI 2 was originally designed to evaluate 3000 subjects but was able to recruit fewer than 1500. To facilitate recruitment, blood glucose criteria for study entry were eliminated (the original DIGAMI required a blood glucose >11 mmol/L [approximately 198 mg/dL] for inclusion), leading to lower mean baseline blood glucose levels in DIGAMI 2 patients. Furthermore, less than 50% of patients assigned to follow-up therapy with subcutaneous insulin actually took insulin 3 or more times daily (versus 4 doses taken daily in the original DIGAMI). Lastly, of patients not assigned to follow-up insulin therapy, approximately 15% took multidose (≥ 3 injections/day) insulin therapy.

Neither treatment group reached DIGAMI 2 target glucose levels, nor was any meaningful separation observed between the study groups for posttreatment fasting blood glucose. As a result, it was not surprising that absolute mortality rates in the study treatment groups were similar at around 20%. However, based on the study limitations described above, it is clear that the subjects in DIGAMI 2 differed from those in the original DIGAMI study. In particular, the lower baseline levels of mean blood glucose in DIGAMI 2 probably contributed to the reduced absolute mortality rates (compared with the original DIGAMI study) observed at the study end. In analysis, DIGAMI 2 patients who did achieve decreased blood glucose levels experienced lower mortality rates; increased blood glucose levels of 3 mmol/L (approximately 54 mg/dL) or increased A1C of 2% was associated with a 20% increase in mortality. However, this finding was not directly attributable to the effects of insulin.

What can we conclude from these studies? There is ample evidence from epidemiologic research that post-MI, hospital-based mortality is increased several-fold in the presence of hyperglycemia. We know from several studies in nondiabetic subjects in the intensive care unit following MI or bypass surgery that the use of insulin saves lives. There are many good scientific reasons for

believing that control of the metabolic environment at the time of the acute coronary syndrome is beneficial. Therefore, in evaluating the results of DIAGMI 2 as opposed to the original DIGAMI, it is vital that we do not abandon the growing use of insulin among patients in the coronary care unit. Fortunately, in many hospitals, the use of insulin in these situations is becoming the standard of care.

IS IT HELPFUL TO OBTAIN LIPID SUBFRACTIONS? SHOULD WE TREAT LOW-DENSITY LIPOPROTEIN CHOLESTEROL TO LOWER TARGETS, AND WHICH TREATMENTS ARE SUCCESSFUL?

There is evidence that parameters of the lipid profile such as particle size and density are related to cardiovascular disease (CVD). Whether obtaining these subfractions routinely in clinical practice contributes to improved outcomes is still an area of debate, with studies ongoing to determine the answer.

However, we do know that the addition of statin therapy in patients with diabetes has been shown to markedly reduce CVD and appears to have a benefit regardless of patients' initial low-density lipoprotein (LDL) level. Recent trial evidence also suggests that lowering LDL levels beyond current goals appears to be beneficial.

RECOMMENDED READING

Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495-1504.

Carmena R, Duriez P, Fruchart JC. Atherogenic lipoprotein particles in atherosclerosis. *Circulation*. 2004;109(23 suppl 1):III2-7.

Colhoun HM, Betteridge DJ, Durrington PN, et al, on behalf of the CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685-696.

Diaz R, Paolasso EA, Piegas LS. Metabolic modulation of acute myocardial infarction. The ECLA (Estudios Cardiológicos Latinoamérica) Collaborative Group. *Circulation*. 1998;98:2227-2234.

Fath-Ordoubabdi F, Beatt KJ. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: an overview of randomized placebo-controlled trials. *Circulation*. 1997;96:1152-1156.

Grundy SM, Cleeman JI, Merz CNB, et al, for the Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation*. 2004;110:227-239.

Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet*. 2003;361:2005-2116.

Malmberg K for the DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. *BMJ*. 1997;314:1512-1515.

Malmberg K, Ryden L, Wedel H, et al, for the DIGAMI 2 Investigators. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J*. 2005;26:650-661.

Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized clinical trial. *JAMA*. 2004;291:1071-1080.

Van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. *Crit Care Med*. 2003;31:359-366.

Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med*. 2001;345:1359-1367.