Consensus Statement on Implication of Landmark Trials in Diabetes

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Abstract
Type 1 and type 2 diabetes mellitus are accompanied by micro vascular and macro-vascular complications which have major contribution to the mortality and morbidity. Many large studies have been conducted with the objectives of measuring the diabetes complications and effects on mortality and morbidity. There is enough evidence from these landmark studies indicating that diabetes complications should be controlled and prevented in diabetes patients.

The aim of this consensus group convened during the National Insulin Summit 2015, Puducherry, was to focus on evaluating the data on major landmark trials in diabetes, examine the objectives, rationale, design and outcomes and to evolve statements on the implications of these results.

Published literature and major landmark studies were reviewed and summarized. Consensus recommendations have been drafted to provide the implications of landmark studies on diabetes. These can aid clinicians to understand better the clinical implications of the landmark studies including Cardiovascular outcome trials (CVOT).

Introduction
Over the years, both type 1 and type 2 diabetes mellitus (T2DM) are accompanied by micro-vascular and macro-vascular complications. Although glucose control remains top priority, long term complications have major contribution to the mortality and morbidity. The prevention of complications has been the objectives of research over the years. Consequently large randomised controlled trials have been conducted to assess whether and how more intensive control of glucose reduces long-term clinical events compared with standard treatment.

The United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) are two landmark trials that convincingly demonstrated that tight glycaemic control has beneficial effects on microvascular outcomes.1,2 These studies also revealed a “legacy effect,” which is a sustained benefit with respect to cardiovascular disease. However, more recent trials like Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease—Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and Veterans Affairs Diabetes Trial (VADT) failed to demonstrate beneficial effects of intensive glucose control on long-term outcomes especially macrovascular complications.3

Around the same time, when it was being realised that glucose-control in diabetes needs to be individualised, role of specific anti-diabetic drug was brought in focus. In 2008 following the safety concerns with Rosiglitazone, United States (US) Food and Drug Administration (FDA) and subsequently European Medicines Agency (EMA) enforced new requirements for CVOT in licensing of new anti-diabetic drugs.4 These regulatory requirements have changed the diabetes trials landscape resulting in the substantial increase in the number of CVOT.

Methods
In order to facilitate and draw the attention of physician community towards the impact of these landmark trials in diabetes, a group of experts from across India held a consensus meeting at the National Insulin Summit congress in Puducherry, India on 7th November 2015.

The objectives of the meeting were to:
1. Evaluate the data on major landmark trials in diabetes
2. Examine the objectives, rationale, design and outcomes
3. Evolve statements on the implications of these results on diabetes care

A broad classification of all the published landmark trials as glucose lowering trials and CVOT was evolved as presented in Figure 1.
Table 1: As compared to UKPDS & DCCT, PATIENTS in ACCORD, ADVANCE VADT were having longer duration of diabetes & close to 1/3rd of patients had macro-vascular disease.

<table>
<thead>
<tr>
<th>Trial name</th>
<th>History of Macro-vascular disease</th>
<th>Baseline HbA1c</th>
<th>HbA1c end of trial Intensive arm</th>
<th>HbA1c end of trial Conventional arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>Not recorded</td>
<td>7.1 ± 1.5</td>
<td>7</td>
<td>7.9</td>
</tr>
<tr>
<td>DCCT</td>
<td>Not recorded</td>
<td>8.9</td>
<td>6.8*</td>
<td>9.2</td>
</tr>
<tr>
<td>ACCORD</td>
<td>35 %</td>
<td>8.1</td>
<td>6.4</td>
<td>7.5</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>32 %</td>
<td>7.5</td>
<td>6.5</td>
<td>7.3</td>
</tr>
<tr>
<td>VADT</td>
<td>40 %</td>
<td>9.4</td>
<td>6.9</td>
<td>8.4</td>
</tr>
</tbody>
</table>

*Duration of diabetes 1-5 years in DCCT secondary prevention group; #: HbA1c in adolescents

History and Background of Glucose Lowering Landmark Trials

During the 1950s and 1960s there was growing cognizance that diabetes complications were presenting the greatest challenge to quality of life. Despite clinical acumen and observation that had demonstrated that allowing glycosuria and very high blood glucose levels led to poor quality of life, many physicians late into the 20th century, believed that perhaps poor control had an advantage in terms of weight loss.

The Availability of Self-monitoring of blood glucose (SMBG) and glycated haemoglobin (HbA1c) in the early 1980’s paved the way for better understanding. Most of the earlier studies included both type 1 and type 2 diabetes together which also hampered the interpretation of the results.

In 1977, Engerman (University of Wisconsin, Madison) demonstrated that development of retinopathy was inhibited in diabetic dogs with good glycaemic control. Almost ten years later in 1987, Prof Cohen (University of Massachusetts) showed that poor glycaemic control contributes to proteinuria and glomerular basement membrane widening. This was followed by early epidemiological evidence, showing relationship between glucose control and microvascular disease, which was the beginning of the changing opinion. In this section, the two landmark trials UKPDS, DCCT will be discussed separately.

Table 1 and 2 provide summary of the design and key baseline parameters in all five glucose lowering trials.

UKPDS

Trial Design

The UKPDS recruited 5,102 newly diagnosed T2DM patients from 23 centers in the United Kingdom (1977-1991) and followed the cohort for about 10 years. The participants who had mean of two fasting plasma glucose (FPG) concentrations of 110–270 mg/dL, after 3 months diet treatment, were randomly assigned intensive policy with a sulphonylurea (chlorpropamide, glibenclamide, or glipizide) or with insulin, or conventional policy with diet. A total of three composite endpoints were used to assess differences between conventional and intensive treatment: any diabetes-related endpoint; diabetes-related death; all-cause mortality.

Microvascular-disease outcome

Patients assigned intensive treatment had a significant 25% risk reduction compared...
Microvascular disease NA 21% reduction in all cause mortality 1.22 (1.01–1.46)

Interpretation Primary outcome 0.90 (0.78–1.04)

DCCT - Legacy effect of good glucose control continues with emergent risk reductions in T2DM.

Table 2: Outcomes in glucose-lowering trials

<table>
<thead>
<tr>
<th></th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome</td>
<td>First occurrence of nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes</td>
<td>Composite of macro vascular events and a composite of microvascular events</td>
<td>Composite of cardiovascular events.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>0.90 (0.78–1.04) P=0.16</td>
<td>0.90 (0.82 to 0.98;) P = 0.01</td>
<td>0.88(0.74 to 1.05) P = 0.14</td>
</tr>
<tr>
<td>Interpretation</td>
<td>No benefit of intensive glucose control on major cardiovascular events</td>
<td>10% relative reduction in the combined outcome of major macro vascular and microvascular events</td>
<td>Intensive glucose control had no significant effect on the rates of major CV events, 1.07(0.81 to 1.42; P = 0.62)</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>1.22 (1.01–1.46) P = 0.04</td>
<td>0.93(0.83 to1.06) P = 0.28</td>
<td>No difference</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>NA</td>
<td>21 % reduction in the incidence of nephropathy</td>
<td>No difference between the groups</td>
</tr>
<tr>
<td>CV Death</td>
<td>1.35 (1.04–1.76) P 0.02</td>
<td>0.88 (0.96 to 1.26) No difference</td>
<td>No difference</td>
</tr>
</tbody>
</table>

with conventional treatment in microvascular endpoints (537 vs 1162 events).

**Macro-vascular disease outcome and other endpoints**

Compared with the conventional group, the risk in the intensive group was 12% lower for any diabetes-related endpoint; 10% lower for any diabetes-related death; and 6% lower for all-cause mortality.

**UKPDS follow up study**

In post-trial monitoring, 3277 patients were asked to attend annual UKPDS clinics for 5 years, but no attempts were made to maintain their previously assigned therapies. At 10 years, the risk reductions in the intensive therapy group were 9% for any diabetes-related end point (p=0.04) and 24% for microvascular disease (P=0.001). The follow-up trial showed that benefits persisted despite the early loss of within-trial differences in HbA1c between the two groups, resulting in “legacy effect”.

**Implications of the results**

- Intensive glucose therapy had a lower risk of microvascular complications in T2DM.
- Legacy effect of good glucose control continues with emergent risk reductions in T2DM.

**DCCT**

The DCCT was a landmark study (1983-1993) which involved 1,441 volunteers with T1DM, aged 13–39 years from 29 medical centres in the United States and Canada. Only those volunteers who had no (Primary prevention cohort) or only early signs of diabetic eye disease (secondary prevention cohort) were included. The study compared the effects of standard control of blood glucose versus intensive control (HbA1c <6.0) on the complications of diabetes. Patients were followed up for a mean period of 6.5 years.

**Micro-vascular disease outcomes:**

In the primary prevention cohort, intensive therapy reduced the mean risk for retinopathy by 76% vs conventional therapy. In the secondary-intervention cohort, intensive therapy slowed the progression of retinopathy by 54% and reduced the development of proliferative or severe non-proliferative retinopathy by 47%.

**Macro-vascular disease outcomes:**

The relative young population of the trial made the detection of any difference in macro-vascular disease unlikely in DCCT, despite which a non-significant 41% lower risk of combined macro-vascular and peripheral vascular events was noticed in the intensive therapy group.

**DCCT follow up study**

Epidemiology of Diabetes Interventions and Complications (EDIC) study was the subsequent observational study, which followed 93% of the DCCT study patients until February 2005. During the mean 17 years of follow-up, fewer CVD events occurred in intensive treatment group. (46 events in 31 patients vs 98 events in 52 patients). EDIC study demonstrated that Intensive diabetes therapy has long-term beneficial effects should be implemented as early as possible in people with T1DM.

Over the years, many other publications from the follow up data of DCCT have shown that the gift of tight glycaemic control on micro and macro-vascular disease continues to give even after up-to 30 years.

**Implications of the results**

- Intensive glucose therapy had a lower risk of microvascular complications in T1DM.
- Intensive diabetes therapy has long-term beneficial effects on the risk of cardiovascular disease in T1DM.
- Benefits good glucose control continues despite an early loss of glycaemic differences, resulted in the introduction of the term “Metabolic memory”.

**History and background of second-generation glucose lowering trials:**

The results of the UKPDS/DCCT made the researchers to look further into this effect of lowering glycemic parameters. During this time it was being established through UKPDS that there is strong correlation between glycemic levels and prevalence of cardiovascular disease (CVD). In the Framingham study, level of glycemia correlated with prevalence of CVD, although only in women (15). Interestingly, in UKPDS the beneficial effect on CVD was found in sub-set of population of metformin sub-group. Similarly, in DCCT the effect on CVD was not statistically significant.

**Trial Design of second-generation glucose lowering drugs**

All subjects in the three trials (ACCORD/ADVANCE/VADT)
were treated to more stringent targets close to Hba1c of 6.5% in the intensive arm, as compared to 7.5% in the other ‘conventional’ arm. As compared to UKPDS/DCCT, patients in ACCORD/ADVANCE/VADT had longer duration of diabetes and close to 1/3rd of patients had macrovascular disease. ACCORD was especially designed to determine the effects of intensive glucose lowering on cardiovascular events or mortality in patients with T2DM. The design was a randomized, multicenter, double 2X2 factorial trial in 10,251 patients with T2DM (Table 2).

ADVANCE (Table 2) had broader objective and was designed to evaluate the primary outcome of a combination of microvascular and major adverse cardiovascular. The VADT was similar in baseline characteristics but subjects had average disease duration of diabetes and higher baseline Hba1c. In such high risk population, with established CV event in 40 percent of the population, the trial was designed to evaluate primary outcome of a composite of CVD events. The intention was to extrapolate effects of intensive glycemic control to high-risk subjects through some ‘miraculous’ discovery.

**Effects on Microvascular outcome**

ADVANCE showed significant reduction in the relative risk of microvascular complications. In ADVANCE, Intensive glycemic control significantly reduced the primary end point (HR 0.90 [95% CI 0.82–0.98], P=0.01), although this was due to a significant reduction in the microvascular outcome primarily development of macroalbuminuria (Table 2).4

The findings of ACCORD and VADT, however were further disappointing. The intensive glycaemia control was stopped in 2008, after a median of 3-7 years follow-up because of an increase in all-cause mortality. ACCORD showed no significant effect of intensive glycaemia therapy on the microvascular outcomes. In VADT, the multiple aspects of microvascular outcomes assessed, the only statistically significant effect of strict glycaemic control was a decrease in the conversion from normo- to micro-or macroalbuminuria. Clearly, it was evident that in patients with longstanding diabetes intensive glycemic control may not result in any apparent benefit.

**Effect on Macrovascular outcomes**

None of these three trials showed a significant benefit of intensive glycemic control on CVD in T2DM (Table 2). The lower-than-predicted CVD rates points out to the fact that comprehensive care for diabetes involves treatment of all vascular risk factors.

ACCORD was halted prematurely based on finding of an increased rate of mortality in the intensive arm compared with the standard arm (1.41 vs. 1.14% per year; 257 vs. 203 deaths over a mean 3.5 years of follow-up)

**Summary of results of second-generation glucose-lowering trials**

None of the trials, ACCORD/ADVANCE/VADT demonstrated a statistically significant reduction in the primary combined cardiovascular end points. Moreover, in ACCORD, intensive therapy resulted in increased overall mortality, mainly contributed by cardiovascular mortality. An explanation has remained elusive. It is still debated, if hypoglycemia was responsible for the adverse outcomes. There are, however, other factors that may have contributed towards this effect, namely more weight gain, or simply put, the greater complexity of therapy, contributed.

**Implications of the results**

What new information did this study add?

- Intensive glucose control (Hba1c<6.5) in patients with pre-existing CVD could increase mortality and cardiovascular events
- Intensive glycemic control cannot be recommended for patients with advanced T2DM and a high risk of CVD. Hence, tight glycose targets must chosen with caution.

This led to newer understanding and new guidelines were drafted where individualization of glycemic targets was noted.

**History and background of CVOTs**

In the past three decades few trials of glucose-lowering drugs used in T2DM have investigated cardiovascular outcomes despite the fact that most patients die from cardiovascular causes in spite of beneficial effects of lipid-reducing and blood pressure- treatments. In 2007 Nissen et al published a meta-analysis, of patients previously treated with Rosiglitazone which showed that treatment with Rosiglitazone increased the risk of myocardial infarction by 43%.

In response and driven by other publications on cardiovascular safety concerns associated with rosiglitazone, USFDA mandated the conduct of CVOTs in licensing of new glucose-lowering drugs in 2008. Subsequent EMA have also adapted similar strategy. Based on these mandates, sponsors need to demonstrate that new antidiabetic therapy for T2DM will not result in an unacceptable increase in cardiovascular risk.

The regulatory requirement to obtain robust cardiovascular safety data to approve new diabetes drugs has resulted in substantial increase in the number of T2DM diabetes cardiovascular outcome trials (CVOT).

**Trial Design CVOTs**

In this section design of ORIGIN (Insulin Glargine), SAVOR-TIMI (Saxagliptin), ELIXA (Alogliptin), TECOS (Sitagliptin) and EMPA-REG (Empagliflozin) will be presented together. Most CVOTs have, placebo-controlled, non-inferiority design with three-point or four-point Major Adverse Cardiovascular Endpoint (MACE) as the primary endpoint.) All the CVOTs included patients with long duration of diabetes of 7-10 years, except ORIGIN, which included patients with pre-diabetes (Table 3).

**Primary outcomes from CVOTs**

The results from the CVOT trials published till date is summarised in Table 4. All trials, except EMPAREG, showed non-inferiority in primary
end point, without any increase in CV risk vs placebo. In EMPA-REG, treatment with empagliflozin reduced primary end-point by 14% achieving superiority vs Placebo in another recent development, Novo Nordisk announced the top-line results from the LEADER trial, which investigated the cardiovascular safety of liraglutide over a period of up to 5 years in more than 9,000 adults with T2DM at high risk of major adverse cardiovascular events. The trial compared the addition of either Liraglutide or placebo to standard of care and demonstrated superiority, with a statistically significant reduction in cardiovascular risk. The details of LEADER will be available later in June 2016.

Secondary outcomes from CVOTs

The outcomes from SAVOR-TIMI showed an incremental 27% risk of hospitalisation due to heart failure in the group treated with Saxagliptin. In EMPA-REG, empagliflozin group showed significantly lower rates of death from cardiovascular causes by 38%, hospitalization for heart failure by 35% and death from any cause 32% relative risk reduction. Results for other studies were neutral in secondary outcome (Table 5).

Implications of the results

What was already known on this topic?

- Few trials of glucose-lowering drugs or strategies in people with T2DM 2 have investigated cardiovascular outcomes
- Till date Metformin is the only drug which has shown to reduce

### Table 3: Key baseline parameters of all the completed CVOTs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Origin</th>
<th>Savor-TIMI</th>
<th>Examine</th>
<th>TECOS</th>
<th>ELIXA</th>
<th>EMPA-REG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Population (n)</td>
<td>12,612</td>
<td>16,492</td>
<td>5,380</td>
<td>14,671</td>
<td>6,068</td>
<td>7,020</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>5</td>
<td>10.3 ± 2.8</td>
<td>7.2 ± 2.8</td>
<td>9.4 ± 2.6</td>
<td>9.3</td>
<td>2.6</td>
</tr>
<tr>
<td>Mean age</td>
<td>64</td>
<td>65 ± 8.5</td>
<td>61</td>
<td>66 ± 8</td>
<td>60.3 ± 9.7</td>
<td>63.1</td>
</tr>
<tr>
<td>Mean HbA1c</td>
<td>6.4</td>
<td>8.0 ± 1.4</td>
<td>8.0 ± 1.1</td>
<td>7.3 ± 0.7</td>
<td>7.7 ± 1.3</td>
<td>8.07</td>
</tr>
<tr>
<td>Mean HbA1c</td>
<td>6.2</td>
<td>2.1</td>
<td>1.5</td>
<td>3</td>
<td>1.9</td>
<td>3.1</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>3 Point MACE</td>
<td>3 Point MACE</td>
<td>3 point MACE</td>
<td>4 point MACE</td>
<td>4 point MACE</td>
<td>3 point MACE</td>
</tr>
<tr>
<td>Secondary endpoint</td>
<td>Cardiovascular (CV) Death, MI or Stroke</td>
<td>Cardiovascular (CV) Death, MI or Stroke</td>
<td>Cardiovascular (CV) Death, MI or Stroke</td>
<td>Cardiovascular (CV) Death, MI or Stroke</td>
<td>Cardiovascular (CV) Death, MI or Stroke</td>
<td>Cardiovascular (CV) Death, MI or Stroke</td>
</tr>
</tbody>
</table>

### Table 4: The results from the CVOT trials published till date

<table>
<thead>
<tr>
<th>ORIGIN</th>
<th>SAVOR TIMI</th>
<th>EXAMINE</th>
<th>TECOS</th>
<th>ELIXA</th>
<th>EMPA-REG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite CV end point</td>
<td>HR 1.02; (CI 0.94 - 1.11)</td>
<td>HR 1.00; (CI 0.89 - 1.12)</td>
<td>HR 0.96; (CI: 0.89 – 1.13)</td>
<td>HR 0.98; (CI: 0.89–1.17)</td>
<td>HR 1.02; [CI: 0.74–0.99]</td>
</tr>
<tr>
<td>Interpretation</td>
<td>No difference</td>
<td>No difference</td>
<td>No difference</td>
<td>No difference</td>
<td>No difference</td>
</tr>
</tbody>
</table>

### Table 5: The key secondary outcome from the CVOTs

<table>
<thead>
<tr>
<th>ORIGIN</th>
<th>SAVOR TIMI</th>
<th>EXAMINE</th>
<th>TECOS</th>
<th>ELIXA</th>
<th>EMPA-REG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization from Heart failure (HF)</td>
<td>HR 0.9; (CI 0.77-1.05)</td>
<td>HR 1.27; [CI: 1.07 – 1.51]</td>
<td>HR 1.07; [CI: 0.79 – 1.46]</td>
<td>HR 1.00; [CI: 0.83–1.20]</td>
<td>HR 0.96; [CI: 0.75–1.23]</td>
</tr>
<tr>
<td>Death from CV cause</td>
<td>HR 1.00; (CI 0.89 -1.13)</td>
<td>HR 1.03; (CI: 0.87 – 1.22)</td>
<td>HR 0.85; (CI 0.66 – 1.10)</td>
<td>HR 1.03; (CI 0.89–1.19)</td>
<td>HR 0.98; [CI: 0.78–1.22]</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>HR 0.98; (CI 0.98 -1.08)</td>
<td>HR 1.11; (CI: 0.96 – 1.27)</td>
<td>HR 0.80; (CI 0.60 – 1.37)</td>
<td>HR 1.01; (CI 0.90–1.14)</td>
<td>NA</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>HR 0.91; (CI 0.76 -1.08)</td>
<td>HR 1.19; (CI: 0.89 – 1.60)</td>
<td>HR 0.90; (CI 0.60–1.37)</td>
<td>HR 0.90; (CI 0.70–1.16)</td>
<td>NA</td>
</tr>
<tr>
<td>Interpretation</td>
<td>No increase or decrease in death due to CV disease</td>
<td>No increase or decrease in death due to CV disease</td>
<td>No increase or decrease in death due to CV disease</td>
<td>No increase or decrease in death due to CV disease</td>
<td>No increase or decrease in death due to CV disease</td>
</tr>
<tr>
<td>Interpretation</td>
<td>No difference</td>
<td>No difference</td>
<td>27% increase in risk of hosp due to HF</td>
<td>No difference</td>
<td>No difference</td>
</tr>
</tbody>
</table>

ForImplications of the results

What was already known on this topic?

- Few trials of glucose-lowering drugs or strategies in people with T2DM 2 have investigated cardiovascular outcomes
- Till date Metformin is the only drug which has shown to reduce
risk for any diabetes-related endpoint

What new information did these studies add?

- The Examination of Cardiovascular Outcomes with Insulin Glargine, Alogliptin, Sitagliptin, and Saxagliptin and Lixisenatide versus Standard of Care showed neutral effects.

- The recently published EMPA-REG outcome trial and the LEADER trial which is expected to be available in June 2016 have both shown superiority of cardiovascular outcomes

Overall Summary

Over the years, various landmark trials have provided useful insights in management of diabetes. The UKPDS has been widely conceived of as mother of all trials and is essentially the nidus for treatment recommendations. The focus moved to trials on individual drugs being followed up in dedicated trials. Metformin and acarbose have also begun such trials.

These trials may add up more evidence to currently add data to support present results or maybe present new findings which will provide more insights in managing diabetes.

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