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Effects of liraglutide on cardiovascular events in patients with type 2 diabetes and polyvascular disease: results of the LEADER trial

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Background and aims: Polyvascular disease can predict cardiovascular (CV) events. In LEADER, liraglutide significantly reduced major adverse CV events (MACE) vs placebo. In a post hoc analysis, we assessed CV outcomes by history of single or polyvascular disease at baseline.

Materials and methods: In LEADER, 9340 patients with type 2 diabetes (T2D) and high CV risk were randomised 1:1 to liraglutide vs placebo, both as add on to standard of care (median follow-up = 3.8 years). The primary outcome (MACE) was a composite of CV death, nonfatal myocardial infarction, or nonfatal stroke. The secondary outcome (expanded MACE) also included hospitalisation for unstable angina, coronary revascularisation, or hospitalisation for heart failure. Cox regression was used to compare CV outcomes in patient risk groups stratified by number of atherosclerotic vascular territories (coronary, cerebrovascular and/or peripheral artery disease). Polyvascular disease was defined as ≥2 and single vascular disease as 1 atherosclerotic vascular territory.

Results: In LEADER, 6775 patients (72.5%) had documented atherosclerotic CV disease (ASCVD). Of these, 1536 patients (23%) had polyvascular and 5239 (77%) had single vascular disease. Patients with polyvascular disease had a higher risk of CV outcomes than those with single vascular disease (MACE: HR 1.52, 95% CI 1.33-1.73; expanded MACE: HR 1.45, 95% CI 1.31-1.62, CV death: HR 1.41, 95% CI 1.13-1.75). Liraglutide reduced MACE consistently in patients with polyvascular (HR 0.82, 95% CI 0.66-1.02) and single vascular disease (HR 0.82, 95% CI 0.71-0.95) vs placebo. In patients without ASCVD at baseline, the HR for liraglutide vs placebo for MACE was 1.08 (95% CI 0.84-1.38). Results were similar for expanded MACE and CV death (Table). No significant interactions were found across risk groups for CV outcomes (Table), with the exception of expanded MACE (p interaction=0.03).

Conclusion: In patients with T2D, polyvascular disease was associated with greater risk of CV outcomes vs single vascular disease. Liraglutide appeared to reduce consistently CV outcomes in patients with single and polyvascular disease vs placebo. A trend towards a neutral response was observed in patients without ASCVD.

Table: Cardiovascular outcomes in patients treated with liraglutide vs placebo by number of vascular territories involved at baseline

Outcome	Vascular disease	n with event/N analysed (%)		HR [95% CI]	Treatment by subgroup interaction
		Liraglutide	Placebo		
MACE	Polyvascular	142/757 (18.8)	173/779 (22.2)	0.82 [0.66–1.02]	
	Single	338/2646 (12.8)	398/2593 (15.3)	0.82 [0.71–0.95]	*p*=0.15
	No ASCVD	128/1265 (10.1)	123/1300 (9.5)	1.08 [0.84–1.38]	
Expanded MACE	Polyvascular	220/757 (29.1)	255/779 (32.7)	0.86 [0.71–1.03]	
	Single	541/2646 (20.4)	633/2593 (24.4)	0.82 [0.73–0.92]	*p*=0.03
	No ASCVD	187/1265 (14.8)	174/1300 (13.4)	1.12 [0.91–1.38]	
CV death	Polyvascular	54/757 (7.1)	60/779 (7.7)	0.92 [0.63–1.32]	
	Single	114/2646 (4.3)	165/2593 (6.4)	0.67 [0.53–0.85]	*p*=0.16
	No ASCVD	51/1265 (4.0)	53/1300 (4.1)	0.99 [0.67–1.45]	

Interaction *p* value is for test of homogeneity of treatment group difference among all 3 subgroups with no adjustment for multiple tests. No ASCVD = no documented evidence of atherosclerotic disease in any of 3 vascular territories at baseline.

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