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Steg, P.G.; Szarek, M.; Valgimigli, M.; Islam, S.; Zeiher, A.M.; Bhatt, D.L.; ... ; ODYSSEY OUTCOMES Investigators

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Clinical Research

Lipoprotein(a) and the Effect of Alirocumab on Revascularization After Acute Coronary Syndrome

P. Gabriel Steg, MD,[a,‡] Michael Szarek, PhD,[b,c,‡] Marco Valgimigli, MD,[d,e] Shahidul Islam, DrPH, MPH, PStat,[f] Andreas M. Zeiher, MD,[g] Deepak L. Bhatt, MD, MPH,[h] Vera A. Bittner, MD, MSPH,[i] Chern-En Chiang, MD, PhD,[j] Rafael Diaz, MD,[k] Shaun G. Goodman, MD, MSc,[l,m] Nina Gotcheva, MD, PhD,[n] Robert A. Harrington, MD,[o] J. Wouter Jukema, MD, PhD,[p,q] Hyo-Soo Kim, MD, PhD,[r] Sang-Hyun Kim, MD, PhD,[s] Joao Morais, MD, PhD,[t,u] Robert Pordy, MD,[v] Michel Scemama, MD,[w] Harvey D. White, DSc,[x] and Gregory G. Schwartz, MD, PhD;[y,‡] for the ODYSSEY OUTCOMES Investigators[§]

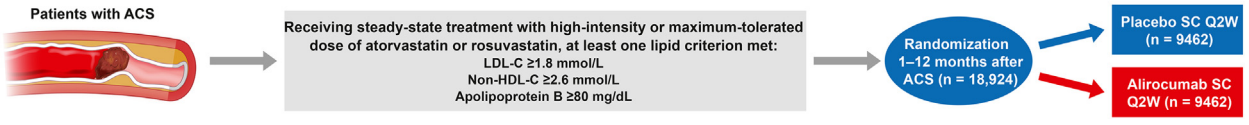
[a] Department of Cardiology, Université Paris-Cité, INSERM-UMR1148, Assistance Publique-Hôpitaux de Paris, Hôpital Bichat, French Alliance for Cardiovascular Trials, and Institut Universitaire de France, Paris, France; [b] CPC Clinical Research and Division of Cardiology, University of Colorado School of Medicine, Aurora, Colorado, USA; [c] State University of New York, Downstate Health Sciences University, Brooklyn, New York, USA; [d] Division of Cardiology, Cardiocentro Ticino Institute, Ente Ospedaliero Cantonale, Lugano, Switzerland; [e] Department of Cardiology,University of Bern, Bern, Switzerland; [f] Division of Health Services Research, NYU Long Island School of Medicine, Mineola, New York, USA; [g] Department of Medicine III, Goethe University, Frankfurt am Main, Germany; [h] Mount Sinai Heart, Icahn School of Medicine at Mount Sinai Health System, New York, New York, USA; [i] Division of Cardiovascular Disease, University of Alabama at Birmingham, Birmingham, Alabama, USA; [j] General Clinical Research Center, Division of Cardiology, Taipei Veterans General Hospital and National Yang Ming Chiao Tung University, Taipei, Taiwan; [k] Estudios Cardiológicos Latinoamérica, Instituto Cardiovascular de Rosario, Rosario, Argentina; [l] Department of Medicine, Canadian VIGOUR Centre, University of Alberta, Edmonton, Alberta, Canada; [m] Division of Cardiology, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; [n] Department of Cardiology, MHAT "National Cardiology Hospital" EAD, Sofia, Bulgaria; [o] Stanford Center for Clinical Research, Department of Medicine, Stanford University, Stanford, California, USA; [p] Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; [q] Netherlands Heart Institute, Utrecht, The Netherlands; [r] Departmentof Cardiology, Seoul National University Hospital, Seoul, Republic of Korea; [s] Division of Cardiology, SMG Seoul National University Boramae Medical Center, Seoul, Republic of Korea; [t] Division of Cardiology, Leiria Hospital Center, Leiria, Portugal; [u] ciTechCare, Polytechnic of Leiria, Leiria, Portugal; [v] Regeneron Pharmaceuticals Inc, Tarrytown, New York, USA; [w] Sanofi, Chilly-Mazarin, France; [x] Green Lane Cardiovascular Services, Auckland City Hospital and Auckland University, Auckland, New Zealand; [y] Division of Cardiology, University of Colorado School of Medicine, Aurora, Colorado, USA

See editorial by Thanassoulis, pages 1325-1327 of this issue.

Lipoprotein(a) and the Effect of Alirocumab on Revascularization After Acute Coronary Syndrome (ACS)

ODYSSEY OUTCOMES compared alirocumab with placebo in 18,924 patients with ACS and elevated atherogenic lipoprotein levels despite optimized statin treatment. In this post hoc analysis, treatment effects are summarized using competing risks proportional hazard models.

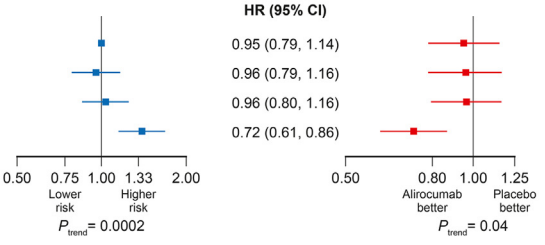
Post hoc analysis of the ODYSSEY OUTCOMES trial



Risk of total* coronary revascularization was increased in patients in the top baseline lipoprotein(a) quartile (as seen in placebo group) relative to patients in the bottom quartile

Benefit of alirocumab over placebo in reducing the risk of total* coronary revascularizations was present in patients with the highest baseline lipoprotein(a)

Baseline lipoprotein(a) Quartile	Events per 100 Patient-Years Alirocumab	Placebo	Placebo group HR (95% CI)	Treatment HR (95% CI)
Quartile 1 (<6.7 mg/dL)	3.2	3.5	Reference	0.95 (0.79, 1.14)
Quartile 2 (6.7 to <21.2 mg/dL)	3.1	3.2	0.96 (0.80, 1.15)	0.96 (0.79, 1.16)
Quartile 3 (21.2 to <59.6 mg/dL)	3.3	3.5	1.03 (0.86, 1.24)	0.96 (0.80, 1.16)
Quartile 4 (≥59.6 mg/dL)	3.4	4.7	1.40 (1.17, 1.67)	0.72 (0.61, 0.86)



*First and recurrent

CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, high-density lipoprotein cholesterol; P_{trend}, *P* for trend; SC Q2W, subcutaneously every 2 weeks.

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ABSTRACT

Background: Many patients require revascularization after index acute coronary syndrome (ACS). Lipoprotein(a) is thought to play a pathogenic role in atherothrombosis. In ODYSSEY OUTCOMES, alirocumab reduced major adverse cardiovascular events after ACS, with greater reduction among those with higher lipoprotein(a) levels. We explored whether risk of revascularization after ACS was modified by the level of lipoprotein(a) and treatment with alirocumab or placebo.

Methods: In ODYSSEY OUTCOMES alirocumab was compared with placebo in 18,924 patients with ACS and elevated atherogenic lipoprotein levels despite optimized statin treatment. In this post hoc analysis, treatment effects are summarized using competing risks proportional hazard models.

Results: A total of 1559 (8.2%) patients had coronary, 204 (1.1%) had limb, and 40 (0.2%) had carotid revascularization. Alirocumab reduced coronary revascularization (2.8 vs 3.2 events per 100 patient-years; hazard ratio [HR], 0.88 [95% confidence interval (CI), 0.80-0.97]; $P = 0.01$) and any revascularization (3.2 vs 3.7 events per 100 patient-years; HR, 0.85 [95% CI, 0.78-0.94]; $P = 0.001$). Baseline lipoprotein(a) quartile was directly associated with risk of coronary or any revascularization in the placebo arm and inversely related to treatment HRs (all P for trend < 0.01). Alirocumab produced the greatest reduction of coronary revascularization in patients with baseline lipoprotein(a) in the top quartile ($\geq$ 59.6 mg/dL; HR, 0.69 [95% CI, 0.57-0.84]), but no apparent reduction in the bottom quartile (HR, 1.00 [95% CI, 0.82-1.22]). Findings were similar for the effect of alirocumab on any revascularization.

Conclusions: Alirocumab reduced revascularization rates after ACS. The risk of revascularization and reduction in that risk with alirocumab were greatest in patients with elevated lipoprotein(a) at baseline.

RÉSUMÉ

Contexte : De nombreux patients ont besoin d'une revascularisation après un premier syndrome coronarien aigu (SCA), et la lipoprotéine A jouerait un rôle dans la pathogenèse de l'athérothrombose. Dans l'étude ODYSSEY OUTCOMES, l'alirocumab a permis de réduire la survenue d'événements cardiovasculaires indésirables majeurs après un SCA, et cette réduction a été plus importante chez les personnes dont le taux de lipoprotéine A était plus élevé. Nous avons cherché à savoir si le risque de revascularisation après un SCA variait en fonction du taux de lipoprotéine A et de l'administration d'alirocumab ou d'un placebo.

Méthodologie : Dans l'étude ODYSSEY OUTCOMES, l'alirocumab a été comparé à un placebo chez 18 924 patients ayant subi un SCA et présentant un taux élevé de lipoprotéines athérogènes malgré un traitement par statine optimisé. Dans cette analyse a posteriori, les effets du traitement sont résumés à l'aide de modèles à risques proportionnels concurrents.

Résultats : Un total de 1 559 patients (8,2 %) ont subi une revascularisation coronarienne, 204 (1,1 %) ont subi la revascularisation d'un membre et 40 (0,2 %) ont subi une revascularisation carotidienne. L'alirocumab a permis de réduire le taux de revascularisation coronarienne (2,8 contre 3,2 événements pour 100 années-patients; rapport des risques instantanés [RRI] : 0,88 [intervalle de confiance (IC) à 95 % : 0,80-0,97]; $P = 0,01$) et celui des autres types de revascularisation (3,2 contre 3,7 événements pour 100 années-patients; RRI : 0,85 [IC à 95 % : 0,78-0,94]; $P = 0,001$). Le quartile de distribution du taux de lipoprotéine A à l'inclusion était directement associé au risque de revascularisation coronarienne ou d'un autre type de revascularisation dans le groupe placebo et inversement lié au RRI du traitement (tendance pour toutes les valeurs de $P < 0,01$). L'alirocumab a entraîné la plus grande réduction du taux de revascularisation coronarienne lorsque le taux initial de lipoprotéine A se situait dans le quartile supérieur ($\geq$ 59,6 mg/dl; RRI : 0,69 [IC à 95 % : 0,57-0,84]), mais aucune réduction apparente lorsqu'il se situait dans le quartile inférieur (RRI : 1,00 [IC à 95 % : 0,82-1,22]). Les effets du traitement par l'alirocumab ont été similaires indépendamment du type de revascularisation.

Conclusions : L'alirocumab a réduit les taux de revascularisation après un SCA. Le risque de revascularisation et la réduction de ce risque avec l'alirocumab étaient les plus élevés chez les patients ayant un taux de lipoprotéine A élevé au départ.

Although low-density lipoprotein (LDL) is considered the principal atherogenic lipoprotein, lipoprotein(a) also influences the risk of major adverse cardiovascular events (MACE) after acute coronary syndrome (ACS). It is thought to play a physiologic role in wound healing and a pathogenic role in atherothrombosis.[1]

LDL cholesterol (LDL-C) and lipoprotein(a) are reduced by inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9). In the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY OUTCOMES) trial (NCT01663402) the PCSK9 inhibitor alirocumab was compared with placebo in patients with recent ACS and elevated atherogenic lipoprotein levels despite high-intensity or maximum tolerated statin therapy. Alirocumab reduced the primary end point of MACE (death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, and hospitalization for unstable angina) as well as secondary end points including ischemia-driven coronary revascularization[2] and all-cause death.[3]

In this analysis of the trial, we describe the effect of alirocumab on the risk of coronary, limb, or carotid revascularization procedures after ACS, the relation of that risk to the level of lipoprotein(a), and whether the latter modified the effect of alirocumab on the risk of revascularization.

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‡These authors contributed equally to this work.

§The ODYSSEY OUTCOMES Committee Members, Investigators, and Contributors are listed in Supplemental Appendix S1.

Corresponding author: Dr P. Gabriel Steg, Département de Cardiologie, AP-HP Hôpital Bichat, 46 Rue Henri Huchard, 75018 Paris, France. Tel.: +33 1 40 25 74 61.

E-mail: gabriel.steg@aphp.fr

See page 1323 for disclosure information.

Methods

Study design

The trial design[4] and primary results[2] have been published. All patients provided written informed consent. All sites obtained ethics committee approval as per local and national guidelines. Briefly, the trial included patients aged 40 years or older who had been hospitalized with ACS and had LDL-C levels $\geq$ 1.81 mmol/L (70 mg/dL), or non-high-density lipoprotein cholesterol $\geq$ 2.59 mmol/L (100 mg/dL), or apolipoprotein B levels $\geq$ 80 mg/dL after at least 2 weeks of stable treatment with atorvastatin 40-80 mg daily, rosuvastatin 20-40 mg daily, or the maximum tolerated dose of one of these statins. Randomization occurred 1-12 months after the index ACS. Patients were excluded if there had been a recurrent ACS or coronary revascularization procedure in the 2 weeks before intended randomization or if coronary revascularization was planned after randomization.

At randomization, patients were assigned to receive blinded treatment with alirocumab 75 mg or matching placebo given using subcutaneous injection every 2 weeks. For patients assigned to receive alirocumab, blinded protocol-specified dose adjustment algorithms were used to target achieved LDL-C levels between 0.65 and 1.29 mmol/L (25-50 mg/dL) and to avoid sustained levels $<$ 0.39 mmol/L (15 mg/dL).[2,4]

Lipoproteins were measured at baseline (randomization visit) and at defined subsequent time points. LDL-C was calculated using the Friedewald formula unless triglycerides exceeded 400 mg/dL (4.52 mmol/L) or calculated LDL-C was $<$ 15 mg/dL (0.39 mmol/L), in which case values were determined using ultracentrifugation/β-quantification. Lipoprotein(a) mass was measured at randomization, 4 months, and 12 months at Covance Central Laboratories using an automated immunoturbidimetric assay[5] on a Siemens BNII (Siemens Healthcare Diagnostics, Erlangen, Germany) validated against the International Federation of Clinical Chemistry and World Health Organization standards.

Outcome definitions

The primary MACE outcome was adjudicated by a blinded clinical events committee. In addition, the committee reviewed all coronary revascularization procedures to adjudicate ischemia-driven coronary revascularization. This prespecified end point, considered outside the prespecified hierarchy of key secondary end points, comprised revascularization procedures performed for new or progressive anginal symptoms, new or progressive abnormalities on stress testing, or recurrent acute ischemia (ie, ACS), but excluded revascularization performed solely for restenosis at a previous percutaneous coronary intervention (PCI) site or revascularization done during other cardiac surgery. In the present analysis, all postrandomization coronary revascularizations (including restenosis and regardless of the presence of angina or ischemia) were also examined as an exploratory end point that was prespecified in the statistical analysis plan. An additional post hoc analysis considered "any" arterial revascularization, which includes, in addition to surgical or nonsurgical coronary revascularization, limb and carotid procedures. Noncoronary (limb or carotid) revascularizations were reported by investigators but not adjudicated. "Total" revascularization refers to first and subsequent repeat revascularizations.

Statistical analysis

Patients were categorized on the basis of revascularization status at randomization: no previous coronary revascularization; revascularization before but not for the qualifying ACS; or revascularization for the qualifying ACS with or without previous revascularization.

Treatment effects on first and total (ie, first and potentially subsequent) coronary and any revascularization procedures were summarized using competing risks proportional hazard models (stratified according to geographic region of enrollment) with deaths treated as competing terminal events to generate hazard ratios (HRs) with Wald 95% confidence intervals (CIs) and *P* values. For total revascularization procedures, marginal models were applied with the robust sandwich estimate for the estimated standard error of the log HR to account for the dependence of event times within individual patients. Accrual of events over time was estimated using cumulative incidence functions, with event rates calculated as the number of events per 100 patient-years of follow-up. Heterogeneity of alirocumab treatment effects according to baseline revascularization category was assessed using competing risks models with interaction terms for relative risk reduction and tests for quantitative interaction for absolute risk reduction (ARR).

Measured or calculated LDL-C level includes a contribution from cholesterol contained in lipoprotein(a). To examine the independent relationships of these 2 lipoproteins to revascularization events we calculated corrected LDL-C (LDL-C_{corr}) using the formula LDL-C_{corr} = LDL-C − 0.3 × lipoprotein(a) mass.[6] Relationships for baseline lipoprotein(a) or LDL-C_{corr} and first and total revascularizations in the placebo group were determined using competing risks models stratified according to geographic region using baseline lipoprotein(a) or LDL-C_{corr} quartile as the predictor variable; *P* values were computed for linear trend in the estimated log HRs across baseline lipoprotein(a) or LDL-C_{corr} quartiles. The tests of linear trend represent interaction tests that account for the ordinal nature of the quartiles. These models were adjusted for the following demographic and clinical variables: coronary revascularization status at randomization, age, sex, race, body mass index, current smoking, history of diabetes, and baseline LDL-C_{corr} (in the lipoprotein(a) model) or baseline lipoprotein(a) (in the LDL-C_{corr} model).

Heterogeneity in the relative effects of alirocumab treatment on first and total revascularizations was assessed according to baseline lipoprotein(a) quartile. Competing risks models stratified according to geographic region were constructed with baseline lipoprotein(a) quartile, treatment, and their interaction as predictors, along with the demographic and clinical variables listed previously. *P* values for linear trend across baseline lipoprotein(a) quartiles were calculated for the estimated log treatment HRs. Similar models were constructed with baseline LDL-C_{corr} quartile.

Results

The trial comprised 18,924 patients randomized at 1315 sites in 57 countries a median of 2.6 (quartile (Q)1-Q3, 1.7-4.3) months after the qualifying ACS. Baseline characteristics of trial participants according to lipoprotein(a) quartile[7] are shown in Supplemental Table S1. Baseline lipoprotein(a) values were 2.0 (Q1-Q3, 2.0-4.8), 12.2 (Q1-Q3, 9.3-15.9), 37.6 (Q1-Q3, 28.3-47.7), and 92.2 (Q1-Q3, 73.2-119.0) mg/dL in the 4 quartiles respectively, whereas baseline LDL-C levels were 2.15 (Q1-Q3, 1.79-2.62) mmol/L (83 [Q1-Q3, 69-101] mg/dL), 2.20 (Q1-Q3, 1.86-2.64) mmol/L (85 [Q1-Q3, 72-102] mg/dL), 2.23 (Q1-Q3, 1.89-2.69) mmol/L (86 [Q1-Q3, 73-104] mg/dL), and 2.38 (Q1-Q3, 2.02-2.82) mmol/L (92 [Q1-Q3, 78-109] mg/dL), respectively. Baseline characteristics overall were well balanced for the alirocumab and placebo groups (Supplemental Table S2). Patients were followed for a median of 2.8 (Q1-Q3, 2.3-3.4) years. As previously described,[2] median lipoprotein(a) at randomization was 21.2 (Q1-Q3, 6.7-59.6) mg/dL, median LDL-C was 2.24 (Q1-Q3, 1.89-2.69) mmol/L (86.5 [Q1-Q3, 73.0-104.0] mg/dL), and median baseline LDL-C_{corr} was 1.95 (Q1-Q3, 1.57-2.42) mmol/L (75.4 [Q1-Q3, 60.6-93.6] mg/dL). During follow-up, 1559 (8.2%) patients had coronary, 204 (1.1%) had limb, and 40 (0.2%) had carotid revascularizations.

Effect of alirocumab on first and total coronary revascularizations

Alirocumab treatment reduced first ischemia-driven coronary revascularization rates (2.8 vs 3.2 events per 100 patient-years; HR, 0.88 [95% CI, 0.80-0.97]; $P = 0.01$; Fig. 1 and Supplemental Fig. S1). Alirocumab also reduced total (including recurrent) ischemia-driven coronary revascularization rates, with 3.2 vs 3.7 events per 100 patient-years with alirocumab and placebo, respectively (HR, 0.87 [95% CI, 0.78-0.97]; $P = 0.008$).

The number of patients who underwent first or total coronary revascularizations including those that were not ischemia-driven by PCI or coronary artery bypass grafting (CABG) as well as ischemia-driven subcategories (ACS-driven or elective) are described in Table 1. There were numerically fewer coronary revascularizations with alirocumab compared with placebo for PCI and CABG, and for urgent (ACS) and elective indications. The largest numerical difference was for urgent PCI. The number of CABG procedures appeared similar among groups, with the caveat of far fewer procedures than for PCI. Angiographic findings are described in Supplemental Table S3. Compared with placebo, there were fewer *de novo* lesions with alirocumab, with small differences in the number of events related to restenosis or stent thrombosis. Among patients who underwent PCI or CABG, the rates of periprocedural complications were low and did not differ according to treatment group (Supplemental Table S4).

Effect of alirocumab on any (coronary and noncoronary) revascularization

The incidence of first and total coronary, limb, and carotid revascularizations according to treatment group is summarized in Table 2. Alirocumab treatment resulted in fewer first revascularizations (3.2 vs 3.7 events per 100 patient-years; HR, 0.85 [95% CI, 0.78-0.94]; $P = 0.001$) and total revascularizations (3.7 vs 4.5 events per 100 patient-years; HR, 0.83 [95% CI, 0.75-0.91]; $P = 0.0002$) (Table 2). The reduction in revascularizations with alirocumab appeared consistent across coronary, limb, and carotid revascularizations.

Effect of lipoprotein(a) and corrected LDL-C on risk of coronary or other arterial revascularization and alirocumab treatment effect

At month 4 of treatment, alirocumab reduced lipoprotein(a) by a median of 5.0 (Q1-Q3, 13.5-0) mg/dL overall, with median reductions of 0 (Q1-Q3, 1.4-0), 5.1 (Q1-Q3, 7.9-2.3), 9.8 (Q1-Q3, 16.2-3.1), and 20.2 (Q1-Q3, 34.1-8.0) mg/dL across increasing baseline lipoprotein(a) quartiles. Importantly, median changes in LDL-C (−1.39 [Q1-Q3, −1.79 to −0.92] mmol/L [−53.7 (Q1-Q3, −69.1 to −35.5) mg/dL], −1.40 [Q1-Q3, −1.84 to −0.96] mmol/L [−54.1 (Q1-Q3, −71.0 to −37.1) mg/dL], −1.38 [Q1-Q3, −1.82 to −0.93] mmol/L [−53.3 (Q1-Q3, −70.3 to −36.0) mg/dL], and −1.40 [Q1-Q3, −1.84 to −0.95] mmol/L [−54.1 (Q1-Q3, −71.0 to −36.7) mg/dL] mg/dL), and LDL-C_{corr} (−1.39 [Q1-Q3, −1.79 to −0.93] mmol/L [−53.7 (Q1-Q3, −69.1 to −35.9) mg/dL], −1.37 [Q1-Q3, −1.79 to −0.94] mmol/L [−52.8 (Q1-Q3, −69.2 to −36.4) mg/dL], −1.33 [Q1-Q3, −1.72 to −0.88] mmol/L [−51.2 (−66.4, −34.0) mg/dL], and −1.23 [−1.65, −0.82] mmol/L [−47.3 (Q1-Q3, −63.6 to −31.5) mg/dL]) were similar across baseline lipoprotein(a) quartiles. In the placebo group, changes from baseline to month 4 were minimal.[2]

In the placebo arm, using the lowest quartile as a reference, there was a uniform risk of first ischemia-driven coronary revascularization in quartiles 1-3 of baseline lipoprotein(a), with markedly greater risk in the top quartile compared with the bottom quartile (HR, 1.45 [95% CI, 1.20-1.76]; $P = 0.0001$ for trend; Fig. 2). Notably, the reduction of first coronary revascularization produced by alirocumab was most pronounced in the top quartile of lipoprotein(a) ($P = 0.001$ for trend; Fig. 2 and Fig. 3D). In that quartile, relative risk reduction was substantial (HR, 0.69 [95% CI, 0.57-0.84], paralleled by an ARR of 1.3 events per 100 patient-years. Moreover, the reduction in first coronary revascularization in the top quartile of lipoprotein(a) became apparent within the first year after randomization (Fig. 3D). Similar observations were made when total coronary revascularizations were considered, with an ARR of 1.3 procedures per 100 patient-years of observation in the highest baseline quartile of lipoprotein(a) and with significant interactions between baseline lipoprotein(a) and the risk of total coronary revascularizations in the placebo group and between baseline lipoprotein(a) and the benefit of alirocumab ($P = 0.0002$ and $P = 0.04$ for trend, respectively [see Graphical Abstract]). Similar relationships for baseline LDL-C_{corr} quartile and first and total revascularizations were evident in the placebo arm; however, unlike lipoprotein(a), there was no evidence of heterogeneity in the treatment effects across quartiles (first revascularization P for trend = 0.55, Supplemental Fig. S2; total revascularizations P for trend = 0.83, Supplemental Fig. S3).

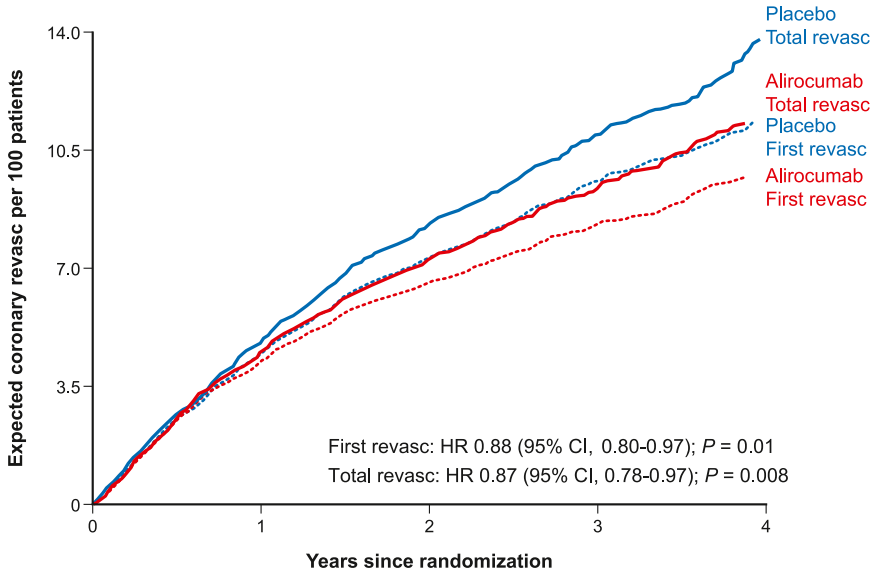

Figure 1. Cumulative incidence of first and total ischemia-driven coronary revascularization (revasc) according to treatment allocation. Hazard ratio (HR) for alirocumab vs placebo. CI, confidence interval.

Regarding all (coronary, limb, and carotid) revascularizations, there was also a relationship within the placebo group for baseline lipoprotein(a) quartile and risk of first (P for trend < 0.0001) and total (P for trend $= 0.0002$) events, and between baseline lipoprotein(a) quartile and benefit of alirocumab for first (P for trend $= 0.003$) and total (P for trend $= 0.03$) events (Fig. 4 and Table 3). Similar to the findings for coronary revascularization, in the

Table 1. Type of and reason for coronary revascularization and first and total events

			Events per 100 patient-years (number of events)			
Event number	Type of revascularization	Reason for revascularization	Alirocumab	Placebo	HR (95% CI)	*P*
First	All (PCI + CABG)	Any	3.2 (811)	3.6 (903)	0.89 (0.81-0.98)	0.0207
		Ischemia-driven	2.8 (727)	3.2 (823)		
		ACS	1.7 (438)	2.1 (521)		
		Elective	1.1 (289)	1.2 (302)		
		Nonischemia-driven	0.3 (84)	0.3 (80)		
	PCI	Any	2.7 (699)	3.1 (785)	0.89 (0.80-0.98)	0.0205
		Ischemia-driven	2.5 (629)	2.8 (721)		
		ACS	1.5 (393)	1.9 (474)		
		Elective	0.9 (236)	1.0 (247)		
		Nonischemia-driven	0.3 (70)	0.3 (64)		
	CABG	Any	0.4 (112)	0.5 (118)	0.94 (0.73-1.22)	0.67
		Ischemia-driven	0.4 (98)	0.4 (102)		
		ACS	0.2 (45)	0.2 (47)		
		Elective	0.2 (53)	0.2 (55)		
		Nonischemia-driven	0.1 (14)	0.1 (16)		
Total	All (PCI + CABG)	Any	3.7 (990)	4.1 (1115)	0.89 (0.81-0.98)	0.0188
		Ischemia-driven	3.2 (875)	3.7 (1003)		
		ACS	2.0 (535)	2.4 (650)		
		Elective	1.3 (340)	1.3 (353)		
		Nonischemia-driven	0.4 (115)	0.4 (112)		
	PCI	Any	3.2 (860)	3.6 (977)	0.89 (0.80-0.98)	0.0190
		Ischemia-driven	2.8 (764)	3.3 (884)		
		ACS	1.8 (482)	2.2 (591)		
		Elective	1.0 (282)	1.1 (293)		
		Nonischemia-driven	0.4 (96)	0.3 (93)		
	CABG	Any	0.5 (130)	0.5 (138)	0.95 (0.75-1.20)	0.67
		Ischemia-driven	0.4 (111)	0.4 (119)		
		ACS	0.2 (53)	0.2 (59)		
		Elective	0.2 (58)	0.2 (60)		
		Nonischemia-driven	0.1 (19)	0.1 (19)		

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention.

Table 2. Treatment effects on first and total ischemia-driven coronary, peripheral artery, and carotid revascularizations

Event	Type of revascularization	Events per 100 patient-years (number of events)		HR (95% CI)	*P*
		Alirocumab	Placebo		
First	Any	3.2 (814)	3.7 (945)	0.85 (0.78-0.94)	0.0010
	Ischemia-driven coronary	2.8 (725)	3.2 (816)	0.88 (0.80-0.97)	0.0134
	Peripheral artery	0.3 (76)	0.4 (106)	0.71 (0.53-0.95)	0.0226
	Carotid	0.1 (13)	0.1 (23)	0.56 (0.28-1.10)	0.09
Total	Any	3.7 (1001)	4.5 (1202)	0.83 (0.75-0.91)	0.0002
	Ischemia-driven coronary	3.2 (875)	3.7 (1003)	0.88 (0.80-0.97)	0.0126
	Peripheral artery	0.4 (110)	0.6 (169)	0.66 (0.49-0.89)	0.0064
	Carotid	0.1 (16)	0.1 (30)	0.54 (0.28-1.03)	0.06

CI, confidence interval; HR, hazard ratio.

lower 3 quartiles of baseline lipoprotein(a), there was minimal effect of alirocumab on all revascularizations; however, in the top quartile of baseline lipoprotein(a) alirocumab reduced that risk substantially (HR, 0.67 [95% CI, 0.56-0.80] for first; HR, 0.69 [95% CI, 0.59-0.82] for total; ARR per 100 patient-years 1.6 for first, 1.7 for total).

Discussion

In this large trial of patients with recent ACS and elevated atherogenic lipoprotein levels despite intensive or maximum tolerated statin therapy, alirocumab reduced the risk of coronary or any (coronary, limb, or carotid) arterial revascularization. First and total (first and recurrent) revascularization events were reduced.

Baseline lipoprotein(a) was associated with the risk of arterial revascularization after ACS, but also significantly modified the effect of alirocumab on revascularization: the greatest and earliest benefit of alirocumab on revascularization was seen in patients with baseline lipoprotein(a) in the top quartile ($\geq$ 59.6 mg/dL). In contrast, there was little or no apparent benefit of alirocumab on revascularization in the lowest quartile of lipoprotein(a) ($<$ 6.7 mg/dL). These findings are particularly notable in light of similar and substantial reductions in LDL-C_{corr} across baseline lipoprotein(a) quartiles. The benefit of alirocumab on revascularization was not associated with baseline LDL-C_{corr} quartiles. This is important because LDL-C incorporates LDL-C_{corr} and lipoprotein(a) cholesterol, but in our observations it suggests that the apparent relationship between reductions in LDL-C and reduction in revascularization with alirocumab might actually be driven by the reduction in lipoprotein(a) cholesterol particles rather than by any change in "true" LDL-C (which is approximated by LDL-C_{corr}).

The relation for elevated lipoprotein(a) and risk of atherosclerotic events has been well documented[8-10] and appears to be monotonic over a broad range of lipoprotein(a) concentrations. Others have previously observed that the association of LDL-C with incident cardiovascular events, including coronary revascularization, is due in part to the contribution of lipoprotein(a) to measured or calculated LDL-C.[11] Likewise, elevated lipoprotein(a) has been previously associated with an increased risk of coronary revascularization.[12] Previous studies relating elevated lipoprotein(a) levels and an increased attributable risk for MACE have categorized elevated lipoprotein(a) levels at values $>$ 50 mg/dL—consistent with the values from the highest quartile in the present analysis.[9]

Previous analyses of ODYSSEY OUTCOMES have shown that baseline lipoprotein(a) predicted first and total MACE,[7,13] and that alirocumab-induced reductions in lipoprotein(a) contributed, independently of LDL-C reduction, to the reduced risk of MACE. In the present analysis, the

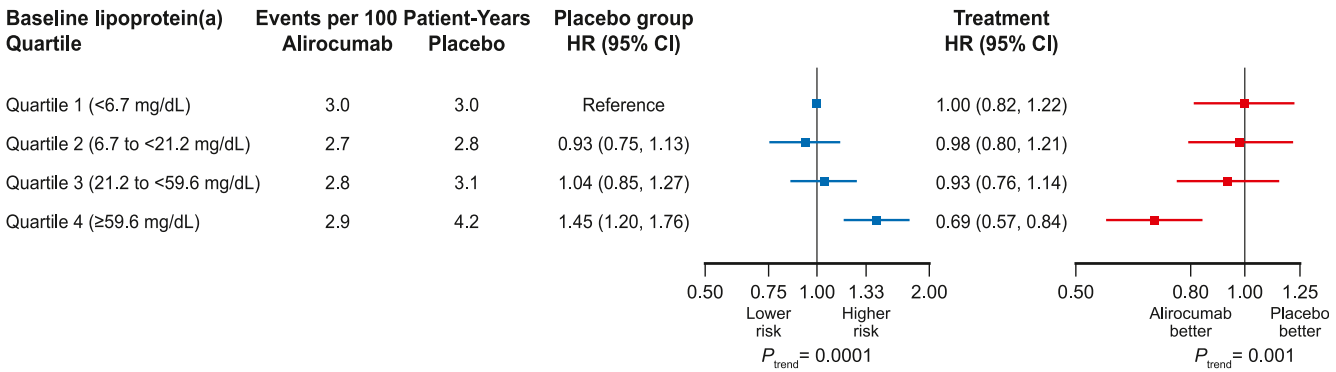

Figure 2. Forest plot relating baseline lipoprotein(a) quartile to the risk of first ischemia-driven coronary revascularization in the placebo group (**left side of the graph**) and the effect of alirocumab on the risk of first ischemia-driven coronary revascularization (**right side of the graph**). Absolute risk reduction (events per 100 patient-years) with alirocumab: 0 for quartile 1, 0.1 for quartile 2, 0.3 for quartile 3, and 1.3 for quartile 4. CI, confidence interval; HR, hazard ratio.

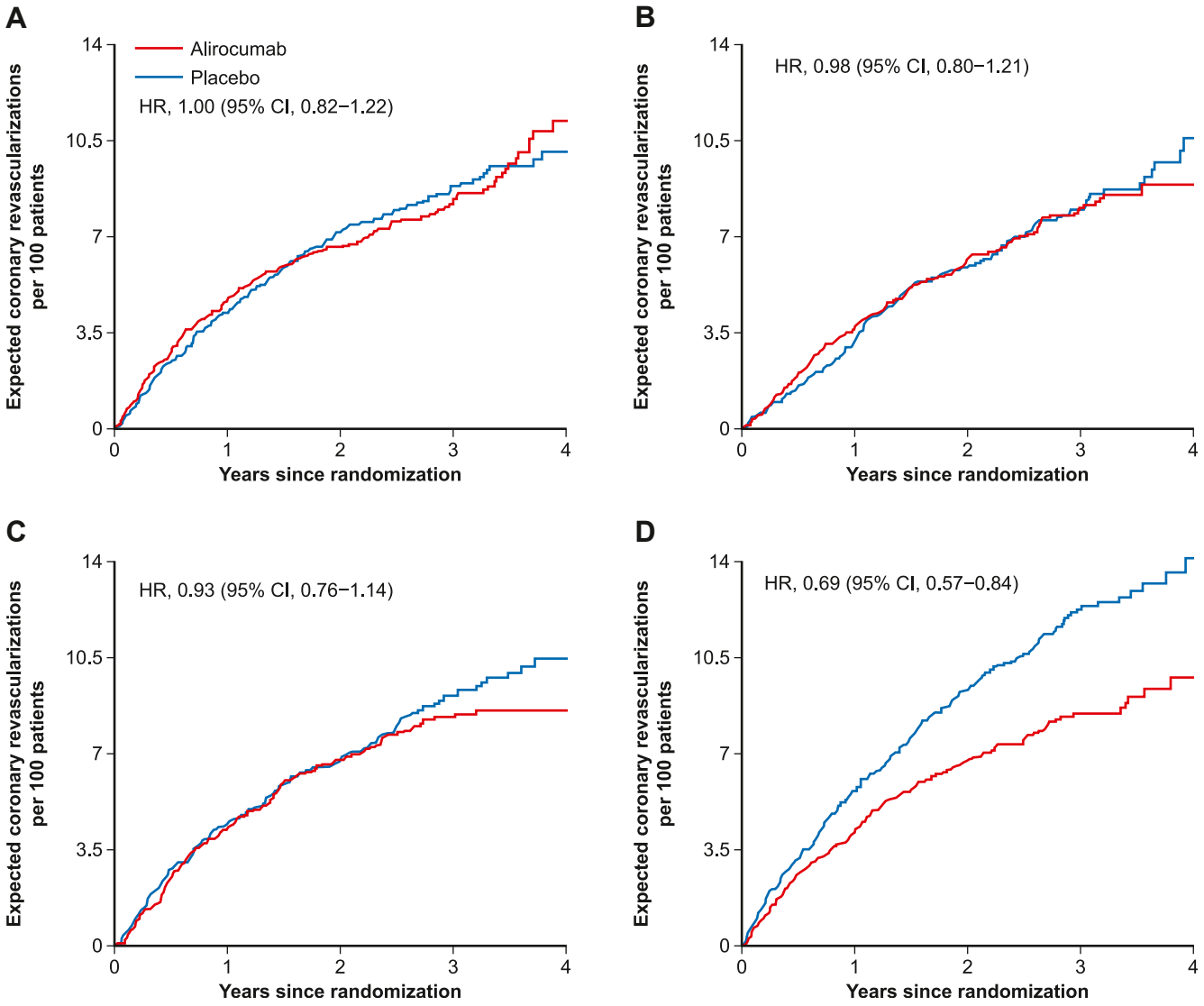

Figure 3. Kaplan-Meier curves for time to first ischemia-driven coronary revascularization according to baseline lipoprotein(a) quartile: (**A**) quartile 1 (< 6.7 mg/dL); (**B**) quartile 2 (6.7 to < 21.2 mg/dL); (**C**) quartile 3 (21.2 to < 59.6 mg/dL); and (**D**) quartile 4 (≥ 59.6 mg/dL). CI, confidence interval; HR, hazard ratio.

benefit of alirocumab on revascularization was nearly confined to patients with baseline lipoprotein(a) levels in the top quartile. However, with rather broad CIs in each quartile, our observations cannot rule out a continuous relationship between for lipoprotein(a) and the benefit of alirocumab on revascularization, akin to that demonstrated for primary MACE[7] and peripheral artery disease events.[14]

Statin treatment is associated with a reduced need for coronary revascularization,[15] and greater statin-induced LDL-C reduction is associated with a greater benefit on coronary revascularization.[16,17] There is also evidence that LDL-lowering with statins reduces the risk of peripheral revascularizations.[18,19] In contrast, there is uncertainty regarding the relationship of lipoprotein(a) levels and risk of peripheral revascularization. Some,[20] but not all,[21] studies have suggested that elevated lipoprotein(a) levels are predictive of a greater risk of peripheral revascularization in patients with peripheral artery disease.

PCSK9 inhibitors such as alirocumab provide substantial reduction of LDL-C[22,23] and modest reduction of lipoprotein(a). In patients with stable atherosclerotic cardiovascular disease, evolocumab reduced coronary revascularization by 22%, with a consistent reduction in urgent and elective procedures, a reduction in the need for complex PCI,[24] and a 24% reduction in the need for CABG.[25] The benefit of evolocumab on revascularization was not associated with baseline LDL-C (dichotomized at 1.81 mmol/L [70 mg/dL]) but associations with lipoprotein(a) levels were not reported.

The effect of alirocumab on revascularization was manifested predominantly by fewer PCIs. The number of CABG procedures might have been too small to detect an effect of treatment. In fact, in the **F**urther Cardiovascular **Ou**tcomes **R**esearch With PCSK9 **I**nhibition in Subjects With **E**levated **R**isk (FOURIER) trial, with more patients who underwent CABG than in ODYSSEY OUTCOMES, there was a

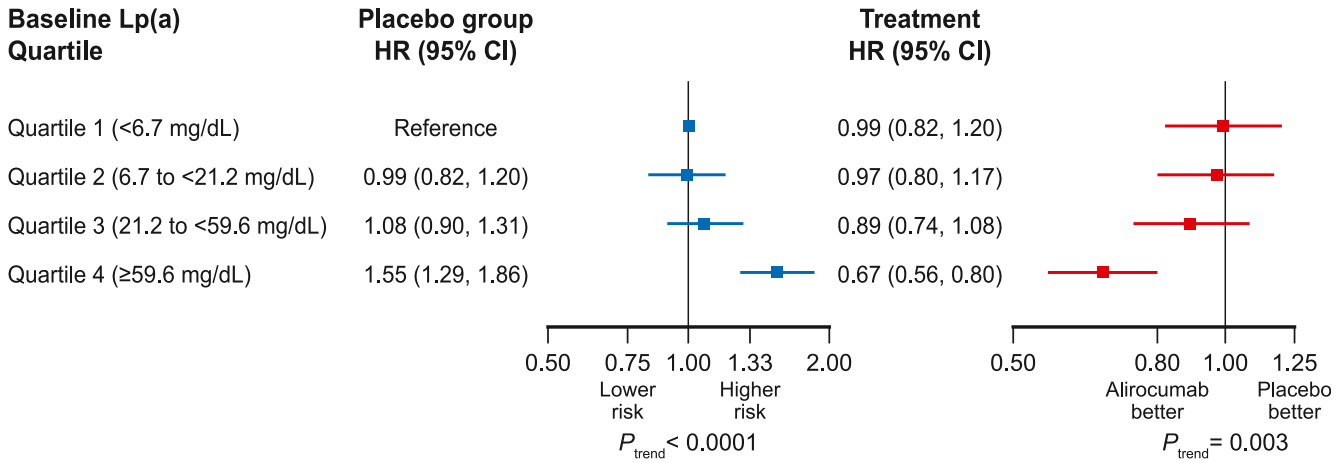

Figure 4. Relationship between baseline lipoprotein(a) quartile and first revascularization in the placebo group, and between baseline lipoprotein(a) quartile and benefit of alirocumab for first coronary, peripheral, and carotid revascularization. CI, confidence interval; HR, hazard ratio.

reduction in CABG with the PCSK9 inhibitor evolocumab[26] and in the Cholesterol Treatment Trialists' meta-analysis of LDL-lowering trials, there was a reduction in revascularization and specifically in PCI and CABG with statins.[27] Considering these previous observations, the lack of clear reduction in CABG with alirocumab in ODYSSEY OUTCOMES might reflect type II error.

Revascularization was the most frequent event at follow-up in ODYSSEY OUTCOMES,[2] an important cause of hospital readmission and a major driver of health care costs.[28,29] As such, reductions in the need for revascularization likely contribute to the cost-effectiveness of lipid-lowering therapies.

Strengths and Limitations

Strengths of this analysis include a large number of revascularizations in a diverse, international cohort, systematic measurement of lipoprotein(a) as well as the standard lipid profile, and rigourous adjudication of coronary revascularization with specific criteria for ischemia-driven revascularization, restenosis, and stent thrombosis. Total coronary revascularizations was a prespecified outcome in the statistical analysis plan, but should be interpreted conservatively because it was not included in the hierarchical analysis of secondary end points. Because of the potent LDL-C lowering effect of alirocumab, and its moderate lipoprotein(a) lowering effect, it is difficult to definitely ascertain the contribution of lipoprotein(a) lowering and LDL-C_{corr} lowering to the improved outcomes with alirocumab. Mediation analyses and, more importantly, future studies using specific and potent therapies to lower lipoprotein(a)[30] will help clarify the role of lipoprotein(a) lowering in the reduction of revascularization. Finally, the correction factor used to compute LDL-C_{corr} does not recognize interindividual variability, and the optimal correction factor remains debated.[31] Finally, we measured mass lipoprotein(a), which is influenced by apolipoprotein(a) isoform size. At high lipoprotein(a) mass, molar concentration is underestimated, and vice versa.[32] However, the magnitude of lipoprotein(a) lowering by alirocumab is not affected by apolipoprotein(a) size.[33,34]

Conclusions

In patients with recent ACS alirocumab reduced the risk of coronary, limb, or carotid revascularizations. Patients with elevated levels of lipoprotein(a) were at high risk for revascularization after ACS, and derived a substantial reduction in that risk with alirocumab use. Conversely, patients with low lipoprotein(a) appeared to derive minimal benefit of alirocumab on revascularization, despite substantial reductions in LDL-C. These observations have substantial implications for the cost-effectiveness of alirocumab, for our understanding of the pathogenic role of lipoprotein(a) in atherosclerosis, and potentially for the selection of the best candidates for therapy.

Table 3. Relationship between baseline lipoprotein(a) quartile and total ischemia-driven coronary, limb, and carotid revascularizations in the placebo group, and between baseline lipoprotein(a) quartile and benefit of alirocumab for total coronary, limb, and carotid revascularizations

Baseline lipoprotein(a) quartile	Placebo group HR (95% CI)	*P* trend	Treatment HR (95% CI)	*P* trend
Quartile 1 (< 6.7 mg/dL)	Reference	0.0002	0.93 (0.77-1.12)	0.03
Quartile 2 (6.7 to < 21.2 mg/dL)	0.99 (0.82-1.19)		0.91 (0.76-1.10)	
Quartile 3 (21.2 to < 59.6 mg/dL)	1.04 (0.86-1.25)		0.92 (0.76-1.10)	
Quartile 4 (≥ 59.6 mg/dL)	1.40 (1.17-1.67)		0.69 (0.59-0.82)	

CI, confidence interval; HR, hazard ratio.

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Ethics Statement

This study complies with the Declaration of Helsinki. All sites obtained ethics committee approval as per local and national guidelines.

Patient Consent

All patients provided written informed consent.

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Disclosures

See Supplemental Appendix S2 for a complete list of author disclosures.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2023.04.018.