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ORIGINAL ARTICLE

Characteristics and Cardiovascular Disease Event Rates among African Americans and Whites Who Meet the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) Trial Inclusion Criteria

Lisandro D. Colantonio[1] · Keri L. Monda[2] · Robert S. Rosenson[3] · Todd M. Brown[4] · Katherine E. Mues[2] · George Howard[5] · Monika M. Safford[6] · Larisa Yedigarova[7] · Michael E. Farkouh[8] · Paul Muntner[1]

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Abstract

Purpose Determine the risk for cardiovascular disease (CVD) events among adults with clinically evident CVD who meet the inclusion criteria for the FOURIER clinical trial on PCSK9 inhibition in a real-world database.

Methods We analyzed data from 2072 African American and 2972 white REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants 45–85 years of age with clinically evident CVD. Study participants meeting the FOURIER inclusion criteria (one major or two minor cardiovascular risk factors, fasting LDL cholesterol ≥ 70 mg/dL or non-HDL cholesterol ≥ 100 mg/dL, triglycerides ≤ 400 mg/dL, and taking statin) were followed for CVD events (myocardial infarction, stroke, coronary revascularization, and CVD death) from baseline in 2003–2007 through 2014.

Results Overall, 771 (37.2%) African Americans and 1200 (40.4%) whites met the FOURIER inclusion criteria. The CVD event rate per 1000 person years was 60.6 (95% CI 53.6–67.6) among African Americans and 63.5 (95% CI 57.7–69.3) among whites. The risk for CVD events among adults meeting the FOURIER inclusion criteria was higher for those with a history of multiple cardiovascular events (hazard ratios among African Americans and whites 1.34 [95% CI 1.05–1.71] and 1.34 [1.10–1.63], respectively), a prior coronary revascularization (1.44 [1.13–1.84] and 1.23 [1.00–1.52], respectively), diabetes (1.38 [1.08–1.76] and 1.41 [1.15–1.72], respectively), reduced glomerular filtration rate (1.63 [1.26–2.11] and 1.29 [1.03–1.62], respectively), and albuminuria (1.77 [1.37–2.27] and 1.33 [1.07–1.65], respectively).

Conclusions The CVD event rate is high among African Americans and whites meeting the FOURIER inclusion criteria. Characteristics associated with a higher CVD risk may inform the decision to initiate PCSK9 inhibition.

Keywords African Americans · Cardiovascular diseases · Mortality · Continental population groups · Epidemiology · Evolocumab

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✉ Lisandro D. Colantonio
lcolantonio@uab.edu

[1] Department of Epidemiology, University of Alabama at Birmingham, 1720 2nd Ave. South, RPHB 527C, Birmingham, AL 35294-0013, USA

[2] Center for Observational Research, Amgen Inc., Thousand Oaks, CA, USA

[3] Mount Sinai Heart, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[4] Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

[5] Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL, USA

[6] Department of Medicine, Weill Cornell Medical College, New York, NY, USA

[7] Amgen Inc., Thousand Oaks, CA, USA

[8] Peter Munk Cardiac Centre, University of Toronto and Heart and Stroke Richard Lewar Centre of Excellence, Toronto, ON, Canada

Introduction

In the Further Cardiovascular Outcomes Research with Proprotein Convertase Subtilisin–Kexin Type 9 (PCSK9) Inhibition in Subjects with Elevated Risk (FOURIER) clinical trial, evolocumab reduced the risk for cardiovascular disease (CVD) events compared with placebo among adults 40 to 85 years of age with clinically evident CVD [1]. In addition to having clinically evident CVD, eligibility criteria for the FOURIER trial included one major or two minor cardiovascular risk factors (as described below) and having suboptimal cholesterol levels while taking an optimized regimen of statin therapy.

Prior studies suggest that it may not be cost-effective to treat all individuals who meet the FOURIER trial inclusion criteria with a PCSK9 inhibitor [2–4]. Therefore, determining the CVD event rate and characteristics associated with a higher risk for CVD events among individuals meeting the FOURIER inclusion criteria can contribute to identify subgroups who may have a larger absolute risk reduction through PCSK9 inhibition. The objectives of the current analysis were to estimate the proportion of adults with clinically evident CVD who meet the inclusion criteria for the FOURIER trial, calculate their CVD event rate, and determine characteristics associated with having a higher CVD risk. To achieve these objectives, we used data from a prospective population-based US cohort of African Americans and whites, the REasons for Geographic And Racial Differences in Stroke (REGARDS) study [5]. African Americans have a higher prevalence of cardiovascular risk factors, including hypertension, diabetes and obesity, a lower use of statin therapy, and a higher risk for CVD events compared with whites [6, 7]. Therefore, analyses were conducted among African Americans and whites, separately.

Methods

Study Population

The REGARDS study enrolled 30,239 African American and white men and women ≥ 45 years of age who were recruited from all 48 contiguous US states and the District of Columbia between January 2003 and October 2007 [5]. REGARDS study participants have been prospectively followed for CVD events and mortality [5, 8]. The REGARDS study protocol was approved by the Institutional Review Boards governing research in human subjects at the participating centers and all participants provided written informed consent.

For the current analysis, we included REGARDS study participants 45 to 85 years of age with clinically evident CVD (as defined below) at baseline who had baseline measurements of total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides, and follow-up for CVD events and mortality. We excluded REGARDS study participants > 85 years of age at baseline because this population was not eligible for the FOURIER trial. Participants with missing data on total cholesterol, HDL cholesterol, or triglycerides at baseline were excluded as we cannot determine whether they meet the FOURIER trial inclusion criteria.

Baseline Assessment in the REGARDS Study

Computer-assisted telephone interviews were administered at baseline by trained staff and used to collect participant information including their age, race, gender, cigarette smoking status, prior diagnosed comorbid conditions (e.g., myocardial infarction [MI], stroke, diabetes, high blood pressure [BP]), history of vascular interventions (e.g., coronary and lower extremity revascularization procedures), and use of oral hypoglycemic and antihypertensive medications, aspirin and insulin.

After completion of the interview, trained health professionals conducted in-home examinations following standardized protocols. Procedures included 2 BP measurements which were averaged, weight and waist circumference measurements, an electrocardiogram, and collection of blood and urine samples. Using blood samples, serum total cholesterol, HDL cholesterol, triglycerides, glucose, high-sensitive C reactive protein (hsCRP), and creatinine were measured. For participants with fasting triglycerides < 400 mg/dL, low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation [9]. Non-HDL cholesterol was calculated as total minus HDL cholesterol. Estimated glomerular filtration rate (eGFR) was calculated using information on age, race, gender, and serum creatinine and the Chronic Kidney Disease Epidemiology equation [10]. Albumin and creatinine were measured in urine samples and used to calculate the albumin-to-creatinine ratio (ACR).

Clinically evident CVD at baseline was defined by a history of MI, stroke, or peripheral artery disease (PAD) to match the FOURIER trial definition [11]. History of MI was defined by self-report of a prior diagnosis of MI, or evidence of a previous MI on the baseline electrocardiogram. History of stroke was defined by self-report of a prior diagnosis of stroke. PAD was defined by self-report of a prior revascularization procedure in the lower extremities. Hypertension was defined by a mean systolic BP ≥ 140 mmHg, mean diastolic BP ≥ 90 mmHg, or self-report of a prior diagnosis of high BP with concurrent use of antihypertensive medication.

During the in-home examination, staff conducted a review of containers for prescription and over-the-counter medications that participants took during the prior 2 weeks. Use of a statin, non-statin lipid-lowering medication (ezetimibe, fibrate, niacin, and cholestyramine), $P2Y_{12}$ inhibitor (antiplatelet agent), beta-blocker, and renin-angiotensin-

aldosterone system (RAAS) inhibitor were defined using medication names recorded during the medication review. Medication dosages were not recorded. The intensity of statin therapy (Supplemental Table 1) was assessed in a subsample of REGARDS study participants who had Medicare pharmacy coverage and a statin prescription fill within 120 days prior to their medication review [12, 13].

FOURIER Trial Inclusion Criteria

Inclusion criteria for the FOURIER trial, as operationalized using REGARDS baseline data, included the following:

1. Having one major or two minor cardiovascular risk factors (Supplemental Table 2).
2. Fasting LDL cholesterol ≥ 70 mg/dL or non-HDL cholesterol ≥ 100 mg/dL.
3. Triglycerides ≤ 400 mg/dL.
4. Statin use.

Data Collected During Follow-Up

Following baseline assessment, REGARDS study participants or proxy respondents were contacted every 6 months via telephone to determine vital status and the occurrence of coronary revascularization (i.e., coronary artery bypass grafting or percutaneous coronary intervention), stroke, and MI events. Suspected events were confirmed using medical records as described previously [8, 14]. The main underlying cause of deaths identified during follow-up was determined through interviews with next-of-kin or proxies, medical records in the last year of life, death certificates, and autopsy reports [8, 15].

We analyzed two composite outcomes to resemble those used in the FOURIER trial. The primary outcome included cardiovascular death, stroke, definite or probable MI, or coronary revascularization. The primary outcome in the FOURIER trial also included hospitalization due to unstable angina, but these events were not assessed in the REGARDS study. The secondary outcome included cardiovascular death, stroke, or definite or probable MI. Adjudicated CVD events and all-cause mortality in REGARDS were available through December 31, 2014.

Statistical Analysis

We calculated the proportion of African Americans and whites 45 to 85 years of age with clinically evident CVD who met the FOURIER inclusion criteria outlined above. The FOURIER trial included participants taking a moderate- or high-intensity statin. Therefore, we calculated the proportion of African American and white REGARDS study participants meeting the FOURIER inclusion criteria who were taking a moderate- or high-intensity statin in the subsample with Medicare pharmacy coverage and a statin prescription fill within 120 days prior to their medication review.

Among REGARDS study participants who met the FOURIER inclusion criteria, we calculated baseline characteristics for African Americans and whites, separately and determined the statistical significance of differences using chi-squared tests, *t* tests, or Wilcoxon's rank sum tests, as appropriate. We also compared the characteristics of participants who met versus did not meet the FOURIER inclusion criteria among African Americans and whites, separately.

The following analyses were restricted to REGARDS study participants who met the FOURIER inclusion criteria. We calculated the cumulative incidence and incidence rate for the primary and secondary composite outcomes, all-cause mortality and each component of the primary outcome (i.e., cardiovascular death, stroke, MI, and coronary revascularization) among African Americans and whites, separately. Proportional hazard regression models with progressive adjustment were used to calculate hazard ratios and 95% confidence intervals (CI) for the primary and secondary outcomes, all-cause mortality and each primary outcome component comparing African Americans versus whites. Model 1 included adjustment for age, gender, region of residence, income, and education. Model 2 included adjustment for the variables in Model 1 and history of MI, stroke, PAD, a history of multiple cardiovascular events, a prior coronary revascularization, smoking, diabetes, hypertension, metabolic syndrome, body weight, total and HDL cholesterol, triglycerides, eGFR < 60 mL/min/1.73 m^2, ACR ≥ 30 mg/g, hsCRP > 2.0 mg/L, and medication use (i.e., non-statin lipid-lowering medication, aspirin or $P2Y_{12}$ inhibitor, beta-blocker, and RAAS inhibitor).

We used proportional hazard regression models to calculate hazard ratios and 95% CIs for the primary and secondary outcomes associated with baseline characteristics among African Americans and whites, separately. Many of these characteristics are highly correlated. Therefore, regression models only included adjustment for age, gender, region of residence, income, and education to allow to identify baseline characteristics that could be used as risk markers in clinical practice. The statistical significance in the difference between hazard ratios for African Americans and whites was determined by including interaction terms between race and each participant characteristic.

For time-to-event analyses, participants were followed from baseline through their first outcome event, death, loss to follow-up, or December 31, 2014, whichever occurred first. The calculation of cumulative incidence functions and hazard ratios for all outcomes except all-cause mortality were conducted accounting for the competing risk for death [16]. All analyses were conducted using SAS v9.4 (SAS Institute Inc., Cary NC). Statistical significance was defined as a p value < 0.10 for interactions and < 0.05 for all other analyses.

Results

Overall, 2072 Africans American and 2972 white REGARDS study participants were 45 to 85 years of age and had clinically evident CVD (Supplemental Fig. 1). Of these participants, 771 (37.2%) African Americans and 1200 (40.4%) whites met the FOURIER trial inclusion criteria (Fig. 1). The main reason for not meeting the FOURIER inclusion criteria was not taking a statin, particularly among African Americans. In the subset of REGARD study participants meeting the FOURIER inclusion criteria who had Medicare pharmacy coverage and a statin prescription fill within 120 days prior to their medication review ($n = 95$), 91% were taking a high- or moderate-intensity statin.

Among REGARDS study participants meeting the FOURIER inclusion criteria, African Americans were younger and less likely to be male, have a history of MI, a prior coronary revascularization, low HDL cholesterol, be taking a non-statin lipid-lowering medication, and aspirin or a $P2Y_{12}$ inhibitor compared to whites (Table 1, left panel). African Americans were more likely than whites to have < $25,000 annual household income, less than high school education, a history of stroke, diabetes, a history of multiple cardiovascular events, hsCRP > 2.0 mg/L, metabolic syndrome, hypertension, and ACR ≥ 30 mg/g. Also, African Americans were more likely to be a smoker, have a higher body weight, total, HDL, LDL and non-HDL cholesterol, and triglycerides, and to be taking a RAAS inhibitor compared with whites.

African Americans and whites in the REGARDS study who met the FOURIER inclusion criteria were older and less likely to be male, a smoker, to be taking aspirin or a $P2Y_{12}$ inhibitor, a beta-blocker, and a RAAS inhibitor compared to previously reported characteristics of FOURIER trial participants (Table 1, right panel). African Americans and whites who met the FOURIER inclusion criteria in the REGARDS study were also more likely to have a history of stroke and to be taking ezetimibe compared with FOURIER trial participants. The characteristics of REGARDS study participants 45 to 85 years of age with clinically evident CVD who met versus those who did not meet the FOURIER inclusion criteria by race is shown in Supplemental Table 3.

Risk for outcomes among participants meeting the FOURIER inclusion criteria

The cumulative incidence of the primary and secondary outcomes, all-cause mortality, cardiovascular death, stroke, and MI was similar among African Americans and whites who met the FOURIER inclusion criteria (Fig. 2). The cumulative incidence of coronary revascularization was lower among African Americans compared with whites. At 2.2 years of follow-up, African Americans and whites meeting FOURIER trial inclusion criteria in the REGARDS study had higher cumulative incidence of the primary and secondary outcomes compared to previously reported results among FOURIER trial participants. After multivariable adjustment, the risk for the primary and secondary outcomes, all-cause mortality, cardiovascular death, stroke, and MI were not statistically significantly different between African Americans and whites meeting the FOURIER inclusion criteria

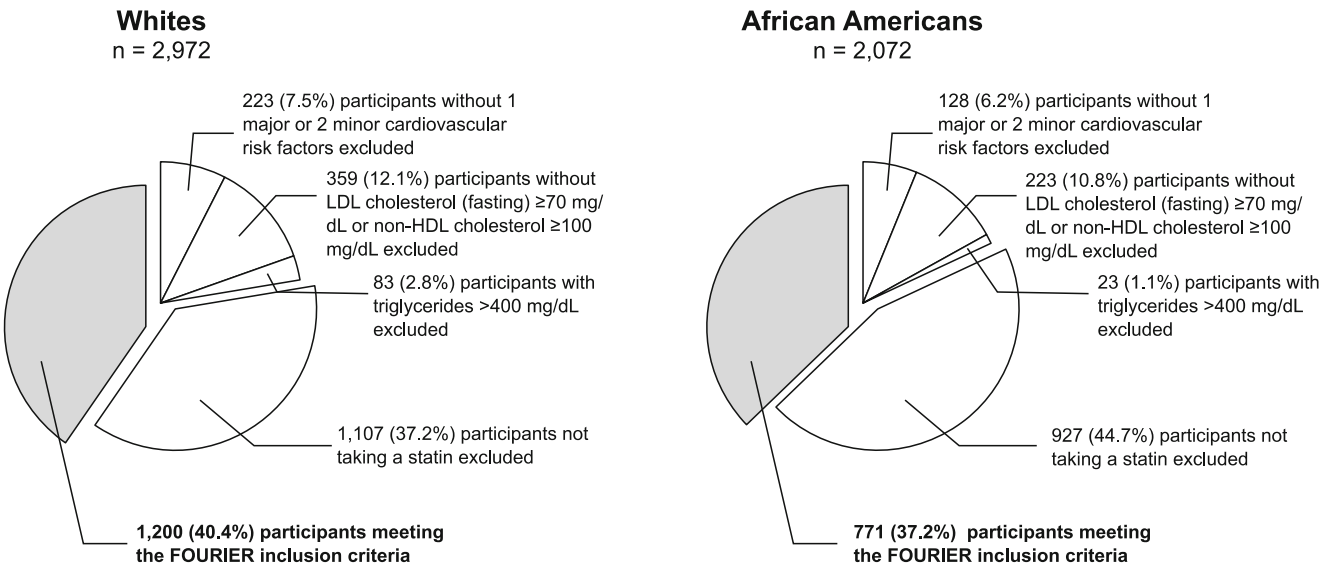

Fig. 1 Inclusion criteria for the FOURIER trial among REGARDS study participants with clinically evident cardiovascular disease. FOURIER, Further cardiovascular OUtcomes Research with proprotein convertase subtilisin/kexin type 9 Inhibition in subjects with Elevated Risk; HDL, high-density lipoprotein; LDL, low-density lipoprotein; REGARDS, REasons for Geographic And Racial Differences in Stroke. Inclusion criteria for the FOURIER trial were applied sequentially and include (1) having one major or two minor cardiovascular risk factors (as defined in Supplemental Table 2), (2) fasting LDL cholesterol ≥ 70 mg/dL or non-HDL cholesterol ≥ 100 mg/dL, (3) triglycerides ≤ 400 mg/dL, and (4) statin use

Table 1 Characteristics of REGARDS study participants with clinically evident cardiovascular disease meeting the FOURIER inclusion criteria (left panel) and FOURIER trial participants (right panel)

	REGARDS study participants			FOURIER trial participants[h]	
Characteristics	White	African Americans	*p* value[g]	Evolocumab	Placebo
N	1200	771		13,784	13,780
Demographics					
Age, years, mean (SD)	69.4 (7.9)	66.9 (8.0)	< 0.001	62.5 (9.1)	62.5 (8.9)
Men, *n* (%)	830 (69.2)	361 (46.8)	< 0.001	10,397 (75.4)	10,398 (75.5)
Geographic region of residence[a] *n* (%)					
Belt	433 (36.1)	233 (30.2)		–	–
Buckle	269 (22.4)	127 (16.5)	< 0.001	–	–
Non-belt region	498 (41.5)	411 (53.3)		–	–
< $25,000 annual household income, *n* (%)	364 (32.0)	410 (56.7)	< 0.001	–	–
Less than high school education, *n* (%)	155 (12.9)	216 (28.0)	< 0.001	–	–
History of cardiovascular disease					
History of myocardial infarction, *n* (%)	926 (77.6)	508 (66.7)	< 0.001	11,145 (80.9)	11,206 (81.3)
History of stroke[b] *n* (%)	325 (27.2)	322 (41.9)	< 0.001	2686 (19.5)	2651 (19.2)
Peripheral artery disease, *n* (%)	139 (11.6)	96 (12.5)	0.55	1858 (13.5)	1784 (12.9)
Major cardiovascular risk factors					
Diabetes, *n* (%)	377 (31.5)	378 (49.1)	< 0.001	5054 (36.7)	5027 (36.5)
Age ≥ 65 years, *n* (%)	864 (72.0)	469 (60.8)	< 0.001	–	–
Current smoking, *n* (%)	200 (16.7)	157 (20.4)	0.03	3854 (28.0)	3923 (28.5)
Multiple cardiovascular events[c] *n* (%)	383 (31.9)	281 (36.4)	0.04	–	–
Minor cardiovascular risk factors					
Coronary revascularization, *n* (%)	733 (61.4)	305 (40.0)	< 0.001	–	–
Low HDL cholesterol[d] *n* (%)	582 (48.5)	322 (41.8)	0.003	–	–
hsCRP > 2.0 mg/L, *n* (%)	595 (50.6)	487 (64.9)	< 0.001	–	–
High LDL or non-HDL cholesterol[e] *n* (%)	129 (10.8)	157 (20.4)	< 0.001	–	–
Metabolic syndrome[f] *n* (%)	655 (54.6)	469 (60.8)	0.006	–	–
Other characteristics					
Weight, kg, mean (SD)	85.9 (17.9)	90.2 (19.9)	< 0.001	85.0 (17.3)	85.5 (17.4)
Hypertension, *n* (%)	852 (71.4)	682 (88.7)	< 0.001	11,045 (80.1)	11,039 (80.1)
Total cholesterol, mg/dL, median (25th–75th pctl)	166 (150, 184)	173 (153, 197)	< 0.001	168 (151, 188)	168 (151, 189)
HDL cholesterol, mg/dL, median (25th–75th pctl)	42 (36, 51)	47 (39, 56)	< 0.001	44 (37, 53)	44 (37, 53)
LDL cholesterol, mg/dL, median (25th–75th pctl)	91 (79, 105)	99 (85, 121)	< 0.001	92 (80, 109)	92 (80, 109)
Non-HDL cholesterol, mg/dL, median (25th–75th pctl)	121 (107, 139)	123 (107, 146)	0.02	–	–
Triglycerides, mg/dL, median (25th–75th pctl)	138 (101, 200)	106 (81, 142)	< 0.001	134 (101, 183)	133 (99, 181)
eGFR < 60 mL/min/1.73 m^2, *n* (%)	268 (22.3)	181 (23.5)	0.56	–	–
ACR ≥ 30 mg/g, *n* (%)	250 (21.6)	241 (33.6)	< 0.001	–	–
Medication use					
Statin type, *n* (%)					
Atorvastatin	443 (36.9)	310 (40.2)	0.14	–	–
Fluvastatin	39 (3.3)	17 (2.2)	0.17	–	–
Lovastatin	94 (7.8)	75 (9.7)	0.14	–	–
Pravastatin	95 (7.9)	57 (7.4)	0.67	–	–
Rosuvastatin	51 (4.3)	37 (4.8)	0.56	–	–
Simvastatin	480 (40.0)	284 (36.8)	0.16	–	–
Any non-statin lipid-lowering medication, *n* (%)	221 (18.4)	68 (8.8)	< 0.001	–	–
Ezetimibe, *n* (%)	98 (8.2)	47 (6.1)	0.09	726 (5.3)	714 (5.2)
Fibrate, *n* (%)	65 (5.4)	7 (0.9)	< 0.001	–	–

Table 1 (continued)

Characteristics	REGARDS study participants			FOURIER trial participants[h]	
	White	African Americans	*p* value[g]	Evolocumab	Placebo
Niacin, *n* (%)	75 (6.3)	17 (2.2)	< 0.001	–	–
Cholestyramine	1 (0.1)	0 (0.0)	0.42	–	–
Aspirin or $P2Y_{12}$ inhibitor, *n* (%)	1002 (83.5)	591 (76.7)	< 0.001	12,766 (92.7)	12,666 (92.0)
Beta-blocker, *n* (%)	618 (51.5)	404 (52.4)	0.70	10,441 (75.8)	10,374 (75.4)
RAAS inhibitor, *n* (%)	703 (58.6)	520 (67.4)	< 0.001	10,803 (78.4)	10,730 (77.9)

ACR, albumin-to-creatinine ratio; *eGFR*, estimated glomerular filtration rate; *FOURIER*, Further cardiovascular OUtcomes Research with proprotein convertase subtilisin/kexin type 9 Inhibition in subjects with Elevated Risk; *HDL*, high-density lipoprotein; *hsCRP*, high-sensitivity C reactive protein; *LDL*, low-density lipoprotein; *pctl*, percentile; *RAAS*, renin-angiotensin-aldosterone system; *REGARDS*, REasons for Geographic And Racial Differences in Stroke; *SD*, standard deviation

[a] Stroke buckle includes coastal North Carolina, South Carolina, and Georgia. Stroke belt includes the remaining parts of the stroke buckle states and Tennessee, Mississippi, Alabama, Louisiana, and Arkansas

[b] The FOURIER trial only included nonhemorrhagic stroke

[c] Multiple cardiovascular events is defined by a history of ≥ 2 myocardial infarction and/or stroke events, or peripheral artery disease in addition to a history of myocardial infarction or stroke

[d] Low HDL cholesterol is defined as HDL cholesterol < 40 mg/dL for men and < 50 mg/dL for women

[e] High LDL cholesterol is defined as fasting LDL cholesterol ≥ 130 mg/dL. High non-HDL cholesterol is defined as fasting or non-fasting non-HDL cholesterol ≥ 160 mg/dL

[f] Metabolic syndrome is defined by having ≥ 3 of the following components: (1) elevated blood pressure, defined as systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or self-reported use of antihypertensive medication; (2) abdominal obesity, defined as waist circumference ≥ 88 cm among women and ≥ 102 cm among men; (3) impaired glucose, defined by a fasting serum glucose ≥ 100 mg/dL (or non-fasting serum glucose ≥ 140 mg/dL), or self-report of a prior diagnosis of diabetes with current use of insulin or oral hypoglycemic medications; (4) low HDL cholesterol, defined as < 40 mg/dL among men and < 50 mg/dL among women; (5) high triglycerides, defined as fasting triglycerides ≥ 150 mg/dL

[g] *p* value comparing white and African American REGARDS study participants meeting the FOURIER inclusion criteria

[h] Characteristics of FOURIER trial participants were adapted from Sabatine et al. [1]

(Table 2). The risk for coronary revascularization was statistically significantly lower among African Americans compared with whites.

Characteristics associated with the primary and secondary outcomes

A history of multiple cardiovascular events, a prior coronary revascularization, diabetes, eGFR < 60 mL/min/1.73 m^2, and ACR ≥ 30 mg/g were associated with a higher risk for the primary outcome among African Americans and whites (Fig. 3). Among African Americans, the risk for the primary outcome was also higher among participants taking aspirin or $P2Y_{12}$ inhibitor, or a beta-blocker. Among whites, the risk for the primary outcome was also higher among men, those with hsCRP > 2.0 mg/L and those taking a non-statin lipid-lowering medication. Higher levels of HDL cholesterol were associated with a lower risk for the primary outcome among African Americans and whites. Hazard ratios for the primary outcome associated with participant characteristics were consistent for African Americans and whites (all interaction *p* values > 0.10). Characteristics associated with the secondary outcome among African Americans and whites meeting the FOURIER inclusion criteria are shown in Supplemental Fig. 2.

Discussion

In the current analysis of a large nationwide cohort study, a substantial proportion of African Americans and whites 45 to 85 years of age with clinically evident CVD met the inclusion criteria for the FOURIER trial. The main reason for not meeting the FOURIER trial inclusion criteria for both African Americans and whites was not being on statin therapy. There were substantial differences in baseline characteristics between African American and white REGARDS study participants who met the inclusion criteria for the FOURIER trial, including demographics, prior history of MI and stroke, and cardiovascular risk factors. Despite these differences, the risk for CVD events was similar among African Americans and whites who met the FOURIER inclusion criteria. Factors associated with a higher risk for CVD events among individuals meeting the FOURIER inclusion criteria were identified and could be used to inform the decision to initiate PCSK9 inhibition in this population.

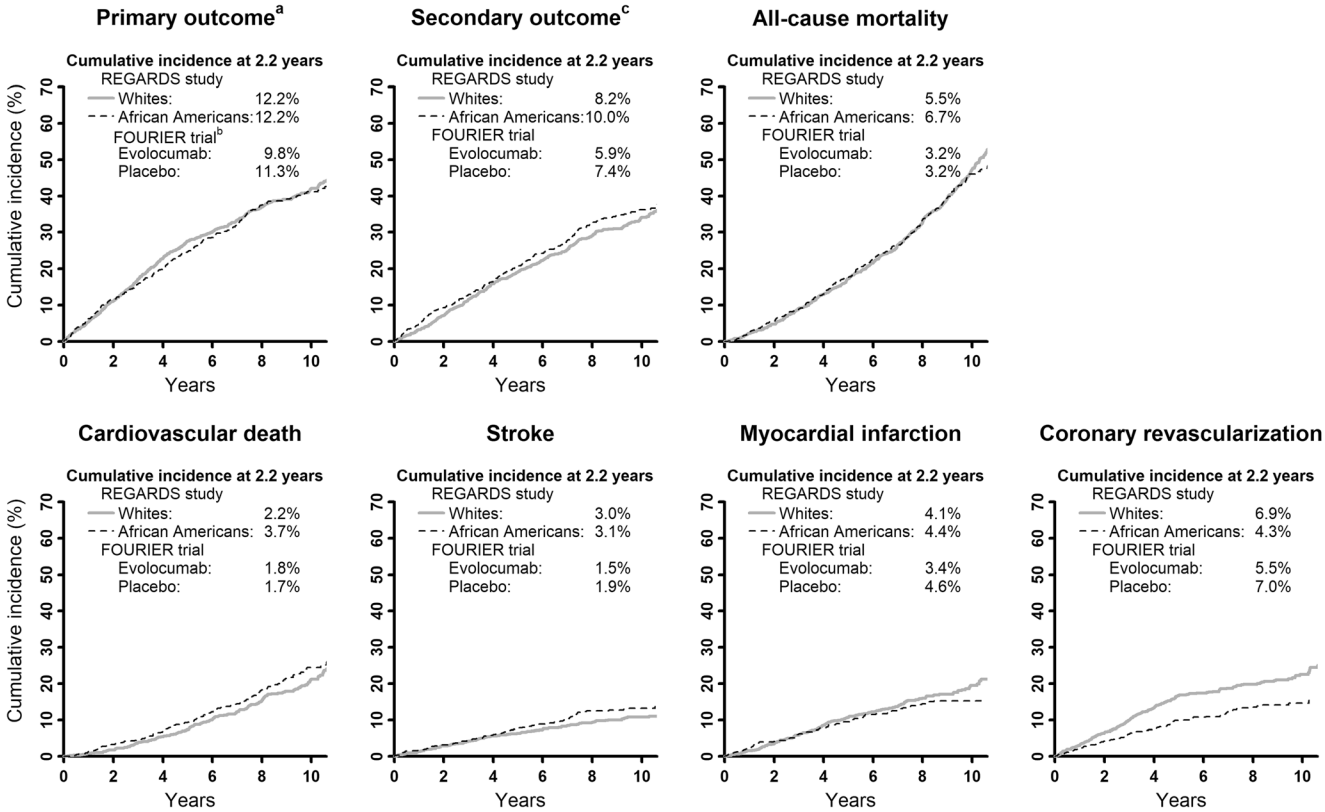

Fig. 2 Cumulative incidence for outcomes among REGARDS study participants with clinically evident cardiovascular disease who met the FOURIER inclusion criteria. FOURIER, Further cardiovascular OUtcomes Research with proprotein convertase subtilisin/kexin type 9 Inhibition in subjects with Elevated Risk; REGARDS, REasons for Geographic And Racial Differences in Stroke. [a]Includes cardiovascular death, stroke, myocardial infarction, or coronary revascularization. [b]Also includes hospitalization for unstable angina. [c]Includes cardiovascular death, stroke, or myocardial infarction. The cumulative incidence of cardiovascular outcomes at 2.2 years among FOURIER trial participants was adapted from Sabatine et al. [1]

In the FOURIER trial, PCSK9 inhibition reduced the risk for the primary and secondary outcomes by 15% and 20%, respectively, compared with placebo among patients with clinically evident CVD taking an optimized regimen of statin therapy [1]. In the current study, a large proportion of African Americans and whites with clinically evident CVD were not taking statins and therefore did not meet the FOURIER inclusion criteria. This finding is consistent with prior studies showing suboptimal use of statin therapy and high rates of statin discontinuation following a CVD event, especially among African Americans [17–20]. Results from the current study suggest that despite the suboptimal use of statin therapy, approximately 40% of African Americans and whites with clinically evident CVD may meet the inclusion criteria for the FOURIER trial. Therefore, results from the FOURIER trial is likely generalizable to a large proportion of African Americans and whites with clinically evident CVD.

There were substantial differences in the baseline characteristics of African Americans and whites who met the FOURIER inclusion criteria in the REGARDS study. Findings from the current analysis are consistent with prior studies showing that African Americans are more likely to have a history of stroke [21, 22], hypertension [23, 24] and albuminuria [25], and less likely to have lower HDL cholesterol [26] compared with whites. African Americans have a higher risk for dying after their first MI compared with whites [27]. This could explain the lower prevalence of a history of MI among African Americans versus whites found in the current analysis. There were also some differences in the characteristics of African American and white REGARDS study participants who met the FOURIER inclusion criteria versus FOURIER trial participants. For example, African Americans and whites who met the FOURIER inclusion criteria in the REGARDS study were more likely to have a history of stroke compared to FOURIER trial participants [1]. This could be explained by FOURIER participants having been recruited using a convenience sampling approach while the REGARDS study enrolled a population-based sample [1, 5].

African Americans were underrepresented in the FOURIER clinical trial [1, 11]. However, there is no reason to anticipate that results from the FOURIER trial may not be generalizable to African Americans. In the current analysis, African Americans and whites who met the FOURIER inclusion criteria had similar rates for the primary and secondary

Table 2 Rates and hazard ratios for cardiovascular outcomes and all-cause mortality among REGARDS study participants who met the FOURIER inclusion criteria

	Whites ($n = 1200$)	African Americans ($n = 771$)
Primary outcome[a]		
Events	460	286
Event rate (95% CI) per 1000 person years	63.5 (57.7, 69.3)	60.6 (53.6, 67.6)
Hazard ratio (95% CI)		
Model 1	1 (reference)	0.98 (0.83, 1.15)
Model 2	1 (reference)	0.92 (0.76, 1.12)
Secondary outcome[b]		
Events	368	250
Event rate (95% CI) per 1000 person years	46.8 (42.0, 51.6)	50.5 (44.3, 56.8)
Hazard ratio (95% CI)		
Model 1	1 (reference)	1.08 (0.90, 1.29)
Model 2	1 (reference)	0.99 (0.80, 1.23)
All-cause mortality		
Events	488	298
Event rate (95% CI) per 1000 person years	55.7 (50.7, 60.6)	54.3 (48.1, 60.5)
Hazard ratio (95% CI)		
Model 1	1 (reference)	1.01 (0.86, 1.19)
Model 2	1 (reference)	0.89 (0.74, 1.08)
Cardiovascular death		
Events	188	139
Event rate (95% CI) per 1000 person years	21.4 (18.4, 24.5)	25.3 (21.1, 29.5)
Hazard ratio (95% CI)		
Model 1	1 (reference)	1.18 (0.93, 1.50)
Model 2	1 (reference)	1.00 (0.75, 1.35)
Stroke		
Events	117	92
Event rate (95% CI) per 1000 person-years	13.9 (11.4, 16.4)	17.6 (14.0, 21.2)
Hazard ratio (95% CI)		
Model 1	1 (reference)	1.34 (0.99, 1.82)
Model 2	1 (reference)	1.06 (0.73, 1.54)
Myocardial infarction		
Events	177	95
Event rate (95% CI) per 1000 person years	21.6 (18.5, 24.8)	18.4 (14.7, 22.1)
Hazard ratio (95% CI)		
Model 1	1 (reference)	0.88 (0.67, 1.16)
Model 2	1 (reference)	0.87 (0.63, 1.20)
Coronary revascularization		
Events	220	89
Event rate (95% CI) per 1000 person years	28.6 (24.8, 32.4)	17.6 (13.9, 21.3)
Hazard ratio (95% CI)		
Model 1	1 (reference)	0.67 (0.52, 0.87)
Model 2	1 (reference)	0.73 (0.54, 0.99)

CHD, coronary heart disease; *CI*, confidence interval; *FOURIER*, Further cardiovascular OUtcomes Research with proprotein convertase subtilisin/kexin type 9 Inhibition in subjects with Elevated Risk; *REGARDS*, REasons for Geographic And Racial Differences in Stroke. The median (maximum) follow-up for mortality is 7.9 (11.8) years

[a] Includes cardiovascular death, stroke, myocardial infarction, or coronary revascularization

[b] Includes cardiovascular death, stroke, or myocardial infarction

Model 1 adjusts for age, gender, geographic region of residence, income, and education

Model 2 adjusts for variables in Model 1 plus history of myocardial infarction, history of stroke, history of peripheral artery disease, multiple cardiovascular events, history of coronary revascularization, smoking, diabetes, hypertension, metabolic syndrome, body weight, total and high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate < 60 mL/min/1.73 m^2 , albumin-to-creatinine ratio ≥ 30 mg/g, highly sensitive C reactive protein > 2.0 mg/L, and medication use, including any non-statin lipid-lowering medication, aspirin or $P2Y_{12}$ inhibitor, beta-blocker, and renin-angiotensin-aldosterone system inhibitor

composite cardiovascular outcomes, all-cause mortality, cardiovascular death, stroke, and MI. However, the rate of coronary revascularization was lower for African American versus white REGARDS study participants who met the FOURIER inclusion criteria. This finding is consistent with prior studies showing that African Americans are less likely to receive a coronary revascularization compared with whites, although the reasons behind this finding are not clearly understood

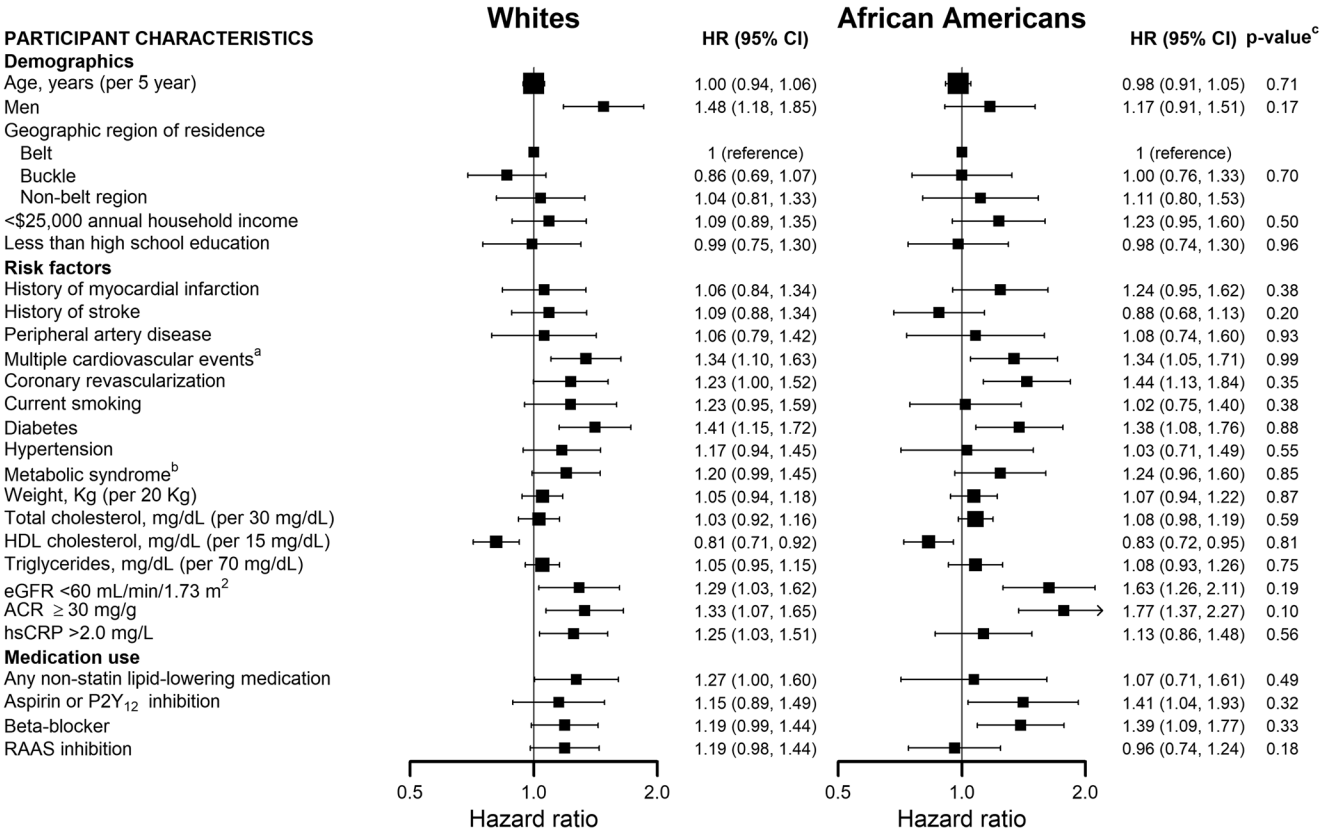

Fig. 3 Hazard ratios for the primary outcome associated with participant characteristics among African Americans and whites who met the FOURIER inclusion criteria. ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; FOURIER, Further cardiovascular OUtcomes Research with proprotein convertase subtilisin/kexin type 9 Inhibition in subjects with Elevated Risk; HDL, high-density lipoprotein; hsCRP, high-sensitivity C reactive protein; LDL, low-density lipoprotein; RAAS, renin-angiotensin-aldosterone system. Hazard ratios adjust for age, gender, geographic region of residence, income, and education. [a]Multiple cardiovascular events is defined by a history of ≥ 2 myocardial infarction and/or stroke events, or peripheral artery disease in addition to a history of myocardial infarction or stroke. Metabolic syndrome is defined by having ≥ 3 of the following components: (1) elevated blood pressure, defined as systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or self-reported use of antihypertensive medication; (2) abdominal obesity, defined as waist circumference ≥ 88 cm among women and ≥ 102 cm among men; (3) impaired glucose, defined by a fasting serum glucose ≥ 100 mg/dL (or non-fasting serum glucose ≥ 140 mg/dL), or self-report of a prior diagnosis of diabetes with current use of insulin or oral hypoglycemic medications; (4) low HDL cholesterol, defined as < 40 mg/dL among men and < 50 mg/dL among women; (5) high triglycerides, defined as fasting triglycerides ≥ 150 mg/dL. [c]*p* values comparing the hazard ratio among African Americans versus whites. The primary outcome includes cardiovascular death, stroke, myocardial infarction, or coronary revascularization

[28–31]. Compared with FOURIER trial participants, African Americans and whites in the REGARDS study who met the FOURIER inclusion criteria had higher CVD event rates. In an analysis conducted by Fonarow et al., patients with commercial health insurance or Medicare Supplemental insurance in the Truven MarketScan database who had a history of CVD also had a higher CVD event rate compared with FOURIER trial participants [3]. Along with the current study, the results from the MarketScan database suggest that the absolute risk reduction associated with PCSK9 inhibition among African Americans and whites with clinically evident CVD in the general population may be larger as compared with what could be expected based on event rates in the FOURIER trial [32].

In clinical practice, it may not be cost-effective to treat all individuals who meet the FOURIER trial inclusion criteria with a PCSK9 inhibitor [2–4]. In the current study, having a history of multiple CVD events, a prior coronary revascularization, diabetes, eGFR < 60 mL/min/1.73 m^2, and ACR ≥ 30 mg/g were associated with a higher risk for CVD events among African American and white REGARDS study participants meeting the FOURIER inclusion criteria. Directing PCSK9 inhibition towards populations with very high CVD risk could result in a larger absolute risk reduction [32]. This could also translate into a lower cost per quality-adjusted life year saved.

The current study has several strengths including using data from a large population-based cohort of African Americans and whites who resided in all 48 contiguous US states and the District of Columbia with long-term follow-up and a rigorous CVD event adjudication process. Despite these strengths, the current study has potential and known limitations. The FOURIER trial included participants with a history of MI, nonhemorrhagic stroke, or PAD. In the current

analysis, a history of stroke was defined by self-report of a prior cerebrovascular event regardless of whether this was ischemic or hemorrhagic as this information is not available in the REGARDS study. This could have contributed to the higher prevalence of history of stroke among REGARDS study participants meeting the FOURIER inclusion criteria versus FOURIER trial participants. Also, the definition of PAD in REGARDS was based on self-report of a prior revascularization procedure in the lower extremities. In the FOURIER trial, PAD was defined as intermittent claudication with ankle-brachial index < 0.85, peripheral artery revascularization, or amputation due to atherosclerotic disease. Therefore, the current analysis may have underrepresented the population with PAD as compared with the FOURIER trial. While FOURIER subjects were on an optimized statin regime, the statin dosage taken by REGARDS study participants at baseline was unavailable and we included all study participants regardless of dose. In a subgroup analysis of participants meeting the FOURIER inclusion criteria who had Medicare pharmacy coverage, over 90% were taking a high- or moderate-intensity statin. Few REGARDS study participants had Medicare pharmacy coverage at baseline as this program started in 2006 and only provides pharmacy benefits to adults ≥ 65 years of age and those with end-stage renal disease or disability [33].

In conclusion, a substantial proportion of African Americans and whites with clinically evident CVD met the FOURIER inclusion criteria. Despite differences in baseline characteristics, African Americans and whites meeting the FOURIER inclusion criteria had a similar risk for CVD events. Among African Americans and whites who met the FOURIER inclusion criteria, those with a history of multiple CVD events, a prior coronary revascularization, diabetes, eGFR < 60 mL/min/1.73 m^2, and ACR ≥ 30 mg/g had a higher risk for CVD events. The results of the current study help to identify sub-groups of African Americans and whites who may receive a larger absolute CVD risk reduction with PCSK9 inhibition.

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Compliance with Ethical Standards

Conflict of Interest KLM, KEM, and LY are employed by Amgen, Inc. KLM and LY also are stockholders of Amgen, Inc. RSR, TMB, MMS, MEF, and PM receive research support from Amgen, Inc. RSR also receives research support from Akcea, Astra Zeneca, Medicines Company, Regeneron and Sanofi, serves on Advisory Boards for Akcea, Amgen, Inc., CVS Caremark, Easy Vitals, Regeneron and Sanofi, receives consulting fees and honoraria from Amgen, Regeneron, C5, CVS Caremark, Kowa and Pfizer, and receives royalties from UpToDate. TMB also receives research support from Astra Zeneca. PM also has received an honorarium from Amgen, Inc. LDC and GH have no disclosures.

Ethical Approval All procedures performed in the current student were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The REGARDS study protocol was approved by the Institutional Review Boards governing research in human subjects at the participating centers.

Informed Consent Informed consent was obtained from all individual participants included in the REGARDS study.

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References

1. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376:1713–22.
2. Kazi DS, Moran AE, Coxson PG, Penko J, Ollendorf DA, Pearson SD, et al. Cost-effectiveness of PCSK9 inhibitor therapy in patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease. JAMA. 2016;316:743–53.
3. Fonarow GC, Keech AC, Pedersen TR, Giugliano RP, Sever PS, Lindgren P, et al. Cost-effectiveness of evolocumab therapy for reducing cardiovascular events in patients with atherosclerotic cardiovascular disease. JAMA Cardiol. 2017;2:1069–78.
4. Arrieta A, Hong JC, Khera R, Virani SS, Krumholz HM, Nasir K. Updated cost-effectiveness assessments of PCSK9 inhibitors from the perspectives of the health system and private payers: insights derived from the FOURIER trial. JAMA Cardiol. 2017;2:1369–74.
5. Howard VJ, Cushman M, Pulley L, Gomez CR, Go RC, Prineas RJ, et al. The REasons for geographic and racial differences in stroke study: objectives and design. Neuroepidemiology. 2005;25:135–43.
6. Carnethon MR, Pu J, Howard G, Albert MA, Anderson CAM, Bertoni AG, et al. Cardiovascular health in African Americans: a scientific statement from the American Heart Association. Circulation. 2017;136:e393–423.
7. Gamboa CM, Colantonio LD, Brown TM, Carson AP, Safford MM. Race-sex differences in statin use and low-density lipoprotein cholesterol control among people with diabetes mellitus in the reasons for geographic and racial differences in stroke study. J Am Heart Assoc. 2017;6:e004264.

8. Safford MM, Brown TM, Muntner PM, Durant RW, Glasser S, Halanych JH, et al. Association of race and sex with risk of incident acute coronary heart disease events. JAMA. 2012;308:1768–74.
9. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499–502.
10. Levey AS, Stevens LA, Schmid CH, Zhang Y(L), Castro AF III, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604–12.
11. Sabatine MS, Giugliano RP, Keech A, Honarpour N, Wang H, Liu T, et al. Rationale and design of the Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk trial. Am Heart J. 2016;173:94–101.
12. Colantonio LD, Kent ST, Kilgore ML, Delzell E, Curtis JR, Howard G, et al. Agreement between Medicare pharmacy claims, self-report, and medication inventory for assessing lipid-lowering medication use. Pharmacoepidemiol Drug Saf. 2016;25:827–35.
13. Xie F, Colantonio LD, Curtis JR, Safford MM, Levitan EB, Howard G, et al. Linkage of a population-based cohort with primary data collection to Medicare claims: the reasons for geographic and racial differences in stroke study. Am J Epidemiol. 2016;184:532–44.
14. Howard VJ, Kleindorfer DO, Judd SE, McClure LA, Safford MM, Rhodes JD, et al. Disparities in stroke incidence contributing to disparities in stroke mortality. Ann Neurol. 2011;69:619–27.
15. Soliman EZ, Howard G, Cushman M, Kissela B, Kleindorfer D, le A, et al. Prolongation of QTc and risk of stroke: the REGARDS (REasons for Geographic And Racial Differences in Stroke) study. J Am Coll Cardiol. 2012;59:1460–7.
16. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94:496–509.
17. Albright KC, Zhao H, Blackburn J, Limdi NA, Beasley TM, Howard G, et al. Racial differences in statin adherence following hospital discharge for ischemic stroke. Neurology. 2017;88:1839–48.
18. Colantonio LD, Huang L, Monda KL, Bittner V, Serban MC, Taylor B, et al. Adherence to high-intensity statins following a myocardial infarction hospitalization among Medicare beneficiaries. JAMA Cardiol. 2017;2:890–5.
19. Rosenson RS, Kent ST, Brown TM, Farkouh ME, Levitan EB, Yun H, et al. Underutilization of high-intensity statin therapy after hospitalization for coronary heart disease. J Am Coll Cardiol. 2015;65:270–7.
20. Yun H, Safford MM, Brown TM, et al. Statin use following hospitalization among Medicare beneficiaries with a secondary discharge diagnosis of acute myocardial infarction. J Am Heart Assoc. 2015;4:e001208.
21. Albright KC, Boehme AK, Tanner RM, Blackburn J, Howard G, Howard VJ, et al. Addressing stroke risk factors in black and white Americans: findings from the National Health and Nutrition Examination Survey, 2009-2010. Ethn Dis. 2016;26:9–16.
22. Huxley RR, Bell EJ, Lutsey PL, Bushnell C, Shahar E, Rosamond W, et al. A comparative analysis of risk factors for stroke in blacks and whites: the atherosclerosis risk in communities study. Ethn Health. 2014;19:601–16.
23. Carson AP, Howard G, Burke GL, Shea S, Levitan EB, Muntner P. Ethnic differences in hypertension incidence among middle-aged and older adults: the multi-ethnic study of atherosclerosis. Hypertension. 2011;57:1101–7.
24. Nwankwo T, Yoon SS, Burt V, Gu Q. Hypertension among adults in the United States: National Health and Nutrition Examination Survey, 2011-2012. NCHS Data Brief. 2013:1–8.
25. United States Renal Data System. Incidence, Prevalence, Patient Characteristics, and Treatment Modalities. 2015. In: USRDS annual data report: Epidemiology of Kidney Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2015.
26. Yu SS, Castillo DC, Courville AB, Sumner AE. The triglyceride paradox in people of African descent. Metab Syndr Relat Disord. 2012;10:77–82.
27. Colantonio LD, Gamboa CM, Richman JS, Levitan EB, Soliman EZ, Howard G, et al. Black-white differences in incident fatal, nonfatal, and total coronary heart disease. Circulation. 2017;136:152–66.
28. Mathews R, Chen AY, Thomas L, et al. Differences in short-term versus long-term outcomes of older black versus white patients with myocardial infarction: findings from the can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of American College of Cardiology/American Heart Association Guidelines (CRUSADE). Circulation. 2014;130:659–67.
29. Anstey DE, Li S, Thomas L, Wang TY, Wiviott SD. Race and sex differences in management and outcomes of patients after ST-elevation and non-ST-elevation myocardial infarct: results from the NCDR. Clin Cardiol. 2016;39:585–95.
30. Patel N, Patel NJ, Macon CJ, Thakkar B, Desai M, Rengifo-Moreno P, et al. Trends and outcomes of coronary angiography and percutaneous coronary intervention after out-of-hospital cardiac arrest associated with ventricular fibrillation or pulseless ventricular tachycardia. JAMA Cardiol. 2016;1:890–9.
31. Nallamothu BK, Lu X, Vaughan-Sarrazin MS, Cram P. Coronary revascularization at specialty cardiac hospitals and peer general hospitals in black Medicare beneficiaries. Circ Cardiovasc Qual Outcomes. 2008;1:116–22.
32. Mark DB, Richman I, Hlatky MA. Proprotein convertase subtilisin/kexin type 9 inhibitor therapy-breakthrough in low-density lipoprotein cholesterol lowering, breakdown in value. JAMA Cardiol. 2017;2:1066–8.
33. Centers for Medicare & Medicaid Services (CMS). Medicare program; Medicare prescription drug benefit. Final rule. Fed Regist. 2005;70:4193–585.