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Commentary

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REWIND Diabetes for Octogenarians

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Older patients with type 2 diabetes mellitus form one of the largest cohorts of the diabetic population. Worldwide, the population of older adults is rapidly growing and so also is the prevalence of diabetes in this cohort as part of the global epidemic. In the United States, older adults (≥65 years) make up more than 25% of the total population with diabetes, and the prevalence in this age category is estimated to double in the next 20 years as the population ages (1). Managing older adults with diabetes present unique challenges due to concomitant comorbidities, frailty, and increased risk of hypoglycemia from overtreatment.

In the last 15 years, we have witnessed advance in diabetes treatment with 3 major classes of therapy being added to our armament in addressing the unmet need of diabetes care. One of these classes is glucagon-like peptide-1 (GLP-1) receptor agonists (RAs). GLP-1 is a naturally occurring peptide secreted from the intestines following food intake, which in turn stimulates insulin secretion from the pancreas to maintain glucose homeostasis. The native GLP-1 has a very short plasma half-life, owning to degradation by the enzyme dipeptidyl peptidase-4 (2). Exploiting this physiological response, various GLP-1 RAs have been developed, with several currently in clinical use. Randomized controlled trials have demonstrated that GLP-1 RAs are highly effective at lowering hemoglobin A1c and facilitating weight loss without causing hypoglycemia in adults with type 2 diabetes, but results may not be generalizable to older adults.

In this issue of the journal, Riddle and colleagues report the efficacy and safety of dulaglutide in older patents: a post-hoc analysis of the REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes) trial (3). REWIND is a randomized, double-blind placebo-controlled trial at 371 sites in 24 countries, recruited just under 10 000 type 2 diabetes patients aged ≥ 50 years with and additional cardiovascular risk factors. Participants were randomly assigned (1:1) subcutaneous injections once a week of either dulaglutide (1·5 mg) or an equal volume of matching placebo as an add-on to country-specific standard of care. In this post-hoc analysis study subjects were stratified by age subgroups (≥65 and <65 years). A total of 5256 randomized patients were ≥65 years. The primary end point was a major adverse cardiovascular event (first occurrence of the composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular disease or unknown causes). During a median follow-up of 5.4 years, dulaglutide treatment showed a similar reduction in the incidence of major adverse cardiovascular events in older (11%) *vs* younger (13%) patients (P = 0.797). The incidence of all-cause mortality, hospitalizations for heart failure, severe hypoglycemia, severe renal events, serious gastrointestinal events, and rate of

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study drug discontinuation were similar between randomized treatment groups within each age subgroup. In addition, previous study has shown that dulaglutide treatment have similar glycemic efficacy in type 2 diabetic patients ≥ 65 years of age compared to those <65 years (4).

The finding from this post-hoc study and the main RWIND trial have numerous implications for the management of type 2 diabetes patients of older age. First, older patients with diabetes are at an increased risk of cardiovascular disease, and a diabetic therapy that reduces the cardiovascular events will have an added benefit to the glycemic control and reduced microvascular complications of diabetes. Second, the risk of cognitive decline increase with age and previous exploratory analysis of the REWIND trial suggests long-term treatment with dulaglutide may reduce cognitive impairment in people with type 2 diabetes (5).Third, diabetes is an independent risk factor for osteoporotic fractures, the risk of which is higher with patients of older age. A case-control study using Danish National Health Service data has shown that the use of GLP-1 RA was not associated with fracture risk as compared to the use of other antihyperglycemic drugs (6). Fourth, older patients are at an increased risk of severe hypoglycemia associated complications, and a treatment with low risk of hypoglycemia and the convenience of once-weekly dosing will further enhance our ability to care for our aging patients.

In conclusion, the work by Riddle and colleagues is significant in demonstrating the safety and effectiveness of dulaglutide in over 65 years of age. However, with the mean age of 71 for the older cohort and the exploratory nature of the post-hoc analysis limit the generalizability of the findings and warrant future studies involving the octogenarian.

Additional Information

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