BRIEF OBSERVATION

THE AMERICAN JOURNAL of MEDICINE®

Effect of Alirocumab on Incidence of Atrial Fibrillation After Acute Coronary Syndromes: Insights from the ODYSSEY OUTCOMES Trial

Renato D. Lopes, MD, PhD,[a] Patrícia O. Guimarães, MD,[b] Gregory G. Schwartz, MD, PhD,[c] Deepak L. Bhatt, MD, MPH,[d] Vera A. Bittner, MD, MSPH,[e] Andrzej Budaj, MD, PhD,[f] Anthony J. Dalby, MD,[g] Rafael Diaz, MD,[h] Shaun G. Goodman, MD,[i,j] Robert A. Harrington, MD,[k] J. Wouter Jukema, MD, PhD,[l,m] Robert Gabor Kiss, MD, PhD,[n] Megan Loy, BAppSc,[o] Robert Pordy, MD,[p] Yann Poulouin, MStat,[q] Michael Szarek, PhD,[r,s] Harvey D. White, DSc,[t] Philippe Gabriel Steg, MD[u,v], for the ODYSSEY OUTCOMES Investigators

[a]Duke University Medical Center, Duke Clinical Research Institute, Durham, NC; [b]Heart Institute, InCor, University of São Paulo Medical School, São Paulo, Brazil; [c]Division of Cardiology, University of Colorado School of Medicine, Aurora, Colo; [d]Brigham and Women's Hospital Heart & Vascular Center and Harvard Medical School, Boston, Mass; [e]University of Alabama at Birmingham, Birmingham, Ala; [f]Centre of Postgraduate Medical Education, Grochowski Hospital, Warsaw, Poland; [g]Life Fourways Hospital, Randburg, South Africa; [h]Estudios Cardiológicos Latin América, Instituto Cardiovascular de Rosario, Rosario, Argentina; [i]Canadian VIGOUR Centre, University of Alberta, Edmonton, Alta, Canada; [j]St. Michael's Hospital, University of Toronto, Toronto, Ont, Canada; [k]Stanford Center for Clinical Research, Department of Medicine, Stanford University, Stanford, Calif; [l]Leiden University Medical Center, Leiden, the Netherlands; [m]Netherlands Heart Institute, Utrecht, the Netherlands; [n]Military Hospital, Budapest, Hungary; [o]Sanofi, Bridgewater, NJ; [p]Regeneron Pharmaceuticals Inc., Tarrytown, NY; [q]IT&M Stats, Neuilly-sur-Seine, France; [r]Downstate School of Public Health, State University of New York, Brooklyn, NY; [s]CPC Clinical Research and Division of Cardiology, University of Colorado School of Medicine, Aurora, Colo; [t]Green Lane Cardiovascular Services, Auckland City Hospital, Auckland, New Zealand; [u]Université de Paris, Assistance Publique-Hôpitaux de Paris, Hôpital Bichat, FACT (French Alliance for Cardiovascular Trials), INSERM U1148, Paris, France; [v]National Heart and Lung Institute, Royal Brompton Hospital, Imperial College, London, UK.

ABSTRACT

BACKGROUND: Using data from the ODYSSEY OUTCOMES trial (NCT01663402), we sought to identify factors associated with the development of incident atrial fibrillation in patients with recent acute coronary syndrome without prior atrial fibrillation and to determine whether alirocumab treatment influenced risk of incident atrial fibrillation.

METHODS: ODYSSEY OUTCOMES compared alirocumab treatment with placebo in 18,924 patients with recent acute coronary syndrome and dyslipidemia despite high-intensity or maximum-tolerated statin therapy. The primary outcome of major adverse cardiovascular events (MACE) comprised death from coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization. Patients were classified as having previous atrial fibrillation (present prior to or at randomization) or no previous atrial fibrillation. A multivariable model was used to determine factors associated with incident atrial fibrillation.

RESULTS: Among 18,262 participants without prior atrial fibrillation at baseline, 499 (2.7%) had incident atrial fibrillation during follow-up. Older age, history of heart failure or myocardial infarction, and higher body mass index were significantly associated with incident atrial fibrillation. Treatment with alirocumab or placebo did not influence the cumulative incidence of atrial fibrillation (hazard ratio 0.91; 95% confidence interval, 0.77-1.09). Patients with vs without a history of atrial fibrillation had a higher incidence of MACE (8.8 vs 3.7 events per 100 patient-years), without significant interaction between atrial fibrillation and randomized treatment on risk of MACE ($P_{interaction}$ = .78).

CONCLUSIONS: While alirocumab did not modify risk of incident atrial fibrillation after acute coronary syndrome, it did reduce the risk of MACE, regardless of prior atrial fibrillation history. History of atrial fibrillation is an independent predictor of recurrent cardiovascular events after acute coronary syndrome.

 • The American Journal of Medicine (2022) 135:915–918

KEYWORDS: Acute coronary syndromes; Alirocumab; Atrial fibrillation

Funding: See last page of article.
Conflicts of Interest: See last page of article.
Authorship: See last page of article.

Requests for reprints should be addressed to Renato D. Lopes, MD, PhD, Duke Clinical Research Institute, 200 Morris Street, Durham, NC 27701.
E-mail address: renato.lopes@dm.duke.edu

https://doi.org/10.1016/j.amjmed.2022.02.016

INTRODUCTION

Proprotein convertase subtilisin−kexin type 9 (PCSK9) inhibitors promote substantial and sustained low-density lipoprotein cholesterol lowering and reduce cardiovascular events in high-risk patients treated with statins.[1,2] The ODYSSEY OUTCOMES trial compared treatment with the PCSK9 inhibitor, alirocumab, with placebo in 18,924 patients with recent acute coronary syndromes and residual dyslipidemia despite high-intensity or maximum-tolerated statin therapy.[1]

Atrial fibrillation is a marker of risk in patients presenting with acute coronary syndrome. An ongoing question has been whether lipid-lowering therapies, either directly or indirectly through prevention of ischemic cardiovascular events, reduce the incidence of atrial fibrillation. Analyses of statin trials have not provided consistent evidence of benefit,[3] and the potential effect of PCSK9 inhibition on the incidence of atrial fibrillation is unknown.

The current analysis determined: 1) factors associated with the development of incident atrial fibrillation in acute coronary syndrome patients without prior atrial fibrillation; 2) whether alirocumab treatment influenced incident atrial fibrillation; 3) whether a history of atrial fibrillation was associated with the risk of major adverse cardiovascular events (MACE); and 4) whether there was any interaction between prior history of atrial fibrillation and the effect of alirocumab on MACE.

CLINICAL SIGNIFICANCE

- Alirocumab treatment after acute coronary syndrome did not affect the incidence of atrial fibrillation.
- Alirocumab reduced the risk of major adverse cardiovascular events after acute coronary syndrome, irrespective of prior atrial fibrillation.
- A history of atrial fibrillation is an independent predictor of recurrent cardiovascular events after acute coronary syndrome.

METHODS

The randomized, double-blind, placebo-controlled ODYSSEY OUTCOMES trial (NCT01663402) compared the efficacy and safety of alirocumab vs placebo in 18,924 patients with recent acute coronary syndrome and elevated atherogenic lipoproteins despite high-intensity or maximum-tolerated statin treatment. Patients were randomly assigned to receive alirocumab or placebo beginning 1-12 months after acute coronary syndrome and were followed for a median of 2.8 years. The primary outcome of MACE comprised death from coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization.[1] Study participants were classified as having previous atrial fibrillation (present prior to or at randomization) or no previous atrial fibrillation. In the latter category, the incidence of atrial fibrillation after randomization was determined from investigator reports of adverse events. A multivariable model was used to determine factors associated with incident atrial fibrillation. Treatment hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for the primary outcome and selected secondary outcomes.

RESULTS

Overall, 662 patients (3.5%) had a history of atrial fibrillation at baseline and 18,262 (96.5%) had no history of atrial fibrillation. Patients with a history of atrial fibrillation were older than those without prior atrial fibrillation (mean [SD] age: 65.7 [9.2] vs 58.2 [9.1] years) and had a greater burden of comorbidities, including cerebrovascular disease (11.6% vs 4.7%), peripheral artery disease (7.9% vs 3.8%), hypertension (83.2% vs 63.6%), and heart failure (35.6% vs 13.8%).

Among participants without prior atrial fibrillation at baseline, 499 (2.7%) had incident atrial fibrillation during follow-up. Older age, history of heart failure or myocardial infarction, and higher body mass index were significantly associated with incident atrial fibrillation. Among the 18,894 patients who received at least one dose of study medication, treatment with alirocumab or placebo did not influence the cumulative incidence of atrial fibrillation (HR 0.91; 95% CI, 0.77-1.09; Figure).

Patients with vs without a history of atrial fibrillation had a higher incidence of MACE (8.8 vs 3.7 events per 100 patient-years), cardiovascular death (2.8 vs 0.9 events per 100 patient-years), myocardial infarction (5.8 vs 2.6 events per 100 patient-years), stroke (1.3 vs 0.5 events per 100 patient-years), all-cause death (4.0 vs 1.3 events per 100 patient-years), and hospitalization for atrial fibrillation (2.9 vs 0.6 events per 100 patient-years). There was no significant interaction between atrial fibrillation and randomized treatment on risk of MACE ($P_{\text{interaction}} = .78$): treatment HR in patients with atrial fibrillation at baseline, 0.81 (95% CI, 0.58-1.12) vs 0.85 (95% CI, 0.78-0.93) in the subgroup without atrial fibrillation at baseline.

DISCUSSION

Our findings confirm prior observations that patients with a history of atrial fibrillation have a higher risk of MACE after acute coronary syndrome.[4,5] Incident atrial fibrillation was associated with older age and a greater burden of cardiovascular comorbidities, but was not influenced by assignment to treatment with alirocumab or placebo despite the benefit of the former on MACE.

As this was a post hoc analysis, our results should be taken to be exploratory. Other limitations include the absence of protocol-specified periodic electrocardiograms or ambulatory electrocardiographic studies, and the absence of systematic adjudication of incident atrial fibrillation

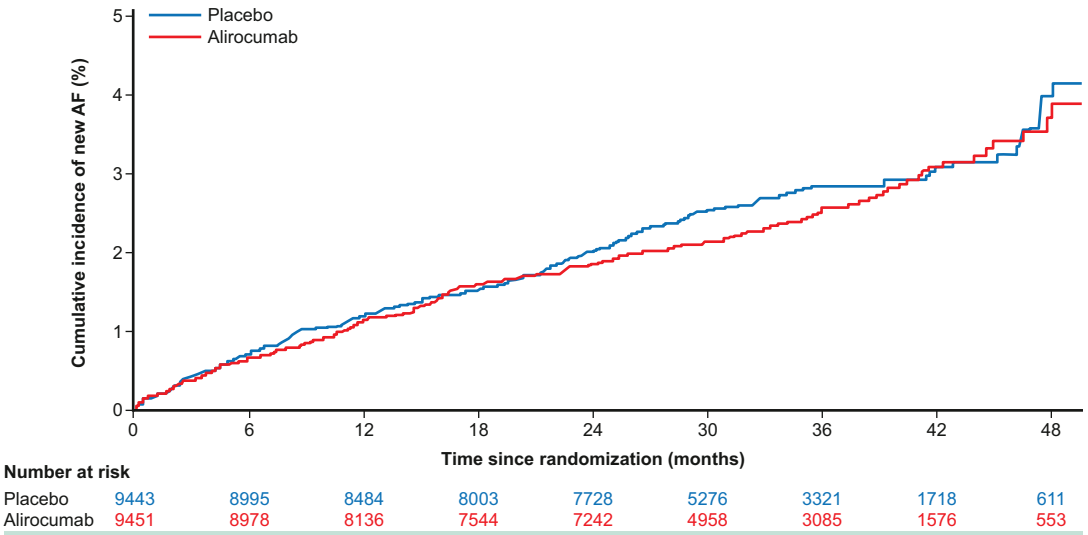

Figure Cumulative incidence of incident atrial fibrillation (AF) by randomized treatment in the safety population (18,894 patients). Hazard ratio 0.91; 95% confidence interval, 0.77-1.09.

events. Future studies with more rigorous atrial fibrillation ascertainment may be warranted.

In conclusion, history of atrial fibrillation is an independent predictor of recurrent cardiovascular events after acute coronary syndrome. While alirocumab did not modify the risk of incident atrial fibrillation after acute coronary syndrome, it did reduce the risk of MACE, regardless of prior atrial fibrillation history.

ACKNOWLEDGMENTS

Editorial support was provided by Sophie Rushton-Smith of Medlink Healthcare Communications, London, and was funded by Sanofi.

References

1. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;379(22):2097–107.
2. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376(18):1713–22.
3. Fang WT, Li HJ, Zhang H, Jiang S. The role of statin therapy in the prevention of atrial fibrillation: a meta-analysis of randomized controlled trials. *Br J Clin Pharmacol* 2012;74(5):744–56.
4. Guimarães PO, Peterson ED, Stevens SR, et al. Antithrombotic treatment gap among patients with atrial fibrillation and type 2 diabetes. *Int J Cardiol* 2019;289:58–62.
5. Lopes RD, Elliott LE, White HD, et al. Antithrombotic therapy and outcomes of patients with atrial fibrillation following primary percutaneous coronary intervention: results from the APEX-AMI trial. *Eur Heart J* 2009;30(16):2019–28.

Funding: This work was supported by Sanofi and Regeneron Pharmaceuticals.

Conflicts of Interest: RDL reports research support from Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, Pfizer; consulting fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Medtronic, Merck, Pfizer, and Portola. POG has no conflicts of interest to report. GGS reports research grants to the University of Colorado from Astra Zeneca, Resverlogix, Silence Therapeutics, Sanofi, and The Medicines Company; editorial support from Sanofi; research grants from the US Department of Veterans Affairs (VA); and is coinventor of pending US patent 62/806,313 ("Methods for Reducing Cardiovascular Risk") assigned in full to the University of Colorado. DLB reports grants from Sanofi and Regeneron during the conduct of the study; grants from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Sanofi Aventis, and The Medicines Company; other from FlowCo, grants and other from PLx Pharma, other from Takeda; personal fees from Duke Clinical Research Institute, Mayo Clinic, Population Health Research Institute; personal fees, non-financial support, and other from the American College of Cardiology; personal fees from Belvoir Publications, Slack Publications, WebMD, Elsevier, other from Medscape Cardiology, other from Regado Biosciences, other from Boston VA Research Institute, personal fees and non-financial support from the Society of Cardiovascular Patient Care, non-financial support from the American Heart Association, personal fees from HMP Global, grants from Roche, personal fees from Harvard Clinical Research Institute (now Baim Institute for Clinical Research), other from Clinical Cardiology, personal fees from the Journal of the American College of Cardiology, other from VA; grants from Pfizer, Forest Laboratories/AstraZeneca, and Ischemix, other from St. Jude Medical (now Abbott), other from Biotronik, grants and other from Cardax and Boston Scientific, grants from Amgen, Lilly, Chiesi, and Ironwood; personal fees from the Cleveland Clinic and Mount Sinai School of Medicine, other from Merck, grants from Abbott and Regeneron, other from Svelte, grants and other from PhaseBio, grants from Idorsia and Synaptic, personal fees from TobeSoft; grants, personal fees, and other from Boehringer Ingelheim, personal fees from Bayer, grants and other from Novo Nordisk, grants from Fractyl, personal fees from Medtelligence/ReachMD and CSL Behring, grants and other from Cereno Scientific, grants from Afimmune and Ferring Pharmaceuticals, other from CSI, grants from Lexicon, personal fees from MJH Life Sciences and Level Ex, grants from Contego Medical, grants and other from CellProthera, personal fees from K2P and the Canadian Medical and Surgical Knowledge Translation Research Group, grants and other from MyoKardia/BMS, grants from Owkin and HLS Therapeutics, grants and other from Janssen, grants from 89Bio, grants and other from Novo Nordisk, grants from Garmin, grants and other from Novartis, grants and other from NirvaMed, other from Philips, personal fees from Arnold and Porter law firm and Piper Sandler, grants from

Stasys, personal fees from Cowen and Company; grants from Faraday Pharmaceuticals, Javelin, Reid Hoffman Foundation, Moderna, Beren, Aker Biomarine, and Recardio; personal fees from DRS.LINQ, grants from Acesion Pharma, personal fees from Assistance Publique-Hôpitaux de Paris, outside the submitted work. VAB reports grant support from Sanofi, Regeneron Pharmaceuticals, Astra Zeneca, DalCor, Esperion, and Novartis; consulting fees from Pfizer; honoraria from Medscape; and fees for participating on a Data Safety Monitoring Board from the National Institutes of Health. AB reports personal fees and non-financial support from Sanofi Aventis, Bristol-Myers Squibb/Pfizer, Bayer, and AstraZeneca; personal fees from Eisai, Novartis, GlaxoSmithKline, Amgen, and Novo Nordisk. AJD reports consulting fees for Acino and Sanofi. RD reports research grants from Sanofi, DalCor Pharmaceuticals, Population Health Research Institute, Duke Clinical Research Institute, the TIMI group, Amgen, Cirius, Montreal Health Innovations Coordinating Center, and Lepetit; and personal fees, as a member of the Executive Steering Committee, from Amgen and Cirius. SGG reports research grant support (eg, steering committee or data and safety monitoring committee) and/or speaker/consulting honoraria (eg, advisory boards) from: Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CSL Behring, Daiichi-Sankyo/American Regent, Eli Lilly, Esperion, Ferring Pharmaceuticals, GlaxoSmithKline, HLS Therapeutics, JAMP Pharma, Janssen/Johnson & Johnson, Merck, Novartis, Novo Nordisk A/C, Pendopharm, Pfizer, Regeneron, Sanofi, Servier, and Valeo Pharma; and salary support/honoraria from the Heart and Stroke Foundation of Ontario/University of Toronto (Polo) Chair, Canadian Heart Research Centre and MD Primer, Canadian VIGOUR Centre, Cleveland Clinic Coordinating Centre for Clinical Research, Duke Clinical Research Institute, New York University Clinical Coordinating Centre, and PERFUSE Research Institute. RAH reports research grants (all data and safety monitoring board related) from AstraZeneca, Janssen, and Bristol-Myers Squibb, serving on advisory boards for Gilead (uncompensated) and WebMD; and serving on the boards of directors (unpaid) for the American Heart Association and Stanford HealthCare. JWJ reports research grants from the Netherlands Heart Foundation, the Interuniversity Cardiology Institute of the Netherlands, and the European Commission Seventh Framework Programme; and research support from Amgen, Astellas, AstraZeneca, Daiichi- Sankyo, Lilly, Merck-Schering-Plough, Pfizer, Roche, and Sanofi. RGK reports none. ML is an employee of Sanofi. RP is an employee of Regeneron Pharmaceuticals. YP is an IT&M Stats employee, and IT&M Stats reports consultancy fees from Sanofi. MS reports serving as a consultant or on advisory boards (or both) for CiVi, Resverlogix, Baxter, Esperion, Sanofi, and Regeneron Pharmaceuticals, Inc. HDW reports grant support paid to the institution for serving on a Steering Committee for the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) from Sanofi-Aventis and Regeneron Pharmaceuticals, for the ACCELERATE study (A Study of Evacetrapib in High-Risk Vascular Disease) from Eli Lilly and Company, for the STRENGTH trial (Outcomes Study to Assess Statin Residual Risk Reduction With EpaNova in High CV Risk Patients With Hypertriglyceridemia) from Omthera Pharmaceuticals, for the CAMELLIA-TIMI study (A Study to Evaluate the Effect of Long-term Treatment With BELVIQ [Lorcaserin HC] on the Incidence of Major Adverse Cardiovascular Events and Conversion to Type 2 Diabetes Mellitus in Obese and Overweight Subjects With Cardiovascular Disease or Multiple Cardiovascular Risk Factors) from Eisai Inc, for the HEART-FID study (Randomized Placebo-Controlled Trial of FCM as Treatment for Heart Failure With Iron Deficiency) from American Regent, and for the ISCHEMIA Trial (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) and the MINT Trial (Myocardial Ischemia and Transfusion) from the National Institutes of Health USA; he also received grants to the institution and personal fees as Steering Committee member for the dal-GenE study (Effect of Dalcetrapib vs Placebo on CV Risk in a Genetically Defined Population With a Recent ACS) from DalCor Pharma UK Inc, for the AEGIS-II study (The Safety and Tolerability of CSL112, a Reconstituted, Infusible, Plasma-Derived Human ApoA-I, After Acute Myocardial Infarction: The ApoA-I Event reducinG in Ischemic Syndromes I) from CSL Behring, for the SCORED trial (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk) and the SOLOIST-WHF trial (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type2 Diabetes Post Worsening Heart Failure) from Sanofi-Aventis Australia Pty Ltd, and for the CLEAR Outcomes Study (Evaluation of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With Bempedoic Acid [ETC-1002] or Placebo) from Esperion Therapeutics Inc.; he was on the Advisory Boards for CSL Behring and Genentech, Inc. (an affiliate of F. Hoffmann-La Roche Ltd, "Roche"; Lytics Post-PCI Advisory Board at European Society of Cardiology. PGS reports grants, personal fees, and non-financial support from Sanofi; grants and personal fees from Amarin, Servier, and Bayer; personal fees from Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Idorsia, Pfizer, and Novartis. In addition, he has a patent use of alirocumab to reduce risk after ACS (royalties to Sanofi) pending.

Authorship: All authors had access to the data and a role in writing the manuscript. RDL: Conceptualization, methodology, investigation, writing - original draft, visualization; POG: Conceptualization, methodology, writing - review & editing, visualization; GGS: Methodology, investigation, writing - review & editing, supervision, project administration, funding acquisition; DLB: Investigation, writing - review & editing; VAB: Investigation, writing - review & editing; AB: Investigation, writing - review & editing; AJD: Investigation, writing - review & editing; RD: Investigation, writing - review & editing; SGG: Investigation, writing - review & editing; RAH: Investigation, writing - review & editing; JWJ: Investigation, writing - review & editing; RGK: Investigation, writing - review & editing; ML: Investigation, resources, writing - review & editing; RP: Investigation, resources, writing - review & editing; YP: Formal analysis, data curation, writing - review & editing; MS: Methodology, formal analysis, data curation; HDW: Investigation, investigation, writing - review & editing; PGS: Methodology, investigation, writing - review & editing, supervision, project administration, funding acquisition.