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Glucagon-like Peptide-1 Medicines for Peripheral Arterial Disease in Type 2 Diabetes: Are They Ready for Prime Time?

Ronald M. Goldenberg, MD, FRCPC, FACE

Introduction

Comorbid peripheral arterial disease (PAD) affects approximately 12.5%–22% of individuals with type 2 diabetes (T2D), and is associated with an increased risk of major adverse limb events (MALE), such as revascularization procedures and lower extremity amputations, as well as heightened cardiovascular events and mortality.[1] Despite this elevated risk, few therapies have been proven to reduce the risk of MALE. Although statins, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and low dose rivaroxaban plus aspirin have been shown to reduce the risk of MALE in individuals with PAD, there remains an unmet need for disease-modifying agents to improve PAD outcomes in people with concomitant T2D and PAD.[1]

Current Diabetes Canada guidelines recommend glucagon-like peptide-1 (GLP-1) medicines for individuals with T2D and established cardiovascular disease (CVD), multiple risk factors, or chronic kidney disease (CKD) due to their proven cardiorenal benefits.[2] Emerging data has shown that GLP-1 medicines reduce the incidence of MALE in individuals with T2D. This review summarizes the totality of evidence for GLP-1 medicines and their impact on MALE, drawing from randomized controlled trials (RCTs) and observational studies.

Randomized Controlled Trials

Results from RCTs are considered the highest level of evidence for evaluating the effects of pharmacotherapies on clinical outcomes. The first indication that a GLP-1 medicine may reduce the risk of lower extremity amputation in individuals with T2D emerged from a post hoc exploratory analysis of the LEADER trial, demonstrating a significant 35% risk reduction in the composite outcome of diabetic foot ulcer plus amputation with liraglutide versus placebo.[3]

Similarly, in the SOUL cardiovascular outcomes trial comparing oral semaglutide versus placebo, a pre-specified secondary outcome of MALE, defined as hospitalization for acute or chronic limb ischemia, was reduced in semaglutide treated individuals (hazard ratio [HR] 0.71, 95% CI 0.53–0.96).[4] Furthermore, a meta-analysis by Goldenberg and Verma encompassing six RCTs comparing a GLP-1 medicine to placebo in individuals with T2D (**Figure 1A**) demonstrated a statistically significant reduction in MALE with low heterogeneity (HR 0.78, 95% CI 0.68–0.90; p=0.0005; I^2=3%).[5]

Two RCTs have studied the impact of GLP-1 medicines on MALE in individuals with T2D and comorbid PAD. A post hoc analysis of the EXSCEL trial demonstrated a non-statistically significant reduction in MALE with once-weekly exenatide (HR 0.83, 95% CI 0.66–1.04).[6] In the STRIDE trial, an exploratory MALE outcome did not show a statistically significant impact from semaglutide therapy; however, this outcome was limited by very low event rates, with only six events among 396 (1.5%) semaglutide treated individuals and five events among 396 (1.3%) placebo treated individuals.[7] Notably, an exploratory outcome reflecting PAD progression, defined as rescue treatment, MALE, or all-cause death, was reduced by 54% with semaglutide (HR 0.46, 95% CI 0.24–0.84). Giugliano et al. subsequently performed a meta-analysis of these two RCTs in individuals with T2D and PAD (**Figure 1A**) and demonstrated a non-significant reduction in MALE (HR 0.84, 95% CI 0.67–1.05; p=0.12; I^2 = 0%). The certainty of evidence was considered low, largely due to the limited number of available RCTs.[8]

Two RCTs have shown a beneficial effect of a GLP-1 medicine on walking distance in individuals with T2D and PAD.[7,9] The STARDUST trial demonstrated an improvement in the secondary outcome of 6-minute walking distance with liraglutide versus control (estimated treatment difference [ETD] 25.1 m, 95% CI 21.8–28.3; p<0.0001) alongside an increase in the primary outcome of peripheral perfusion, as measured by transcutaneous oxygen pressure.[9] Similarly, the STRIDE RCT reported a significantly greater maximum walking distance in the semaglutide group versus the placebo group (ETR 1.13, 95% CI 1.06–1.21; p=0.0004). A subsequent meta-analysis by Giugliano et al. pooling these two RCTs also demonstrated a significantly greater walking distance with the GLP-1 group versus the control group (ETR 1.10, 95% CI 1.05–1.15; p<0.001; I^2=5.8).[8] Interestingly, the improvements in walking distance observed in both STARDUST and STRIDE extended beyond the effects attributable to weight loss and glycemic control alone.

Observational Studies

Observational studies represent a lower level of evidence than RCTs due to the potential for residual confounding, even when using propensity score methods or multivariate regression techniques. Despite this limitation, it is reassuring that there have been a large number of observational studies supporting a beneficial effect of GLP-1 medicines on MALE in people with T2D. Baviera et al. have reported the results from an observational analysis of two Italian cohorts, demonstrating that first-time users of GLP-1 medicines experienced significantly reduced rates of lower limb complications compared to users of other antihyperglycemic agents (AHAs) with relative risk reductions ranging from 31%–33%.[10] Observational studies comparing rates of MALE between GLP-1 medicines and sodium-glucose cotransporter-2 (SGLT2) inhibitors have shown conflicting results. While several studies have shown no significant differences between these two AHA classes,[11-14] others have demonstrated a reduction in the risk of MALE with GLP-1 medicines.[15–18]

These discrepant results are likely explained by different methodologies as well as variations in unmeasured confounders across the studies. In a meta-analysis of observational studies conducted in populations with T2D, Dutta et al reported a statistically significant 30% reduction (p=0.005, I^2=0%) in MALE (**Figure 1B**) and a 42% reduction (p<0.0001; I^2=0%) in amputations associated with GLP-1 therapy.[19]

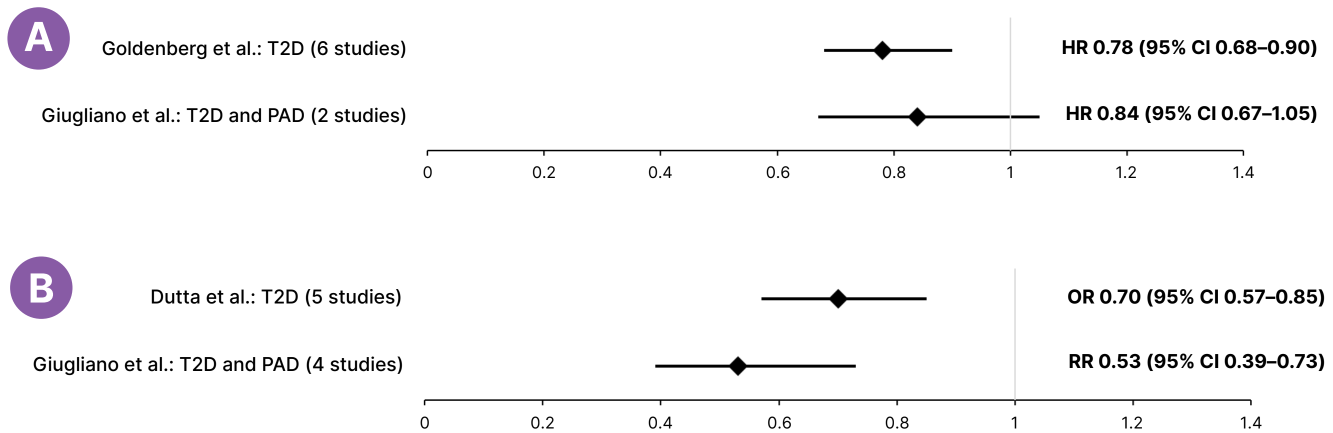

Figure 1. Summary of meta-analyses assessing the effects of GLP-1 medicines and MALE in people with T2D or T2D and PAD, based on **A)** RCTs, and **B)** observational studies; *courtesy of Ronald Goldenberg, MD, FRCPC, FACE.*

Abbreviations: GLP-1: glucagon-like peptide-1; **HR:** hazard ratio; **MALE:** major adverse limb events; **OR:** odds ratio; **PAD:** peripheral arterial disease; **RCTs:** randomized controlled trials; **RR:** risk ratio; **T2D:** type 2 diabetes.

Observational studies have also been performed in populations with T2D and comorbid PAD. The SMILE retrospective cohort study demonstrated a significant 33% reduction in MALE with semaglutide therapy compared to other AHAs (HR 0.77, 95% CI 0.61–0.97; p=0.029), along with a 50% reduction in lower extremity amputations (HR 0.50, 95% CI 0.30–0.83; p=0.008).[20]

Similarly, in a diabetes subgroup analysis of a retrospective observational study conducted in a PAD population, GLP-1 treated individuals experienced a 28% reduction in MALE compared to a control group not receiving GLP-1 therapy (HR 0.72, 95% CI 0.64–0.81; p<0.01).[21] In a retrospective cohort study in a population with T2D and foot ulcers, Lewis et al. reported a 55% reduction in amputation risk in semaglutide users compared to non-users (relative risk [RR] 0.45, 95% CI 0.37–0.55; p<0.001).[22] They also demonstrated reductions in other wound-related complications. In addition, a retrospective cohort study reported that tirzepatide was associated with a significant reduction in MALE (HR 0.44, 95% CI 0.33–0.59, p<0.001) compared to non-users in a population with diabetes and PAD. These findings support the concept that the benefits of GLP-1 medicines include GLP-1/GIP co-agonists in addition to GLP-1 receptor mono-agonists.[23] Consistent with this, other observational studies have shown similar benefits of GLP-1 medicines in populations with T2D and PAD.[24-26] Furthermore, a meta-analysis by Giugliano et al. of four observational studies in populations with T2D and PAD demonstrated a 47% reduction (p<0.001) in lower extremity amputations (**Figure 1B**).[8]

Mechanisms for Benefit on PAD Outcomes

The beneficial effects of GLP-1 medicines on glycemic control and body weight may indeed be a contributor to the clinical benefits observed in individuals with CVD or risk factors for CVD. However, the potential for vascular benefits of GLP-1 medicines that extend beyond improvements in glycemia or weight loss remains an ongoing area of research. Proposed mechanisms for improved vascular function include anti-inflammatory effects, reduced immune activation, improved endothelial function, as well as indirect effects on vascular regenerative progenitor cells.[27] In the STARDUST trial, liraglutide treatment was associated with significant improvements in markers of both inflammation and angiogenesis.[28]

Conclusions

PAD and MALE are highly prevalent complications in individuals with T2D. Evidence from secondary outcomes of MALE in RCTs, meta-analyses of RCTs, and observational studies demonstrates that GLP-1 medicines are associated with reductions in MALE among populations with T2D, including those with comorbid PAD. Current clinical guidelines prioritize GLP-1 medicines for cardiorenal protection in individuals with T2D and either established CVD, multiple risk factors, or CKD. With the current evidence for GLP-1 medicines and their benefits on PAD outcomes, these agents should be considered an important component of our therapeutic armamentarium for reducing MALE in people with T2D.

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