

Effects of an intravenous infusion of a potassium-glucose-insulin solution on the electrocardiographic signs of myocardial infarction

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Am J Cardiol. 1962;9:166-181

This paper, which is a little more than a collection of case reports, was published in 1962 and its results were largely forgotten until the DIGAMI study (Diabetic patients receiving Insulin-Glucose infusion during Acute Myocardial Infarction) revealed strong evidence for the therapeutic effect of insulin and glucose during acute myocardial infarction.

The rationale of the study was as follows. After acute coronary artery occlusion, polarization of the myocardial fibers in the areas supplied by the occluded vessel is reduced. The degree of diastolic polarization varies in the different zones of the infarcted area and determines whether the zone is completely unexcitable (dead zone) or is activated with a delay (injury zone) or presents only alterations in its recovery or repolarization (ischemic zone). The concentration of potassium ions inside the fiber is about 30 times that outside the fiber. This ratio contributes to the resting polarization of the muscle fibers. There is considerable evidence to suggest that the polarization of the muscle fibers of the human heart is mainly due to the K^+ / K_0^+ ratio and to the permeability to K^+ , which is sufficiently higher than the permeability to other ions to permit a transmembrane K^+ potential. Thus, any decrease in diastolic polarization must be followed by a decrease in the potassium ratio. Combined administration of potassium together with glucose and insulin was expected to increase resting polarization and affect potassium ratios within the myocardium. The protocol was to give 40 mmol of KCl and 20 units of soluble insulin together with 1000 mL of either 5% or 10% glucose. When less fluid was indicated, 500 mL of 10% glucose solution was used.

This study included a series of 7 case reports, in which all patients received this treatment and electrocardiograms were followed. The electrocardiogram was considered to be stabilized with this additional treatment. The authors were impressed by the absence or disappearance of arrhythmias together with an increased sense of well-being perceived by the patients. The authors concluded that

the cardiac fiber membranes of infarcted zones still viable were actually helped towards restoring the normal permeability to potassium during the resting and recovery period following infarction.

This paper, largely forgotten for the past 30 years, has gained much more credence and respect following the DIGAMI study, which has shown a beneficial effect of glucose and insulin infusion in diabetic patients treated in the coronary care unit setting.

1962

44-year-old Nelson Mandela is jailed
for 5 years for activism;
Amnesty International is created;
and Jamaica gains independence
from Britain after 307 years



Diabetes and cardiovascular disease. The Framingham study

W.B. Kannel, D.L. McGee

JAMA. 1979;241:2035-2038

In this subset analysis from the father (or should I say mother) of all epidemiological studies—the Framingham study—diabetes was clearly defined as a major cardiovascular risk factor. This study reported on 20-year follow-up data from the Framingham epidemiological study, which had been in continuous operation since 1948. A cohort of 5209 men and women aged 30 to 62 years had been followed up biennially to determine in what way patients who go on to develop cardiovascular disease differ from those who remain free from the disease. Clinical cardiovascular end points were diagnosed from the biennial examinations as well as information from hospital admissions, medical examiners' reports, and other sources. Before diagnoses were made final they were submitted to a panel review of all the available information. The diagnosis of diabetes in the Framingham study was based on a history of treatment with oral hypoglycemic agents or insulin or the finding of elevated random blood sugar levels on two successive visits. People who exhibited these characteristics were then reviewed by the investigators and a final diagnosis of diabetes was made.

At the initial time of examination, 957 cases of cardiovascular disease were found among the 5209 patients of the study. In the course of the 20-year follow-up, the impact of diabetes on the major cardiovascular end points was determined by the sizes of the (age-adjusted) relative risks of disease for diabetics versus nondiabetics, and it was apparent that diabetes doubles the risk of total cardiovascular disease in men and almost triples it in women. The relative risk of cardiovascular death was also roughly doubled for men and more than tripled for women, even after age adjustment. The examination of the impact of diabetes on each of the major cardiovascular sequelae showed that its greatest effect in terms of relative risk was on intermittent claudication. Hypertension had the highest attributable risk for all of the cardiovascular events. Diabetes had the lowest attributable risk among males for all of the cardiovascular events except intermittent claudication. However, among females, the risk attributable to diabetes exceeded that of

cigarette smoking. Thus, in summary, based on 20 years of surveillance of the Framingham cohort relating subsequent cardiovascular events to prior evidence of diabetes, a two- to threefold increased risk of clinical atherosclerotic disease was reported. The relative impact was substantially greater for women than for men.

This pivotal study was the first to really define and quantify diabetes as a major cardiovascular risk factor. Following this paper, numerous other prospective and mechanistic studies were launched to further examine the role of diabetes in the development of cardiovascular disease.

1979

Sony launches the first Personal Stereo in Japan;
the success of Rubik's Cube makes its Hungarian
inventor a multimillionaire;
and "The Deer Hunter" wins the Best Picture Oscar

Mortality from coronary heart disease and stroke in relation to degree of glycaemia: the Whitehall study

J.H. Fuller, M.J. Shipley, G. Rose, R.J. Jarrett, H. Keen

BMJ. 1983;287:867-870

For the first time in 1983, a study related risk of stroke in addition to coronary heart disease to the degree of glycaemia. If the Framingham study was the father of all epidemiological studies, the Whitehall study was a close relation. In this prospective study, 18 403 male civil servants aged between 40 and 64 years were examined between 1967 and 1969. Their records were tagged at the central registry of the National Health Service and a virtually complete 10-year follow-up was available for comparison by the study group. At the initial screening examination, the following parameters were assessed: ECG, arterial blood pressure, body mass index, oral glucose tolerance test (OGTT, 50 g glucose, 2-hour blood glucose), and fasting lipid profile. For the purposes of the study 3 groups were defined: those who had diabetes (224 subjects); those with glucose intolerance (999 subjects with blood glucose concentrations at 2 hours ranging between 5.4 and 11.0 mmol/L); and a normoglycemic group (17 051 subjects whose blood glucose concentrations were below 5.4 mmol/L at 2 hours).

Mortality from stroke and coronary heart disease at 10 years showed a nonlinear relation to 2-hour blood glucose values with a significantly increased risk for glucose-intolerant subjects with concentrations between 5.4 and 11.0 mmol/L (and for diabetics [blood glucose greater than 11.1 mmol/L]). This study also confirmed the finding that systolic blood pressure was significantly related to the development of stroke as men in the highest systolic blood pressure quintile had 12 times, and treated hypertensive patients 25 times, the mortality from stroke compared with those in the lowest two quintiles. In addition, stroke mortality was increased by 2.5 times in those smoking 10 or more cigarettes a day compared with nonsmokers.

Multiple logistic analysis was performed with the variables significantly predictive of mortality from both stroke and coronary heart disease, ie, age, systolic blood pressure, treatment for blood pressure, and a blood glucose value of greater than 5.4 mmol/L. Within the glucose-intolerant

and diabetic groups, the risk factors most strongly related to subsequent deaths from coronary heart disease were age and blood pressure, with less consistent relation to smoking, cholesterol concentrations, and obesity. Although several studies had reported, prior to this one, an increased prevalence of diabetes among cases of stroke, the definition of diabetes previously used was variable and the data patchy. Thus, this was the first large-scale study that showed increased death from stroke associated with elevated blood glucose values on the OGTT.

This very large epidemiological study was the first to show unequivocally that mortality rates from coronary heart disease had a nonlinear relation to 2-hour blood glucose values with a significantly increased risk in glucose-intolerant subjects and patients with diabetes. It also confirmed the important role of blood pressure, smoking, and cholesterol concentrations on cardiovascular disease in patients with diabetes. As a result of this study, clinical practice changed and people became much more aggressive in treating patients with glucose intolerance and, in particular, those with hypertension.

1983

Klaus Barbie is charged
with crimes against humanity;
“ET” encourages people to “phone home”
and wins four Oscars;
and Spanish artist Joan Miró dies, aged 90



Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial

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Diabetes Care. 1993;16:434-444

With its very large study population, the massive Multiple Risk Factor Intervention Trial (MRFIT) study had great advantages over others. Its disadvantage was the nonrandom way people were recruited. Participants in this cohort study were screened between 1973 and 1975 and followed up for an average of 12 years. The study cohort consisted of 361 662 men aged between 35 and 57 who were seen at 20 centers throughout the USA. Participation in screening for this study was essentially on a voluntary basis. The most common recruitment procedure was from employment groups or communities. After exclusions for previous myocardial infarction and missing data, the final cohort was 347 978 men. Of these, 5163 had diabetes. Those with diabetes were on average 3 years older and had a slightly higher systolic blood pressure (+5.8 mm Hg). The percentage of the cohort reported as having diabetes increased progressively as age rose.

Over the 12-year follow-up, crude coronary heart disease and coronary vascular disease death rates were approximately 5 times higher in men with diabetes compared with men without diabetes. After adjustment for age, race, systolic blood pressure, serum cholesterol levels, and number of cigarettes per day, the relative risks were 3.2 for coronary heart disease and 3.0 for coronary vascular death. A significant independent association of diabetes with coronary vascular disease death was demonstrated. The effect of other risk factors was examined using univariate and multivariate analyses. Within each stratum homogeneous for cardiovascular risk, cardiovascular disease mortality was found to be considerably higher for patients with diabetes, including the stratum with optimal profile of the other risk factors (cigarette smoking, hypertension, and serum cholesterol).

Thus, the main findings of MRFIT confirmed that diabetes is a strong independent risk factor for cardiovascular disease mortality over and above the effect of serum cholesterol, blood pressure, and cigarette use. In addition,

this large cohort study clearly showed that serum cholesterol, blood pressure, and cigarette smoking are significant strong, independent predictors of mortality in men with and without diabetes. The large cohort allowed this definitive study to answer the question as to the exact effect of diabetes on cardiovascular risk.

1993

Janet Reno becomes
the first female US Attorney General;
the Dallas Cowboys beat the Buffalo Bills 52-17
to win the Super Bowl;
and Italian car pioneer Ferruccio Lamborghini dies,
aged 76

NIDDM and its metabolic control predict coronary heart disease in elderly subjects

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Diabetes. 1994;43:960-967

Scandinavia is an ideal environment in which to study epidemiological questions as by and large it can boast well-documented records and people there are relatively easy to contact and willing to take part in studies. Hence this study, which was set up to answer an important question, namely, whether non-insulin-dependent diabetes mellitus (NIDDM) and its metabolic control had an important influence on mortality and morbidity from ischemic heart disease in elderly subjects, is one of a whole series of important epidemiological studies that have originated from Scandinavia. This study was conducted in Kuopio in Eastern Finland, where 1910 subjects born between 1912 and 1921 were randomly selected from a population register that included all the inhabitants. A postal questionnaire was sent out and 83 subjects were excluded because they were too ill to participate. Eventually, 1299 of the eligible 1827 subjects participated with an overall participation rate of 71%. Subjects attended for a baseline examination between 1988 and 1989, and a follow-up study was then conducted between 1990 and 1991. Of the 1298 subjects participating in the baseline study, 1069 were nondiabetic and 229 had non-insulin-dependent diabetes mellitus (NIDDM). During the follow-up, 3.4% of the nondiabetics and 14.8% of the NIDDM subjects died of coronary heart disease (CHD) or had a nonfatal myocardial infarction. Surprisingly, the incidence of CHD or nonfatal myocardial infarction and all CHD events did not differ significantly between various glucose tolerance groups. Thus, men with abnormal glucose tolerance did not seem to have excess incidence of CHD events. In contrast, however, women with abnormal glucose tolerance had an excess incident rate of all CHD events. Odds ratios risk for CHD death, nonfatal myocardial infarction, and all CHD events, were 11.7, 4.7, and 5.4, respectively. In diabetic subjects, the risk factors were evaluated using univariate analysis. Glycosylated hemoglobin and duration of diabetes were the most significant baseline risk factors associated with both CHD and CHD events. Rates of both CHD death and all CHD in NIDDM subjects calculated by tertiles of glycosylated hemoglobin and duration of diabetes

revealed striking results. There was a significant dose-response relationship between glycosylated hemoglobin as well as the duration of diabetes.

Thus, this study concluded that NIDDM in old age, particularly in women, was a strong risk factor for CHD mortality and morbidity. Furthermore, the study gave strong evidence for the importance of metabolic control in the risk of CHD events in elderly subjects with NIDDM. High glycosylated hemoglobin appears to predict CHD in elderly NIDDM subjects. The upshot was that based on the findings of this study, diabetologists adopted a more aggressive management of elderly patients in trying to achieve good metabolic control.

1994

Comet fragments crash into Jupiter
and produce giant fireballs;
US marines take control of Haiti
without firing a single shot;
and Rose Kennedy,
matriarch of the Kennedy clan,
dies, aged 104



Angiographic findings and outcome in diabetic patients treated with thrombolytic therapy for acute myocardial infarction: the GUSTO-I experience

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J Am Coll Cardiol. 1996;28:1661-1669

GUSTO (Global Utilization of Streptokinase and TPA for Occluded arteries) was the first trial that sought to determine why patients with diabetes have approximately twice the mortality of nondiabetic patients in the setting of an acute myocardial infarction. The study was an invasive angiographic study and looked at patients receiving thrombolysis for acute myocardial infarction. Early infarct-related artery patency and reocclusion rates, together with global and regional ventricular function were measured. In addition, 30-day mortality rates were also recorded.

The GUSTO angiographic trial involved 2431 patients; of these, 12.8% (310) had diabetes and 2116 did not. However, the diabetic cohort had a significantly higher proportion of female and elderly patients, were more often hypertensive, came to hospital later, and had more congestive heart failure, together with a higher number of previous myocardial infarction and bypass surgery procedures. Surprisingly, 90-minute postthrombolysis patency flow grade rates in patients with and without diabetes were not significantly different. In addition, the reocclusion rates, although numerically different, did not reach statistical significance. Ejection fraction at 90 minutes after thrombolysis was similar, as was regional ventricular function. Diabetic patients had less compensatory hyperkinesia in the noninfarct zone compared with controls. Despite this, there was no significant difference in ventricular function at 5th- and 7th-day follow-up between the two groups. The striking finding, however, was that the 30-day mortality rate was 11.3% in diabetic patients versus 5.9% in nondiabetic patients. This difference is similar to that reported in previous studies and was highly significant. These were the first data to demonstrate that diabetes is an independent determinant of early (30-day) mortality after myocardial infarction, even after adjustment for angiographic characterization. This study strongly supported numerous previous studies, which demonstrated increased mortality in patients with diabetes in the setting of acute myocardial infarction. Previously, the excess mortality had been

attributed to larger infarct size, more frequent pump failure, as well as a greater number of comorbid conditions. This study using angiographic variables showed that the excess mortality noted in diabetic patients with acute myocardial infarction could not be explained by differences in early patency response to thrombolytic therapy, increased injury in response to ischemia and reperfusion, comorbid medical conditions, or the greater extent of coronary artery disease.

GUSTO showed that thrombolytic therapy was equally efficacious in restoring early infarct-related artery patency in patients with and without diabetes. There was no significant difference in the regional ventricular response to injury or reperfusion in diabetic patients compared with nondiabetic patients. However, there was a significantly blunted hyperkinetic response in the noninfarcted zone immediately after ischemic injury. This phenomenon may contribute to the increased prevalence of congestive heart failure seen in patients with diabetes and possibly to mortality. Thus, GUSTO clearly defined that thrombolysis in the early stages of acute myocardial infarction is as efficacious in diabetic as in nondiabetic patients, but that diabetes is nevertheless a powerful independent risk factor for early mortality. There is still a lot of work to be done in trying to find out why!

1996

Madeleine Albright becomes
the first female US Secretary of State;
hundreds of people are taken hostage
in the Japanese Embassy in Lima, Peru;
and a 6-year-old boy in the US
is punished for "sexual harassment,"
after kissing a schoolmate

Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S)

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Diabetes Care. 1997;20:614-620

Diabetic patients are subjected to an excessive coronary heart disease risk, which is thought to be in part explained by the adverse effects of diabetes on serum lipids and other general cardiovascular risk factors.

Serum lipid abnormalities in type 2 diabetes are characterized by decreased high-density lipoprotein (HDL) cholesterol and elevated total and very-low-density lipoprotein (VLDL) triglyceride levels, whereas total cholesterol and low-density lipoprotein (LDL) cholesterol levels do not differ significantly from those of nondiabetic subjects. Serum total cholesterol has been shown to be a powerful predictor of coronary heart disease mortality and morbidity in both diabetic and nondiabetic patients. However, at every level of total cholesterol, diabetic patients have a 2 to 3 times higher coronary heart disease risk than nondiabetic subjects.

The Scandinavian Simvastatin Survival Study (4S) was designed to investigate the effect of cholesterol lowering with simvastatin on mortality and morbidity in patients with coronary heart disease. A total of 4444 patients with previous myocardial infarction or angina with serum cholesterol levels in the region of 5.5 to 8.0 mmol/L and serum triglycerides of less than 2.5 mmol/L were randomly allocated to receive simvastatin or placebo. This paper was a subgroup analysis of the data on diabetic patients included in the 4S study.

Recruitment and randomization of this study took place between 1988 and 1989. Patients were men and women aged between 35 and 70 years, with previous myocardial infarction or angina. Of the total of 4444 patients only 202 had diabetes. Of these, 97 were randomized to placebo and 105 to simvastatin. Over the 5.4-year median follow-up period, simvastatin treatment produced changes in the serum lipids in diabetic patients to a similar extent to those observed in nondiabetic patients. Over the whole course of the trial, simvastatin-treated nondiabetic patients had a reduction in total and LDL cholesterol of 24% and 34%, respectively, and this compared favorably with the diabetic patients in whom the reductions were

27% and 36%, respectively. HDL cholesterol and triglycerides altered by +8% and -9%, respectively, compared with +7% and -11% in the diabetic patients, respectively. Thus, simvastatin was effective in altering the lipid profile in a favorable way in diabetic and nondiabetic patients. Over the 5.4-year median follow-up period, the relative risk in simvastatin-treated diabetic patients from mortality was 0.5. The relative risk for a major coronary heart disease event was 0.45 and for any atherosclerotic event was 0.63. The corresponding relative risks in nondiabetic patients were similarly reduced, but if anything not quite as dramatically as those in diabetic patients. Allowing for the significantly reduced number of diabetic patients in the study, the findings are quite striking and show that the results of cholesterol lowering with simvastatin may indeed improve the prognosis of diabetic patients with coronary heart disease to a greater extent than nondiabetic subjects. Even though patients were excluded if they had elevated triglycerides, which is commonly found in diabetic patients, these results are highly meaningful and have altered clinical practice so that much more attention has been given toward the use of statins in diabetic patients. Similar results have been found from other large studies (such as the CARE trial published in *N Engl J Med*).

1997

16-year-old Martina Hingis
becomes the youngest Wimbledon Champion
this century;
Paul McCartney receives a knighthood;
and fashion designer Gianni Versace
is shot dead in Miami



Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)

UK Prospective Diabetes Study (UKPDS) Group

Lancet. 1998;352:837-853

The UK Prospective Diabetes Study (UKPDS) was the largest and longest study in the history of diabetes. The study was conceived and designed in the 1970s and actually started in 1977, to finally report its major findings in 1998. When the UKPDS was designed, there was tremendous uncertainty about the appropriate metabolic goals for patients with type 2 diabetes. The aim was to find out whether an intensive policy of management with tighter blood glucose control had advantages over a less stringent strategy. The underlying hypothesis was that lowering the blood glucose to the normal range with any one of several medicines would reduce the likelihood of diabetes-related complications, specifically microvascular complications and the macrovascular events that are the major cause of mortality and morbidity in type 2 diabetes. The study design was complex; essentially, 3867 newly diagnosed type 2 diabetic patients from 23 participating centers were randomly allocated to an intensive treatment group, which could be with either a sulphonylurea, or insulin, or a less stringent policy starting with diet. Hard end points for both microvascular and macrovascular disease were used and all analyses were by intention to treat. Over the 10-year period of follow-up, glycosylated hemoglobin (HbA_{1c}) was 7.0% (6.2%-8.2%) in the intensively treated group, compared with 7.9% (6.9%-8.8%) in the conventionally treated group. In comparison with the conventionally treated group, the risk for any diabetes-related end point was 12% lower. Most of the risk reduction in any of the diabetes-related aggregate end points was due to a 25% risk reduction in microvascular end points. Most of this reduction was due to fewer patients requiring photocoagulation.

There were no obvious differences for any of the aggregate end points between the three therapies. Patients in the intensive group had more hypoglycemic episodes than those in the conventional group, and weight gain was significantly higher in the intensive group (mean 2.9 kg). Of these, patients assigned to insulin had a greater gain in weight (4 kg) than those assigned to chlorpropamide (2.6 kg) or glibenclamide (1.7 kg). Thus, the benefit of the

intensive policy seems to be mainly due to improvements in microvascular outcomes with only borderline support for a decrease in macrovascular disease.

Thus, the main finding from this pivotal study is that intensive therapy of type 2 diabetes is beneficial, despite the associated weight gain (metformin is advantageous in not causing as much weight gain as insulin or sulphonylureas—but this was reported in a supplementary analysis (UKPDS 34)). Despite the substantial reduction in the frequency of microvascular complications in the intensively treated group, there was no obvious benefit in terms of macrovascular disease. We can take heart, however, from the findings that insulin or insulin and sulphonylurea treatment did not have any detrimental effects on cardiovascular outcomes, reassuring those who questioned whether the intensive therapy methods of the Diabetes Control and Complications Trial (DCCT) could be directly translated to type 2 diabetes. Like all pivotal studies, as many questions were raised as were answered, and the study does not firmly establish the choice of any one therapy in the treatment of type 2 diabetes.

1998

British au pair Louise Woodward is convicted
of manslaughter in Boston, USA;
the Chicago Bulls win the NBA title
with an 87-86 victory over Utah Jazz;
and Nelson Mandela marries Grace Michel
on his 80th birthday

Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38)

UK Prospective Diabetes Study Group

BMJ. 1998;317:703-713

Although only a subsidiary part of the main United Kingdom Prospective Diabetes Study (UKPDS), this study actually revealed the more dramatic results. Cardiologists have always been telling us diabetologists over many years that the circulation is more important than glucose homeostasis, and this study provides some grist to their mill! The subjects in this study included 1148 hypertensive patients with type 2 diabetes who were enrolled in the UKPDS. Patients were randomized to either tight blood pressure control (less than 150/85 mm Hg) with the use of an angiotensin-converting enzyme inhibitor or a β -blocker as main treatment, or to a less tight control group aiming at a blood pressure of less than 180/105 mm Hg. Patients were followed up for a median of 8.4 years and predefined clinical end points—fatal and nonfatal—related to diabetes and all-cause mortality were measured.

The results of this study show that the mean blood pressure during follow-up was significantly reduced in the group assigned to tight blood pressure control (144/82 mm Hg) compared with the group assigned to less tight control blood pressure (154/87 mm Hg). Reduction in risk in the group assigned to tight control compared with the less tight control group was 24% for diabetes-related end points and 32% for deaths related to diabetes. The reduction in stroke was 44% in the intensively treated group, and that in microvascular end points was 37%. The other major finding of this study was that after 9 years of follow-up, 30% of patients in the group assigned to tight control required three or more treatments to lower blood pressure to achieve the target. Thus, a policy of tight blood pressure control appears to reduce the risk of complications of diabetes to an even possibly greater extent than tight blood glucose control.

This paper has important implications for the treatment of diabetes and has led to all diabetologists being more aggressive in their blood pressure management. The other aspect of this study that has led to a wholesale change in clinical practice and perception of drug therapy

is the fact that multiple combinations of different antihypertensive agents are often required for effective treatment of hypertension in patients with diabetes.

1998

Derek Bentley is cleared of murder
45 years after being hanged;
Britain celebrates 50 years of the NHS;
and Martin Luther King's killer,
James Earl Ray, dies in prison, aged 70



Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the DIGAMI study

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Circulation. 1999;99:2626-2632

DIGAMI (Diabetic patients receiving Insulin-Glucose infusion during Acute Myocardial Infarction study) launched a thousand insulin prescriptions in every Coronary Care Unit across the world and made a large impact on the clinical care of diabetic patients undergoing myocardial infarction.

DIGAMI was a multicenter, randomized controlled study of the effect of intensive insulin treatment on mortality and morbidity in patients with diabetes presenting with acute myocardial infarction within the preceding 24 hours. Patients were stratified into four groups on the basis of risk classification and previous use of insulin. High-risk patients fulfilled more than two of the following criteria: age greater than 70 years, history of previous acute myocardial infarction, history of congestive heart failure, or ongoing treatment with digoxin. The predefined stratified groups were: (i) no insulin and low risk; (ii) no insulin and high risk; (iii) insulin and low risk; and (iv) insulin and high risk. Patients were randomized to intensive insulin treatment consisting of an insulin and glucose infusion, followed by multidose subcutaneous insulin for 3 months. Patients assigned to the control group received conventional treatment at the discretion of the physician in charge. Thrombolysis, β -blockade, and aspirin were initiated as soon as possible in the absence of any contraindications. The study population was followed for 1 year with outpatient visits scheduled at 3 and 12 months after randomization. In this paper, the long-term follow-up was described. The mean time of follow-up was 3.4 years (range 1.6-5.6 years) and did not differ between patients within the full strata. Of the 620 patients originally entered, 314 were allocated to the control and 306 to the intensive insulin treatment. The prevalence of previously undiagnosed diabetes in this group was 11% (66 out of the 620 patients). In total, 270 of the patients in the insulin group and 264 in the control group had definite acute myocardial infarction, with the number of possible acute myocardial infarctions being 9 and 23, respectively. At the time of hospital discharge, 80% of all patients were on aspirin, 70% were on β -blockers, and 31% received angiotensin-

converting enzyme (ACE) inhibitors in addition to the antidiabetic treatment. During the long-term follow-up there were 240 deaths (39%); of these, 138 were in the control group (mortality 44%) and 102 were in the intensive group (mortality 33%). This difference was highly significant with a $P < 0.011$. This corresponded to a relative mortality reduction of 28%. The most striking effect was observed in patients without prior insulin treatment and with a low predicted cardiovascular risk. Such subjects in the intensive group had a relative reduction of mortality of 51%. The association between long-term mortality and baseline glycometabolic state revealed striking associations. Among all patients, the most powerful predictors of an unfavorable outcome were a high blood glucose level at admission and onset of heart failure during the hospital phase.

The DIGAMI study and the papers that have resulted from it have brought cardiologists and diabetologists together with the single purpose of trying to improve blood glucose control in coronary care units (CCU). The workload of many diabetes specialist nurses has gone up considerably as a result of these observations, and in any hospital, the CCU is the site of many people being initiated onto insulin treatment. It is a salutary note that intensive insulin treatment achieves a reduction in mortality of diabetic patients with acute myocardial infarction almost equivalent to the use of thrombolysis. There is much theoretical evidence to support the intensification of blood glucose control in patients undergoing myocardial infarction, but it was not until the DIGAMI study addressed it with significant power that the true importance was formally demonstrated.

1999

Andre Agassi wins the French Open,
but not Wimbledon;
the 30th anniversary
of Apollo 11's moon landing is celebrated;
and Gwyneth Paltrow is in tears,
in a pink dress, at the Oscar ceremonies