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RESEARCH LETTER

WILEY

Evaluation of evolocumab on saphenous vein graft patency following coronary artery bypass graft surgery in people living with and without diabetes in the NEWTON-CABG CardioLink-5 trial

Hwee Teoh PhD[1,2] | Subodh Verma MD[1,3,4] | G. B. John Mancini MD[5] | Adrian Quan MPhil[1] | Michael Szarek PhD[6,7,8] | Randi Elituv BScN[1,9] | Meena Verma[10] | Elizabeth Misner[1] | Aishwarya Krishnaraj PhD[1,4] | Peter Jüni MD[11,12] | Michael J. Koren MD[13] | Stephen J. Nicholls MBBS[14] | Deepak L. Bhatt MD[8] | C. David Mazer MD[4,15,16,17] | Lawrence A. Leiter MD[2,18,19]

[1]Division of Cardiac Surgery, St Michael's Hospital-Unity Health Toronto, Toronto, Ontario, Canada

[2]Division of Endocrinology and Metabolism, St Michael's Hospital-Unity Health Toronto, Toronto, Ontario, Canada

[3]Department of Surgery, University of Toronto, Toronto, Ontario, Canada

[4]Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada

[5]Division of Cardiology, Centre for Cardiovascular Innovation, Dilawri Cardiovascular Institute, University of British Columbia, Vancouver, British Columbia, Canada

[6]Division of Cardiology, University of Colorado School of Medicine, Aurora, Colorado, USA

[7]CPC Clinical Research, University of Colorado School of Medicine, Aurora, Colorado, USA

[8]Mount Sinai Fuster Heart Hospital, Icahn School of Medicine at Mount Sinai, New York, New York, USA

[9]North York Diagnostic and Cardiac Centre, Toronto, Ontario, Canada

[10]Royal College of Surgeons in Ireland, Dublin, Ireland

[11]Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, Ontario, Canada

[12]Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, Oxford, UK

[13]Jacksonville Center for Clinical Research, Flourish Research Group, Jacksonville, Florida, USA

[14]Victorian Heart Institute, Monash University, Melbourne, Victoria, Australia

[15]Department of Anesthesia, St Michael's Hospital-Unity Health Toronto, Toronto, Ontario, Canada

[16]Department of Anesthesiology and Pain Medicine, University of Toronto, Toronto, Ontario, Canada

[17]Department of Physiology, University of Toronto, Toronto, Ontario, Canada

[18]Department of Medicine, University of Toronto, Toronto, Ontario, Canada

[19]Department of Nutritional Sciences, University of Toronto, Toronto, Ontario, Canada

Correspondence
Lawrence A. Leiter, St Michael's Hospital Medical Centre, 61 Queen Street East, Toronto, ON M5C 2T2, Canada.
Email: lawrence.leiter@unityhealth.to

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1 | BACKGROUND

Compared to people without diabetes, those living with diabetes have smaller coronary vessels and experience more aggressive atherosclerosis, more diffuse coronary lesions, and more extensive disease.[1] Almost half of the individuals undergoing coronary artery bypass graft (CABG) surgery live with diabetes[2] and this proportion is likely to continue rising. Of note, CABG surgery remains the recommended cornerstone treatment of individuals living with diabetes and multivessel coronary artery disease.[3,4]

Low-density lipoprotein cholesterol (LDL-C) is a reliable predictor of long-term major adverse cardiac or cerebrovascular events (MACCEs) among those who have undergone CABG.[5] In a pooled analysis of three randomised clinical trials (RCTs) that followed a total of 4050 individuals living with established coronary heart disease and type 2 diabetes, lower LDL-C levels 1 year following revascularisation procedures was associated with significantly less MACCE.[6] The same study further reported that when compared to optimal medical therapy, CABG was associated with MACCE reductions as long as LDL-C had declined unlike percutaneous coronary intervention where MACCE benefits were only evident among those who achieved a 1 year post-revascularisation LDL-C of less than 70 mg/dL.[6]

Saphenous veins remain widely used conduits for CABG surgery despite their persistently high failure rates. A 2023 pooled analysis of seven RCTs revealed that approximately 20% of saphenous vein grafts (SVGs) failed within a median time to CABG imaging of 1.02 years.[7] This is concerning since graft failure is associated with adverse cardiac events and mortality. Furthermore, there is currently no therapy that can prevent SVG failure.

The impetus for this pre-specified sub-analysis of the NEWTON-CABG CardioLink-5 (Effect of Evolocumab on Saphenous Vein Graft Patency Following Coronary Artery Bypass Surgery; ClinicalTrials.gov NCT03900026)[8] trial was the persistent paucity of information on the longevity of bypass graft patency in the setting of diabetes. This sub-analysis therefore sought to evaluate SVG disease rates, SVG patency and SVG plaque volumes in addition to the efficacy of evolocumab versus placebo by baseline diabetes status.

2 | METHODS

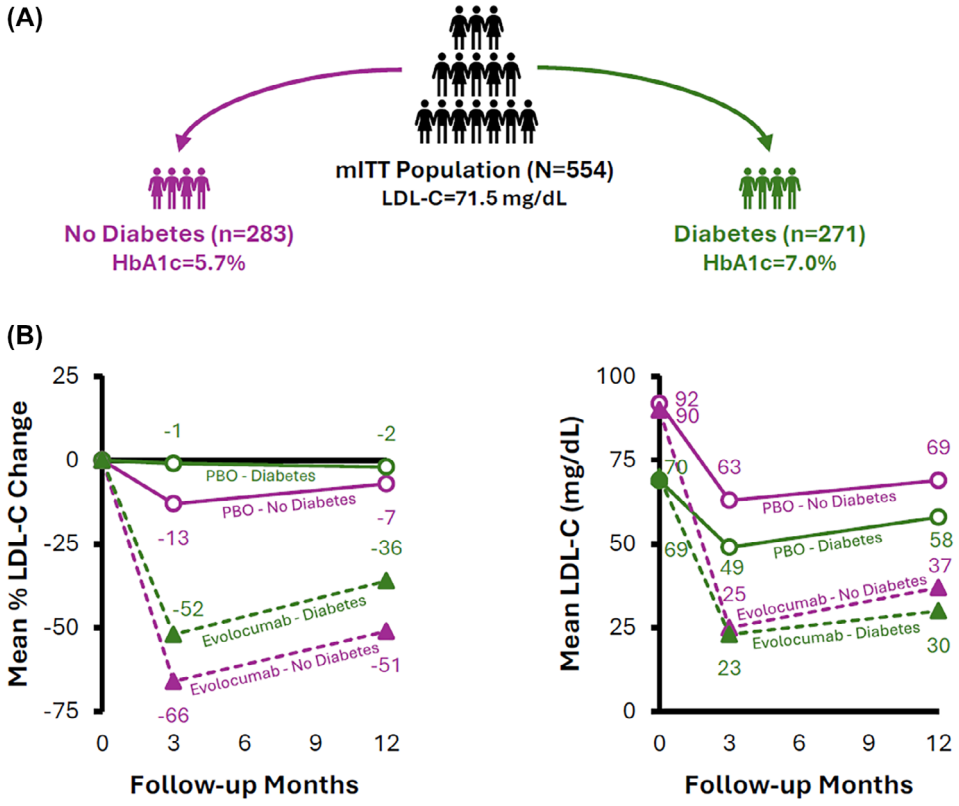
NEWTON-CABG CardioLink-5 was a multicentre, double-blind, randomised trial that involved early initiation of the proprotein convertase subtilisin/kexin type 9 inhibitor evolocumab (140 mg every 2 weeks) versus placebo in statin-treated (moderate to high intensity) adults who had undergone CABG surgery with at least two SVGs.[8] There was no pre-specified LDL-C entry criterion. Country- and site-specific ethics boards approved the protocol. Participants provided written informed consent prior to study entry.

The primary efficacy endpoint (vein graft disease rate, VGDR) was the proportion of SVGs with 50% or greater stenosis or total occlusion 24 months after the index CABG procedure. The secondary efficacy endpoints were: the proportion of SVGs that were totally (100%) occluded at 24 months; the proportion of participants with at least one totally (100%) occluded SVG at 24 months; and the hierarchical composite of cardiovascular death, myocardial infarction, coronary revascularisation, number of SVGs with 100% stenosis at the end-of-study visit, number of SVGs with 50%–99% stenosis at end of study, number of totally (100%) occluded arterial grafts at end of study, and total plaque volume at end of study (each assessed by total wins for each treatment group and WIN ratio).

3 | RESULTS

The median baseline LDL-C for the entire NEWTON-CABG CardioLink-5 cohort was 71.5 mg/dL and, as previously reported, evolocumab did not improve 24-month SVG patency, reduce total occlusion rates, or lower the proportion of participants with at least one occluded SVG.[8]

Efficacy analyses for this sub-analysis were performed on the modified intention-to-treat population, that is, the 554 randomised participants from Canada, Australia, Hungary, and the United States who received at least one dose of the investigational product (evolocumab or placebo) and had at least one evaluable SVG 24 months post-surgery (Figure 1A). The median age was 66 years, approximately 15% were women, and the median time from CABG surgery to randomisation was 13 days. Participants with a diabetes diagnosis in their charts or an HbA1C 6.5% or higher were included in the "Diabetes" group ($n = 271$; median HbA1c 7.0%); others were classified as having "No Diabetes" ($n = 283$; median HbA1c 5.7%). The "Diabetes" group compared with the "No Diabetes" group had fewer white participants (62.2% vs. 76.3%) and significantly higher body mass index (median 28.6 vs. 27.8 kg/m^2), systolic blood pressure (median 126 vs. 120 mmHg), and circulating levels of triglycerides (median 142 vs. 129 mg/dL), as well as lower LDL-C (median 59 vs. 83 mg/dL) and non-high-density lipoprotein cholesterol (median 88 vs. 109 mg/dL) levels (all $p < 0.05$). Proportionally less of the "No Diabetes" than "Diabetes" group had previously undergone a percutaneous coronary intervention (13.1% vs. 20.7%; $p < 0.002$). Over 96% of both groups were on ASA and one-third on a $P2Y_{12}$ inhibitor (no diabetes 34.4%; diabetes 27.8%). Among those with "No Diabetes," 0.4% were treated with a sodium-glucose cotransporter-2 inhibitor (SGLT2i) whereas 29.9%, 27.3%, 5.2%, and 2.2% of the "Diabetes" group were treated with insulin, an SGLT2i, a glucagon-like peptide-1 receptor agonist (GLP-1RA), and both an SGLT2i and GLP-1RA, respectively. The temporal percentage changes in and achieved LDL-C levels are summarised in Figure 1B. The efficacy of evolocumab versus placebo on the primary endpoint (proportion of SVGs with at least 50% stenosis/evaluated grafts) was comparable between the groups (Figure 2A). As shown in Figure 2B, the "Diabetes" group had similar VGDRs (odds ratio [OR] 95% confidence interval [CI] = 0.95 [0.70, 1.29]) at 24 months to the "No Diabetes" group. The percentages of completely occluded SVGs (OR [95% CI] = 0.86 [0.61, 1.20]), proportions of participants with at least one completely (100%) occluded SVG, and composite clinical wins (WIN ratio [95% CI] = 1.04 [0.86,



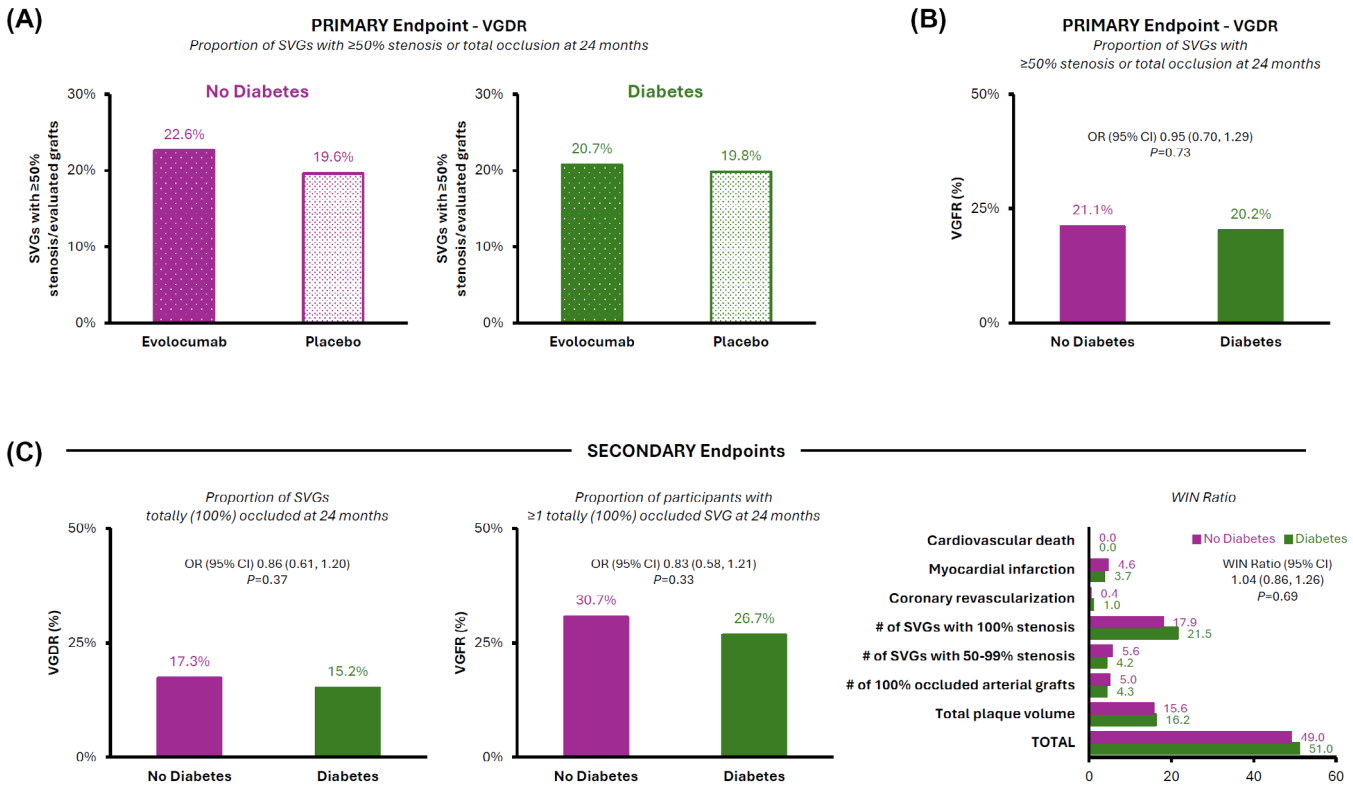


FIGURE 1 (A) NEWTON-CABG CardioLink-5 Diabetes versus No Diabetes Subgroups and (B) temporal percentage change in and achieved LDL-C levels by baseline diabetes status. HbA1C, glycated haemoglobin; LDL-C, low-density lipoprotein cholesterol; PBO, placebo.

FIGURE 2 NEWTON-CABG CardioLink-5 efficacy outcomes by baseline diabetes status. (A) Efficacy of evolocumab versus placebo on VGDR and impact of evolocumab versus placebo on the NEWTON-CABG CardioLink-5. (B) Primary (VGDR) and (C) secondary outcomes. CI, confidence interval; OR, odds ratio; SVG, saphenous vein graft; VGDR, vein graft disease rate.

1.26]) for the "Diabetes" and "No Diabetes" groups were comparable (Figure 2C).

4 | DISCUSSION

People living with diabetes experience a higher mortality rate and greater need for repeat revascularisation procedures post-coronary revascularisation.[9] In the current work, SVG failure rates were similar in the "No Diabetes" and "Diabetes" groups. This is noteworthy and in stark contrast to the risk for stent-related thrombosis where the gap between individuals living with diabetes and without diabetes, while persistent, has narrowed.[10] The overall neutral results of NEWTON-CABG CardioLink-5 may reflect the low baseline LDL-C values and relatively short follow-up duration. SVG failures appeared to be unaffected by evolocumab despite the expected steep LDL-C decrease and slow recovery after month 3, suggesting that SVG quality and technical factors, rather than LDL-C levels, may have been more critical to early SVG failure. Regardless, that SVG disease burden remained high despite the median baseline LDL-C of 77.3 mg/dL underscores the need for robust study of cardiac revascularisation options for people living with versus without diabetes and for investigations seeking alternate biological targets and mechanistic interventions to improve clinical care and narrow knowledge gaps.

5 | CONCLUSIONS

Individuals living with diabetes are a growing high-risk population with elevated rates of surgical mortality and post-cardiac surgery readmissions. The NEWTON-CABG CardioLink-5 trial demonstrated in a post-CABG statin-treated population that the LDL-C-lowering efficacy of evolocumab was independent of diabetes status and that there was no diabetes status-treatment interaction for the primary endpoint. The data herein should not and do not detract from the established cardiovascular benefits of intensive LDL-C lowering in individuals who undergo CABG, regardless of whether they have diabetes or not.

AUTHOR CONTRIBUTIONS

Hwee Teoh, Subodh Verma, C. David Mazer, and Lawrence A. Leiter developed the concept of the analysis. Michael Szarek performed the analysis. Hwee Teoh wrote the first draft of the manuscript. All authors reviewed the results and interpreted the findings; reviewed/edited the manuscript and approved the final version of the manuscript. Subodh Verma, C. David Mazer, and Lawrence A. Leiter are the guarantors of the work and, as such, had full access to all data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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DATA AVAILABILITY STATEMENT

Trial data may be available for academic non-commercial purposes upon execution of a data sharing agreement.

ORCID

Hwee Teoh https://orcid.org/0000-0003-1036-4767
Subodh Verma https://orcid.org/0000-0002-4018-8533
Adrian Quan https://orcid.org/0000-0001-8008-028X
Michael Szarek https://orcid.org/0000-0002-0046-0264
Aishwarya Krishnaraj https://orcid.org/0000-0003-3763-478X
Michael J. Koren https://orcid.org/0000-0001-5023-7178
Stephen J. Nicholls https://orcid.org/0000-0002-9668-4368
Deepak L. Bhatt https://orcid.org/0000-0002-1278-6245
C. David Mazer https://orcid.org/0000-0003-2566-4308
Lawrence A. Leiter https://orcid.org/0000-0002-1040-6229

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