The ORIGIN study: Useful learning points despite null findings?

In this section, a panel of multidisciplinary team members give their opinions on a recently published paper. In this issue, we focus on correcting dysglycaemia using basal insulin, and the associated cardiovascular and safety outcomes.

Basal insulin and cardiovascular and other outcomes in dysglycaemia

ORIGIN Trial Investigators (2012) *N Engl J Med* **367**: 319–28

NEJM

Insulin glargine: Cardiovascular and safety outcomes

1 The authors of the ORIGIN (Outcome Reduction with an Initial Glargine Intervention) study set out to investigate whether early management of people with impaired glucose tolerance using basal insulin safely reduced incident cardiovascular (CV) outcomes.

2 Study participants from over 40 countries were enrolled from 573 clinical sites (n=12 537). All were aged ≥50 years, had impaired glucose tolerance, impaired fasting glucose or a diagnosis of early T2D, alongside existing CV risk factors.

3 Individuals were randomised to receive either insulin glargine treatment or standard care. Those in the insulin-treatment arm added an evening glargine injection to their normal insulin regimen and increased the dose once weekly. The target fasting plasma glucose level was 5.3 mmol/L.

4 Over a median follow-up of 6.2 years, rates of incident CV outcomes, cancers, cases of diabetes, hypoglycaemic episodes and weight were recorded and compared between the two groups.

5 The rates of death from CV causes, non-fatal myocardial infarction or non-fatal stroke were comparable between the insulin glargine and standard care arms (2.94 versus 2.85 per 100 person-years, respectively). The rate of incident cancers did not differ significantly between the two groups.

6 Of the people without baseline diabetes, significantly fewer who were randomised to insulin glargine developed diabetes by the first oral glucose tolerance test compared with those receiving standard care (25% versus 31%, P=0.006).

7 The authors concluded that in people with impaired plasma glucose levels, treatment with basal insulin had a neutral effect on CV outcomes compared with standard care. Basal insulin did reduce incident diabetes but this was associated with greater weight gain and a higher rate of hypoglycaemic episodes.

"Will the ORIGIN (Outcome Reduction with an Initial Glargine Intervention) study change practice? I doubt it, but it does provide some reassurance regarding the safety of insulin glargine."

Jiten Vora, Professor of Diabetes, Royal Liverpool University Hospital, Liverpool

The basic aim of the ORIGIN (Outcome Reduction with an Initial Glargine Intervention) study was the prevention of CV events with insulin-mediated normoglycaemia in people with prediabetes or an early diagnosis of diabetes. This was based on the premise that restoring insulin deficiency in dysglycaemia reduces the need for pancreatic insulin so it can better buffer glucose changes, and consequently reduce the toxic oxidant effects of glucose. This was an appropriate trial following data from the previous studies such as UKPDS (UK Prospective Diabetes Study) and the DCCT (Diabetes Control Complications and Trial). Overall, the authors considered whether insulin replacement targeting fasting glycaemia to below 5.3 mmol/L with insulin glargine would reduce CV outcomes more than standard treatment approaches to dysglycaemia.

The primary study outcome was a composite of cardiovascular death, myocardial infarction or stroke together with revascularisation or hospitalisation for congestive heart failure. Secondary outcomes included a microvascular composite outcome, the development of new T2D and all-cause death. A total of 10 321 people had prior diabetes and 1452 had impaired fasting glucose levels and/or impaired glucose tolerance. The standard care group received treatment at the discretion of their physician. The insulin glargine group self titrated basal insulin, increasing it by 1 to 2 units twice weekly with a fasting glucose target of 5.3 mmol/L. Insulin treatment was also utilised in the standard care group.

In people who received insulin glargine, the median insulin dose at the end of the trial was 28 units per day in a person weighing 70 kg. The glycaemic results in this group were remarkable, with target fasting glucose achieved and maintained for over 6.5 years. The fasting glucose levels ranged between 4.4 and 5.8 mmol/L in the insulin glargine arm, compared with 5.7–7.9 mmol/L in the standard care arm, and an ultimate value of 5.3 mmol/L and 6.8 mmol/L in each group, respectively.

HbA_{1c} levels ranged between 37 and 48 mmol/mol (5.5% and 6.5%) in the insulin glargine treatment arm and from 40 to 52 mmol/mol (5.8% to 6.9%) in the standard care arm, with remarkable stability in both groups over the study period. All categories of hypoglycaemia were significantly greater in the insulin glargine arm; however, hypoglycaemia rates in groups were considerably lower than those reported in previous studies, including the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, UKPDS and VADT (Veterans Affairs Diabetes Trial). In the ORIGIN trial, rates of hypoglycaemia were similar to those seen in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) study, and absolute risk reduction of hypoglycaemia was 0.7%.

The median weight gain in the glargine-treated patients was

1.6 kg (interquartile range, -2 to 5.5 kg) whilst there was a 0.5 kg loss in the standard care arm (interquartile range, -4.3 to 3.2 kg). The study also examined the development of new diabetes in patients with impaired fasting glucose levels and/or impaired glucose tolerance. After a washout period of insulin withdrawal, a 28% reduction in new diabetes was seen in the insulin glargine group – this will clearly require further follow-up. The researchers found no significant differences in any primary or secondary CV outcomes between the two treatment arms.

Whilst further analysis of the data will reveal other specific end-points, the essential summary of findings documents that insulin glargine treatment was able to maintain normoglycaemia, but had a neutral effect on CV outcomes in people with prediabetes or with recently diagnosed diabetes. This was associated with a modest increase in hypoglycaemia and weight, but this was lower than has been seen in previous studies. Furthermore, there was no increase in any incident cancers, cancer-related death, neoplasia of lung, colon, breast, prostate, or melanomas.

Thus, whilst basal insulin largely had a neutral effect on CV events and cancers, a pertinent point to note from the ORIGIN study is the remarkably effective glycaemic control achieved in the standard care arm of the study. The study has also provided important safety data on insulin glargine, though in a population with prediabetes or early diagnosed diabetes. Further follow-up of the study participants would be appropriate, and this has been planned in the ORIGINALE (ORIGIN And Legacy Effects) study.

Will the ORIGIN study change practice? I doubt it, but it does provide some reassurance regarding the safety of insulin glargine.

"A continued longer follow-up of people in the ORIGIN study would, however, be useful to confirm ongoing basal insulin safety in the post-trial period with respect to cancers"

Naveed Sattar, Professor of Metabolic Medicine, University of Glasgow, Glasgow

The ORIGIN (Outcome Reduction with an Initial Glargine Intervention) study trialled the use of basal insulin (glargine) early in the course of diabetes management, but also included a minority of individuals at an elevated risk of diabetes (about one in eight participants). All people had cardiovascular disease (CVD) risk factors, and nearly 60% had a prior CVD event, enabling researchers to determine whether "provision of sufficient basal insulin to normalize fasting plasma glucose levels may reduce cardiovascular events" over a median follow-up of 6.2 years.

The results of this very well-conducted study showed absolutely no difference in CVD event rates between the insulin and standard care arms, with virtually identical Kaplan–Meier survival lines for all the main outcomes. Data also demonstrated near identical incident cancer rates in the two study arms, providing a strong signal of the safety of basal insulin over several years of exposure – when trials are adequately powered, such findings always trump epidemiological observations, which are inherently constrained by residual confounding and bias. A continued longer follow-up of people in the ORIGIN study would, however, be useful to confirm ongoing basal insulin safety in the post-trial period with respect to cancers – not all people will be fully reassured by the initial cancer outcomes due to the modest trial length. Such a follow-up may also be useful to address any microvascular benefits of basal insulin, although, given the minimal changes in HbA_{1c} over the course of the study, these are highly unlikely. But are there other useful learning points from this study?

Firstly – and perhaps most importantly – is whether, given what we know now about the relationship between glycaemia and CVD risk, there was ever any chance of the ORIGIN study demonstrating a vascular benefit of basal insulin. Put simply, recent data have shown that glucose or glycaemia levels within the upper reaches of the normal range are only very weakly associated with vascular risk (Emerging Risk Factors Collaboration, 2010). A post-hoc analysis of the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) study data, however, suggested that there may also be a threshold association of HbA_{1c} with CVD risk in those with diabetes, with CVD risk only elevating once HbA_{1c} is beyond 53 mmol/mol (7.0%; Zoungas et al, 2012). With the benefit of hindsight, the ORIGIN study may not have been conducted built on the premise of a linear relationship between glycaemia and vascular risk, which is now likely to be incorrect. Of interest, HbA_{1c} values fell slightly from 46 to 44 mmol/mol (6.4% to 6.2%) in those randomised to insulin versus a small rise from 46 to 49 mmol/mol (6.4% to 6.5%) in the standard care arm – all levels were well below the threshold for vascular risk escalation in diabetes patients, as proposed by the ADVANCE study group.

Secondly, we should note that the minimal rise in median HbA_{1c} in the standard care arm is impressive (as is the net weight loss in this study arm over 6.2 years), and perhaps reflects the compliant and willing nature of the participants in this study – notably, all agreed to be randomised to potential insulin therapy.

Thirdly, considering the postulated benefits of basal insulin on lipid, inflammation, thrombotic and vascular pathways (over and above its glucose-lowering effect), it is fair to question whether the ORIGIN study would ever have shown a vascular benefit of basal insulin (Sattar et al, 2008). Indeed, it did not lower vascular risk in the study cohort, whereas greater weight gain and hypoglycaemia rates, albeit modest in both cases, were seen in those randomised to basal insulin.

Fourthly, the authors correctly concluded that the overall results from the ORIGIN study were unambiguous and conclusive in that they do not support use of basal insulin in early diabetes care.

Finally, the legacy of the ORIGIN study is that it has provided data that further emphasise that, rather than focusing on low glycaemia targets in those with well-controlled diabetes and vascular disease, improved lipid and blood glucose management, and smoking cessation are better placed to lower CVD risk in people with diabetes.

Emerging Risk Factors Collaboration (2010) Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* **375**: 2215–22

Sattar N, Wannamethee SG, Forouhi NG (2008) Novel biochemical risk factors for type 2 diabetes: pathogenic insights or prediction possibilities? *Diabetologia* **51**: 926–40

Zoungas S, Chalmers J, Ninomiya T et al (2012) Association of HbA1c levels with vascular complications and death in patients with type 2 diabetes: evidence of glycaemic thresholds. *Diabetologia* **55**: 636–43