Journal of Clinical & Experimental Cardiology

OPEN ACCESS Freely available online

Perspective

Cardiovascular Effects of Novel Diabetes Medications: Implications for Integrated Care

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DESCRIPTION

The intricate relationship between diabetes mellitus and cardiovascular disease has long been recognized, with cardiovascular complications representing the leading cause of morbidity and mortality among patients with diabetes. Historical approaches to diabetes management focused primarily on glycemic control, with the assumption that improved glucose levels would translate to reduced cardiovascular risk. However, this paradigm was challenged when several glucose-lowering medications demonstrated neutral or even potentially harmful cardiovascular effects despite their efficacy in improving glycemic parameters. This revelation prompted regulatory agencies to mandate Cardiovascular Outcome Trials (CVOTs) for all new diabetes medications, a requirement that has fundamentally transformed the landscape of diabetes therapeutics and their intersection with cardiovascular medicine.

Sodium-Glucose Co-Transporter 2 (*SGLT2*) inhibitors, which reduce glucose reabsorption in the proximal tubule of the kidney, have demonstrated consistent cardiovascular benefits across multiple agents and patient populations. The cardioprotective mechanisms of *SGLT2* inhibitors appear multifaceted and largely independent of their glucose-lowering effects. Proposed mechanisms include favorable hemodynamic effects through osmotic diuresis and natriuresis, reduced arterial stiffness, decreased sympathetic nervous system activity, direct ionic effects on myocardial cells (Na^+/H^+ exchange inhibition), improved cardiac energetics through increased ketone utilization, and attenuated inflammation and oxidative stress. Perhaps most remarkably, dedicated heart failure trials have demonstrated benefits of *SGLT2* inhibitors in patients with heart failure regardless of diabetes status, establishing these agents as foundational therapy for heart failure across the spectrum of ejection fraction.

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs), which enhance glucose-dependent insulin secretion and suppress glucagon release while promoting satiety and weight loss, have similarly demonstrated cardiovascular benefits, though with a somewhat different profile than *SGLT2* inhibitors. The leader trial demonstrated that liraglutide reduced Major Adverse Cardiovascular Events (MACE) by 13% in patients with type 2 diabetes and established cardiovascular disease or high cardiovascular risk, with significant reductions in cardiovascular death. Subsequent trials with semaglutide, albiglutide, and dulaglutide showed similar reductions in MACE, while trials with lixisenatide and extended-release exenatide demonstrated cardiovascular safety but not superiority.

The cardiovascular effects of GLP-1 RAs appear to be mediated primarily through atherosclerotic risk reduction rather than the heart failure benefits observed with *SGLT2* inhibitors. Proposed mechanisms include improved endothelial function, reduced inflammation and oxidative stress, stabilization of atherosclerotic plaques, and favorable effects on traditional cardiovascular risk factors including blood pressure, weight, and lipid profile. Recent evidence from the select trial demonstrates that semaglutide reduces cardiovascular events even in non-diabetic patients with established cardiovascular disease and overweight or obesity, suggesting that these benefits extend beyond diabetes management to broader cardiometabolic risk reduction.

The implementation of these evidence-based recommendations, however, faces several challenges in real-world practice. Despite their proven benefits, utilization of *SGLT2* inhibitors and GLP-1 RAs remains suboptimal, particularly among patients at highest cardiovascular risk who stand to benefit most. Barriers to implementation include clinical inertia, concerns about cost and insurance coverage, complex prescribing patterns involving multiple specialists, and limited awareness of cardiovascular benefits among non-endocrinologists. Additionally, certain patient populations remain underrepresented in clinical trials, including those with advanced kidney disease, heart failure with preserved ejection fraction, and established cardiovascular disease without diabetes. The expanding indications of these medications beyond diabetes management highlight the need for integrated care models that transcend traditional specialty boundaries. The concept of "cardiometabolic medicine" is gaining traction, reflecting the recognition that diabetes and

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Received: 03-Mar-2025, Manuscript No. JCEC-25-37160; **Editor assigned:** 05-Mar-2025, PreQC No. JCEC-25-37160 (PQ); **Reviewed:** 19-Mar-2025, QC No. JCEC-25-37160; **Revised:** 26-Mar-2025, Manuscript No. JCEC-25-37160 (R); **Published:** 02-Apr-2025, DOI:10.35248/2155-9880.25.16.941

Citation: Srinivasan A (2025). Cardiovascular Effects of Novel Diabetes Medications: Implications for Integrated Care. J Clin Exp Cardiolog. 16:941.

cardiovascular disease frequently coexist and share underlying pathophysiological mechanisms. This integrated approach requires collaborative decision-making between cardiologists, endocrinologists, primary care physicians, and other healthcare providers involved in the care of patients with diabetes and cardiovascular disease.

CONCLUSION

Several models of integrated care have been proposed and implemented, ranging from cross-specialty education initiatives to dedicated cardiometabolic clinics staffed by cardiologists and endocrinologists working in tandem. Electronic health record-based decision support tools can facilitate appropriate prescription of cardioprotective diabetes medications based on patient characteristics and existing conditions. Additionally, team-based care models involving pharmacists, advanced practice providers, and care coordinators can enhance medication management, address barriers to adherence, and provide comprehensive patient education.