Editorial

Glucagon-Like Peptide-1 Receptor Agonists: A New Era in Cardiometabolic and Cardiovascular Care

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Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have evolved from glucose-lowering medications for diabetes into foundational cardiometabolic therapies, supported by robust evidence of cardiovascular protection from major clinical trials.[1] Their dual capacity to reduce hyperglycemia and promote substantial weight loss is particularly relevant in regions like Iran and the Middle East, where the prevalence of obesity (~25%), overweight (~60%), and diabetes (~10%) is rising rapidly; regional diabetes prevalence is projected to increase by more than 80% by 2050.[1,2]

By enhancing glucose-dependent insulin secretion, suppressing glucagon release and appetite, lowering blood pressure, improving lipid profiles, and exerting anti-inflammatory vascular effects, GLP-1 RAs such as liraglutide, semaglutide, and dulaglutide offer a comprehensive strategy for mitigating the intertwined risks of metabolic and cardiovascular disease.[3]

Cardiovascular Outcomes: Landmark Trials and Latest Evidence

Since 2015, multiple large randomized trials have established GLP-1 RAs as cardioprotective therapies beyond their glucose-lowering role in diabetes. Studies such as LEADER (liraglutide), SUSTAIN-6 (semaglutide), and REWIND (dulaglutide) demonstrated significant reductions in major adverse cardiovascular events (MACE)—including cardiovascular death, myocardial infarction, and stroke—of roughly 12% in relative risk compared with placebo.[4–6] These benefits were most evident for myocardial infarction and stroke, although heart failure (HF) outcomes were initially neutral. On this foundation, current guidelines recommend GLP-1 RAs for patients with type 2 diabetes and established atherosclerotic cardiovascular disease or high cardiovascular risk. This paradigm shift reframed GLP-1 RAs as cardiometabolic agents, catalyzing trials beyond traditional diabetes care.[7]

Recent studies have dramatically expanded the clinical relevance of these agents. The SELECT trial showed that semaglutide, 2.4 mg weekly, reduced the risk of 3-point MACE by 20% in more than 17,000 overweight or obese adults without diabetes, extending cardiovascular protection to a nondiabetic population.[8] In the STEP-HFpEF trial, semaglutide at a high dose markedly improved symptoms, exercise capacity, and weight loss in patients with obesity and HF with preserved ejection fraction (HFpEF), representing a breakthrough for a condition with few effective treatments. Collectively, these findings reinforce the broad cardiovascular utility of GLP-1 RAs across diabetes, obesity, and HF by targeting the shared metabolic and inflammatory pathways that drive cardiovascular disease.[9]

The SUMMIT trial assessed tirzepatide, a dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 (GIP/GLP-1) receptor agonist, in 731 patients with obesity and HFpEF, with or without diabetes.[1] At doses up to 15 mg weekly for 52 weeks or more, tirzepatide demonstrated a remarkable 13.9% reduction in body weight versus 2.2% with placebo (absolute difference, 11.6%; P<0.001), surpassing the weight loss achieved with semaglutide. Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS) scores improved by 19.5 points compared with 12.7 points with placebo (treatment effect, +6.9 points; $P < 0.001$). Tirzepatide also reduced the composite of cardiovascular death or HF events by 38% (HR, 0.62 [95% CI, 0.41 to 0.95]) and significantly lowered HF hospitalization rates (8.0% vs 14.2%; HR, ~0.54). Although cardiovascular mortality was low in both groups, the overall profile favors the cardioprotective potential of tirzepatide, likely due to its dual mechanism and enhanced metabolic effects. Notably, tirzepatide reduced high-sensitivity C-reactive protein by approximately 39%, indicating decreased systemic inflammation, a hallmark of obesity-driven HFpEF.[10]

Obesity is a well-known risk factor for atrial fibrillation (AF), and weight loss has been shown to reduce AF burden.[10] GLP-1 RAs, via substantial weight reduction and possibly direct antiarrhythmic effects, are now being investigated in this context.

A notable recent study, TRANSFORM-AF, reported that GLP-1 RA use was associated with a 13% reduction in AF–related events—a composite of AF hospitalizations, cardioversions, and ablations—over 3 years compared with similar patients not receiving a GLP-1 RA.[11] Interestingly, the observed AF benefit in TRANSFORM-AF occurred with only modest weight loss (4% greater than that in controls), suggesting GLP-1 RAs might confer antiarrhythmic benefits beyond weight reduction. Patients with morbid obesity (body mass index >40) appeared to derive even greater AF risk reduction. Although these findings come from an observational study and await confirmation in randomized trials, they open a tantalizing new front: using GLP-1 RAs as part of a comprehensive strategy to manage AF in patients with obesity. At a minimum, this reinforces the concept that cardiometabolic optimization through medications such as GLP-1 RAs should accompany procedural interventions for arrhythmias.[11]

Safety in Practice

The primary adverse effects of GLP-1 RAs are gastrointestinal. Nausea, early satiety, and occasional vomiting are common during dose escalation. These adverse effects are usually transient and manageable; nonetheless, in some patients, they may persist or be severe. Approximately 5% to 10% of patients may be unable to tolerate GLP-1 RAs because of gastrointestinal symptoms. In SELECT, as noted, 17% of participants receiving semaglutide discontinued the drug compared with 8% receiving placebo.

Other safety considerations include a small risk of acute pancreatitis (a causal link is not firmly established, but caution is advised in patients with a history of pancreatitis) and a contraindication in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN 2) syndrome, owing to thyroid C-cell tumor findings in rodent studies. Rapid weight loss can predispose patients to gallstones. Monitoring for gallbladder disease is, therefore, prudent if patients develop upper abdominal symptoms.

Unlike sodium-glucose cotransporter 2 inhibitors (SGLT2is), GLP-1 RAs do not cause hypotension and have a neutral effect on heart rhythm aside from a mild increase in heart rate. Importantly, extensive trials have found no increase in serious adverse cardiovascular events with GLP-1 RAs.[3–8]

Conclusion

GLP-1 RAs have transformed cardiovascular care, evolving from diabetes drugs into potent cardiometabolic therapies. By reducing myocardial infarction, stroke, and HF symptoms while promoting weight loss, these agents address both the metabolic and cardiovascular roots of disease. Landmark trials—including SELECT, SOUL, and STEP-HFpEF—have confirmed benefits across populations with and without diabetes. Despite challenges such as cost and access, the strong safety and efficacy profiles of GLP-1 RAs make them essential tools in contemporary cardiology. These agents are no longer merely glucose-lowering drugs but integral cardiovascular therapies supporting a comprehensive, preventive approach to cardiometabolic disease.

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