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

Subodh Verma, MD PhD[1]; Deepak L. Bhatt, MD, MPH[2]; Stephen C. Bain, MD[3]; John B. Buse, MD PhD[4]; Johannes F.E. Mann, MD[5]; Steven P. Marso, MD[6]; Michael A. Nauck, MD[7]; Neil R. Poulter, F.Med.Sci[8]; Richard E. Pratley, MD[9]; Bernard Zinman, MD[10]; Marie M. Michelsen, MD[11]; Tea Monk Fries, MD PhD[11]; Søren Rasmussen, MSc PhD[11]; Lawrence A. Leiter, MD[12]; the LEADER Publication Committee on behalf of the LEADER Trial Investigators

[1]Division of Cardiac Surgery, St. Michael's Hospital; and Departments of Surgery and Pharmacology & Toxicology, University of Toronto, Toronto, Ontario, Canada

[2]Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston, Massachusetts, USA

[3]Institute of Life Science, Swansea University, Swansea, UK

[4]University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA

[5]Friedrich Alexander University of Erlangen, Erlangen, Germany

[6]HCA Midwest Health Heart & Vascular Institute, Kansas City, MO, USA

[7]Diabetes Center Bochum-Hattingen, St. Josef-Hospital, Ruhr-University Bochum, Bochum, Germany

[8]Imperial College London, London, UK

[9]Florida Hospital Translational Research Institute for Metabolism and Diabetes, Orlando, Florida, USA

[10]Lunenfeld Tanenbaum Research Institute, Mount Sinai Hospital and University of Toronto, Toronto, Ontario, Canada

[11]Novo Nordisk A/S, Søborg, Denmark

[12]Li Ka Shing Knowledge Institute, St. Michael's Hospital, and University of Toronto, Toronto, Canada

Corresponding author: Subodh Verma, MD PhD FRCSC, Professor, University of Toronto, Cardiac Surgeon, St. Michael's Hospital, 30 Bond Street, 8th Floor, Bond Wing, Toronto, ON, M5B 1W8, Canada. Email: VermaSu@smh.ca. Telephone: +1-857-307-1992

The presence of polyvascular disease, defined as atherosclerosis involving more than one distinct vascular territory, is a strong, independent predictor of cardiovascular events.[1-4] In the LEADER trial,[5] the human glucagon-like peptide 1 analog liraglutide reduced cardiovascular events in patients with type 2 diabetes (T2D) at high cardiovascular risk. In this post hoc analysis of LEADER, we evaluated the effects of liraglutide stratified by number of atherosclerotic vascular territories (coronary, cerebrovascular, and/or peripheral)

Data and analytic methods supporting this study's findings are available from the corresponding author upon reasonable request. LEADER (ClinicalTrials.gov NCT01179048) was a randomized trial of liraglutide (1.8 mg or maximum tolerated dose) versus placebo in 9340 patients with T2D and high cardiovascular risk (median follow-up=3.8 years).[5] The primary outcome was a composite of cardiovascular death, non-fatal myocardial infarction (MI), or non-fatal stroke (major adverse cardiovascular events, MACE). The key secondary expanded outcome (expanded MACE) also included hospitalization for unstable angina, coronary revascularization, or hospitalization for heart failure.

The ethics committee or institutional review board at each participating center approved the trial protocol. Patients provided informed consent. Cardiovascular outcomes were prospectively adjudicated by an independent, blinded event adjudication committee. Atherosclerotic vascular territories included coronary (MI, ≥50% coronary artery stenosis, percutaneous coronary intervention or coronary artery bypass graft surgery, angina pectoris, or asymptomatic ischemia), cerebrovascular (stroke, transient ischemic attack, ≥50% intracranial or carotid artery stenosis) and peripheral arteries (≥50% peripheral artery stenosis). Information was extracted from patients' baseline medical history. Risk groups were determined by number of

vascular territories involved: polyvascular disease as two or more, single vascular disease as one, and a group with no documented atherosclerotic cardiovascular disease (ASCVD).

The hazard ratios (HRs) comparing risk groups were calculated using a Cox proportional hazards model with treatment and risk group as factors. The treatment effect of liraglutide versus placebo within risk groups was estimated using Cox proportional hazards regression model with treatment, risk group, and the interaction of both as factors.

In LEADER, 6775 patients (72.5%) had documented ASCVD. In patients with ASCVD, 1536 (23%) had a baseline history of polyvascular disease, and 5239 (77%) had single vascular disease. For the total population, the distribution of vascular territory involvement is shown in Figure, A. Briefly, 5364 patients (57.4%) had a history of coronary artery disease, 1968 (21.1%) had cerebrovascular disease, 1184 (12.7%) had peripheral artery disease, and 2665 (27.5%) had no documented ASCVD. At baseline, in patients with polyvascular disease versus single vascular disease, mean age±standard deviation was higher (65.1±7.7 versus 63.5±7.3 years), more patients were male (68.8 versus 67.9%), current or previous smokers (67.1 versus 60.1%), had an estimated glomerular filtration rate <60 ml/min/1.73m^2 (27.1 versus 19.0%), had history of heart failure (26.4 versus 16.5%), MI (47.2 versus 39.7 %), stroke (33.5 versus 10.0%), or peripheral artery disease (47.1 versus 8.5%), and there was a higher frequency of cardiovascular medication use (95.6 versus 92.7% for antihypertensive therapy, 83.8 versus 79.2% for lipid-lowering therapy, and 79.7 versus 75.7 % for antiplatelet therapy). Baseline hemoglobin A_{1c} was similar between groups.

Patients with polyvascular disease had a higher risk of cardiovascular outcomes than those with single vascular disease (MACE: HR 1.52, 95% confidence interval [CI] 1.33–1.73; expanded MACE: HR 1.45, 95% 1.31–1.62, cardiovascular death: HR 1.41, 95% CI 1.13–1.75) (Figure, B, C).

Liraglutide reduced MACE consistently in patients with polyvascular (HR 0.82, 95% CI 0.66–1.02) and with single vascular disease (HR 0.82, 95% CI 0.71–0.95). Results were similar for expanded MACE and cardiovascular death (Figure, C). The risk reduction in MACE and expanded MACE was similar to that of the total trial population in LEADER (Figure, C).[5] The corresponding data for non-fatal MI and stroke are displayed in Figure, C.

In patients without ASCVD at baseline, the HR for liraglutide versus placebo for MACE was 1.08 (95% CI 0.84–1.38), with similar results for expanded MACE and cardiovascular death (Figure, C). However, no significant interaction was found among risk groups, except for expanded MACE ($p_{interaction}$=0.03), which could be a chance finding since no adjustment for multiple testing was performed or may suggest a difference in treatment effects across risk groups, driven by the group without ASCVD (Figure, C). The reason for a neutral response in patients without ASCVD could be that the baseline risk was lower, and to establish any potential effect might require a longer treatment period or larger sample size. Nevertheless, patients with T2D benefit from liraglutide treatment regarding glycemic control, potential weight reductions, and better blood pressure control.

In patients with T2D and documented ASCVD, the presence of polyvascular disease was associated with greater cardiovascular risk versus those with single vascular disease. Liraglutide appeared consistently to reduce major cardiovascular outcomes in both patients with polyvascular and single vascular disease.

Acknowledgments

Editorial assistance, limited to formatting and collation of co-author comments, was supported financially by Novo Nordisk and provided by Gillian Groeger and Izabel James, of Watermeadow

Medical, an Ashfield Company, part of UDG Healthcare plc, during preparation of this article. Dr. Verma wrote the first draft. The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and have approved the final version.

Sources of funding

The LEADER trial was funded by Novo Nordisk.

Disclosures

S Verma: research grants and/or speaking honoraria from Boehringer Ingelheim/Eli Lilly, AstraZeneca, Janssen, Merck, Novartis, Novo Nordisk, Sanofi, Valeant and Amgen [all significant].

D Bhatt: advisory board for Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; board of directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; chair: American Heart Association Quality Oversight Committee; data monitoring committees: Cleveland Clinic, Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, Population Health Research Institute; honoraria: American College of Cardiology (senior associate editor, clinical trials and news, ACC.org; vice-chair, ACC Accreditation Committee), Belvoir Publications (editor in chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications

(editor in chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (guest editor; associate editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (chief medical editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (secretary/treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (deputy editor), NCDR-ACTION Registry Steering Committee (chair), VA CART Research and Publications Committee (chair); research funding: Abbott, Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company; royalties: Elsevier (editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); site co-investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott); trustee: American College of Cardiology; unfunded research: FlowCo, Merck, PLx Pharma, Takeda.

S Bain: research grant (includes principal investigator, collaborator or consultant and pending grants as well as grants already received) from Healthcare and Research Wales (Welsh Government) [Significant] and Novo Nordisk [Significant]; other research support from Healthcare and Research Wales (Welsh Government) infrastructure support [significant]; honoraria from Novo Nordisk [significant], Sanofi [significant], Lilly [significant], Boehringer Ingelheim [significant], and Merck [significant]; ownership interest: Gycosmedia (diabetes on-line news service) [significant].

J Buse: consulting fees paid to his institution and travel support [all modest] from Novo Nordisk, Eli Lilly, Bristol-Myers Squibb, GI Dynamics, Elcelyx, Merck, Metavention, vTv Therapeutics, PhaseBio, AstraZeneca, Dance Biopharm, Quest Diagnostics, Sanofi-Aventis, Lexicon Pharmaceuticals, Orexigen Therapeutics, Takeda Pharmaceuticals, Adocia, and Roche; grant support [all modest] from Eli Lilly, Bristol-Myers Squibb, GI Dynamics, Merck, PhaseBio,

AstraZeneca, Medtronic, Sanofi, Tolerex, Osiris Therapeutics, Halozyme Therapeutics, Johnson & Johnson, Andromeda, Boehringer Ingelheim, GlaxoSmithKline, Astellas Pharma, MacroGenics, Intarcia Therapeutics, Lexicon, Scion NeuroStim, Orexigen Therapeutics, Takeda Pharmaceuticals, Theracos, Roche, and the National Institutes of Health (UL1TR001111); fees and stock options: PhaseBio [modest]; boards of the AstraZeneca Healthcare Foundation and Bristol-Myers Squibb Together on Diabetes Foundation [both modest].

J Mann: research grants from Celgene, Europ Union, McMaster University Canada, AbbVie, Novo Nordisk, Roche, and Sandoz; personal fees (includes committee member and/or speaker fees) from Boehringer Ingelheim, Astra, Amgen, ACI, Fresenius, Celgene, Gambro, AbbVie, Medice, Novo Nordisk, Roche, Sandoz, Lanthio, Sanifit, Relypsa, and ZS Pharma [all significant].

S Marso: consulting fees from Novo Nordisk and St Jude Medical; research support from Novo Nordisk, Terumo, The Medicines Company, AstraZeneca and Bristol Myers-Squibb [all significant].

M Michelsen: Novo Nordisk employee [significant].

T Monk Fries: Novo Nordisk employee [significant] and shareholder [modest].

M Nauck: advisory boards or consultancy for AstraZeneca [modest], Boehringer Ingelheim [modest], Eli Lilly & Co. [significant], Fractyl [modest], GlaxoSmithKline [modest], Menarini/Berlin Chemie [modest], Merck, Sharp & Dohme [significant], and Novo Nordisk [significant]; speakers' bureau for AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., Menarini/Berlin Chemie [all modest], Merck, Sharp & Dohme, and Novo Nordisk A/S [both significant]. His institution has received grant support from AstraZeneca, Eli Lilly & Co., Menarini/Berlin-Chemie, Merck, Sharp & Dohme, Novartis Pharma, and Novo Nordisk A/S.

N Poulter: President of the International Society of Hypertension; personal speaker fees from Servier [modest], Takeda [modest] and Novo Nordisk [significant]; advisory boards for AstraZeneca [modest] and Novo Nordisk [significant]; research grants for his research group relating to T2D from Diabetes UK, NIHR EME, Julius Clinical, and the British Heart Foundation with a pending grant from Novo Nordisk [significant].

R Pratley: research grant from Gilead Sciences, Lexicon Pharmaceuticals, Ligand Pharmaceuticals Inc., Lilly, Merck, Novo Nordisk, Sanofi-Aventis US LLC, and Takeda; speaker for AstraZeneca, Novo Nordisk, and Takeda; consultant for AstraZeneca, Boehringer Ingelheim, Eisai, Inc., GlaxoSmithKline, Janssen Scientific Affairs LLC, Ligand Pharmaceuticals Inc., Lilly, Merck, Novo Nordisk, Pfizer, and Takeda. All payments are made directly to his employer (Florida Hospital).

S Rasmussen: Novo Nordisk employee and shareholder [both significant].

B Zinman: consulting fees from Merck [modest], Novo Nordisk [significant], Sanofi-Aventis [modest], Eli Lilly [modest], AstraZeneca [modest], Janssen [modest], and Boehringer Ingelheim [significant].

L Leiter: consultant and speaker fees from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, and Servier [all modest]; consultant fees from Regeneron [modest]; research grant or support from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Esperion, GlaxoSmithKline, Janssen, Kowa, Merck, Novartis, Novo Nordisk, Resverlogix, Sanofi, and The Medicines Company [all modest].

References

1. Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM, Wilson PW, Alberts MJ, D'Agostino R, Liau CS, Mas JL, Rother J, Smith SC, Jr., Salette G, Contant CF, Massaro JM, Steg PG, REACH Registry Investigators. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA*. 2010;304:1350-1357.

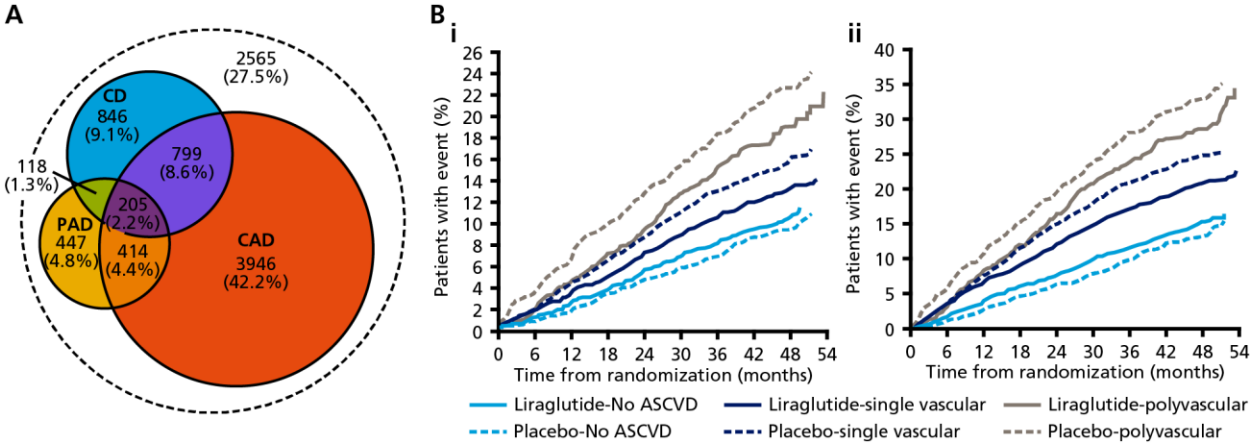
2. Kaasenbrood L, Boekholdt SM, van der Graaf Y, Ray KK, Peters RJ, Kastelein JJ, Amarenco P, LaRosa JC, Cramer MJ, Westerink J, Kappelle LJ, de Borst GJ, Visseren FL. Distribution of estimated 10-year risk of recurrent vascular events and residual risk in a secondary prevention population. *Circulation*. 2016;134:1419-1429.

3. Verma S, Mazer CD, Al-Omran M, Inzucchi SE, Fitchett D, Hehnke U, George JT, Zinman B. Cardiovascular outcomes and safety of empagliflozin in patients with type 2 diabetes mellitus and peripheral artery disease: a subanalysis of EMPA-REG OUTCOME. *Circulation*. 2017. doi: 10.1161/CIRCULATIONAHA.117.032031.

4. Cavender MA, Steg PG, Smith SC, Jr., Eagle K, Ohman EM, Goto S, Kuder J, Im K, Wilson PW, Bhatt DL, REACH Registry Investigators. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the reduction of atherothrombosis for continued health (REACH) registry. *Circulation*. 2015;132:923-931.

5. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB, LEADER Steering Committee, LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311-322.

Figure: Analysis of LEADER data stratified by number of atherosclerotic vascular territories (no ASCVD: no documented evidence of atherosclerotic disease in any of three vascular territories [coronary artery, cerebrovascular or peripheral artery]; single vascular disease: atherosclerotic disease in one of the three vascular territories; polyvascular disease: atherosclerotic disease in two or more of the specified vascular territories)**. Panel A,** Venn diagram of number (%) of patients according to number of vascular territories involved at baseline. **Panel B,** Kaplan-Meier estimates of time to first primary MACE (composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke): **(i)**, and expanded MACE (composite of the primary, with hospitalization for unstable angina, coronary revascularization, or hospitalization for heart failure also included) and **(ii),** based upon number of number of vascular territories involved at baseline. **Panel C,** cardiovascular outcomes by number of vascular territories involved. Hazard ratios and 95% CIs are based on Cox regression analyses. Interaction *p*-value is for test of homogeneity of treatment group difference among all 3 subgroups (no ASCVD, single vascular disease, and polyvascular disease) with no adjustment for multiple tests. ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CD, cerebrovascular disease; CI, confidence interval; MACE, major adverse cardiovascular event; PAD, peripheral artery disease.



C

	n with event/N analyzed (%) Liraglutide	Placebo	Hazard ratio [95% CI]	Treatment by subgroup interaction
Primary MACE				
Total trial population	608/4668 (13.0)	694/4672 (14.9)	0.87 [0.78–0.97]	
Polyvascular	142/757 (18.8)	173/779 (22.2)	0.82 [0.66–1.02]	
Single vascular	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				
Total trial population	948/4668 (20.3)	1062/4672 (22.7)	0.88 [0.81–0.96]	
Polyvascular	220/757 (29.1)	255/779 (32.7)	0.86 [0.71–1.03]	
Single vascular	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]	
Cardiovascular death				
Total trial population	219/4668 (4.7)	278/4672 (6.0)	0.78 [0.66–0.93]	
Polyvascular	54/757 (7.1)	60/779 (7.7)	0.92 [0.63–1.32]	
Single vascular	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]	
Non-fatal myocardial infarction				
Total trial population	281/4668 (6.0)	317/4672 (6.8)	0.88 [0.75–1.03]	
Polyvascular	61/757 (8.1)	94/779 (12.1)	0.65 [0.47–0.89]	
Single vascular	173/2646 (6.5)	174/2593 (6.7)	0.96 [0.78–1.19]	*p*=0.10
No ASCVD	47/1265 (3.7)	49/1300 (3.8)	0.99 [0.66–1.47]	
Non-fatal stroke				
Total trial population	159/4668 (3.4)	177/4672 (3.8)	0.89 [0.72–1.11]	
Polyvascular	44/757 (5.8)	42/779 (5.4)	1.06 [0.70–1.62]	
Single vascular	81/2646 (3.1)	104/2593 (4.0)	0.76 [0.56–1.01]	*p*=0.24
No ASCVD	34/1265 (2.7)	31/1300 (2.4)	1.14 [0.70–1.85]