JACC: ADVANCES VOL. 2, NO. 9, 2023

ORIGINAL RESEARCH

OUTCOMES AND QUALITY

Sex Differences in Cardiovascular Outcomes and Cholesterol-Lowering Efficacy of PCSK9 Inhibitors

Systematic Review and Meta-Analysis

Frederick Berro Rivera, MD,[a] Sung Whoy Cha, MD,[b] John Paul Aparece, MD,[c] Aubrey Rocimo, MD,[d] Bradley Ashley Ong, MD,[d] Jem Marie Golbin, MD,[d] Pia Gabrielle Alfonso, MD,[d] Byambaa Enkhmaa, MD, PhD, MAS,[e] Safi U. Khan, MD, MS,[f] Miguel Cainzos-Achirica, MD, MPH, PhD,[g] Annabelle Santos Volgman, MD,[h] Ann Marie Navar, MD, PhD,[i] Nishant P. Shah, MD[j]

ABSTRACT

BACKGROUND Guideline-recommended low-density lipoprotein cholesterol (LDL-C) thresholds are often not achieved in women. The proprotein convertase subtilisin/kexin type-9 inhibitor (PCSK9i) monoclonal antibodies can help further reduce LDL-C and major adverse cardiovascular events (MACE) although differences in efficacy by sex and type are less understood.

OBJECTIVES The authors sought to determine if there are differences in the efficacy of LDL-C lowering and reduction in the risk of MACE by sex and type of PCSK9i.

METHODS A comprehensive literature search was done through October 17, 2022, for published trials comparing PCSK9i vs control. Outcomes assessed were LDL-C reduction and incidence of MACE following the use of PCSK9i vs placebo, stratified by sex and type of PCSK9i used.

RESULTS We identified 16 trials with 54,996 adults, and 15,143 (27.5%) of them were female. PCSK9i significantly reduced MACE compared to placebo in both women (HR: 0.86, 95% CI: 0.74-0.97, $P < 0.001$) and men (HR: 0.85, 95% CI: 0.79-0.91, $P < 0.001$) with no significant sex difference (MD −0.01, 95% CI: −0.14 to −0.13, $P = 0.930$). PCSK9i also significantly reduced LDL-C levels in both sexes at 12 weeks (females: MD −62.57, 95% CI: −70.24 to −54.91, $P < 0.001$; males: MD −66.19, 95% CI: −72.03 to −60.34, $P < 0.001$) and 24 weeks (females: MD −47.52, 95% CI: −52.94 to −42.09, $P < 0.001$; males: MD −54.07, 95% CI: −59.46 to −48.68, $P < 0.001$). Significant sex difference was seen in the LDL reduction of PCSK9i for both 12 weeks (males vs females: MD −4.55, 95% CI: −7.34 to −1.75, $P < 0.01$) and 24 weeks (males vs females: MD −7.11, 95% CI: −9.99 to −4.23, $P < 0.001$).

CONCLUSIONS The use of PCSK9i results in significant LDL-C and MACE reduction in both males and females. While there is no significant sex difference in MACE reduction, LDL-C reduction is greater in males than in females. Our data support the equal use of PCSK9i in all eligible patients, regardless of sex. (JACC Adv 2023;2:100669)

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2023.100669

ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

LDL-C = low-density lipoprotein cholesterol

MACE = major adverse cardiovascular events

MD = mean difference

MI = myocardial infarction

PCSK9i = proprotein convertase subtilisin/kexin type-9 inhibitor

RCT = randomized controlled trial

Elevated low-density lipoprotein cholesterol (LDL-C) level is a principal risk factor for atherosclerotic cardiovascular disease and a primary target for preventive therapies.[1] Although statins are the first-line lipid-lowering agents for reducing the risk of atherosclerotic cardiovascular disease, high residual risk remains a concern in many statin-treated patients.[2] The proprotein convertase subtilisin/kexin type-9 inhibitors (PCSK9i) are highlighted in the 2022 American College of Cardiology Expert Consensus Decision Pathway as adjunctive therapies to statins to be used sooner in high-risk patients to help achieve lower LDL-C goals.[3] Alirocumab and evolocumab are monoclonal antibody PCSK9is approved by the United States Food and Drug Administration in 2015. In addition to statins, these agents led to dose-dependent reductions in LDL-C levels by up to 60% in clinical trials.[2] For high-risk patients on maximum statin therapy or who are statin intolerant, these agents also reduce nonfatal myocardial infarction (MI) and stroke.[4] What is unclear is if there are differences in PCSK9i efficacy between sex and type of agent.[5] Moreover, females remain consistently underrepresented in lipid-lowering therapy trials.[6] Thus, this meta-analysis of randomized controlled trials (RCTs) was done to assess for any differences in the efficacy of LDL-C lowering and major adverse cardiovascular events (MACEs) reduction with PCSK9i between males and females and by type of PCSK9i.

METHODS

This study was reported under the Preferred Reporting Items for a Review and Meta-Analysis (PRISMA), and the checklist was followed[7] (Supplemental Figure 1, Supplemental Table 1). Certainty of evidence was rated using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) framework.[7,8] This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO),[9] with the identification number CRD42023388794.

DATA SOURCES AND SEARCHES. The literature search was performed using PubMed/MEDLINE, Ovid/Embase, and Google Scholar databases from database inception until October 17, 2022. Search terms included "PCSK9 inhibitor", "PCSK9 antibody", "Evolocumab", "Alirocumab", "Bococizumab", "AMG145", "Repatha", "REGN727", "SAR236553", "RN 316", "PF-04950615", and synonyms. PCSK9is that are not monoclonal antibodies, such as inclisiran, were not included. Citations of selected articles and any relevant studies that evaluated MACE and LDL-C lowering using PCSK9is were reviewed. After removing duplicates, records were reviewed at the title and abstract level, followed by the screening of full text based on our study criteria.

STUDY SELECTION. Eligible trials included only published articles comparing treatment with PCSK9is and control in adult patients aged 18 years or older. Trials were required to evaluate PCSK9is as medication versus placebo, ezetimibe, or usual care (fenofibrate; omega-3 fatty acid; nicotinic acid) with or without statin therapy. In addition, the studies must have reported at least one of the 2 outcomes: LDL-C reduction or MACE. Studies were excluded if they did not report a control arm or lacked sex-stratified analyses. We excluded RCTs with participants younger than 18 years and those reporting interim or post hoc analysis. Cross-over trials were also excluded due to the nature of the outcomes considered. Review articles, case reports, letters to the editor, commentaries, proceedings, laboratory studies, and other nonrelevant studies were excluded. No language restrictions were imposed.

DATA EXTRACTION. Key participant and intervention characteristics and reported data on efficacy outcomes were extracted independently by 2

From the [a]Department of Medicine, Lincoln Medical Center, Bronx, New York, USA; [b]Department of Medicine, Cebu Institute of Medicine, Cebu City, Cebu, Philippines; [c]Department of Internal Medicine, Texas Tech University Health Sciences Center El Paso, El Paso, Texas, USA; [d]Department of Medicine, University of the Philippines System, Manila, National Capital Region, Philippines; [e]Section of Endocrinology, Diabetes & Metabolism, UC Davis Health Systems, Davis, California, USA; [f]Department of Cardiology, Houston Methodist DeBakey Heart & Vascular Center, Houston, Texas, USA; [g]Cardiólogo y epidemiólogo cardiovascular, Hospital del Mar/Parc de Recerca Biomèdica de Barcelona, Barcelona, Spain; [h]Division of Cardiology, Rush University Medical Center, Chicago, Illinois, USA; [i]Department of Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA; and the [j]Division of Cardiology, Duke University Medical Center, Durham, North Carolina, USA.
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.

Manuscript received March 9, 2023; revised manuscript received July 31, 2023, accepted August 26, 2023.

investigators (S.W.C. and J.P.A.) using standard data-extraction templates. Any disagreements were resolved by discussion or, if required, by a third author (F.B.R.). Data on the following variables were extracted: first author's name, year of publication, journal, study phase, interventional and control treatments, randomization method, analysis tool, number of randomized patients, and demographic and clinical data (eg, age, sex). In case of uncertainties regarding the study data, we contacted the authors of the specific study for additional information.

OUTCOME MEASURES. Outcomes assessed in this study were: 1) LDL-C-lowering effects of PCSK9i measured as percent change from baseline; and 2) incidence of MACE following the use of PCSK9i vs control, stratified by sex. MACE was defined as a composite of cardiovascular death, MI, stroke, or coronary revascularization. For FOURIER trial (Sabatine et al[10]), the primary efficacy endpoint was the composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. The median duration of follow-up was 2.2 years. Sabatine et al[10] used HR and estimated the risks in males and females separately. For the ODYSSEY trial (Schwartz et al[11]), the primary endpoint was a composite of death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. The median duration of follow-up was 2.8 years. The investigators also used HR and estimated the risks in males and females separately. In addition, subgroup analyses were performed for applicable studies stratified by sex on: 1) type of PCSK9i; and 2) LDL-C-lowering effect of PCSK9i vs ezetimibe.

BIAS ASSESSMENT. All included studies reported a central randomization process, and outcomes were objectively determined. The included studies reported all primary and secondary outcomes as prespecified in their protocols, so the risk of bias for selective reporting was judged as low. Two authors (S.W.C. and J.P.A.) independently assessed the risk of bias based on the Cochrane Risk of Bias Tool (Supplemental Figures 2 and 3) for studies that fulfilled the inclusion criteria. Disagreements between the 2 reviewers were resolved by consensus. In case of persistent disagreement, arbitration by a third reviewer (F.B.R.) was performed.

STATISTICAL ANALYSIS. RevMan version 5.4 and Stata version 17.0 were used to conduct the included studies' meta-analysis, heterogeneity tests, and sensitivity analyses. For all outcomes, the significance level was set at a P value of <0.05. Statistical heterogeneity was identified through the forest plots and a standard chi-square test with a significant level of $P < 0.10$. The extent of heterogeneity was based on the I^2 statistic, wherein a value of more than 50% was interpreted as substantial heterogeneity. We pooled all estimates using a random effects model. We measured HR and mean differences (MD) with 95% CIs. Prespecified subgroup analyses were performed according to the type of PCSK9i and PCSK9i vs ezetimibe.

RESULTS

A literature search through October 17, 2022, yielded 1,183 potentially relevant references on PCSK9i therapy (Supplemental Figure 1). Of these, 229 duplicates were removed. A total of 908 studies with unrelated interventions, outcomes, populations, nonoriginal data (eg, meta-analysis or review), descriptive or observational study design, and study protocols were excluded. A total of 46 studies were left, and 30 pooled analyses were removed for not meeting the eligibility criteria. The remaining 16 related studies were retrieved as full-text publications for detailed evaluation. Overall, 16 studies were included in the final meta-analysis. From the 16 studies, 54,996 eligible individuals were included for analysis, among which 15,143 or 27.5% were females. The total percentage of females in each study ranged from 17.4% to 66.4%. **Table 1** includes study characteristics and sex distribution.

LDL-C REDUCTION AT 12 AND 24 WEEKS. Four studies[12-15] reported percentage changes in LDL-C after 12 weeks of PCSK9i versus control and their corresponding MD. All 4 studies reported significantly decreased LDL-C levels after 12 weeks of PCSK9i therapy in both sexes (females: MD −62.57, 95% CI: −70.24 to −54.91, $P < 0.001$ [**Figure 1A**]; males: MD −66.19, 95% CI: −72.03 to −60.34, $P < 0.001$ [**Figure 1B**]), with an overall greater reduction in males than in females (males vs females: MD −4.55, 95% CI: −7.34 to −1.75, $P < 0.01$, [**Figure 1C**]). Eight studies[16,17-23] reported percentage changes in LDL-C after 24 weeks of PCSK9i versus control and their corresponding MD. All 8 studies reported significantly decreased LDL-C levels after 24 weeks of PCSK9i therapy in both sexes (females: MD −47.52, 95% CI: −52.94 to −42.09], $P < 0.001$ [**Figure 2A**]; males: MD −54.07, 95% CI: −59.46 to −48.68, $P < 0.001$ [**Figure 2B**]) with an overall greater reduction in males than in females (males vs females: MD −7.11, 95% CI: −9.99 to −4.23, $P < 0.001$ [**Figure 2C**]).

JACC: ADVANCES, VOL. 2, NO. 9, 2023
NOVEMBER 2023:100669

TABLE 1 Characteristics of Included Studies

First Author, Year	Population	N	Women (%)	Intervention	Control	Outcome	LDL-C Reductions From Baseline
Bays et al, 2015[23]	Patients with very high CVD risk and LDL-C levels of ≥70 mg/dL or high CVD risk and LDL-C of ≥100 mg/mL	355	34.9%	Alirocumab plus Atorvastatin	Ezetimibe, doubling atorvastatin dose, or switching to rosuvastatin	Percent change in LDL-C from baseline to week 24	Add-on alirocumab reduced LDL-C levels by 44.1% and 54.0%, respectively
Boccara et al, 2020[17]	PLHIV and hypercholesterolemia/ mixed dyslipidemia taking maximally tolerated statin therapy	467	17.4%	Evolocumab	Placebo	Percent change in LDL-C from baseline to week 24	56.9% in evolocumab vs placebo
Cannon et al, 2015[24]	Patients with high cardiovascular risk and elevated LDL-C despite maximal doses of statins	720	26.4%	Alirocumab	Ezetimibe	Percent change in LDL-C from baseline to week 24	50.6% in the alirocumab arm
Chen et al, 2019[12]	Patients with T2DM and dyslipidemia on background statin	451	51.0%	Evolocumab	Placebo	Percent change in LDL-C from baseline to week 12	73% vs 12% in the alirocumab 140Q2W vs placebo arm, respectively, 65.4% vs 8.4% in the alirocumab 420OQ2W vs placebo arm, respectively
Giugliano et al, 2012[13]	Patients with history of hypercholesterolemia and fasting LDL-C ≥2.2 mmol/L on stable dose of statin for ≥4 wk	1,262	25.4%	Evolocumab	Placebo	Percent change in LDL-C from baseline to week 12	41.8%, 60.2%, 66.1%, 41.8%, 50%, and 50.3% in evolocumab 70/105/140 mg biweekly, 280/350/ 420 mg monthly vs placebo
Kastelein et al, 2015[20]	HeFH patients without a history of CV events and those who suffered an MI or ischemic stroke if LDL-C levels were not at goal	735	44.9%	FH I Alirocumab FH II Alirocumab	FH I placebo FH II placebo	Percent change in LDL-C from baseline to week 24	FH I 48.8% and 9.1% in the alirocumab and ezetimibe arm, respectively. FH II 48.7% and 2.8% in the alirocumab and ezetimibe arm, respectively
Kereiakes et al, 2015[21]	Patients with established CHD or CHD risk equivalents and hypercholesterolemia	316	34.2%	Alirocumab	Placebo	Percent change in LDL-C from baseline to week 24	45.9% in alirocumab vs placebo
Koren et al, 2014[14]	Patients with fasting LDL-C ≥100 and <190 mg/dL and Framingham risk scores ≤10%	614	66.4%	Evolocumab	Placebo	Percent change in LDL-C from baseline to week 12	Evolocumab treatment reduced LDL-C from baseline, on average, by 55%-57% more than placebo
Raal et al, 2015[15]	HeFH and were on a stable lipid-lowering therapy for ≥4 wk with fasting LDL ≥2.6 mmol/L	329	42.3%	Evolocumab	Placebo	Percent change in LDL-C from baseline to week 12	59.2% in evolocumab biweekly vs placebo and 61.3% in evolocumab monthly vs placebo
Ray et al, 2018[16]	Patients with T2DM and mixed dyslipidemia not optimally managed my maximally tolerated statin therapy	413	49.1%	Alirocumab	Usual lipid-lowering care	Percent change in LDL-C from baseline to week 24	43% in alirocumab vs usual care
Robinson et al, 2015[22]	Patients at high risk of CV events on maximally tolerated statin therapy	2,341	37.7%	Alirocumab	Placebo	Percent change in LDL-C from baseline to week 24	61% vs 0.8% in the alirocumab vs placebo arm, respectively
Roth et al, 2014[25]	Hypercholesterolemic patients at moderate cardiovascular risk not receiving statins or other lipid-lowering therapy	18,924	25.2%	Alirocumab	Ezetimibe	Percent change in LDL-C from baseline to week 24	47.2% alirocumab arm

Continued on the next page

TABLE 1 Continued

First Author, Year	Population	N	Women (%)	Intervention	Control	Outcome	LDL-C Reductions From Baseline
Roth et al, 2016[19]	Hypercholesterolemic patients at moderate to very high cardiovascular risk	803	39.3%	Alirocumab	Placebo	1) Percent change in LDL-C from baseline to week 24 in no statin group 2) Percent change in LDL-C from baseline to week 24 in with statin group 3) Percent change in LDL-C from baseline to averaged weeks 21-24 in no statin group 4) Percent change in LDL-C from baseline to averaged weeks 21-24 in no statin group in with statin group	1) 52.7% vs 0.3% in the alirocumab vs placebo arm, respectively 2) 58.8% vs 0.1% in the alirocumab vs placebo arm, respectively 3) 56.9% vs 1.6% in the alirocumab vs placebo arm, respectively 4) 65.8% vs 0.8% in the alirocumab vs placebo arm, respectively
Sabatine et al, 2017[10]	Patients with atherosclerotic CVD and LDL ≥70 mg/dL on statin therapy	564	25.0%	Evolocumab	Placebo	1) Composite of CV death, MI, stroke, hospitalization for UA or coronary revascularization 2) Composite of CV death, MI, or stroke	1) 9.8% vs 11.3% in evolocumab vs placebo arm, respectively 2) 5.9% vs 7.4% in evolocumab vs placebo arm, respectively
Schwartz et al, 2018[11]	Patients who had an ACS 1-12 mo prior, LDL ≥70 mg/dL, a non-HDL cholesterol ≥100 mg/dL, or an apolipoprotein B level of ≥80 mg/dL, on high intensity or maximally tolerated statin therapy	18,924	25.2%	Alirocumab	Placebo	Composite of death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization	9.5% vs 11.1% in alirocumab vs placebo arm, respectively
Stroes, 2016[32]	Patients with hypercholesterolemia not on statin therapy	233	44.2%	Alirocumab	Placebo	Percent change in LDL-C from baseline to week 24	51.7%, 53.5%, and 4.7% in the alirocumab 150Q4W, 75Q2W, and placebo arm, respectively

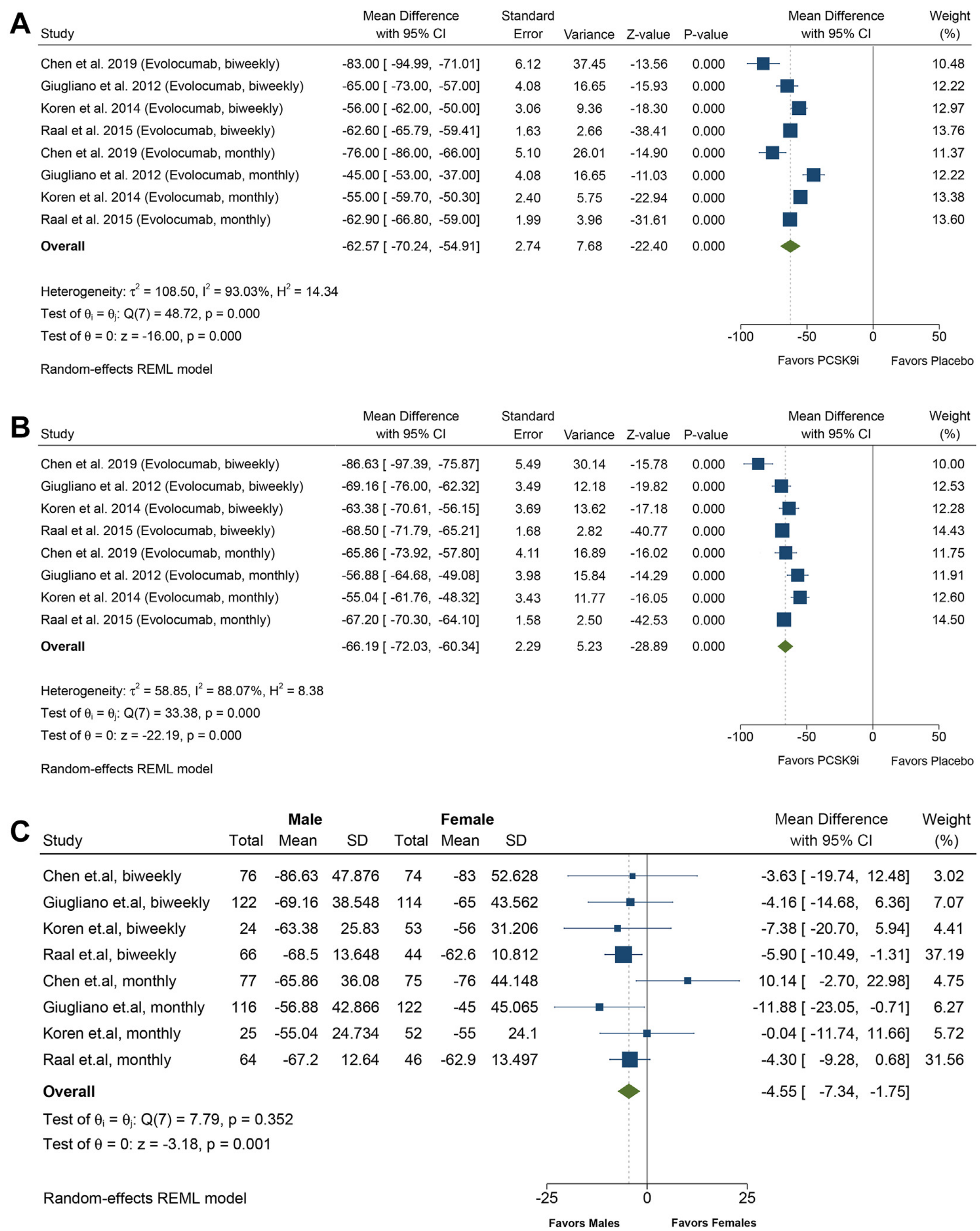
ACS = acute coronary syndrome; CHD = cardiovascular heart disease; CV = cardiovascular; FH = familial hypercholesterolemia; HDL = high-density lipoprotein; HeFH = hereditary familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PLHIV = person living with HIV; UA = unstable angina.

MAJOR ADVERSE CARDIOVASCULAR EVENTS. Two studies[10,11] reported incidence of MACE and their corresponding HR after treatment with a PCSK9i versus placebo. Both studies reported a similar reduction in MACE after PCSK9i in both sexes (females: HR 0.86, 95% CI: 0.74-0.97] $P < 0.001$ [Figure 3A]; males: HR 0.85, 95% CI: 0.79-0.91, $P < 0.001$ [Figure 3B]). However, further analysis showed no significant sex differences in MACE following PCSK9i use (males vs females: MD −0.01, 95% CI: −0.14 to 0.13, $P = 0.930$ [Figure 3C]).

SUBGROUP ANALYSIS: PCSK9i VS EZETIMIBE. Three studies[23-25] reported percentage changes in LDL-C after 24 weeks of biweekly PCSK9i versus ezetimibe. All 3 studies reported significantly decreased LDL-C levels in both sexes (females: MD −23.28, 95% CI: −29.70 to −16.87, $P < 0.001$ [Figure 4A]; males: MD −32.18, 95% CI: −37.10 to −27.25, $P < 0.001$ [Figure 4B]) with an overall greater reduction in males than in females (males vs females: MD −8.61, 95% CI: −16.99 to −0.24, $P < 0.05$ [Figure 4C]).

SUBGROUP ANALYSIS: BY PCSK9i TYPE. For subgroup analyses by type of PCSK9i, 7 studies used alirocumab, and one[17] used evolocumab. All 7 studies reported significantly decreased LDL-C levels after 24 weeks in both sexes (females: MD −46.69, 95% CI: −52.55 to −40.84, $P < 0.001$ [Figure 5A]; males: MD −53.75, 95% CI: −59.79 to −47.70, $P < 0.001$ [Figure 5B]). Likewise, administration of evolocumab resulted in significantly decreased LDL-C levels after 24 weeks in both sexes (females: MD −54.83, 95% CI −64.47 to −45.19, $P < 0.001$ [Figure 5A]; males: MD −56.62, 95% CI: −61.79 to −51.45, $P < 0.001$ [Figure 5B]). Further analysis revealed an overall greater LDL-C reduction in males compared to

FIGURE 1 PCSK9 Inhibitor vs Placebo



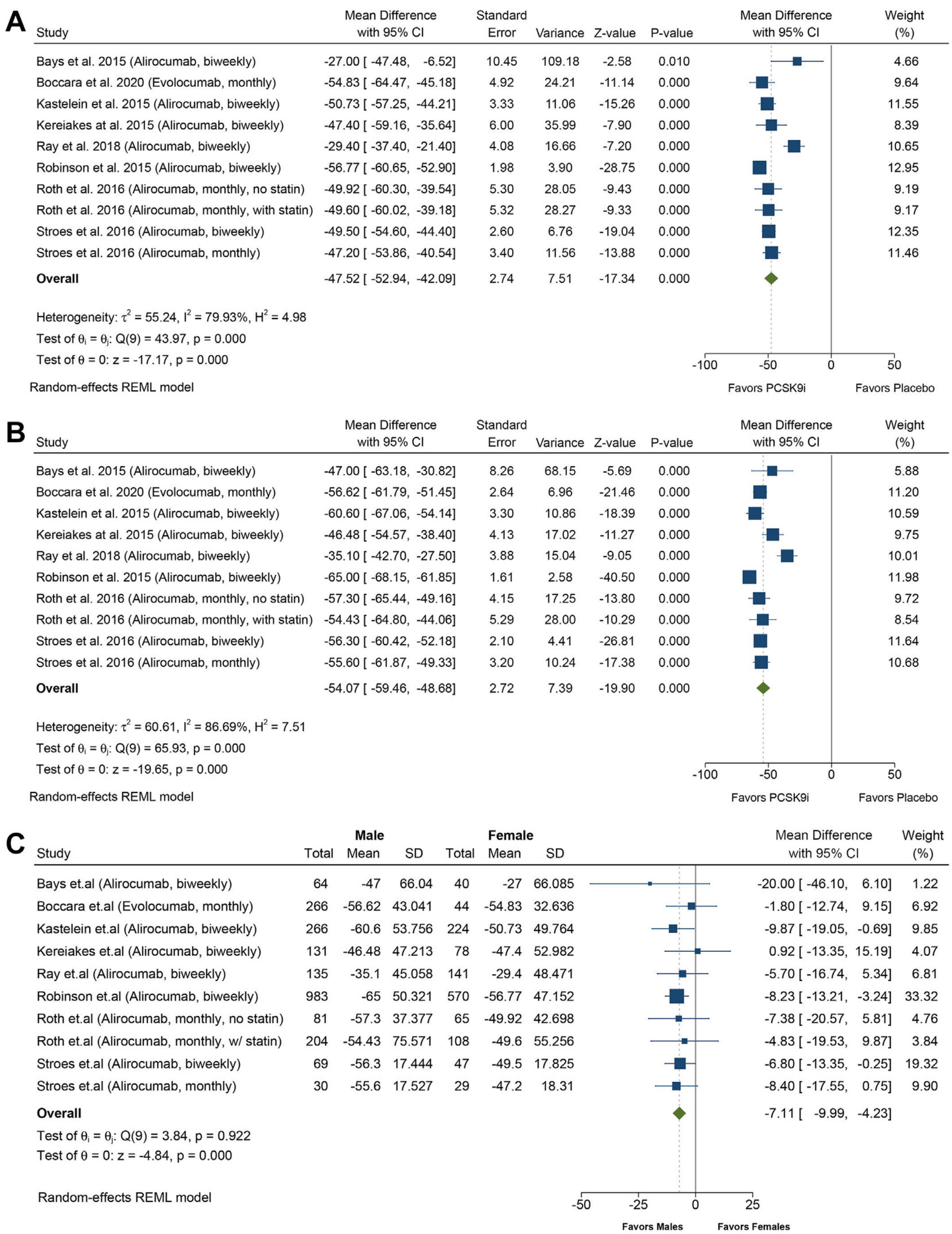
(A) LDL-C reduction in females after 12 weeks of therapy; (B) LDL-C reduction in males after 12 weeks of therapy; (C) sex difference in LDL-C reduction after 12 weeks of therapy. LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type-9.

females for alirocumab (males vs females: MD −7.53, 95% CI: −10.51 to −4.55], $P < 0.001$ [Figure 5C]) and no significant difference for evolocumab (males vs females: MD −1.79, 95% CI: −9.56 to −5.98, $P = 0.650$ [Figure 5C]).

DISCUSSION

The present study includes both clinical outcomes data among patients treated with PCSK9i globally and assesses its efficacy by sex (Central Illustration).

FIGURE 2 **PCSK9 Inhibitor vs Placebo**



A

Study	Mean Difference with 95% CI	Standard Error	Variance	Z-value	P-value	Weight (%)
Bays et al. 2015 (Alirocumab, biweekly)	-27.00 [-47.48, -6.52]	10.45	109.18	-2.58	0.010	4.66
Boccara et al. 2020 (Evolocumab, monthly)	-54.83 [-64.47, -45.18]	4.92	24.21	-11.14	0.000	9.64
Kastelein et al. 2015 (Alirocumab, biweekly)	-50.73 [-57.25, -44.21]	3.33	11.06	-15.26	0.000	11.55
Kereiakes at al. 2015 (Alirocumab, biweekly)	-47.40 [-59.16, -35.64]	6.00	35.99	-7.90	0.000	8.39
Ray et al. 2018 (Alirocumab, biweekly)	-29.40 [-37.40, -21.40]	4.08	16.66	-7.20	0.000	10.65
Robinson et al. 2015 (Alirocumab, biweekly)	-56.77 [-60.65, -52.90]	1.98	3.90	-28.75	0.000	12.95
Roth et al. 2016 (Alirocumab, monthly, no statin)	-49.92 [-60.30, -39.54]	5.30	28.05	-9.43	0.000	9.19
Roth et al. 2016 (Alirocumab, monthly, with statin)	-49.60 [-60.02, -39.18]	5.32	28.27	-9.33	0.000	9.17
Stroes et al. 2016 (Alirocumab, biweekly)	-49.50 [-54.60, -44.40]	2.60	6.76	-19.04	0.000	12.35
Stroes et al. 2016 (Alirocumab, monthly)	-47.20 [-53.86, -40.54]	3.40	11.56	-13.88	0.000	11.46
Overall	-47.52 [-52.94, -42.09]	2.74	7.51	-17.34	0.000	

Heterogeneity: $\tau^2 = 55.24$, $I^2 = 79.93\%$, $H^2 = 4.98$
Test of $\theta_i = \theta_j$: Q(9) = 43.97, p = 0.000
Test of $\theta = 0$: z = -17.17, p = 0.000

Random-effects REML model

B

Study	Mean Difference with 95% CI	Standard Error	Variance	Z-value	P-value	Weight (%)
Bays et al. 2015 (Alirocumab, biweekly)	-47.00 [-63.18, -30.82]	8.26	68.15	-5.69	0.000	5.88
Boccara et al. 2020 (Evolocumab, monthly)	-56.62 [-61.79, -51.45]	2.64	6.96	-21.46	0.000	11.20
Kastelein et al. 2015 (Alirocumab, biweekly)	-60.60 [-67.06, -54.14]	3.30	10.86	-18.39	0.000	10.59
Kereiakes at al. 2015 (Alirocumab, biweekly)	-46.48 [-54.57, -38.40]	4.13	17.02	-11.27	0.000	9.75
Ray et al. 2018 (Alirocumab, biweekly)	-35.10 [-42.70, -27.50]	3.88	15.04	-9.05	0.000	10.01
Robinson et al. 2015 (Alirocumab, biweekly)	-65.00 [-68.15, -61.85]	1.61	2.58	-40.50	0.000	11.98
Roth et al. 2016 (Alirocumab, monthly, no statin)	-57.30 [-65.44, -49.16]	4.15	17.25	-13.80	0.000	9.72
Roth et al. 2016 (Alirocumab, monthly, with statin)	-54.43 [-64.80, -44.06]	5.29	28.00	-10.29	0.000	8.54
Stroes et al. 2016 (Alirocumab, biweekly)	-56.30 [-60.42, -52.18]	2.10	4.41	-26.81	0.000	11.64
Stroes et al. 2016 (Alirocumab, monthly)	-55.60 [-61.87, -49.33]	3.20	10.24	-17.38	0.000	10.68
Overall	-54.07 [-59.46, -48.68]	2.72	7.39	-19.90	0.000	

Heterogeneity: $\tau^2 = 60.61$, $I^2 = 86.69\%$, $H^2 = 7.51$
Test of $\theta_i = \theta_j$: Q(9) = 65.93, p = 0.000
Test of $\theta = 0$: z = -19.65, p = 0.000

Random-effects REML model

C

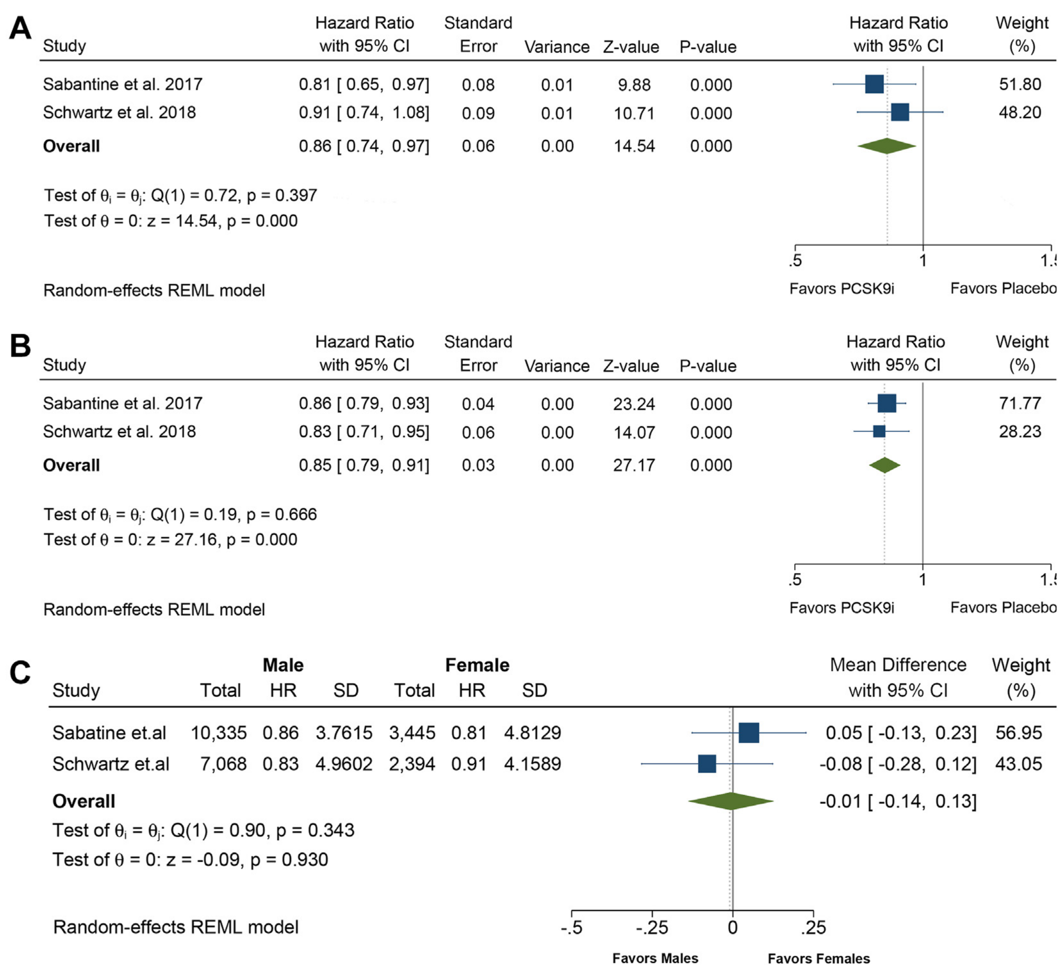
Study	Male Total	Male Mean	Male SD	Female Total	Female Mean	Female SD	Mean Difference with 95% CI	Weight (%)
Bays et.al (Alirocumab, biweekly)	64	-47	66.04	40	-27	66.085	-20.00 [-46.10, 6.10]	1.22
Boccara et.al (Evolocumab, monthly)	266	-56.62	43.041	44	-54.83	32.636	-1.80 [-12.74, 9.15]	6.92
Kastelein et.al (Alirocumab, biweekly)	266	-60.6	53.756	224	-50.73	49.764	-9.87 [-19.05, -0.69]	9.85
Kereiakes et.al (Alirocumab, biweekly)	131	-46.48	47.213	78	-47.4	52.982	0.92 [-13.35, 15.19]	4.07
Ray et.al (Alirocumab, biweekly)	135	-35.1	45.058	141	-29.4	48.471	-5.70 [-16.74, 5.34]	6.81
Robinson et.al (Alirocumab, biweekly)	983	-65	50.321	570	-56.77	47.152	-8.23 [-13.21, -3.24]	33.32
Roth et.al (Alirocumab, monthly, no statin)	81	-57.3	37.377	65	-49.92	42.698	-7.38 [-20.57, 5.81]	4.76
Roth et.al (Alirocumab, monthly, w/ statin)	204	-54.43	75.571	108	-49.6	55.256	-4.83 [-19.53, 9.87]	3.84
Stroes et.al (Alirocumab, biweekly)	69	-56.3	17.444	47	-49.5	17.825	-6.80 [-13.35, -0.25]	19.32
Stroes et.al (Alirocumab, monthly)	30	-55.6	17.527	29	-47.2	18.31	-8.40 [-17.55, 0.75]	9.90
Overall							-7.11 [-9.99, -4.23]	

Test of $\theta_i = \theta_j$: Q(9) = 3.84, p = 0.922
Test of $\theta = 0$: z = -4.84, p = 0.000

Random-effects REML model

(A) LDL-C reduction in females after 24 weeks of therapy; (B) LDL-C reduction in males after 24 weeks of therapy; (C) sex difference in LDL-C reduction after 24 weeks of therapy.

FIGURE 3 **PCSK9 Inhibitor vs Placebo**

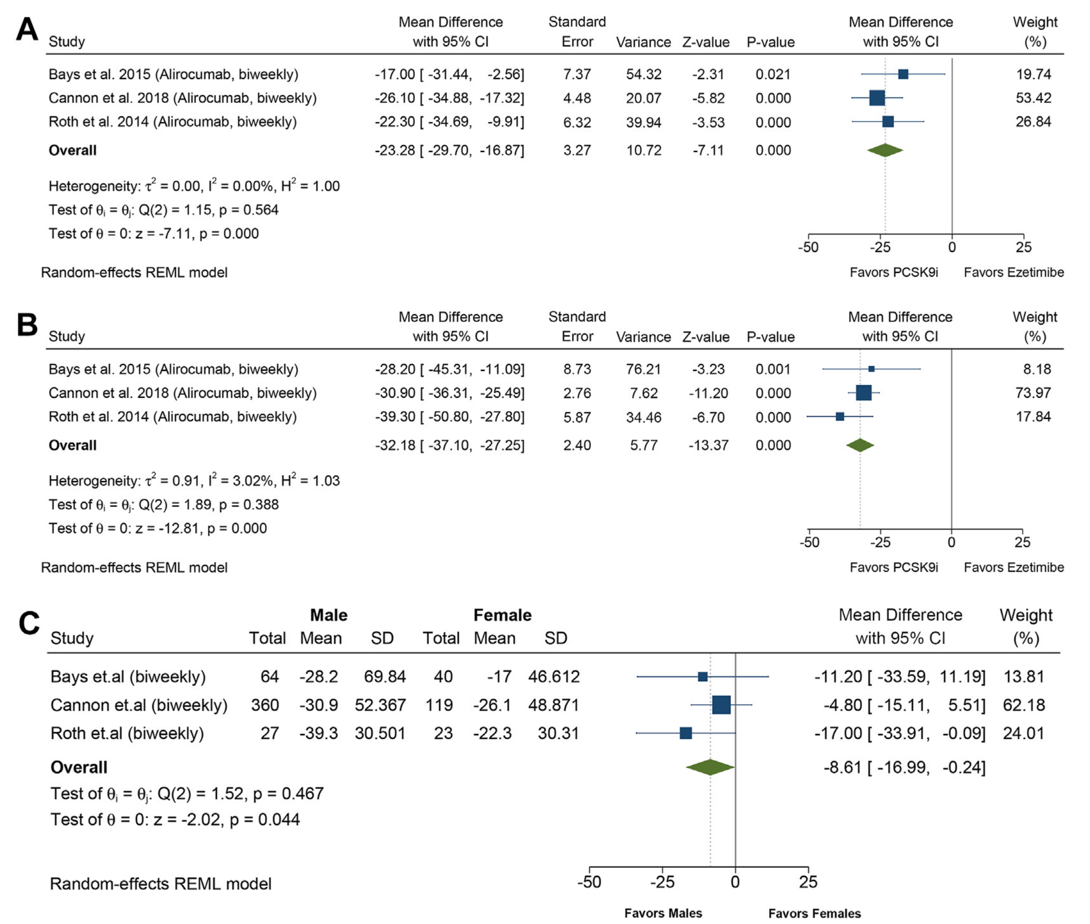


(A) Major adverse cardiovascular events (MACE) in females; (B) MACE in males; (C) sex difference in MACE.

To date, this is the first meta-analysis to explore these outcomes and further support the benefit of PCSK9i use. Our results show that there are significant and similar reductions in MACE across both sexes. Furthermore, our results show significant reductions in LDL-C in both males and females, with greater reduction in males than in females.

Multiple trials have evaluated the efficacy of monoclonal antibody PCSK9is. These include the ODYSSEY (Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome) trial, FOURIER (Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease) trial, and SPIRE (Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients) trial, which used alirocumab, evolocumab, and bococizumab, respectively.[10,11,26] All trials reported a reduction in LDL-C levels and cardiovascular events. The ODYSSEY and SPIRE trials revealed greater benefits among those with higher LDL-C baseline values (>100 mg/dL),[8,24] while the FOURIER trial showed consistent benefits among subgroups.[10] Given the benefit of these agents, current guidelines recommend their use, especially if target LDL-C levels are not achieved on maximally tolerated statin.[3] The results of this study support the equal use of PCSK9is across sex in reducing both LDL-C and MACE. Observational studies have suggested differences in LDL-C reduction by sex.[27,28,29] Consistent with previous data, our results showed significantly greater mean reduction in males than in females regardless of frequency and duration of PCSK9i

FIGURE 4 **PCSK9 Inhibitor vs Ezetimibe**

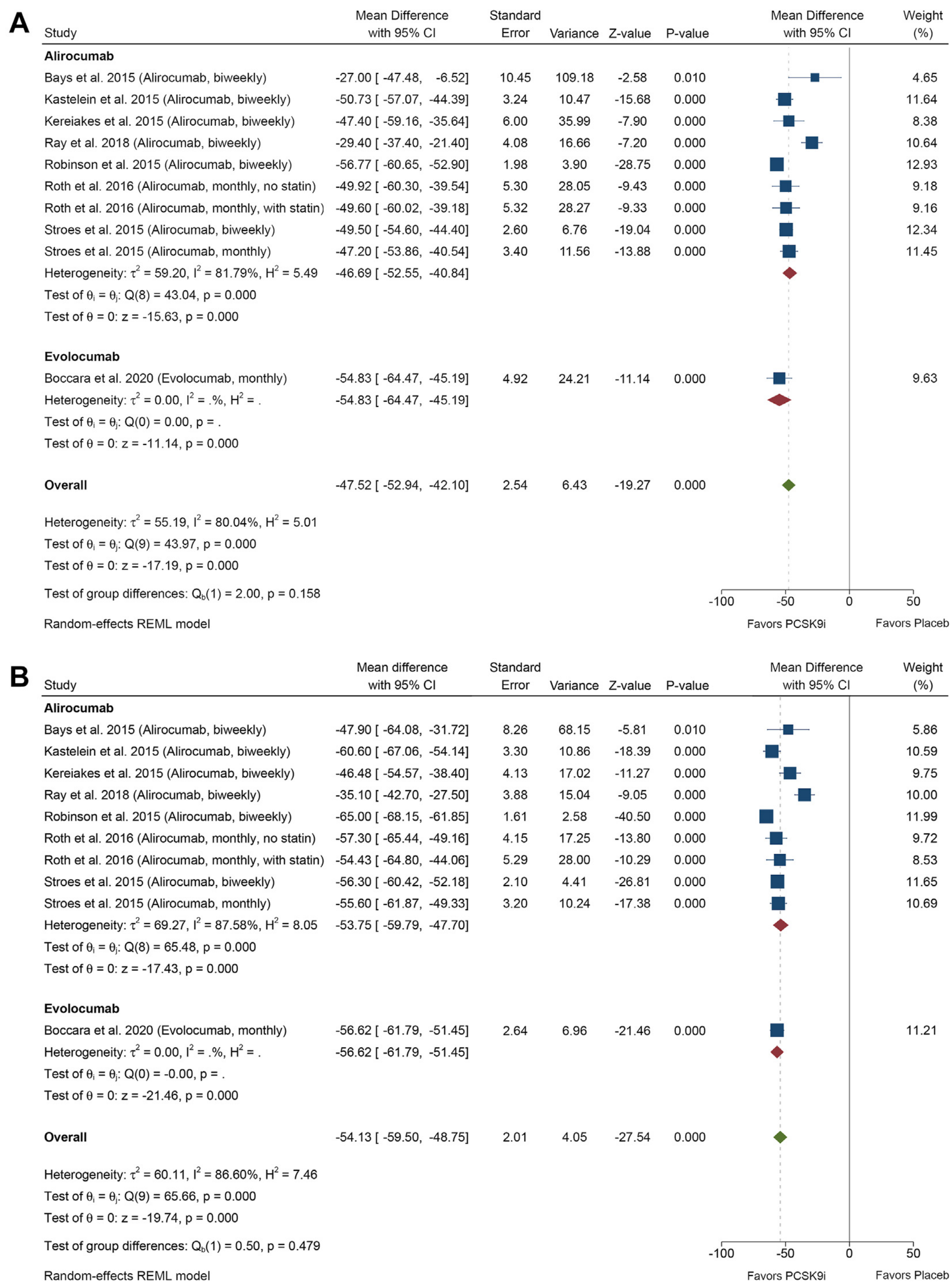


(A) LDL-C reduction in females after 24 weeks of therapy; (B) LDL-C reduction in males after 24 weeks of therapy; (C) sex difference in LDL-C reduction after 24 weeks of therapy.

administration. Furthermore, our findings extend on what was shown by Sever et al that, on average, the treatment difference in LDL-C was 59 to 60 mg/dL for males and from 50 to 52 mg/dL in females who received evolocumab. Moreover, no statistical evidence of treatment effect modification by sex was observed for cardiovascular death, MI, stroke, unstable angina requiring rehospitalization, and coronary revascularization.[30] The LIPID-REAL registry study conducted at 18 different hospitals using evolocumab and alirocumab revealed that the mean reduction in LDL-C was lower in females than in males (47.4% vs 56.9%).[27] Also, a pooled analysis of 10 ODYSSEY Phase 3 trials showed that females and males given alirocumab achieved an average on-treatment LDL-C <50 mg/dL in 36.5% and 58.7%, respectively.[31] Similar findings were also reported in a multicenter study in Spain, where the mean LDL-C reduction was lower in females than in males (46% vs 57%), with an even greater reduction among those with cardiovascular disease (68.9% vs 48.0%).[28] Females are consistently underrepresented in RCTs assessing lipid-lowering therapies, limiting the results.[6]

Regardless of the absolute change in LDL-C, there was still a significant LDL-C reduction across both sexes. The specific mechanisms behind the sex-specific differences in LDL-C reduction are not yet fully known; however, some studies have shown that circulating PCSK9 levels were higher among females than among males.[29] Furthermore, different factors can predict circulating PCSK9 levels in females and males. The mean corpuscular hemoglobin concentration and cigarette pack-years were

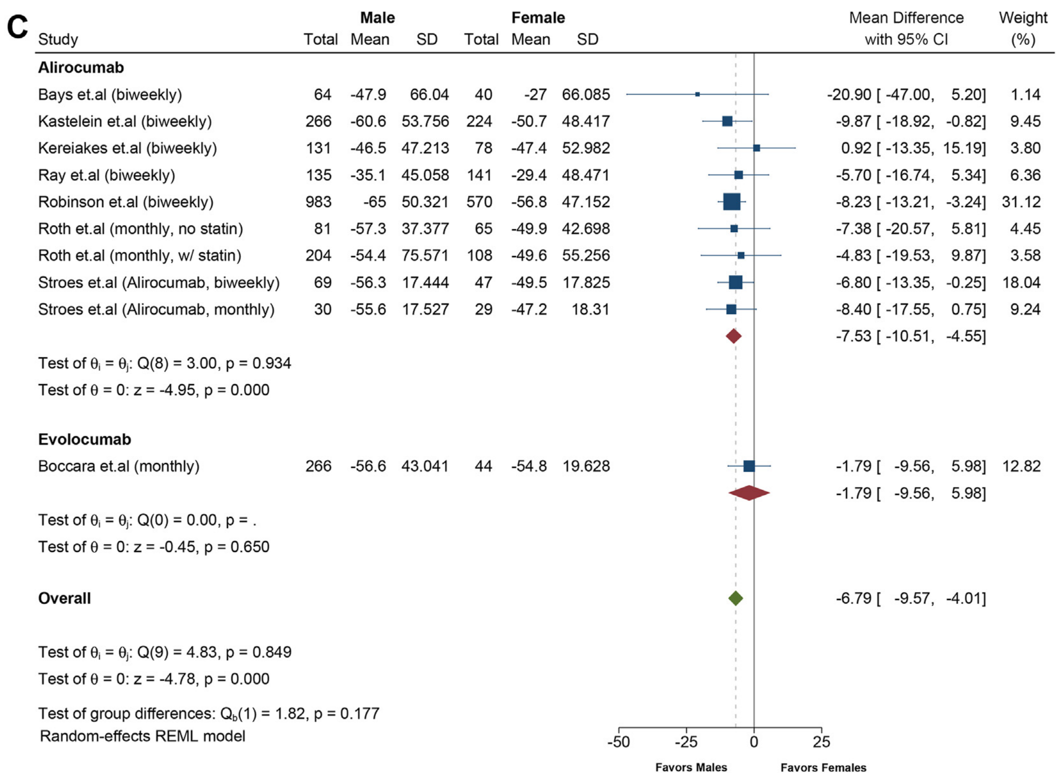
FIGURE 5 PCSK9 Inhibitor vs Placebo



(A) LDL-C reduction in females after 24 weeks of therapy, by type of PCSK9 inhibitor; (B) LDL-C reduction in males after 24 weeks of therapy, by type of PCSK9 inhibitor; (C) sex difference in LDL-C reduction after 24 weeks of therapy, by type of PCSK9 inhibitor.

Continued on the next page

FIGURE 5 Continued



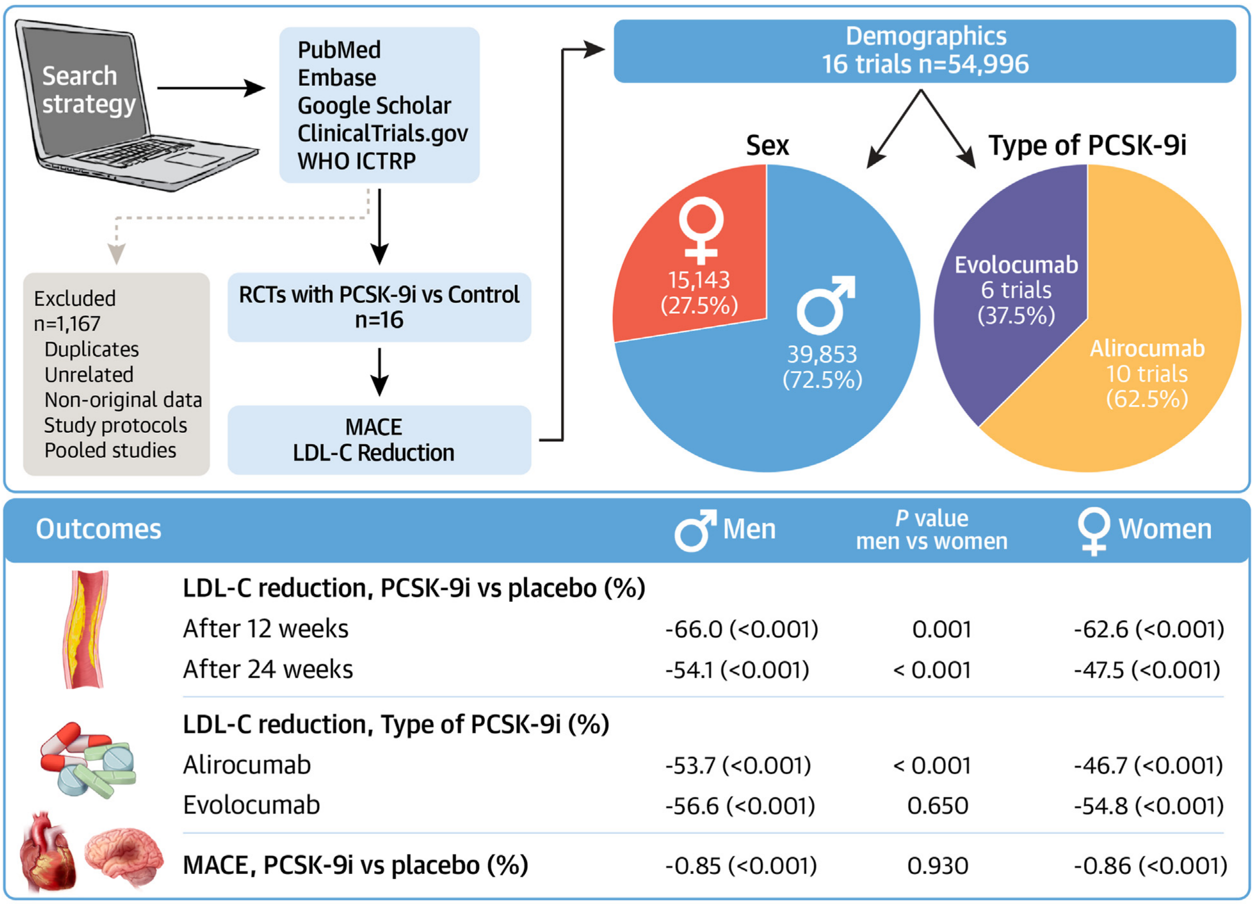
independent predictors in females, while hypercholesterolemia and physical activity were independent predictors in males.[29] These differences suggest that some of the variations in the sex-specific responses to PCSK9i may be due to different levels of circulating PCSK9 among the sexes. However, further research is needed to elucidate these differences.

When evaluating PCSK9i by type across sex, our results showed that both alirocumab and evolocumab resulted in significant LDL-C reduction in both sexes compared to placebo. Moreover, analysis for sex difference by PCSK9i type showed a greater LDL-C reduction in males than in females for alirocumab (MD −7.53, 95% CI: −10.51 to −4.55, $P < 0.001$), but not with evolocumab (MD −1.79, 95% CI: −9.56 to −5.98, $P = 0.650$). However, the number of studies included in the evolocumab group (n = 1) may not provide conclusive data in this group.

As noted, both the FOURIER and ODYSSEY trials showed a prominent reduction in MACE with PCSK9is.[16,12] The FOURIER trial showed a similar reduction in MACE among males and females with evolocumab.[16] However, the ODYSSEY trial showed a greater MACE reduction in males (HR: 0.83, 95% CI: 0.74-0.92) than in females (HR: 0.91, 95% CI: 0.77-1.08) with Alirocumab.[12] In our study, there was a significant reduction in MACE compared to placebo with PCSK9i for both sexes, but no significant sex differences were found (MACE, males vs females: MD −0.01, 95% CI: −0.14 to 0.13, $P = 0.930$).

STRENGTH AND LIMITATIONS. To our knowledge, this is the first meta-analysis to report on sex-differences in LDL-C reduction and MACE in participants receiving PCSK9i therapy. There are several limitations that are important to note. This is a study-level meta-analysis, and we could not access individual patient data. Additional limitations include heterogeneity in PCSK9i studies in both males and females. Publication bias may also be present, but the extent of which could not fully be quantified. However, every effort possible was made to limit bias by utilizing a robust analytical approach to adjust for potential moderators through subgroup analyses.

CENTRAL ILLUSTRATION **Sex Difference on Cardiovascular Outcomes of PCSK9 Inhibitors**



Rivera FB, et al. JACC Adv. 2023;2(9):100669.

A total of 54,996 participants from 16 trials were included in the study. Main outcomes include incidence of MACE and mean LDL-C reduction of PCSK9i vs placebo stratified by sex. LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular event; PCSK9i = proprotein convertase subtilisin/kexin type-9 inhibitor; RCT = randomized controlled trial.

CONCLUSIONS

The use of PCSK9i results in significant LDL-C and MACE reduction in both males and females. While there is no significant sex difference in MACE reduction, LDL-C reduction is greater in males than in females. Our data support the equal use of PCSK9i in all eligible patients, regardless of sex.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Frederick Berro Rivera, Department of Medicine, Lincoln Medical Center, 234 East 149th Street, The Bronx, New York 10451, USA. E-mail: frederick.berro.rivera@gmail.com. @FredRiveraMD.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Clinicians should consider PCSK-9 inhibitors in eligible patients not achieving the desired LDL-C level equally across both sexes. Despite a lower LDL-C reduction in women than in men, both sexes have a significant reduction in LDL-C and MACE with these agents. Thus, these results support current guideline recommendations.

TRANSLATIONAL OUTLOOK: PCSK-9 inhibitors continue to show great promise but may have different effects on various subgroups. Large-scale studies utilizing individual patient data can further expand the current understanding of PCSK-9i utilization across these populations.

REFERENCES

1. Atar D, Jukema JW, Molemans B, et al. New cardiovascular prevention guidelines: how to optimally manage dyslipidaemia and cardiovascular risk in 2021 in patients needing secondary prevention? *Atherosclerosis*. 2021;319:51-61.

2. Dixon DL, Pamulapati LG, Bucheit JD, et al. Recent updates on the use of PCSK9 inhibitors in patients with atherosclerotic cardiovascular disease. *Curr Atheroscler Rep*. 2019;21(5):16.

3. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2022 ACC expert consensus decision pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2022;80(14):1366-1418.

4. Khan SU, Yedlapati SH, Lone AN, et al. PCSK9 inhibitors and ezetimibe with or without statin therapy for cardiovascular risk reduction: a systematic review and network meta-analysis. *BMJ*. 2022;377:e069116.

5. Fulcher J, O'Connell R, Voysey M, et al. Efficacy and safety of LDL-lowering therapy among males and females: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet*. 2015;385(9976):1397-1405.

6. Khan SU, Khan MZ, Raghu Subramanian C, et al. Participation of and older participants in randomized clinical trials of lipid-lowering therapies: a systematic review. *JAMA Netw Open*. 2020;3(5):e205202.

7. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.

8. Schwingshackl L, Rüschemeyer G, Meerpohl JJ. [How to interpret the certainty of evidence based on GRADE (Grading of Recommendations, Assessment, Development and Evaluation)]. *Urologe A*. 2021;60(4):444-454.

9. Sideri S, Papageorgiou SN, Eliades T. Registration in the international prospective register of systematic reviews (PROSPERO) of systematic review protocols was associated with increased review quality. *J Clin Epidemiol*. 2018;100:103-110.

10. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376(18):1713-1722.

11. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379(22):2097-2107.

12. Chen Y, Yuan Z, Lu J, et al. Randomized study of evolocumab in patients with type 2 diabetes and dyslipidaemia on background statin: prespecified analysis of the Chinese population from the BERSON clinical trial. *Diabetes Obes Metab*. 2019;21(6):1464-1473.

13. Giugliano RP, Desai NR, Kohli P, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. *Lancet*. 2012;380(9858):2007-2017.

14. Koren MJ, Lundqvist P, Bolognese M, et al. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. *J Am Coll Cardiol*. 2014;63(23):2531-2540.

15. Raal FJ, Stein EA, Dufour R, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2015;385(9965):331-340.

16. Ray KK, Leiter LA, Müller-Wieland D, et al. Alirocumab vs usual lipid-lowering care as add-on to statin therapy in individuals with type 2 diabetes and mixed dyslipidaemia: the ODYSSEY DM-DYSLIPIDEMIA randomized trial. *Diabetes Obes Metab*. 2018;20(6):1479-1489.

17. Boccara F, Kumar PN, Caramelli B, et al. Evolocumab in HIV-infected patients with dyslipidemia: primary results of the randomized, double-blind BEIJERINCK study. *J Am Coll Cardiol*. 2020;75(20):2570-2584.

18. Stroes E, Robinson JG, Raal FJ, et al. Consistent LDL-C response with evolocumab among patient subgroups in PROFICIO: a pooled analysis of 3146 patients from phase 3 studies. *Clin Cardiol*. 2018;41(10):1328-1335.

19. Roth EM, Moriarty PM, Bergeron J, et al. A phase III randomized trial evaluating alirocumab 300 mg every 4 weeks as monotherapy or add-on to statin: ODYSSEY CHOICE I. *Atherosclerosis*. 2016;254:254-262.

20. Kastelein JJ, Ginsberg HN, Langslet G, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. *Eur Heart J*. 2015;36(43):2996-3003.

21. Kereiakes DJ, Robinson JG, Cannon CP, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: the ODYSSEY COMBO I study. *Am Heart J*. 2015;169(6):906-915.e13.

22. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372(16):1489-1499.

23. Bays H, Gaudet D, Weiss R, et al. Alirocumab as add-on to atorvastatin versus other lipid treatment strategies: ODYSSEY OPTIONS I randomized trial. *J Clin Endocrinol Metab*. 2015;100(8):3140-3148.

24. Cannon CP, Cariou B, Blom D, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. *Eur Heart J*. 2015;36(19):1186-1194.

25. Roth EM, Taskinen MR, Ginsberg HN, et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24 week, double-blind, randomized phase 3 trial. *Int J Cardiol*. 2014;176(1):55-61.

26. Ridker PM, Revkin J, Amarenco P, et al. Cardiovascular efficacy and safety of bococizumab in high-risk patients. *N Engl J Med*. 2017;376(16):1527-1539.

27. Cordero A, Fernández Del Olmo MR, Cortez Quiroga GA, et al. Sex differences in low-density lipoprotein cholesterol reduction with PCSK9 inhibitors in real-world patients: the LIPID-REAL Registry. *J Cardiovasc Pharmacol*. 2022;79(4):523-529.

28. Boklage S, Elassal J, Gervasio J, Gupta R. Abstract 203: gender differences in PCSK9 inhibitor prescribing. *Circ Cardiovasc Qual Outcomes*. 2017;10(suppl_3):A203.

29. Ferri N, Ruscica M, Coggi D, et al. Sex-specific predictors of PCSK9 levels in a European population: the IMPROVE study. *Atherosclerosis*. 2020;309:39–46.

30. Sever P, Gouni-Berthold I, Keech A, et al. LDL-cholesterol lowering with evolocumab, and outcomes according to age and sex in patients in the FOURIER trial. *Eur J Prevent Cardiol*. 2021;28(8):805–812. https://doi.org/10.1177/2047487320902750

31. Vallejo-Vaz AJ, Ginsberg HN, Davidson MH, et al. Lower on-treatment low-density lipoprotein cholesterol and major adverse cardiovascular events in women and men: pooled analysis of 10 ODYSSEY phase 3 alirocumab trials. *J Am Heart Assoc*. 2018;7(18):e009221.

32. Stroes E, Guyton JR, Lepor N, et al. Efficacy and safety of alirocumab 150 mg every 4 weeks in patients with hypercholesterolemia not on statin therapy: the ODYSSEY CHOICE II study. *J Am Heart Assoc*. 2016;5(9):e003421. https://doi.org/10.1161/JAHA.116.003421

KEY WORDS cardiovascular events, PCSK9 inhibitors, sex difference, tertiary prevention

APPENDIX For a supplemental table and figures, please see the online version of this paper.