ADVANCE to ADVANCE-ON: Unfolding the “Legacy Story” in Diabetes

Sanjay Kalra*

Received: 27 March 2019; Accepted: 06 February 2023

ABSTRACT

Type 2 diabetes mellitus (T2DM) is a progressive disease. The importance of early intensive glucose lowering in preventing vascular complications in diabetes is well established. Sulfonylureas (SU) is recommended by most guidelines and widely used for the management of T2DM. However, there has been ambiguity around the long-term benefits with regard to microvascular and macrovascular outcomes with SUs. The United Kingdom Prospective Diabetes Study (UKPDS) provided evidence of sustained cardiovascular (CV) and microvascular benefits of previous intensive glycemic control with SUs or insulin in T2DM patients. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release (MR) Controlled Evaluation (ADVANCE) trial, another landmark study in T2DM patients and its posttrial observational follow-up (FU) study (ADVANCE-Observational Study [ADVANCE-ON]) together provide definite evidence for sustained renal benefits of glimepiride MR based intensive glucose control initiated early during the course of diabetes. These effects, however, may be specific to glimepiride. Evidence from other studies and reviews also suggests that glimepiride MR may hold a distinct place among currently available SUs and reinforce its utility in diabetes management.

Journal of the Association of Physicians of India (2023): 10.59556/japi.71.0319

INTRODUCTION

Diabetes is a growing health issue worldwide. The global diabetes prevalence in 2021 was estimated to be 536.6 million people, which is expected to rise to 783.2 million in 2045.1 Diabetes mellitus is associated with micro and macrovascular complications leading to debilitating or often fatal outcomes.2

Type 2 diabetes mellitus (T2DM) accounts for 90–95% of cases.3 A comprehensive approach addressing hyperglycemia along with lipid, blood pressure, and weight abnormalities, and additionally preventing or delaying the associated complications, can help manage T2DM as a whole.4–6

Sulfonylureas (SUs) are secretagogues that act by stimulating insulin secretion from pancreatic β-cells. Since their introduction in clinical practice in the 1950s, SUs have remained the mainstay of pharmacotherapy in the management of T2DM. Despite the advent of several new antihyperglycemic drugs, SUs remains the most prescribed oral antihyperglycemic agents for managing T2DM.7,8 Modern SUs, including glimepiride modified release (MR) and glimepiride, have been preferred. Nevertheless, there has been ambiguity regarding their long-term benefits, especially on the cardiovascular (CV) and mortality risks associated with SUs. Many contrasting reports have been published about this. In a meta-analysis comparing SU vs non-SU agents, the use of SUs was associated with increased mortality and risk for stroke in patients with T2DM; however, the overall incidence of major CV events was similar for both the agents.9 Few reports suggest an increased risk of CV events, mortality, and hypoglycemia with certain SUs.10,11 A review of 15 head-to-head trials comparing SUs with active comparators reported no increased CV risk with SUs.12

This review aims to revisit the available data on the long-term microvascular and macrovascular effects of intensive hypoglycemic therapy in T2DM, particularly with the modern SU, glimepiride MR, and provide clinically relevant insights.

THE UNITED KINGDOM PROSPECTIVE DIABETES STUDY (UKPDS): LEGACY EFFECT OF INTENSIVE GLYCEMIC CONTROL IN NEWLY DIAGNOSED T2DM

Large, randomized trials on diabetes patients have demonstrated that early intensive glucose lowering confers microvascular benefits.13,14 In the UKPDS, patients with newly diagnosed T2DM were randomly assigned for intensive glucose lowering with either an SU (chlorpropamide or glibenclamide) or insulin, or conventional diet-based therapy. A 25% risk reduction in overall microvascular complications was observed with intensive vs conventional treatment in patients with newly diagnosed diabetes.15 This reduction in microvascular risk was maintained over ~10 years of posttrial follow-up (FU).16 Long-term CV [15% reduction in myocardial infarction (MI)] benefits with previous intensive therapy emerged during the 10-year posttrial FU.16

United Kingdom Prospective Diabetes Study (UKPDS) 44-year FU demonstrated that the legacy effect of implementing intensive blood glucose control soon after diagnosis continues to remain for up to 44 years. Early intensive blood glucose control with insulin or sulfonylurea led to 11% fewer deaths and 26% fewer diabetic complications like kidney failure or vision loss. The use of metformin led to 31% fewer heart attacks and 25% fewer deaths. This glycemic legacy effect strengthened the early intervention in diabetes.17

OTHER LANDMARK TRIALS: WHAT THEY ADD TO THE EXISTING KNOWLEDGE

In the early 21st century, three large long-term trials were conducted by Action to Control CV Risk in Diabetes (ACCORD), Veterans Affairs Diabetes Trial (VADT), and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), to evaluate the relationship between intensive glycemic control and CV outcomes in T2DM patients at high risk for CV events.18–20 A long-term FU study was commissioned for each of these trials to evaluate possible legacy effects.21–23 The results from these trials and their posttrial FU studies are summarized in Table 1.

In contrast to the results from previous epidemiological studies and the UKPDS, no significant CV benefit was observed with intensive glucose lowering in the initial active comparison phase of the ACCORD trial or the VADT.14,18,19 In fact,
the glucose-lowering arm of the ACCORD trial was terminated early, and all patients were transitioned to a standard glucose control regimen due to increased all-cause (hazard ratio [HR], 1.20 [95% confidence interval [CI], 1.04–1.39]; p = 0.01) and CV mortality (1.49 [1.19–1.87]; p < 0.0001) with intensive treatment. The risk of CV mortality with prior intensive therapy remained high at the end of the posttrial FU (1.20 [1.03–1.39]; p = 0.02).21 In the VADT, a significant reduction in major CV events was noted with previous intensive vs standard therapy (0.83 [0.70–0.99]; p = 0.04) nearly 10 years after completion of the active intervention phase.22

A post hoc analysis of the ACCORD study revealed that intensive glycemic control did not reduce composite microvascular outcomes or renal failure but delayed the onset of albuminuria and certain measures of retinopathy.24 A total of 5 years of intensive glycemic treatment in the VADT was associated with reduced progression to macroalbuminuria but did not significantly alter the onset or progression of retinopathy.25

Table 1: Baseline characteristics and outcomes from landmark trials in T2DM

<table>
<thead>
<tr>
<th>Characteristic/outcome</th>
<th>UKPDS18,19</th>
<th>ACCORD20,23</th>
<th>VADT21,24</th>
<th>ADVANCE22,25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>3867</td>
<td>10,251</td>
<td>1791</td>
<td>11,140</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Age, years</td>
<td>53</td>
<td>62</td>
<td>60</td>
<td>66</td>
</tr>
<tr>
<td>Duration of diabetes, years</td>
<td>NA⁴</td>
<td>10</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Baseline HbA1c%</td>
<td>7.1</td>
<td>8.3</td>
<td>9.4</td>
<td>7.5</td>
</tr>
<tr>
<td>Trial characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Design</td>
<td>Prospective RCT in patients with newly diagnosed T2DM</td>
<td>Multicenter, RCT in T2DM patients with established CV disease or CV risk factors</td>
<td>Open-label RCT in patients with poorly controlled T2DM</td>
<td>Multinational RCT in T2DM patients</td>
</tr>
<tr>
<td>Treatments for glycemic control (I vs S)</td>
<td>Metformin, SU, or insulin vs diet</td>
<td>Multiple drugs in both arms</td>
<td>Multiple drugs in both arms</td>
<td>Current therapy + gliclazide vs current therapy (physician-directed)</td>
</tr>
<tr>
<td>Glycemic target (I vs S)</td>
<td>Fasting plasma glucose: &lt;6 mmol/L vs &lt;15 mmol/L</td>
<td>A1c: &lt;6% vs 7–7.9%</td>
<td>A1c: &lt;6% vs &lt;9%</td>
<td>A1c: &lt;6.5% vs per local guidelines</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Micro and macrovascular complications</td>
<td>Composite of MI, stroke, or CV death</td>
<td>Composite of MI, stroke, CV death, hospitalization for HF, revascularization, or amputation</td>
<td>Major macrovascular and microvascular events</td>
</tr>
<tr>
<td>Duration of FU, years</td>
<td>10.0</td>
<td>~20</td>
<td>3.7</td>
<td>5.6</td>
</tr>
<tr>
<td>Results</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (I vs. S),%</td>
<td>7.0 vs 7.9</td>
<td>~8.0</td>
<td>6.4 vs 7.5</td>
<td>~8.1 vs 8.3</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>−12%*</td>
<td>−9%*</td>
<td>nd</td>
<td>−17%*</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>nd</td>
<td>−13%*</td>
<td>+22%*</td>
<td>nd</td>
</tr>
<tr>
<td>CV death</td>
<td>nd</td>
<td>NA</td>
<td>+49%*</td>
<td>nd</td>
</tr>
<tr>
<td>MACE</td>
<td>nd</td>
<td>−15% (0.01)</td>
<td>−20%*</td>
<td>nd</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>−25%*</td>
<td>−24%*</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Nephropathy/ESKD</td>
<td>nd</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* p < 0.01 for intensive vs standard glucose-lowering groups; * the UKPDS included patients with newly diagnosed T2DM; * in UKPDS, the composite microvascular endpoint included vitreous hemorrhage, retinal photoagulation, and renal failure; CV, cardiovascular; ESKD, end-stage kidney disease; FU, follow-up; HbA1c, glycated hemoglobin; HF, heart failure; I, intensive glycemic control; MACE, major adverse cardiovascular event; MI, myocardial infarction, NA, data not available; nd, no significant difference between intensive and standard treatment groups; S, standard glycemic control

Evaluation (ADVANCE) to Advance-Observational Study (ADVANCE-ON): Further Unraveling the Legacy Story

The ADVANCE trial evaluated the effect of an intensive [gliclazide MR-based regimen; target glycated hemoglobin (HbA1c) ≤6.5%] vs standard glucose control (target HbA1c per local guidelines) on vascular outcomes in patients with T2DM.20 A total of 11,140 patients were randomized at 215 centers across 20 countries, including 471 Indian patients. After a median FU of 5 years, the mean HbA1c level was significantly lower in the intensive group vs the standard group (6.5 vs 7.3%). The Incidence of the primary endpoint, a composite of major macrovascular and microvascular events, was significantly

Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release (MR) Controlled
## Summary

The results from the ADVANCE study showed that early intensive treatment with a gliclazide MR-based regimen provides effective glycemic control and confers vascular benefits in patients with T2DM. The long-term posttrial FU during the ADVANCE-ON study also showed a favorable legacy effect on hard renal endpoints, such as ESKD, without increased risk of CV events or mortality. Gliclazide MR is associated with a lower risk of hypoglycemia compared to other SUs. Overall, the results confirm the legacy effects of gliclazide MR, reinforcing its utility in routine diabetes management.

## References


### Gliclazide: beyond ADVANCE-ON

Several reports have suggested that gliclazide is unique among all SUs. A population-based observational study that compared the impact of gliclazide vs glimepiride on kidney outcomes supported the nephroprotective effect of gliclazide which was observed in the ADVANCE study. Gliclazide was associated with reduced risk of doubling of creatinine in patients with preserved kidney function (eGFR ≥60 mL/minute/1.73 m²), good glycemic control (HbA1c <7%), and in older patients (>60 years). In another population-based study of Danish residents, gliclazide was associated with a lower risk of CV events compared to other insulin secretagogues, irrespective of the presence of CV risk. A systematic review comparing gliclazide with other SUs reported significantly lower hypoglycemia events and equal or greater glycose-lowering effect with gliclazide. Further, the authors concluded that amongst the currently available SUs, gliclazide had the lowest potential for macrovascular and microvascular events, including CV mortality. This potential beneficial effect may be attributed to its binding specificity for the pancreatic SU receptor (SUR1) and not for SU receptors in the myocardium (SUR2A) or blood vessels (SUR2B). Understandably, the Dutch, South African guidelines, and South Asian Federation of Endocrine Societies consensus statement specifically recommend gliclazide as the preferred SU for the management of type 2 diabetes.


