Placing the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial in context

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Abstract

The results of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial were presented at the American Diabetes Association meeting in June 2012. The purpose of this study was to assess whether there would be any reduction in cardiovascular (CV) events if insulin glargine was started early in the course of diabetes. Therefore, the selected patients were those who were at high risk of CV events, but with impaired fasting glucose, impaired glucose tolerance or recent onset of type 2 diabetes. After 6.5 years, no differences were seen in primary outcomes, namely CV death, myocardial infarction, stroke, revascularisation procedures or hospitalisation for heart failure. However, the early institution of insulin therapy using glargine was found to be an effective means of maintaining glycaemic control in this patient group. As expected, patients on glargine insulin experienced slightly increased rates of both non-severe and severe hypoglycaemia, and slight weight gain. Neither of these problems was considered to be a limiting factor in the early use of glargine insulin. A second arm of the study was designed to assess the role of omega-3 fatty acids in the prevention of CV events. The results of this arm showed no benefit and do not support the use of omega-3 fatty acids as prophylactic therapy in these patients. While the ORIGIN trial is unlikely to alter clinical practice regarding the treatment of either dysglycaemia or new-onset diabetes, it has demonstrated that glargine insulin is relatively safe when used early in diabetes and can maintain near-normal glycaemic control for over six years, without increased cancer risk and with a neutral effect on CV outcomes.

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Introduction

The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial is the fourth in a series of megatrials that was designed to assess the effect of intensive glycaemic control on cardiovascular (CV) outcomes in patients with type 2 diabetes. It follows the Action to Control Cardiovascular Risk in Diabetes (ACCORD),[1] Action in Diabetes and Vascular disease: preterAx and DiamicroN MR Controlled Evaluation (ADVANCE)[2] and Veterans Affairs Diabetes Trial (VADT)[3] trials, all of which failed to show any convincing evidence for CV disease (CVD) protection with intensified glycaemic control.

The ORIGIN study differed from the previous studies in that they were designed to assess whether intensified glycaemic control could reduce or delay the incidence of CV events in patients with longstanding (8-10 years) type 2 diabetes and who had previous CVD. The ACCORD, ADVANCE and VADT trails have been debated extensively in the literature and will not be considered further in this review. The difference with the ORIGIN study is that while it also recruited high-risk individuals, this patient cohort was people with impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or recently diagnosed diabetes. Thus, insulin glargine was administered to a population of patients who were not treated with insulin usually. Furthermore, intensive glycaemic control was not the purpose of the study. The purpose was rather to answer the question whether insulin replacement therapy that targets fasting normoglycaemia (≤ 5.3 mmol/l) with insulin glargine could reduce CV outcomes more than standard treatment approaches to dysglycaemia. Therefore, the ORIGIN trial was designed primarily to explore the effect of insulin therapy with glargine, rather than to compare the effect of glucose lowering, as studied in other trials.

A second leg of the study explored whether adding omega-3 fatty acids would reduce CV death.

This was a multicentre 6.5-year international trial that recruited over 12 500 patients. At the 19 sites in South Africa, 601 patients were recruited, the fifth highest in the world. The trial design, protocol and results were presented at the American Diabetes Association annual meeting in Philadelphia in June 2012 and have been published.[4,5] They are available to those who wish to study them in detail and will not be reproduced here.

The effect of glargine insulin on cardiovascular outcomes

In terms of primary outcomes, specified as CV death, myocardial infarction, stroke, revascularisation procedures or hospitalisation for heart failure, no significant difference was documented between those receiving glargine insulin vs. those on standard care (Figure 1). As might have been expected, symptomatic hypoglycaemia occurred more commonly in patients in the glargine arm of the study. Non-severe hypoglycaemia was reported in 17/100 patient years vs. 5/100 patient years in subjects on standard therapy, while severe hypoglycaemia occurred in 1/100 patient years for those on glargine vs. 0.3/100 patient years in patients on standard therapy. While the difference was statistically significant, in clinical terms, it is suggested that the occurrence of hypoglycaemia was not a limiting factor in the use of glargine insulin. However, there was a threefold increase in both severe and non-severe hypoglycaemia in patients in the glargine arm of the study, and for every 25 patients treated with glargine, there was one severe episode of hypoglycaemia. This needs to be taken into account when considering if there are any possible advantages of initiating early insulin therapy with glargine. Patients on glargine also showed a mean weight gain of 1.6 kg, compared to a weight loss of 0.5 kg in subjects on standard treatment, but again a weight differential of 2.1 kg over the duration of the study, while statistically significant, is probably not of major clinical concern.

The inability in the glargine arm to reduce the incidence of CV events over the 6.5-year duration of the study was not unexpected. Notwithstanding the fact that these were people with new-onset diabetes, or even those with dysglycaemia only, the presence of pre-existing vascular disease was mandatory for inclusion in this study. This created the same problem of trying to reverse established vascular disease in only 6.5 years, as was seen in the ADVANCE, ACCORD and VADT studies.

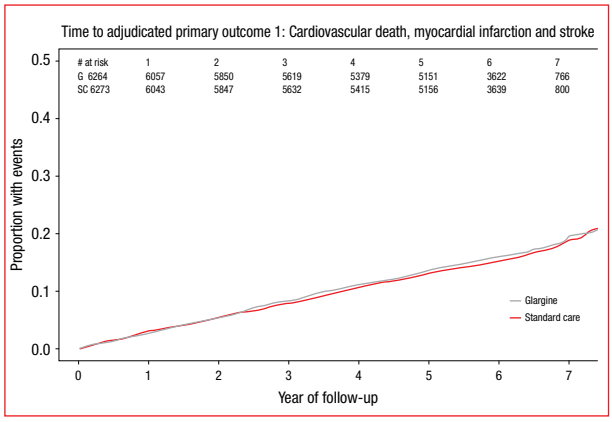

Figure 1: Differences in primary outcomes between the standard and the glargine groups

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Even in the United Kingdom Prospective Diabetes Study (UKPDS),[6] which recruited newly diagnosed patients without demonstrable vascular disease, it took 20 years to manifest a significant reduction in myocardial infarction rates.

The ORIGIN study also fell into the trap of the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction 2 (DIGAMI 2)[7] study. The Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction 1 (DIGAMI 1)[8] study showed that patients treated with intensive insulin therapy after a myocardial infarction had better outcomes than those whose treatment reverted to that of standard care. Following this, many units switched all post-myocardial infarction patients to insulin as a matter of course.

The follow-on study (DIGAMI 2) was a larger and longer trial, to prove the point that long-term insulin was beneficial post-infarction. By the time DIGAMI 2 was conceived, most units were treating post-infarction patients "intensively", so it was very difficult to find a "standard care" group. Furthermore, overall risk factor control had improved. As a result, there was little difference between the haemoglobin A_{1c} (HbA_{1c}) levels in the standard vs. those in the intensive group in DIGAMI 2. There was also no difference in outcome post-infarction, whether the patients were treated with intensive insulin or so-called "standard care" with oral agents.

In the ORIGIN study, the differences in HbA_{1c} between the standard and the glargine groups were minimal (Figure 2), so that any effect on the incidence of CVD would have been entirely due to the glargine. The conclusion that was drawn by the authors of DIGAMI 2, probably quite correctly, was that good control mattered, but it was irrelevant how it was achieved. This probably applies equally to the ORIGIN trial, which will now be extended as an observational follow-up for several more years and will be called the ORIGIN And Legacy Effects (ORIGINALE) trial. What the ORIGIN Trial demonstrated was that glargine insulin was relatively

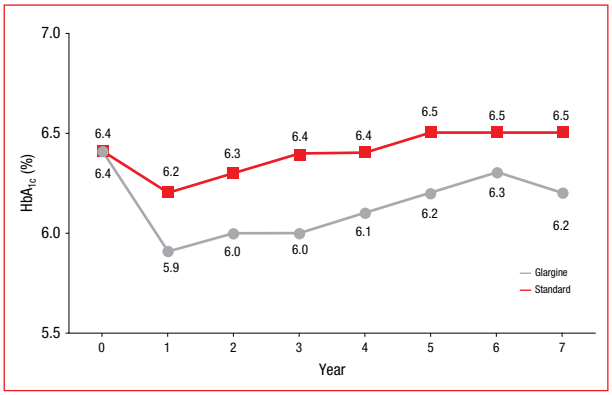

Figure 2: Differences in haemoglobin A_{1c} between the standard and the glargine groups

safe to use, either as first-line therapy, or early in the therapeutic algorithm. It also ended the debate on glargine and cancer by showing no difference in cancer rates between the two groups, although the short-term nature of the trial (only 6.5 years) needs to be taken into account when drawing that conclusion. This trial also demonstrated that it was both possible and safe to reduce the HbA_{1c} to below 6.5% in high-risk patients without increasing either CV events or the mortality rate.

The effect of early glargine therapy in patients with dysglycaemia

Recently, there has been interest in the use of insulin in early type 2 diabetes and the potential that this might have in preserving beta-cell function. Several papers[9,10] have demonstrated that if used early, insulin may promote a period of type 2 diabetes remission. However, until the ORIGIN results were published, it was unclear whether or not starting insulin during the prediabetic phase of dysglycaemia would be of benefit.

Initially, the ORIGIN trial reported a 28% reduction in progression to diabetes in this group of patients. However, this was assessed within a month of completion of the trial, and when reassessed at 100 days after the trial was stopped, the number of patients in remission was only 20%. Therefore, it is unclear what the long-term remission rates might be. This should be measured against a 58% reduction in progression to diabetes with intensive lifestyle changes in both the Diabetes Prevention Program (DPP)[11] and the Finnish Diabetes Prevention Study,[12] and a 31% reduction in progression in the metformin arm of the DPP.

The role of omega-3 fatty acids

Previous trials have suggested a possible benefit from the use of omega-3 fatty acids as a secondary prevention option. The (*Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto*) GISSI trial showed a 15% reduction in all-cause mortality in post-myocardial infarction patients.[13] A recent meta-analysis of published data indicated a 9% CV mortality benefit.[14] In contrast to this, the ORIGIN trial showed no benefit and does not support the use of omega-3 fatty acids as prophylactic therapy in these patients. However, the previous trials recruited a slightly different patient population, namely those who had had a myocardial infarction in the previous three months, or those who had had heart failure. In addition, the dose of omega-3 fatty acids that was given was higher in previous trials. Furthermore, participants in ORIGIN were taking more concomitant cardioprotective medication than those in previous trials. Potentially, this could have reduced the incidence of death from CV causes, thereby reducing the statistical power to detect any effect of the omega-3 fatty acids.

Conclusion

It is unlikely that the ORIGIN results will alter clinical practice regarding the treatment of either dysglycaemia or new-onset diabetes. Nevertheless, while largely a negative study, there were some positive findings. This study has shown that glargine insulin is relatively safe when used early in diabetes and can maintain near-normal glycaemic control for over six years without increased cancer risk and with a neutral effect on CV outcomes. There was only a modest increase in hypoglycaemia and weight with its use. Glargine also slows the progression of dysglycaemia. Targeting an HbA_{1c} of 6.5% in this group of high-risk patients with vascular disease appears to be a safe option. The routine use of omega-3 fatty acids in high-risk patients is not supported by the outcomes of this trial.

Disclosure

Dr Larry Distiller has consulted and lectured for Sanofi South Africa and has been appointed as the national ORIGIN trial spokesman for Sanofi South Africa.

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