

Lisette Romo PA-S

<https://www.nejm.org/doi/full/10.1056/NEJMoa2200433>

## **Glycemia Reduction in Type 2 Diabetes — Glycemic Outcomes**

This article highlights the GRADE (Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study), which is a large randomized controlled trial (RCT) that was conducted in 36 different locations across the United States in type 2 diabetic patients, assessing the difference between diabetes medications. This trial focused on comparing how effective four different oral medications from various drug classes perform when added to the first-line medication, Metformin. One of the most common chronic conditions seen in patients is Type 2 Diabetes Mellitus, which affects 30 million Americans, with many medications available. It is provider-dependent when treating a newly diagnosed patient, since there are so many, but it is important to consider what is most beneficial for patients. Given how prevalent this condition is, understanding their effectiveness is crucial, but studies assessing their long-term use have been far between.

This RCT was conducted on 5,047 participants living with type 2 diabetes over a five-year span, who were taking Metformin with HbA1c levels of 6.8-8.5% range. The demographic was diverse, with the majority of participants being white (65%), black (19.8%), and Hispanic (18.6%). Participants were randomly split into four treatment groups: Insulin: Glargine, Sulfonylurea: Glimepiride, GLP-1: Liraglutide, and DPP-4 inhibitor: Sitagliptin. Two outcomes were being measured: the first was based on how long the medication took for HbA1c levels to reach  $\geq 7.0\%$ , which demonstrates a loss of glycemic control. The other secondary outcome measured how long it took for the HbA1c levels to increase further than 7.5%, indicating worsening diabetes control.

The GRADE trial resulted in insulin glargine and liraglutide being more effective in achieving and maintaining glycemic control by reducing the HbA1c below 7% in comparison to glimepiride and sitagliptin. The group on Glimeperide experienced hypoglycemic side effects whereas patients on liraglutide experienced weight loss and gastrointestinal symptoms, but it was cardioprotective with a lower risk of cardiovascular disease and heart failure. While those two medications worked very well as adjunctive treatment to Metformin, the study highlights the cons. Unfortunately, by five years, more than half of the patients in all four groups had poor glycemic control even in a controlled clinical trial setting, not because the medications were no longer effective, but due to the progressive nature of diabetes; approximately 71% of patients ended up with an HbA1c over 7%.

Overall, the study concluded that glargine and liraglutide were solid second-line treatments to metformin. When considering starting patients on medications, shared-decision making between patient and provider was emphasized, along with side effects, costs, side effects, and efficacy as add on therapy to metformin. This was a practical study with results that coincide

with current guidelines for each medication class. Although limitations include a lack of blinding because it is a randomized trial, and the inclusion of only one drug from each medication class, this may restrict the results.