Generalizability of the FOURIER trial to routine clinical care: Do trial participants represent patients in everyday practice?

Xiaoxi Yao, PhD, [a,b] Bernard J Gersh, MB, ChB, DPhil, FRCP, [c] Francisco Lopez-Jimenez, MD, [c] Nilay D Shah, PhD, [a,b,d] and Peter A Noseworthy, MD [a,c] *Rochester and Cambridge, MA*

Background In the FOURIER trial, evolocumab, a proprotein convertase subtilisin-kexin type 9 inhibitor, reduced cardiovascular events in patients with atherosclerotic cardiovascular disease (ASCVD). We aimed to examine how closely patients in routine practice resemble the FOURIER trial participants and to assess the observed cardiovascular risks based on trial eligibility and underrepresentativeness.

Methods Using a large US administrative database with linked laboratory data, we identified adult patients with ASCVD between January 1, 2012, and December 31, 2016. We identified the excluded and underrepresented populations and examined the risk of cardiovascular events (a composite endpoint of myocardial infarction [MI], stroke, angina, and coronary revascularization) based on trial eligibility and underrepresentativeness.

Results Only 15.2% of 233,977 patients met the FOURIER eligibility. Nearly 60% of the ineligible patients met at least 2 exclusion criteria. Among trial-eligible patients, elderly patients, women, minorities, and those without prior MI were underrepresented in FOURIER. Patients who would have been excluded from FOURIER had a diverse risk profile but, on average, had a lower cardiovascular risk than those who would have qualified (hazard ratio [HR] 0.84 [0.81-0.88], $P < .001$). Among the underrepresented patients, women and patients without prior MI had a lower cardiovascular risk (HR 0.77 [0.71-0.82], $P < .001$; HR 0.67 [0.63-0.72], $P < .001$, respectively). Only 47.2% of patients were on moderate-/high-intensity statins.

Conclusions One in 7 ASCVD patients in practice would have qualified for FOURIER. The excluded and underrepresented populations were at a particularly low or high cardiovascular risk. Statin therapy was underused, and physicians may need to evaluate adherence before adding a proprotein convertase subtilisin-kexin type 9 inhibitor. (Am Heart J 2019;209:54-62.)

From the [a]Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN, [b]Division of Health Care Policy and Research, Department of Health Sciences Research, Mayo Clinic, Rochester, MN, [c]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, and [d]OptumLabs, Cambridge, MA.

Subject terms: Lipids and Cholesterol, Secondary Prevention, Atherosclerosis, Myocardial Infarction, Ischemic Stroke

Funding source: This study was funded by the Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery. The design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication were solely the responsibility of the authors listed.

Conflict of interest disclosure: Dr Gersh serves on the data and safety monitoring board for Janssen Research & Development, Mount Sinai St Luke's, Boston Scientific, Teva, St Jude Medical, Thrombosis Research Institute, Duke Clinical Research Institute, Kowa Research Institute, and Cardiovascular Research Foundation and provides general consulting for Janssen Scientific Affairs (formerly known as Ortho-McNeil), Xenon Pharmaceuticals, and Sirtex Medical.

All authors have no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, and no other relationships or activities that could appear to have influenced the submitted work.

Submitted May 17, 2018; accepted September 30, 2018.

Reprint requests: Peter A. Noseworthy, MD, Associate Professor of Medicine, Department of Cardiovascular Diseases, Electrophysiology, Mayo Clinic College of Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905.

E-mail: Noseworthy.peter@mayo.edu

0002-8703

https://doi.org/10.1016/j.ahj.2018.09.015

In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk (FOURIER) trial, evolocumab, a proprotein convertase subtilisin-kexin type 9 inhibitor (PCSK9i), reduced the risk of cardiovascular events when added to statin therapy in 27,564 patients with atherosclerotic cardiovascular disease (ASCVD).[1] There has been a long-standing debate whether reducing low-density lipoprotein cholesterol (LDL-C), regardless of the means, would reduce cardiovascular events, and this landmark trial was the first to provide formal evidence that evolocumab confers cardiovascular benefit. However, the trial participants may represent only a narrow spectrum of patients encountered in everyday practice. Considering the high cost of the drug, a rigorous assessment of the trial generalizability is needed before the results could be translated to broad patient populations.

The generalizability of a randomized controlled trial is particularly problematic to patients who were excluded from or underrepresented in the trial. Therefore, we aimed to examine the proportion of ASCVD patients in routine clinical practice who would have been excluded

from FOURIER, and identified trial-eligible but underrepresented patient groups. Essentially, we seek to answer the questions commonly asked by clinicians when assessing whether the trial results could apply to their patients: "would my patient have been included in this trial?" and, if so, "are patients like mine well enough represented in the trial so that the findings are applicable?"

Another key driver of the divergent treatment benefits observed in randomized controlled trials and routine practice is that the trials may have selected patients who would benefit most from the experimental treatment. For example, patients at high risk of cardiovascular events may derive more benefits (ie, absolute risk reduction) from the addition of a PCSK9i than low-risk patients even if the relative risk reduction is similar across the risk spectrum. Therefore, a secondary aim is to examine the observed cardiovascular risk based on trial eligibility and underrepresentativeness to better understand the potential benefit from further risk reduction with a PCSK9i in broad populations.

Methods

Study population

We identified adult patients (age $\geq$ 21 years) with ASCVD between January 1, 2012, and December 31, 2016, using OptumLabs Data Warehouse (OLDW), which contains >160 million privately insured and Medicare Advantage enrollees of all ages and races from all 50 states.[2,3] *ASCVD* was defined as history of myocardial infarction (MI), angina, coronary revascularization, ischemic stroke, transient ischemic attack (TIA), and peripheral artery disease (PAD). This definition was based on the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guideline on the treatment of blood cholesterol.[4]

The date of assessing trial eligibility was defined as the index date. We required patients to have at least 12-month enrollment in health insurance plans prior to the index date. We also required patients to have lipid measurements within 90 days prior to the index date, including LDL-C, high-density lipoprotein cholesterol (HDL-C), total cholesterol, and triglycerides. The index date was the first day when patients satisfied the 12-month enrollment and lipid measurement criteria after the start of the study period (ie, January 1, 2012). The mean time from the lipid measurement to the index date was 8.5 days. After determining the index date and the baseline period (ie, the 12 months before index date), we limited the cohort to patients with ASCVD at baseline. ASCVD was defined using previously described and validated algorithms.[5-7]

The index date was essentially an arbitrary date to assess trial eligibility, but the time when patients receive a recent cholesterol measurement is often the time when physicians and patients make decisions on subsequent treatment. Not all ASCVD patients had a recent lipid measurement, but it is highly unlikely that physicians would make a treatment decision without measuring lipids first. Not all patients with insurance claims data had linked laboratory results, but the availability of laboratory results depends on the contracts between laboratory testing facilities and OLDW. In our prior investigation, patients with and without linked laboratory results had similar demographic and clinical characteristics. Patients' geographic location (ie, closer to a laboratory testing facility that submits data to OLDW) is mostly predictive of whether patients had linked laboratory data. As such, the selection of patients should not have introduced any undue bias.

The Mayo Clinic Institutional Review Board exempted this study from approval. Informed consent was not required because the study used preexisting, deidentified data.

Patient characteristics

We used patients' claims and laboratory results over the baseline period to capture their medical history and assess trial eligibility. Not all patients had laboratory tests such as serum creatinine (available in 94% of patients) and thyroid-stimulating hormone test (available in 61% of patients). Patients who did not receive these tests were likely those without clinically evident renal or thyroid dysfunction, and the proportion of patients who met the exclusion criteria due to renal failure or untreated thyroid disease was very small. Medication use (ie, statin, β-blocker, angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, aldosterone antagonist) was defined based on the prescription fills within 90 days before the index day. The intensity of statin was defined based on the 2013 ACC/AHA guidelines.[4]

Statistical analysis

Potential eligibility for the trial was determined based on the trial inclusion and exclusion criteria. Detailed description of the trial eligibility criteria and the operational definition used in this study were shown in Appendix Table III. We assessed the percentages of patients who failed to meet trial eligibility for each criterion, and patients could be ineligible because of multiple criteria. We calculated the percentages of patients who met the trial eligibility in the overall population, as well as in subgroups defined by age, sex, race, type of atherosclerosis, and LDL-C.

To examine which subgroups of patients were potentially eligible but underrepresented in the trial, we compared the characteristics of trial-eligible patients to the FOURIER participants. The patient characteristics examined were selected based on the characteristics reported in the FOURIER trial. We calculated both the absolute and relative differences between the 2 groups to identify the key drivers of underrepresentativeness.

FOURIER only included patients on moderate- or high-intensity statin therapy; however, statin therapy is underused in routine clinical care.[8] Therefore, we assessed the proportion of patients using moderate-/high-intensity statin by age, sex, race, type of atherosclerosis, and baseline LDL-C level. Because the 2013 ACC/AHA guidelines recommended high-intensity statin for ASCVD patients ≤75 years and moderate intensity is reasonable in patients >75 years, we further evaluated the proportion of patients received guideline-recommended statin therapy.[4]

We examined the risks of cardiovascular events during follow-up, that is, from the day after index date until the end of insurance enrollment or the end of the study period (ie, December 31, 2016). The primary outcome was a composite end point of MI, stroke, angina, or coronary revascularization. The secondary outcome was a composite end point of MI and stroke. The 2 outcomes were selected based on the primary efficacy end point and the key secondary efficacy end point used in the FOURIER trial. MI, stroke, and angina were defined as a hospitalization with a primary or secondary diagnosis of these conditions. Coronary revascularization was defined using procedure billing codes. Because our data source did not include a reliable assessment of the cause of death, cardiovascular death was not included in the outcomes, but in FOURIER, evolocumab did not demonstrate a reduction in cardiovascular death (hazard ratio [HR] 1.05 [0.88-1.25]).

We calculated cumulative risks up to 5 years and stratified by potential trial eligibility. We compared the risks between patients who met the trial eligibility to those who did not using Cox proportional-hazards regression. Because the risks were likely affected by the reasons for trial ineligibility, we also performed regression analyses using reasons for trial ineligibility as independent variables. We also investigated the risk for major underrepresented groups, for example, comparing the risks between men and women and between patients with and without prior MI among trial-eligible patients. We also descriptively compared the cardiovascular risk between the trial-eligible patients to the FOURIER placebo arm. We used matching-adjusted indirect comparison analysis to adjust for age, gender, MI, hypertension, diabetes, and statin intensity so that the weighted trial-eligible OLDW population had similar baseline characteristics as the trial participants.[9,10]

Sensitivity analysis

First, because a major reason for trial ineligibility was no moderate- or high-intensity statin therapy, as a sensitivity analysis, we limited to patients who were treated with a moderate- or high-intensity statin and assessed the proportion of patients meeting trial eligibility. This analysis provided some insights into how many patients would qualify for the trial if the statin criterion was met.

Second, some patients did not meet trial eligibility because they did not have a history of MI, ischemic stroke, or PAD but were considered having ASCVD due to a history of angina, coronary revascularization, or TIA. We included these patients in the main analysis because the guideline recommendations on lipid-lowering therapy are the same for patients with different subtypes of ASCVD.[4] In the sensitivity analysis, we focused only on patients with a history of MI, ischemic stroke, or PAD and assessed the proportion of meeting trial eligibility.

Third, the cohort included patients over the past 5 years. There is the reasonable expectation that the increasing availability of generic statin, reduced out-of-pocket cost, and the 2013 ACC/AHA guideline recommendations could increase the use of moderate- or high-intensity statin over time.[8,11] We assessed the proportion of patients meeting trial eligibility and the proportion of statin users by year.

We did not exclude patients who used a PCSK9i because the use often happened toward the end of follow-up and the adoption was slow. Only 161 (<0.1%) patients ever used a PCSK9i. We did a sensitivity analysis using these patients' first prescription of PCSK9i as the index date, assessed their eligibility for FOURIER at the time of prescription, and described their characteristics.

No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Results

Proportion of patients meeting FOURIER eligibility criteria

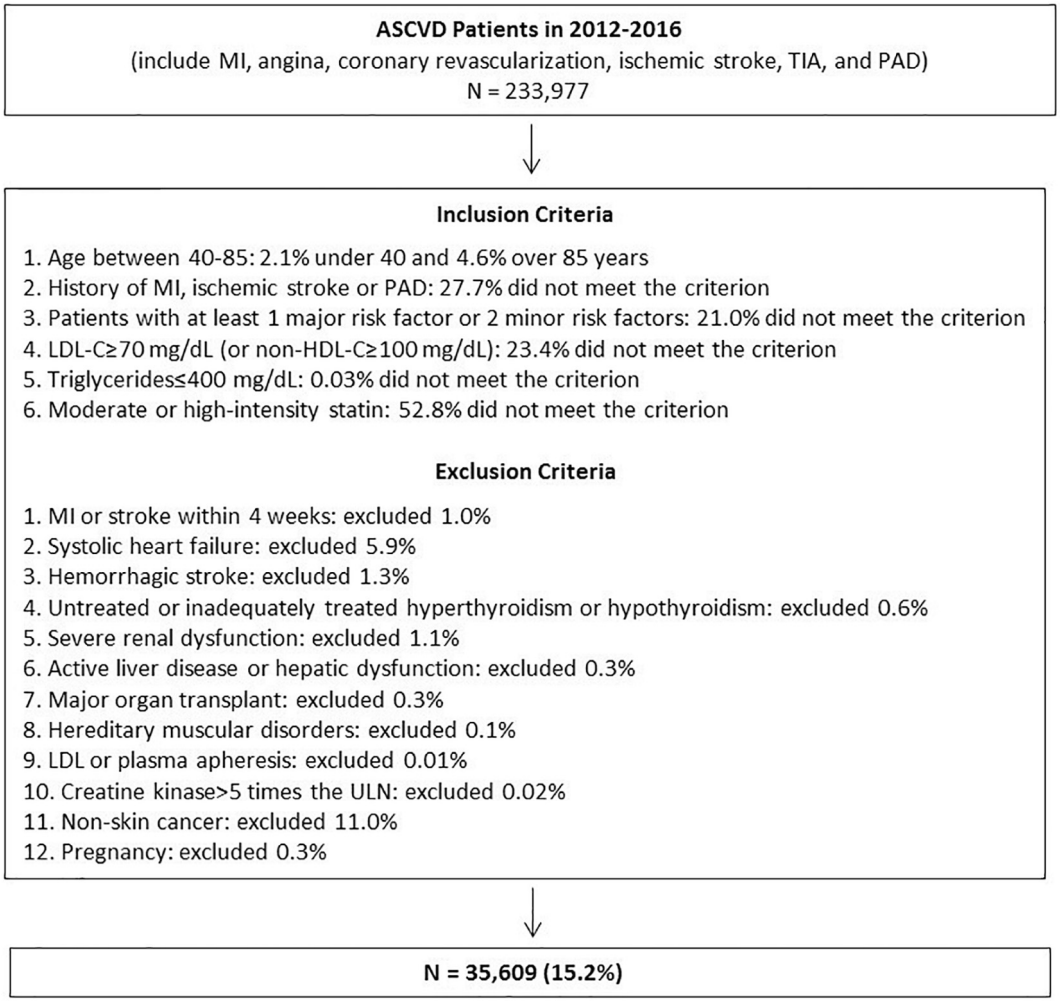
We identified 233,977 adult patients with ASCVD, of whom 35,609 (15.2%) would have met all the eligibility criteria (Figure 1). Approximately 56.1% of the ineligible patients were excluded due to 2 or more reasons. Major reasons for ineligibility included not treated with moderate- or high-intensity statin (52.8%), lack of history of MI, ischemic stroke or PAD (27.7%), absence of additional risk factors (21.0%), low cholesterol level (23.4%), nonskin cancer (11.0%), and systolic heart failure (5.9%). Table I and Appendix Figure 1 illustrate the percentages of patients meeting trial eligibility in subgroups.

A small proportion of patients with LDL-C < 70 mg/dL met trial eligibility because they had non–HDL-C ≥ 100 mg/dL. Subgroups of patients who were younger (<55 years) or older (>75 years), who had very low (<70 mg/dL) or high (≥160 mg/dL) LDL-C, and who had angina or TIA had a lower proportion of patients meeting trial eligibility (Figure 2).

Trial-eligible but underrepresented subgroups

Table II compares the baseline characteristics of FOURIER participants to the trial-eligible patients in our

Figure 1



Flowchart showing the eligibility criteria for FOURIER applied to adult patients with clinical ASCVD in routine clinical care, 2012-2016.

cohort. The trial-eligible OLDW patients were on average older than FOURIER participants (mean age 68.6 ± 9.9 vs 62.5 ± 8.9 years) and consisted of a higher proportion of women (46.4% vs 24.5%) and minorities (33.4% vs 15.0%) but a lower proportion of patients with a history of MI (42.0% vs 81.3%); the baseline lipid measures were similar, for example, the median LDL-C was 88 (interquartile range [IQR] 77-105) mg/dL versus 92 (IQR 80-109 mg/dL). The characteristics of patients who would be excluded from FOURIER were shown in Appendix Table IV.

Only 47.2% of patients were on a moderate- or high-intensity statin, and only 24.8% were on guideline-0 recommended statin doses (Appendix Table V). The proportion of patients using statin was particularly low in patients with high LDL-C, suggesting that many patients had high LDL-C due to the underuse of statin therapy.

Risk of cardiovascular events based on trial eligibility and underrepresentativeness

Over a mean 1.8 ± 1.3 years of follow-up (median 1.5 [IQR 0.75-2.7] years), we observed 18,579 cardiovascular events (event rate 4.65 per 100 person-years), of which 11,699 were MI or stroke (event rate 2.85 per 100 person-years).

Patients who would have been excluded from FOURIER had a lower risk of cardiovascular events than those who would have qualified (5-year risk: 17.9% vs 21.2%; HR 0.84 [0.81-0.88], $P < .001$). However, the risk in the excluded patients depended on the reasons for ineligibility (Appendix Table I). Patients who were excluded due to various low risk features (age <40 years, no history of MI, ischemic stroke, or PAD, no major risk factors or less than 2 minor risk factors, low cholesterol levels, no prior treatment with moderate- or high-

Table I. Percentages of patients meeting FOURIER eligibility in subgroups

Characteristics	ASCVD patients n (%)	Percentages of meeting FOURIER eligibility
Overall	233,977 (100%)	15.2%
Age, y		
<55	35,729 (15.3%)	9.9%
55-65	55,317 (23.6%)	14.7%
66-75	75,537 (32.3%)	19.5%
>75	67,394 (28.8%)	13.6%
Sex		
Men	123,342 (52.7%)	15.5%
Women	110,635 (47.3%)	14.9%
Race/ethnicity		
Asian	7156 (3.1%)	12.6%
Black	32,467 (13.9%)	16.7%
Hispanic	27,021 (11.5%)	15.0%
White	156,603 (66.9%)	15.1%
Other/unknown	10,730 (4.6%)	14.2%
Type of ASCVD		
MI	66,940 (28.6%)	22.3%
Ischemic STROKE	52,920 (22.6%)	20.3%
PAD	66,911 (28.6%)	20.9%
Angina	58,832 (25.1%)	7.1%
Coronary revascularization	23,679 (10.1%)	17.3%
TIA	38,842 (16.6%)	9.6%
LDL-C, mg/dL		
<70	62,501 (26.7%)	4.5%
70-100	83,001 (35.5%)	26.0%
100-160	76,682 (32.8%)	13.2%
≥160	11,793 (5.0%)	9.1%

intensity statin) had lower risk of cardiovascular events;, whereas patients who were excluded due to various high risk features (age >85 years, recent MI or stroke, systolic heart failure, hemorrhagic stroke, renal failure, and nonskin cancer) had a higher risk of cardiovascular events.

The risk of cardiovascular events in real-world trial-eligible patients was similar to the FOURIER placebo arm (3-year risk: 14.4% vs 14.6%; Appendix Figure 1). This analysis assessed 3-year risks because the trial only reported risks up to 3 years. The risk of the secondary outcome, MI or ischemic stroke, was also similar to the secondary efficacy end point in the trial (8.9% vs 9.9%). After we adjusted the real-world trial-eligible patients to have similar baseline characteristics as the trial participants, the risks were still similar. The 3-year risk was 16.1% and 7.7% for the primary and secondary outcomes, respectively.

We also investigated the cardiovascular risk in major groups of patients who met the trial eligibility but were underrepresented, that is, elderly, women, minorities, and patients without prior MI. We focused on these 4 groups because the underrepresentativeness was likely due to the underenrollment of these patients in the trial, whereas the difference in the prevalence of other comorbidities (eg, diabetes) or medications (eg, statins) was likely due to the underenrollment of these 4 groups or the underuse of optimal medical therapies.

We found that the underrepresented patients, particularly women and patients without a history of MI, had a lower risk of cardiovascular events. The 5-year risk was 18.4% for women and 23.8% for men (HR 0.77 [0.71-0.82], $P < .001$), 18.9% for patients without a history of MI, and 24.5% for patients with prior MI (HR 0.67 [0.63-0.72], $P < .001$, Appendix Table II).

Sensitivity analysis

In patients who were treated with moderate-/high-intensity statin, only 32.2% would have qualified for the trial. Among the ineligible patients, key reasons for ineligibility included low cholesterol levels (49.3%); lack of history of MI, ischemic stroke, or PAD (35.9%); absence of additional risk factors (27.5%); nonskin cancer (15.4%); systolic heart failure (10.2%); and a very young or old age (6.1%).

In patients who had a history of MI, ischemic stroke, or PAD, that is, excluding patients who only had angina, TIA, or coronary revascularization, the proportion of trial-eligible patients was 21% (Appendix Table VI). Among the ineligible patients, key reasons for ineligibility included no moderate- or high-intensity statin therapy (64.1%), low cholesterol levels (32.0%), absence of additional risk factors (17.6%), nonskin cancer (14.6%), systolic heart failure (8.9%), and younger or older age (8.7%).

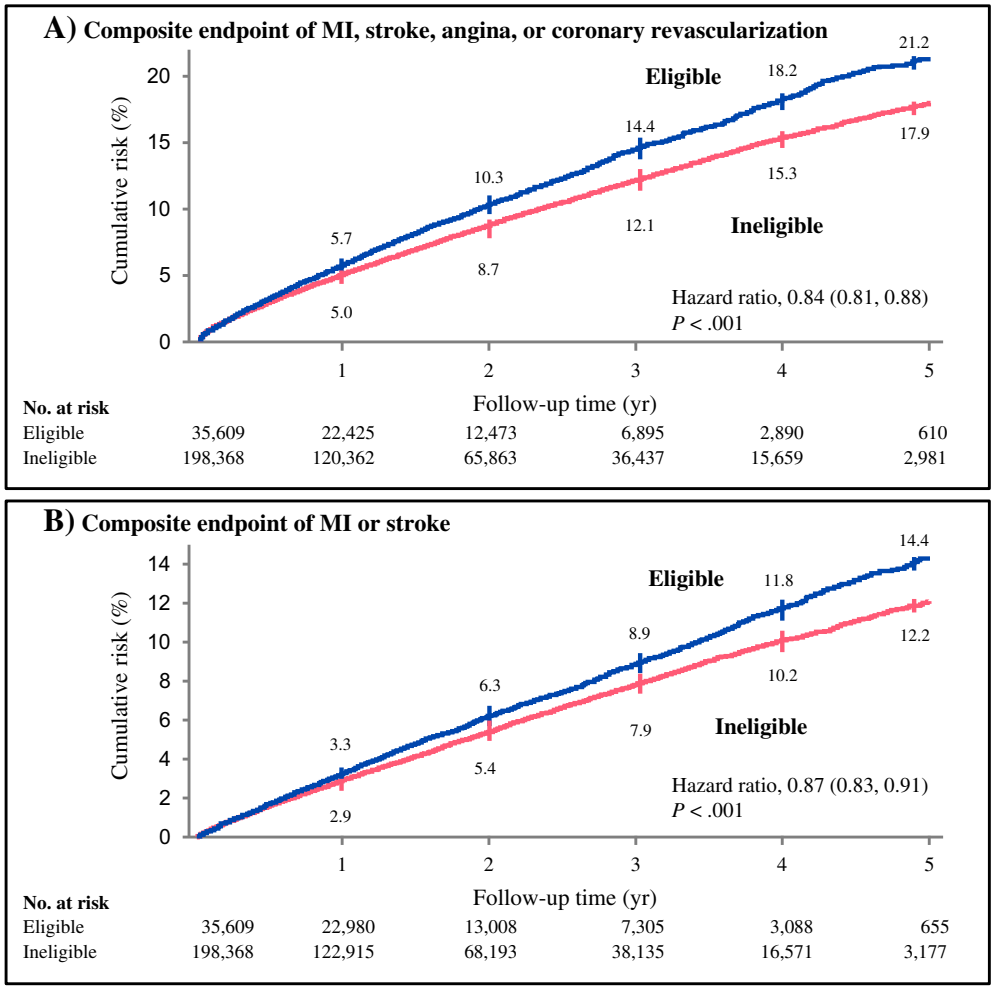
The proportion of trial-eligible patients did not change appreciably over time (Appendix Table VII). Although the use of high-intensity statin therapy did increase somewhat over time, it remained suboptimal, at only 22.1% of patients ≤75 years, at the end of the study period in 2016 (in comparison to 15.1% in 2012). This observed proportion was lower than that previously reported in the post-MI setting[11] but may better reflect the long-term use in broad populations. The decreased proportion of trial-eligible patients in patients >75 years was due to the increased proportion of patients with multiple comorbidities.

Among the 161 ASCVD patients who were prescribed a PCSK9i and had linked lipid results at that time, 90% would have been excluded from FOURIER. Among the ineligible patients, 60% would have met at least 2 ineligibility criteria; major reasons included no moderate- or high-intensity statin therapy (73.8%); lack of history of MI, ischemic stroke, or PAD (44.1%); low cholesterol levels (26.9%); systolic heart failure (11.0%); and nonskin cancer (4.8%). The mean age of the patients was 64.2 years; 41.6% were female; 32.3% were minorities; and 47.8% had MI. The median LDL was 117 (IQR 68-154); 17.4% used ezetimibe; 55.3% did not use any statin or ezetimibe (Appendix Table VIII).

Discussion

The FOURIER trial, which enrolled nearly 30,000 patients from 49 countries, has the potential to

Figure 2



Risks of cardiovascular events by whether patients would have met FOURIER eligibility criteria.

revolutionize the approach to cardiovascular risk reduction in millions of patients. Therefore, thoughtful interpretation and judicious translation of the trial findings are paramount. Our study is the first to examine how closely patients in routine clinical practice resemble those enrolled in FOURIER and to assess the observed cardiovascular risks based on trial eligibility and underrepresentativeness. We found that only a minority of patients would have qualified for the trial. Elderly patients, women, minorities, and those without prior MI were underrepresented in the trial. The excluded and underrepresented populations were at particularly low or high cardiovascular risk. Most patients who received a PCSK9i in practice would not have qualified for FOURIER.

These findings should not detract from the value of this well-conducted and important clinical trial but rather underscore the challenge in translating such trial results to everyday practice. Because the absolute benefit of a therapy is a function of a patient's baseline risk and the relative risk reduction, many patients encountered in practice may derive fewer benefits from PCSK9i due to the low baseline risk. It is also uncertain whether PCSK9i will achieve a similar relative risk reduction in the excluded or underrepresented populations as in FOURIER.

Our finding that the majority of patients would not have qualified for FOURIER is consistent with a recent report using the US Veterans Affairs data,[12] but our broader cohort is more representative of routine practice. Although many patients were ineligible for FOURIER because they were not treated with moderate- or high-intensity statins, even among patients who were, 2 in 3 would have been excluded for other reasons. Our main analysis was not restricted to patients treated with statins because we aimed to inform providers regarding what

Table II. Comparison of FOURIER trial participants and OLDW trial-eligible patients to identify major underrepresented groups

Characteristics	FOURIER placebo arm (n = 13,780)	OLDW trial-eligible patients (n = 35,609)	Absolute difference in prevalence	Ratio of prevalence
Age, mean ± SD	62.5 ± 8.9	68.6 ± 9.9		
Age ≥ 65 y	44.5%	70.1%	−25.6%	0.6
Female sex	24.5%	46.4%	−21.9%	0.5
Nonwhite race	15.0%	33.4%	−18.4%	0.4
Type of atherosclerosis				
MI	81.3%	42.0%	39.3%	1.9
Ischemic stroke	19.2%	30.2%	−11.0%	0.6
PAD	12.9%	39.2%	−26.3%	0.3
Median lipid measures (IQR), mg/dL				
LDL-C	92 (80-109)	88 (77-105)		
Total cholesterol	168 (151-189)	167 (151-189)		
HDL-C	44 (37-53)	46 (38-57)		
Triglycerides	133 (99-181)	135 (97-191)		
Cardiovascular risk factors and medications				
Hypertension	80.1%	93.4%	−13.3%	0.9
Diabetes mellitus	36.5%	49.6%	−13.1%	0.7
β-Blocker	75.4%	42.2%	33.2%	1.8
ACE inhibitor or ARB, aldosterone antagonist	77.9%	62.5%	15.4%	1.2
Statin use				
High intensity	69.1%	28.8%	40.3%	2.4
Moderate intensity	30.7%	71.2%	−40.5%	0.4
Low intensity	0.2%	–		
No statin		–		
Ezetimibe	5.3%	3.3%	2.0%	1.6

A negative absolute difference or a ratio <1 suggests potential underrepresentativeness of certain subgroups. *ACE*, Angiotensin-converting enzyme; *ARB*, angiotensin-receptor blocker.

proportion of their patients would be potential candidates for PCSK9i based on trial eligibility criteria, as well as inform payers regarding what proportion of their enrollees would potentially require a PCSK9i.

The study has important implications for future research and practice. First, the FDA label states that evolocumab is indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease, which are a much broader population than the FOURIER trial population. However, until more evidence becomes available, extrapolation to populations excluded from the trial should be cautious. A recent secondary analysis of FOURIER suggested that in patients with LDL-C <70 mg/dL, evolocumab reduced the cardiovascular risk to a similar degree as in patients who have LDL-C ≥70 mg/dL.[13] However, all the FOURIER patients with LDL-C <70 mg/dL had non–HDL-C ≥100 mg/dL. In our study, only 4.5% of patients with LDL-C <70 mg/dL would have qualified for FOURIER. As such, future studies are needed to investigate whether the FOURIER results are applicable to excluded populations.

Second, as in many other clinical trials,[14,15] women, minorities, and elderly patients were underrepresented in FOURIER. Patients who did not have a history of MI were also underrepresented. In FOURIER, the treatment effect was largely consistent across these subgroups.[1] However, the small number of patients in certain subgroups may make it difficult to detect potential heterogeneity in treatment effects. The similar baseline lipid profile and subsequent cardiovascular risks between the FOURIER placebo arm and trial-eligible patients in our cohort suggest that the trial results may apply to the trial-eligible patients, but future studies are needed to assess whether there is any heterogeneity in treatment effects.

Third, although patients with ASCVD, by definition, are all at high risk, this population is still diverse, and the excluded and underpresented patients are often at particularly low or high risk. In our study, trial-eligible patients were all treated with statins, whereas many trial-ineligible patients were not treated; however, on average, trial-eligible patients still had a higher cardiovascular risk. If statins were to be more widely used, the cardiovascular risk without PCSK9i treatment would have been even lower in the trial-ineligible patients.[16] Therefore, even with a similar relative risk reduction, the absolute risk reduction achieved by PCSK9i will likely be smaller because of low baseline risk. Considering the cost of the drugs, the use may not be justified in low-risk patients. At the same time, the excluded populations also included patients at particularly high risk, such as those with recent MI or stroke, heart failure, hemorrhagic stroke, and renal failure, for whom future studies may be warranted.

Fourth, fewer than half of the patients in this study were treated with moderate- or high-intensity statin

therapy. Consistent with other studies, the use of high-intensity statin was even lower and has only slightly ticked up in recent years.[8,11] Many patients may be undertreated because of nonadherence, and physicians may need to evaluate adherence before determining the lack of efficacy of statin therapy and the need for adding PCSK9i. For patients who have adverse effects or difficulty adhering to statin, PCSK9i could potentially be helpful. However, such approach is controversial, and the reduction in cardiovascular risk has not been demonstrated in the statin-intolerant population.[17]

Last, a previous study found that at a cost of $14,350 per year, adding PCSK9i to statins was estimated to prevent cardiovascular events compared with ezetimibe at $414,000 per QALY.[18] In our database, we found a similar cost for PCSK9i, but because of the small sample size and short follow-up in the PCSK9i user group, we were not able to obtain new estimates for the risk reduction or cost-effectiveness in routine practice. Ezetimibe may be considered before initiating a PCSK9i, particularly because it is now available as a generic. The 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway provided some guidance on the choice of the initial nonstatin agent. For example, if patients require >25% additional lowering of LDL-C, a PCSK9i may be preferred, whereas ezetimibe may be the choice of the initial nonstatin agent for patients who prefer the ease of use of an oral agent and a lower cost. Our study has some limitations that warrant discussion. First, this study only included privately insured and Medicare Advantage patients in the United States. The distribution of age, sex, and minorities in the OLDW population is largely consistent with the general US population. Furthermore, the proportion of trial-eligible patients may be even lower in the patients not included in our study because the use of statin is lower in low-income Medicaid or uninsured population,[8] and the proportion being excluded because of certain medical conditions (eg, renal failure) may be higher in Medicare Fee-for-Service population. Although we do not expect the main findings to be substantially different in another country, future studies are needed assessing patients outside the United States.

Second, we were not able to assess some of the trial eligibility criteria using administrative data, such as current daily cigarette smoking and uncontrolled hypertension. Furthermore, the study relied on administrative data to identify comorbidities and outcomes, which may be subject to misclassification. However, we used established algorithms that are commonly used and demonstrated good performance in previous studies.[5-7] Furthermore, the misclassification should be nondifferential and should not have any undue impact on our comparison between trial-eligible and trial-ineligible patients. The similar risks between the OLDW trial-eligible group and the FOURIER placebo arm also provide some assurance of the validity of the data.

Despite the limitations, the current study also has several strengths, including the large sample of ASCVD patients managed in diverse routine practice settings. Our cohort is less selective than most registries because registries often focus on cardiology practices for recruitment and patients have to sign informed consent and agree to be actively followed. The data are also unique in that few other data sources are able to integrate patients of all ages and races from all 50 states while linking to laboratory results. As such, our findings would apply to many patients encountered in everyday practice.

Conclusions

Only 1 in 7 ASCVD patients in practice would have qualified for FOURIER. Most patients who received a PCSK9i would not have qualified for FOURIER. Elderly patients, women, minorities, and those without a history of MI were underrepresented in the trial. The excluded and underrepresented populations were at particularly low or high cardiovascular risk, and the translation to these patients should be cautious. Statin therapy was underused, and physicians may need to evaluate statin adherence before adding PCSK9i.

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.09.015.

References

1. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713-22.
2. Wallace PJ, Shah ND, Dennen T, et al. Optum Labs: building a novel node in the learning health care system. Health Aff (Millwood) 2014;33:1187-94.
3. Optum. *Optum Research Data Assets*. 2015.
4. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2889-934.
5. Fan J, Arruda-Olson AM, Leibson CL, et al. Billing code algorithms to identify cases of peripheral artery disease from administrative data. J Am Med Inform Assoc 2013;20:e349-54.
6. Kiyota Y, Schneeweiss S, Glynn RJ, et al. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. Am Heart J 2004;148:99-104.
7. Kumamaru H, Judd SE, Curtis JR, et al. Validity of claims-based stroke algorithms in contemporary medicare data reasons for geographic and racial differences in stroke (REGARDS) study linked with medicare claims. Circ Cardiovasc Qual Outcomes 2014;7:611-9.
8. Salami JA, Warraich H, Valero-Elizondo J, et al. National trends in statin use and expenditures in the US adult population from 2002 to

2013: insights from the medical expenditure panel survey. JAMA Cardiol 2017;2:56-65.
9. Signorovitch JE, Wu EQ, Yu AP, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. PharmacoEconomics 2010;28:935-45.
10. Malangone E, SS. *Matching-adjusted indirect comparison analysis using common SAS® 9.2 procedures*. 2011.
11. Rosenson RS, Farkouh ME, Mefford M, et al. Trends in use of high-intensity statin therapy after myocardial infarction, 2011 to 2014. J Am Coll Cardiol 2017;69:2696-706.
12. Virani SS, Akeroyd JM, Nambi V, et al. Estimation of eligibility for proprotein convertase subtilisin/kexin type 9 inhibitors and associated costs based on the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk): insights from the Department of Veterans Affairs. Circulation 2017;135:2572-4.
13. Giugliano RP, Keech A, Murphy SA, et al. Clinical efficacy and safety of evolocumab in high-risk patients receiving a statin: secondary analysis of patients with low LDL cholesterol levels and in those already receiving a maximal-potency statin in a randomized clinical trial. JAMA Cardiol 2017;2(12):1385-91.
14. Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. Arch Intern Med 2002;162:1682-8.
15. Whyte J, Woodcock J, Wang J. Review of the drug trials snapshots program of the US Food and Drug Administration: women in cardiovascular drug trials. JAMA Intern Med 2017;177:724-7.
16. Cannon CP, Khan I, Klimchak AC, et al. Simulation of lipid-lowering therapy intensification in a population with atherosclerotic cardiovascular disease. JAMA Cardiol 2017;2:959-66.
17. Waters DD, Hsue PY, Bangalore S. Pcsk9 inhibitors for statin intolerance? JAMA 2016;315:1571-2.
18. Kazi DS, Moran AE, Coxson PG, et al. Cost-effectiveness of PCSK9 inhibitor therapy in patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease. JAMA 2016;316:743-53.