Long-Term MV Results From the Diabetes Prevention Program Outcomes Study

Written by Nicola Parry

In a session highlighting the results from the Diabetes Prevention Program Outcomes Study [DPPOS; NCT00038727], Kieren J. Mather, MD, Indiana School of Medicine, Indianapolis, Indiana, USA, shared data indicating that, although no significant differences in early microvascular (MV) outcomes were observed among the lifestyle intervention, metformin, or placebo groups, there was a reduction in MV complications in women in the intensive lifestyle intervention arm.

The Diabetes Prevention Program (DPP) was a primary prevention study—a landmark, multicenter, randomized clinical trial examining the roles of an intensive lifestyle intervention or metformin in preventing or delaying the development of type 2 diabetes mellitus (T2DM) in a high-risk population due to the presence of impaired glucose tolerance (IGT) [Knowler WC et al. *N Engl J Med*. 2002]. In the study, 3234 individuals with IGT were randomly assigned to three treatment groups: intensive lifestyle modification, metformin 850 mg twice daily, or placebo. The mean age of the participants was 51 years, 68% of whom were women, and 45% of whom were members of minority groups. The DPP ended 1 year early, after approximately 3 years of study, showing that lifestyle modification reduced T2DM onset by 58% (95% CI, 48 to 66) whereas metformin reduced its onset by 31% (95% CI, 17 to 43). These effects were similar in men and women, and in all racial and ethnic groups.

At the conclusion of the DPP, 2776 (87%) of the original participants were enrolled in the DPPOS, a long-term follow-up of the DPP to examine whether the delay in the development of T2DM seen during the DPP could be sustained, and to evaluate the long-term effect of the original DPP intervention on the later development of T2DM, cardiovascular disease (CVD) and its risk factors and MV complications, and the economic implications of these changes. All patients previously in the DPP placebo group were transferred to the lifestyle intervention group.

After approximately 15 years of follow-up, Dr. Mather noted that the prevalence of MV disease was not significantly different in the lifestyle intervention, metformin, or placebo groups (11.3% vs 13% vs 12.4%; p = = .08). However, he noted that, for unknown reasons, the lifestyle intervention was effective in reducing MV complications in women (21% vs placebo; p = .03; 22% vs metformin; p = 0.02). Additionally, the mean prevalence of MV outcomes was approximately 50% higher in men. There was also a 28% lower prevalence of MV disease in individuals who did not progress to diabetes compared with those who did, and this effect was present in all three treatment groups.

Dr. Mather emphasized the paradoxical results. On one hand, the interventions reduced diabetes development over time, and the prevalence of MV disease was lower in people who were not later diagnosed with T2DM as compared with those who were. Yet, a similar pattern of differential rates of complications was not seen among the different groups. The specific reasons for this remain unknown; however, Dr. Mather remarked that overall the HbA1C levels achieved in the study were relatively low and in a range that, according to data in the medical literature, is associated with low rates of MV complications. Also, the cohort is still relatively early in the course of dysglycemia, with only minimally elevated HbA1C, so there is little difference in HbA1C levels between the groups, which perhaps also contributes to the lack of significant difference.

In summarizing the overall results of the study, Marinella G. Temposa, PhD, George Washington University, Washington, DC, USA, highlighted that the results of the DPP and DPPOS show that primary prevention or delay of T2DM is possible in people at high risk for diabetes, including those with impaired fasting glucose (IFG) and IGT, both in the short and long term. The data have shown that

Official Peer-Reviewed Highlights From
American Diabetes Association.
74th scientific SESSIONS
JUNE 13-17, 2014 · SAN FRANCISCO, CA

intensive lifestyle modification or metformin can reduce or delay the onset of T2DM for up to15 years. Consequently, despite the diabetes pandemic, the disease is not necessarily inevitable among individuals at high risk.

Dr. Temposa noted that the relative benefits of lifestyle modification and metformin demonstrated during DPP decreased during DPPOS due to the reduction in rates seen in the placebo group. The prevention of T2DM was also shown to be cost saving with metformin, whereas both lifestyle intervention and metformin were cost-effective.

The findings of the study also highlighted the key role of T2DM prevention in the development of complications. In addition to a reduced risk of MV disease, participants who were later diagnosed with T2DM, as compared with those who were not, had a higher severity of coronary artery calcification (CAC). And compared with lifestyle, metformin also improved CAC severity in men. The risk of MV disease, specifically retinopathy and nephropathy, and CAC were increased with worsening dysglycemia and longer diabetes duration in this study.

However, Dr. Temposa stressed that, despite 15 years of follow-up, the answers to many questions remain unknown, such as the optimum time to introduce prophylaxis for long-term complications associated with T2DM. It will be important to determine the effects of long-term metformin treatment on CVD and cancer, as well as the effect of the transition from prediabetes to T2DM on the risk for various disease outcomes. Following the clinical course of T2DM will also be necessary, particularly to determine the effects of risk factors on its development and its complications in more advanced stages. Finally, examining the effects of T2DM prevention or delay on longer-term MV outcomes and newly recognized complications, such as functional impairment and quality of life, will definitively address the question of the benefit of T2DM prevention under an intent-to-treat approach, she added.

The abnormal regulation of glycemia follows a protracted time course, and the evolution from IGT through to T2DM and from early complications to morbidity and mortality can take decades. Before the DPP, the diagnosis of T2DM typically occurred only when early complications were recognized. This is considered to be between 1 and 10 years before the biochemical onset of T2DM, but 5 to 10 years after the onset of prediabetes. Examining the evolution of dysglycemia, such as its occurrence during these studies, allows for identifying potential targets for intervention. Understanding how to prevent or delay T2DM and when to intervene to reduce long-term morbidity and mortality in a cost-effective manner may be the most important public health question in diabetes, Dr. Temposa concluded.