Insulin Therapy and Cardiovascular Outcome Trials (CVOTs): Any Harm, Anytime?

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Background

The therapeutic management of diabetes may on its own increase the risk of cardiovascular (CV) risk markers – directly or indirectly – through their pharmacological actions (e.g. side effects as hypoglycaemia), or some metabolic changes (e.g. weight-gain, increased BP, etc.). As these risks may not have been anticipated or immediately noticed during clinical trials, 1 post hoc analyses and epidemiological follow up of clinical trials have raised concerns about the CV safety of some drugs used in the management of diabetes.

Of great popularity among all glucose lowering agents (GLTs) is insulin, which Alvarez et al described as the “the most potent anti-hyperglycaemic agent clinically available” [1,2]. It is therefore not surprising to note that as both the incidence and prevalence of T2DM globally rise, alongside increasing life expectancy and longer duration of chronic disease, the use of insulin in the management of T2DM has continued to increase over the past 2 decades with over 30% of people with T2DM currently on it [2]. Insulin improves glycaemic control but is associated with weight gain and hypoglycaemia – known risk factors for CV diseases [3]. As insulin use in the management of diabetes rises, data on its CV outcomes have largely been inconsistent in both clinical trials and observational studies [4,5]. In view of the controversial publication on the adverse cardiovascular events induced by rosiglitazone [6], the American Food and Drug Administration and Control (FDA) in 2008 mandated that, before approval of any new anti-diabetic therapy, CVOTs should be carried on all GLTs in order to demonstrate their CV benefits or risks [7]. Post-hoc analyses and epidemiological follow-up studies of these trials, in some cases, have either validated or refuted earlier study outcomes, making one to ponder if it is too early to conclude on the outcomes of most CVOTs.

CVOTs vs. Post-hoc analyses/Epidemiological Follow-up Studies

Why has this “most potent anti-hyperglycaemic agent” not been solely subjected to CVOT? With the exception of DEVOTE, and the ORIGIN trials, most CVOTs failed to compare only insulin with another GLT. Whilst earlier prospective trails as The United Kingdom Prospective Diabetes Study (UKPDS) [8], which compared insulin or sulphonylurea (intensive care) vs standard care showed reduction in the risk of microvascular event in the intensive glucose control arm but none for macrovascular events and all-cause mortality; Surprisingly, in a post hoc analysis (after a follow-up duration of 16.8years), a 15% reduction in the risk of MI (p = 0.01) was observed in the intensive arm (Table 1).

In DIGAMI 1, [9] intensive insulin infusion was associated with a 28% reduction in all-cause mortality which was later confirmed in a 20-year post follow-up study which showed longer survival in the insulin (7.0 vs 4.1years) vs. conventional groups [10]; but DIGAMI 2 trial [11] failed to show any benefit. Another landmark trial, the ACCORD study [12] was prematurely terminated due to excess mortality (up to 35%) in the intensive arm of the trial (95%CI: 1.04–1.76). While it was also believed that the risks of hypoglycaemia and weight gain (in excess of 10kg) which were higher in the intensive arm could have driven this, a post hoc analysis on the association between hypoglycaemia and increased mortality showed that hypoglycaemia was associated with excess mortality in both arms. Also, in people who had just a single episode of severe hypoglycaemia, the risk of deaths was lower in the intensive arm [13], implying that hypoglycaemia may not have accounted for the excess mortality recorded. To explore the possible likely reasons, another post hoc analysis among all the trial participants showed that those with baseline HbA1c levels greater than 8.5% had a 65% increased risk of deaths. Coincidentally, these participants were found to be in the intensive therapy arm and did not have an improved HbA1c levels (HbA1c < 7%) throughout the trial. Also, unlike in the standard care arm, 1% increase in HbA1c in the intensive therapy arm was associated with a 66% greater risk of mortality thereby suggesting that factors which are associated with the persistence of high HbA1c may have driven the excess mortality seen in this arm [14].

However, the ADVANCE trial [15] showed significant reductions in the risks of microvascular diseases in the intensive arm, but none...
for macrovascular events; all-cause mortality and CV deaths even after epidemiological follow up.

The ORIGIN Trial [16] showed no statistically significant difference in a 3-point composite of MI, stroke and CV death or a 5-point composite which included hospitalisation for HF and revascularisation for CV death signalling a turning point on the concerns around the use of insulin and was able to douse the concerns raised on its cardiovascular safety.

**Table 1:** Summary of outcomes of major CVOTs involving insulin and results of epidemiological follow-up and post hoc analyses.

| Study | Microvascular Outcomes | Macrovascular Outcomes | Effect on Mortality | Epidemiological Follow-Up/Post Hoc Analyses |
|-------|------------------------|------------------------|---------------------|---------------------------------------------|
| UKPDS | Reduced microvascular endpoint | No effect on MI* | None | Reduced microvascular disease |
| DIGAMI-1 | Not available | Not available | Reduced mortality | Not available |
| ACCORD | Reduced retinopathy, nephropathy, neuropathy | No effect on MACE** | Increased mortality | Reduced retinopathy |
| ADVANCE | Reduced nephropathy | No effect on MACE | None | Reduced end-stage renal disease |
| VADT | Reduced progression of albuminuria | No effect on MACE | None | Reduced MACE |
| ORIGIN | No effect | No effect on MACE | None | Not available |

*MI: Myocardial infarction

**MACE: Major Adverse Cardiovascular Events

Source: Adapted from Fisher [17].

**Is Insulin Now Safe?**

![Figure 1: The effects of intensive versus standard glycemic control on (a) major cardiovascular events (CV death or non-fatal MI or non-fatal stroke) and (b) MI (fatal or non-fatal); (ACCORD Action to Control Cardiovascular Risk in Diabetes, ADVANCE Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation, CI confidence interval, CV cardiovascular, HbA1c glycated hemoglobin, MI myocardial infarction, UKPDS United Kingdom Prospective Diabetes Study, VADT Veteran Affairs Diabetes Trial) Source: Turnbull et al. [19].](image)
From the above, it can be easily deduced that insulin, being part of the intensive control arm of the UKPDS, ACCORD, ADVANCE, VADT and ORIGIN trials did not to show any clear risk for major CV events compared to conventional therapy [8,12,15,17,18] after long-term follow-up or post-hoc analyses. In spite of the excess mortality recorded by ACCORD study, it still showed significant reductions in microvascular complications alongside the UKPDS [8,12]. Similarly, the ADVANCE study showed a reduction in the risk of composite macro- and microvascular events but failed to show any other CV benefit [15] while DIGAMI trial showed no significant benefit with intensive care on all-cause mortality [9,10].

This evidence was later made clearer in a meta-analysis of the 27,049 participants in the ACCORD, ADVANCE, UKPDS and VADT trials [19] which showed a 9% reduction (HR: 0.91, 95%CI: 0.84-0.99) in the risk of major CV events in the intensive therapy group compared to standard care (Figure 1). Nonetheless, this is believed to have been driven, to a large extent, by the 15% reduction in the risk of MI in these populations because no similar significant beneficial effects were reported for stroke, CV deaths or heart failure [19-21].

Currently, there is no meta-analysis of these trials which included the findings of the ORIGIN study. As stated above, the ORIGIN was the first CVOT which compared only insulin vs others, and whose primary outcome was CV events. In this large trial, 12,537 participants with CV risk factors were randomised to either once daily injection of insulin glargine or standard care (lifestyle modification, and/or metformin and/or sulfonylurea). Therefore, with the inclusion of the ORIGIN trial (see Figure 2), I have been able to show that the overall effect remained slightly non-significantly changed as the risk of major CV event was only slightly reduced from 9 to 5% (HR: 0.95, 95%CI: 0.88 -1.03).

**Figure 2:** The effects of intensive versus standard glycaemic control on major cardiovascular events (CV death or non-fatal MI or non-fatal stroke) including the ORIGIN Trial [18].

**If No Harm, Why No Clear CV Benefit?**

Why did these trials fail to report any clear CV benefit? Possible explanations come to mind: first, there was lack of concordance between these trials evidenced by the following:

Firstly, the different follow-up periods: the mean follow-up duration in ACCORD was 3.5 years while the median/mean follow-up durations for ORIGIN, UKPDS, ADVANCE, DIGAMI and VADT trials were 6.2, 10.0, 5, 2.1 and 5.6 years respectively. The short follow up duration in some trials could not have been enough to explore the biological plausibility of the outcomes recorded. Secondly, there were variations in the study populations e.g. the duration of diabetes ranged from zero in UKPDS to up to 10 years in ACCORD and VADT. Thirdly, the presence of other comorbidities and risk factors differed in these populations. For instance, 32% of the ADVANCE trial study population had CV disease at the background, 40% in VADT, and 35% in ACCORD; while more than half of the participants (58.8%) in ORIGIN. Fourthly, there were minor variations in age (range: 53.3 to 66 years) and use of other non-GLTs. In addition to this, the target outcomes in these trials were non-individualised. As the management of diabetes evolves and becomes more individualised and patient-centred, these trials (as at the time they were conducted) were unable to take into account individual variations and unmet needs in treatment. In addition to this, there was the lack of consideration on the different mechanisms of action of the GLTs beside their already known effects on glucose control.

Finally, there was lack of uniformity or consensus on what constitutes the intensive and standard therapy arms of these trials; differences in the definition of the primary outcome and its components; differences in criteria for allocation to a treatment regimen [2,21-24]. In summary, judging by the proportion of patients with background CV diseases in these trials, it was thought this could have influenced the effect of intensive therapy. To explore this, a sub-study of VADT showed that intensive glycaemic control was associated with reduced CV events in those with no background history of CV (e.g. atherosclerosis) [25]. This implied that early initiation of intensive therapy in those with no CV history was associated improved CV outcomes.

This was supported by Turnbull et al. [19] in a meta-analysis of ACCORD, ADVANCE, UKPDS and VADT trials, showed a significant benefit in major CV events in the intensive therapy arm in those without a background CV diseases and shorter duration of diabetes (HR: 0.84, 95% CI: 0.75 – 0.94) vs those with CV diseases and longer duration of diabetes (HR: 1.0, 95% CI: 0.89 – 1.13). Perhaps, more
importantly, a sub-analysis on the ACCORD study by Riddle et al. showed that mortality outcome increased in patients whose HbA1c levels increased despite allocation to the intensively controlled arm. This suggests that factors like insulin resistance (obesity as a surrogate marker) may have also played an important role.

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