Effects of GLP-1 receptor agonists on kidney and cardiovascular disease outcomes: a meta-analysis of randomised controlled trials

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If you take a diabetes drug and give it to eighty-five thousand people across eleven trials — people with failing kidneys, damaged hearts, and more than a decade of high blood sugar behind them — does it protect them, or does it just lower their glucose? That question sounds simple. The answer, it turns out, is anything but.

A meta-analysis led by Badve and colleagues, pulling together every major randomized controlled trial of glucagon-like peptide-1 receptor agonists, or GLP-1 receptor agonists for short, just answered it. And the answer is cleaner than most people expected.

GLP-1 receptor agonists are a class of drugs that mimic a gut hormone the body releases after eating. They stimulate insulin secretion, suppress appetite, and promote weight loss. The drugs in this analysis include names you may have heard: semaglutide, liraglutide, dulaglutide, exenatide, and several others. They were first approved to lower blood sugar in type 2 diabetes. However, as large trials accumulated, something else kept appearing in the data — signals in the heart and kidney numbers that had nothing obvious to do with glucose. That is what this analysis set out to quantify.

The scale of the evidence base matters here. Eleven randomized, placebo-controlled trials. Forty-three thousand three hundred and thirty-nine patients were assigned to a GLP-1 receptor agonist, and forty-two thousand and thirty-four were assigned to a placebo. The average participant was sixty-three years old, had been

living with diabetes for about twelve and a half years, and carried a body mass index of around thirty-two and a half. Kidney function at baseline averaged an estimated glomerular filtration rate, the standard measure of how well the kidneys filter blood, of seventy-seven milliliters per minute per one point seven three square meters. Nearly one in four participants already had an estimated glomerular filtration rate below sixty, the threshold for chronic kidney disease. Almost three quarters had established cardiovascular disease. These were not low-risk research volunteers. These were patients already in trouble.

One trial, SELECT, enrolled people without diabetes entirely — a deliberate extension of the evidence base to a broader population. Its inclusion, as we'll see, only sharpened the picture.

The primary cardiovascular outcome tracked across trials was MACE: major adverse cardiovascular events, which is the composite of heart attack, stroke, and cardiovascular death. That is the number cardiologists watch most closely, and the result is as clear as this kind of evidence gets. GLP-1 receptor agonists reduced MACE with a hazard ratio of zero point eight six — a ninety-five percent confidence interval running from zero point eighty to zero point ninety-two. In plain terms, that translates to a fourteen percent relative reduction in the rate of these events, which means fourteen fewer events per thousand people treated. The number needed to treat was seventy-four patients over roughly twenty-five months to prevent a single MACE. The GRADE certainty rating — the framework researchers use to express confidence in pooled findings — was high. That is the top of the scale.

Now, let’s break it down. For cardiovascular death, the hazard ratio was zero point eight six, translating to six fewer deaths per thousand treated, with high certainty. For nonfatal heart attack, the hazard ratio was zero point eight seven, resulting in a thirteen percent relative reduction. For nonfatal stroke, the hazard ratio was zero point eight eight, indicating roughly twelve percent lower risk, which equals about three fewer strokes per thousand people. For hospitalization for heart failure, the hazard ratio was zero point eight seven, leading to four fewer admissions per thousand, with high certainty. And for all-cause mortality, the hazard ratio was zero point eight seven, indicating nine fewer deaths per thousand, again with high certainty.

What makes these numbers striking is not any single one of them — it's that they all point in the same direction across every outcome, across multiple drugs, and across populations with or without diabetes. Including SELECT moved the composite MACE estimate from zero point eighty-seven to zero point eighty-six. It did not change the story. That consistency is the signal.

Now let’s talk about the kidneys — and this is where the finding becomes genuinely important for a different set of patients.

Kidney failure in diabetes is progressive and largely irreversible. It is the leading cause of dialysis in wealthy countries. Often, it is treated as a downstream consequence of glucose dysregulation, something that happens after years of inadequate control. What this meta-analysis shows is that GLP-1 receptor agonists act on kidney outcomes independently, and with a meaningful effect size.

The composite kidney outcome — a pre-specified endpoint that bundled kidney failure, sustained large declines in estimated glomerular filtration rate, and other serious renal events — was reduced with a hazard ratio of zero point eighty-one, with a confidence interval running from zero point seventy-two to zero point ninety-two, when all nine applicable trials including SELECT were pooled. That is a nineteen percent relative risk reduction. The GRADE certainty was rated high. The absolute effect was roughly five fewer composite kidney events per thousand people treated.

Worsening of kidney function specifically — defined as a sustained, clinically significant decline in filtration capacity — showed a hazard ratio of zero point seventy-eight, with a confidence interval running from zero point sixty-eight to zero point ninety-one. That also had high certainty. Among participants with the worst baseline kidney function, twenty-two point seven percent had an estimated glomerular filtration rate below sixty at entry. Nine point three percent were in the macroalbuminuria category, meaning their kidneys were already leaking substantial amounts of protein into urine — itself an early warning of accelerating damage.

Kidney failure as a standalone endpoint showed a hazard ratio of zero point eighty-four, with a confidence interval from zero point seventy-two to zero point ninety-eight — which indicates about a sixteen percent relative reduction. However, the certainty rating steps down to moderate, downgraded for imprecision. The number needed to treat to prevent one kidney failure event was five hundred and three when SELECT was excluded, rising to six hundred and sixty-three when it was included, with confidence intervals so wide they stretch into the thousands. The signal is real, but the individual event rate is low enough that the absolute benefit is modest and the uncertainty is substantial. That is honest science. The finding deserves attention; it does not deserve overstatement.

The robustness checks bear examination. The team ran a leave-one-out sensitivity analysis — re-running the kidney composite estimate eleven times, each time dropping one trial from the pool, to check whether any single study was carrying the result. It wasn't. Omitting SUSTAIN-6 produced a hazard ratio of zero point sev-

enty-nine. Omitting REWIND produced zero point eighty-five. Every leave-one-out analysis remained statistically significant, with p-values at or below zero point zero two five, and hazard ratios clustering between zero point seventy-nine and zero point eighty-five. No single trial made or broke the finding.

Across the full set of outcomes, heterogeneity was rated as not serious, meaning the results across individual trials were more consistent than divergent. For the outcomes that matter most — MACE, cardiovascular death, all-cause mortality, composite kidney disease, and worsening kidney function — the certainty was high. For kidney failure alone, it was moderate. That gradation matters when clinicians and patients are weighing treatment decisions.

So what does this actually change? These drugs were prescribed for glucose control. What this meta-analysis establishes, across eighty-five thousand participants and eleven trials, is that GLP-1 receptor agonists reduce cardiovascular events, reduce cardiovascular death, reduce all-cause mortality, and reduce composite kidney outcomes — all with high certainty. The number needed to treat to prevent one major cardiovascular event was seventy-four over two years. That is a clinically meaningful number. The drug is doing something well beyond lowering a blood sugar reading.

The population studied was dominated by people with established cardiovascular disease — about three quarters of participants. Only one trial specifically enrolled patients with high-risk or very high-risk chronic kidney disease. So the evidence base is strongest where it has been most tested: patients with existing heart disease and moderate kidney impairment. Effects in lower-risk populations, in earlier stages of kidney disease, and over time horizons longer than roughly two years remain open questions.

But for the patients who resemble those enrolled in these trials, the evidence now permits a clear clinical expectation: GLP-1 receptor agonists lower the risk of heart attack, stroke, cardiovascular death, and progressive kidney disease. Not as a side effect. As the point.

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