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Arrhythmias and heart rate increase in the LEADER trial and relation to risk of cardiovascular events

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Background and aims: Epidemiological data suggest that a higher resting heart rate is associated with a higher risk of cardiovascular (CV) events and death. Glucagon-like peptide-1 receptor agonists can increase heart rate. In the LEADER trial, liraglutide significantly reduced the risk of major adverse CV events ([MACE]; CV death, non-fatal myocardial infarction and non-fatal stroke) by 13% vs placebo (PBO) in people with type 2 diabetes (T2D) and high CV risk.
Materials and methods: In a post hoc analysis from LEADER, we evaluated the frequency of arrhythmias and, for patients with heart rate increases <10 or ≥10 bpm at 6 months, the risk of CV events. In LEADER, 9340 patients with T2D and high CV risk were randomised 1:1 to add liraglutide or PBO to standard of care, and followed for 3.5-5 years. Serious adverse events and non-serious medical events of special interest related to heart rate were systematically collected and reviewed. Cox regression analysis was used to evaluate the risk of CV events in patients with heart rate increases <10 bpm or ≥10 bpm at 6 months.
Results: Mean heart rate increased by 3 bpm for liraglutide vs PBO. The overall frequency of cardiac arrhythmias was 4.9% in both arms, based on adverse event reporting. The types and rates of arrhythmias reported were generally similar in both arms, with low numbers for most arrhythmias and numerically fewer events of ventricular tachycardia and cardiac arrest in the PBO and liraglutide arms, respectively (Table). In total, 3002 (64.3%) patients receiving liraglutide and 3683 (78.8%) receiving PBO had a heart rate increase from baseline <10 bpm at 6 months. Among these patients, liraglutide significantly decreased the risk of MACE (HR [95% CI]: 0.84 [0.73-0.96], p=0.01) and non-significantly decreased the risk of heart failure hospitalisation (0.81 [0.65-1.02]; p=0.07) vs PBO. A total of 1435 (30.7%) patients receiving liraglutide and 750 (16.1%) receiving PBO had a heart rate increase from baseline ≥10 bpm at 6 months. In this subgroup, liraglutide non-significantly decreased the risk of MACE (HR [95% CI]: 0.92 [0.72-1.17], p=0.51) and heart failure hospitalisation (0.94 [0.63-1.43], p=0.78) vs PBO.
Conclusion: The increased mean heart rate observed with liraglutide was not accompanied by an overall higher frequency of arrhythmias vs PBO. Liraglutide decreased the risk of CV events vs PBO in both subgroups regardless of heart rate increase <10 or ≥10 bpm.

Table: Arrhythmia adverse events (AEs) with frequency ≥0.2%

	Liraglutide N=4668				Placebo N=4672			
	N	%	E	R	N	%	E	R
Cardiac arrhythmias*	228	4.9	293	16.4	229	4.9	279	15.7
Atrial fibrillation	91	1.9	115	6.5	99	2.1	116	6.5
Ventricular tachycardia	18	0.4	29	1.6	8	0.2	11	0.6
Atrial flutter	17	0.4	20	1.1	17	0.4	19	1.1
Cardiac arrest	20	0.4	20	1.1	31	0.7	31	1.7
Cardio-respiratory arrest	15	0.3	15	0.8	13	0.3	15	0.8
Bradycardia	11	0.2	11	0.6	11	0.2	11	0.6
Arrhythmia	10	0.2	11	0.6	6	0.1	6	0.3
Atrioventricular block complete	10	0.2	10	0.6	9	0.2	9	0.5

Full analysis set. *Serious AEs or non-serious medical events of special interest related to cardiac arrhythmia identified by reviewing events reported within group 'cardiac arrhythmias'. E, No. of events; N, No. of patients; R, rate of events/1000 patient-years of observation; %, proportion of patients.

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