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BRIEF REPORT

Lipoprotein(a) Levels and Time to Cardiovascular Benefit With Alirocumab in Patients With Recent Acute Coronary Syndrome

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Patients with acute coronary syndromes (ACS) are at high risk of further cardiovascular events, despite current evidence-based therapies, thus indicating a need for additional treatments. Lipoprotein(a), a persistent cardiovascular risk factor,[1] appears to modify the cardiovascular benefit of proprotein convertase subtilisin/kexin type 9 (PCSK9)-directed monoclonal antibodies (MAbs), with greater relative and absolute reductions in major adverse cardiovascular events (MACE) and major adverse limb events (MALE) over 2 to 5 years' treatment when lipoprotein(a) is elevated.[2-4] From both patient and physician perspectives, a relevant question is how soon after initiating a PCSK9 MAb may such an augmented benefit appear?

To address this question, we assessed the time to benefit of alirocumab on MACE and MALE after ACS according to baseline lipoprotein(a) level in a post hoc analysis of the ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; NCT01663402) trial,[5] which received Institutional Review Board approval in each participating country and included 18,924 patients with elevated lipids despite statin therapy, randomized 1 to 12 months after ACS to alirocumab or placebo subcutaneously every 2 weeks. In this analysis, patients were dichotomized by baseline lipoprotein(a) ≥30 mg/dL (n = 8,051) vs <30 mg/dL (n = 10,873) or ≥50 mg/dL (n = 5,709) vs <50 mg/dL (n = 13,215). A level of 30 mg/dL is an inflection point for cardiovascular risk[1] and is considered the upper limit of normal, whereas 50 mg/dL is considered a threshold for risk enhancement in current guidelines.[6] Treatment HRs with 95% CIs for MACE (cardiovascular death, myocardial infarction, fatal or nonfatal ischemic stroke, unstable angina, or ischemia-driven coronary revascularization) and MALE (critical limb ischemia, revascularization, or amputation for ischemia) were estimated from proportional hazards models with

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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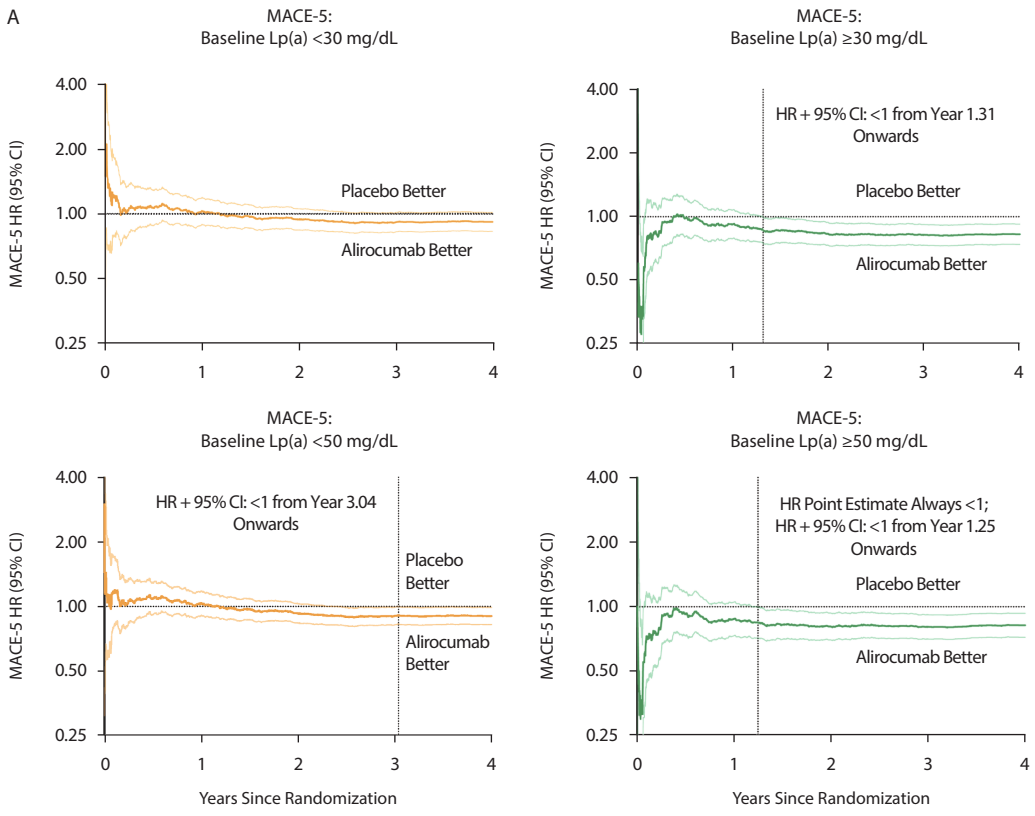
FIGURE 1 Time to Benefit of Alirocumab Treatment in Patients With a Recent Acute Coronary Syndrome



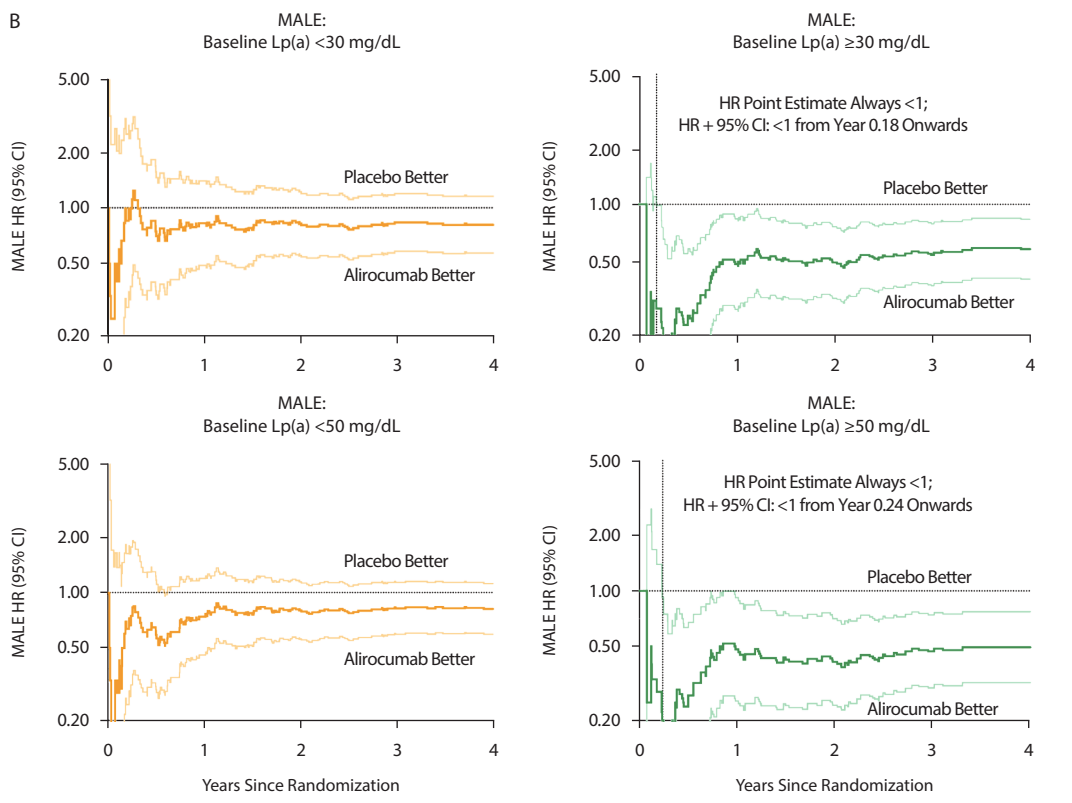
Time-varying treatment HRs for alirocumab vs placebo are shown for (A) major adverse cardiovascular events (MACE, cardiovascular death, myocardial infarction, fatal or nonfatal ischemic stroke, unstable angina, or ischemia-driven coronary revascularization) and (B) major adverse limb events (MALE, critical limb ischemia, revascularization, or amputation for ischemia) for patients with lipoprotein(a) (Lp[a]) levels dichotomized at 30 mg/dL and at 50 mg/dL. Time to benefit was defined as the time after randomization at which the estimated HR + 95% CI remained <1 for all subsequent time. The data suggest earlier time to benefit with alirocumab for MACE and MALE among patients with higher versus lower Lp(a). In addition, overall treatment HRs were more robust with higher Lp(a) levels. For MACE, HRs were 0.82 (95% CI: 0.74-0.92) and 0.92 (95% CI: 0.83-1.02) for Lp(a) ≥30 mg/dL vs <30 mg/dL, respectively, and 0.82 (95% CI: 0.72-0.93) and 0.91 (95% CI: 0.83-0.99) for Lp(a) ≥50 mg/dL vs <50 mg/dL, respectively. Similarly, MALE treatment HRs were 0.57 (95% CI: 0.40-0.83) and 0.83 (95% CI: 0.58-1.17) for Lp(a) ≥30 mg/dL vs <30 mg/dL, respectively, and 0.50 (95% CI: 0.32-0.77) and 0.83 (95% CI: 0.60-1.13) for Lp(a) ≥50 mg/dL vs <50 mg/dL, respectively.

Continued on the next page

truncated follow-up[7] for successive days after randomization (eg, the day 14 model included events through day 14, with follow-up beyond day 14 censored) and plotted in each lipoprotein(a) category. Time to benefit was determined as the day after randomization where the treatment HR and 95% CI remained <1 for all subsequent days, without correction for multiple comparisons. Analogous methods have been applied to other trials.[7]

At baseline, the mean age was 58 years, and 89% of patients received high-intensity statin treatment. Low-density lipoprotein cholesterol (LDL-C) and lipoprotein(a) were well balanced between treatment groups. In the <30 mg/dL lipoprotein(a) stratum, median (Q1-Q3) baseline LDL-C and lipoprotein(a) levels were 85 mg/dL (Q1-Q3: 71-102 mg/dL) and 8 mg/dL (Q1-Q3: 2-15 mg/dL), respectively. At 4 months, LDL-C and lipoprotein(a) reductions were −54 mg/dL (Q1-Q3: −70 to −37 mg/dL) and −2.5 mg/dL (Q1-Q3: −6.3 to 0 mg/dL) with alirocumab and 0 mg/dL (Q1-Q3: −13 to 14 mg/dL) and 0 mg/dL (Q1-Q3: −2.1 to 1.5 mg/dL) with placebo.

FIGURE 1 Continued



In the ≥30 mg/dL lipoprotein(a) stratum, baseline LDL-C and lipoprotein(a) were 89 mg/dL (Q1-Q3: 76-107 mg/dL) and 67 mg/dL (Q1-Q3: 47-99 mg/dL). At 4 months, LDL-C and lipoprotein(a) reductions were −53 mg/dL (Q1-Q3: −71 to −36 mg/dL) and −14.9 mg/dL (Q1-Q3: −26.5 to −4.6 mg/dL) with alirocumab and 1 mg/dL (Q1-Q3: −11 to 14 mg/dL) and −2.8 mg/dL (Q1-Q3: −12.6 to 7 mg/dL) with placebo.

In the <50 mg/dL lipoprotein(a) stratum, baseline LDL-C and lipoprotein(a) were 85 mg/dL (Q1-Q3: 71-102 mg/dL) and 11 mg/dL (Q1-Q3: 4-24 mg/dL), respectively. At 4 months, LDL-C and lipoprotein(a) reductions were −54 mg/dL (Q1-Q3: −70 to −36 mg/dL) and −3.1 mg/dL (Q1-Q3: −7.9 to 0 mg/dL) with alirocumab and 0 mg/dL (Q1-Q3: −13 to 14 mg/dL) and 0 mg/dL (Q1-Q3: −2.6 to 2.1 mg/dL) with placebo. In the ≥50 mg/dL lipoprotein(a) stratum, baseline LDL-C and lipoprotein(a) were 90 mg/dL (Q1-Q3: 77-109 mg/dL) and 84 mg/dL (Q1-Q3: 64-113 mg/dL). At 4 months, LDL-C and lipoprotein(a) reductions were −54 mg/dL (Q1-Q3: −71 to −37 mg/dL) and −18.2 mg/dL (Q1-Q3: −31.5 to −6.7 mg/dL) with alirocumab and 1 mg/dL (Q1-Q3: −11 to 14 mg/dL) and −4.1 mg/dL (Q1-Q3: −15.4 to 7.4 mg/dL) with placebo.

Throughout a median 2.8 years of follow-up, there were 2,775 MACE and 246 MALE, and treatment HRs were more robust for the higher lipoprotein(a) categories (**Figures 1A and 1B**). For MACE, **Figure 1A** shows that the treatment HR and 95% CI were <1 from 1.31 and 1.25 years onward in patients with lipoprotein(a) ≥30 and ≥50 mg/dL, respectively. For patients with baseline lipoprotein(a) <30 or <50 mg/dL, treatment HR and 95% CI were never <1, or they took 3.04 years to remain <1, respectively. Because women have higher lipoprotein(a) levels than men, we assessed the 3-way interaction of treatment*sex*lipoprotein(a) strata on MACE and found none.

Figure 1B shows analogous data for MALE. In patients with lipoprotein(a) ≥30 or ≥50 mg/dL, treatment HR and 95% CI for MALE remained <1 from 0.18 and 0.24 years onward, respectively. In contrast, treatment HR and 95% CI for MALE were

never <1 in patients with baseline lipoprotein(a) <30 or <50 mg/dL.

Thus, in patients with ACS and lipoprotein(a) levels ≥30 or ≥50 mg/dL, alirocumab treatment appeared to be associated with earlier and greater relative risk reductions for MACE and MALE than in patients with lower lipoprotein(a) levels. These post hoc observations have several potential clinical implications.

First, the data support recent guidelines that consider lipoprotein(a) ≥50 mg/dL a risk-enhancing factor warranting consideration of intensified lipid-lowering therapy, including addition of a PCSK9 inhibitor to statin therapy. Second, cardiovascular risk following ACS is nonlinear, with higher risk in the first 6 to 12 months and lower risk thereafter. Consequently, early initiation of PCSK9 inhibition after ACS may be particularly useful in patients with elevated lipoprotein(a) to mitigate risk when it is highest. Third, LDL-C reductions with alirocumab were similar in each lipoprotein(a) stratum, so shorter time to benefit among those patients with elevated lipoprotein(a) is not explained by differential LDL-C lowering.

The current data do not reveal whether earlier and greater risk reduction by alirocumab in the presence of elevated lipoprotein(a) is the result of the modest reduction in circulating lipoprotein(a) levels or whether elevated lipoprotein(a) is a marker for atherosclerotic plaques amenable to rapid stabilization by PCSK9 inhibition. The latter concept is suggested by recent imaging data indicating that patients with high lipoprotein(a) levels have high-risk coronary plaque characteristics, even when LDL-C levels are controlled.[8-10] Notably, only approximately one-half of the patients with lipoprotein(a) ≥30 or ≥50 mg/dL would have met qualification thresholds for ongoing lipoprotein(a)-lowering ongoing outcomes trials.[7] Future studies may determine whether patients currently considered to have mildly to moderately elevated lipoprotein(a) benefit from lipoprotein(a) lowering.

Study limitations include post hoc analyses; hence, findings must be considered exploratory. Because the patient group was unselected for high lipoprotein(a), few patients had very high lipoprotein(a). The patient group was unselected for peripheral artery disease; therefore, there were relatively few MALE, and early benefit on MALE should be interpreted with caution. Furthermore, differences in group sample sizes by lipoprotein(a) cutoffs may affect the power within individual groups to assess outcomes Finally, we did not account for multiple comparisons that could inflate the possibility of a type 1 error.

In conclusion, PCSK9 inhibition with alirocumab was associated with an earlier time to benefit for MACE and MALE in patients with elevated lipoprotein(a), observations warranting prospective confirmation.

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GlaxoSmithKline, Hims, SERB, SFJ, Summa Therapeutics, and Worldwide Clinical Trials; has served on data monitoring committees for Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research, Boston Scientific (Chair, PEITHO trial), Cleveland Clinic, Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ABILITY-DM trial, funded by Concept Medical; for ALLAY-HF, funded by Alleviant Medical), Novartis, Population Health Research Institute, and Rutgers University (for the National Institutes of Health–funded MINT Trial); has received honoraria from the American College of Cardiology (ACC; Senior Associate Editor, *Clinical Trials and News*; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, *Harvard Heart Letter*), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), CSL Behring (American Heart Association lecture), Duke Clinical Research Institute, Engage Health Media, HMP Global (Editor in Chief, *Journal of Invasive Cardiology*), Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Oakstone CME (Course Director, Comprehensive Review of Interventional Cardiology), Philips (Becker's Webinar on artificial intelligence), Population Health Research Institute, WebMD (CME steering committees), Wiley (steering committee); has served as Deputy Editor for *Clinical Cardiology* and *Progress in Cardiovascular Diseases;* has been named on a patent for sotagliflozin assigned to Brigham and Women's Hospital, which assigned it to Lexicon (neither he nor Brigham and Women's Hospital receive any income from this patent); has received research funding from Abbott, Acesion Pharma, Afimmune, Alnylam, Amarin, Amgen, AstraZeneca, Atricure, Bayer, Boehringer Ingelheim, Boston Scientific, CellProthera, Cereno Scientific, Chiesi, Cleerly, CSL Behring, Faraday Pharmaceuticals, Fractyl, Idorsia, Janssen, Javelin, Lexicon, Lilly, Medtronic, Merck Sharp & Dohme, MiRUS, Moderna, Novartis, Novo Nordisk, Pfizer, PhaseBio, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, 89Bio; has received royalties from Elsevier (Editor, *Braunwald's Heart Disease*); and has served as site coinvestigator for Cleerly. 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Dr Goodman has received research grant support (eg, steering committee or data safety monitoring board membership) or speaker or consulting honoraria (eg, advisory board membership) from Amgen, Anthos Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CSL Behring, Daiichi-Sankyo/American Regent, Lilly, Esperion, Ferring Pharmaceuticals, HLS Therapeutics, JAMP Pharma, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pendopharm/Pharmascience, Pfizer, Regeneron, Sanofi, Servier, and Valeo Pharma; and has received salary support or 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 Center for Clinical Research, Duke Clinical Research Institute, New York University Clinical Coordinating Centre, PERFUSE Research Institute, and the TIMI Study Group (Brigham Health). Dr Harrington has served on data safety monitoring boards for the Baim Institute, Colorado Prevention Center Clinical Research, and Merck/BWH; has a research relationship through randomized controlled trials with Edwards Lifesciences and Janssen; has served as a consultant for Atropos Health, Basking Biosciences, Bitterroot Bio, BridgeBio Pharma, Corsera Health, Element Science, HeartBeam, Medscape/WebMD; and has served on the Board of Directors of the American Heart Association, Cytokinetics, and Marea Therapeutics. Dr Jukema's department has received research grants from and/or was speaker (with or without lecture fees) on (CME accredited) meetings sponsored or supported by Abbott, Amarin, Amgen, Athera, Biotronik, Boston Scientific, Dalcor, Daiichi-Sankyo, Edwards Lifesciences, GE Healthcare Johnson and Johnson, Lilly, Medtronic, Merck-Schering-Plough, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Shockwave Medical, the Netherlands Heart Foundation, CardioVascular Research the Netherlands, the Netherlands Heart Institute, and the European Community Framework KP7 Program. 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