Access to Nonstatin Lipid-Lowering Therapies in Patients at High Risk of Atherosclerotic Cardiovascular Disease

Joshua W. Knowles, MD, PhD
William B. Howard, PhD
Lala Karayan, MPH
Seth J. Baum, MD
Katherine A. Wilemon, BS
Christie M. Ballantyne, MD
Kelly D. Myers, BS

High-intensity statins are recommended for all patients with familial hypercholesterolemia (FH), and nonstatin lipid-lowering therapies (LLTs) are indicated when there is an inadequate response to statins.[1,2] In the pre-PCSK9 inhibitor (PCSK9i) era, only ≈40% of FH patients achieved an low-density lipoprotein cholesterol (LDL-C) level <100.[3] In part, on the basis of the need for additional therapeutic options in high-risk FH patients, PCSK9 inhibitors were approved for treatment of heterozygous and homozygous FH in 2015. Nevertheless, emerging anecdotal data suggest that access to nonstatin LLTs has been a challenge for FH patients, although this has not been systematically evaluated. The FOCUS study (FH Optimal Care of the US) was designed by The FH Foundation to assess current treatment patterns of FH patients, and allowed us to assess rejection rates of PCSK9 inhibitors in those with FH or atherosclerotic cardiovascular disease (ASCVD).

The FOCUS data set couples diagnostic information and pharmacy claims adjudication data from QuintilesIMS Inc. for >140 million unique individuals including diagnoses, procedures, laboratory tests, and prescriptions. Of these, 1.12 million individuals had a claim for either a PCSK9i or ezetimibe, forming the basis for our analyses (Figure). These data span the period March 1, 2012, to June 30, 2016, with the exception of pharmacy claim adjudication histories (August 1, 2014, to July 31, 2016) and laboratory data (January 1, 2012, to May 31, 2015). Patients were assigned to 2 cohorts (presumed FH or ASCVD) on the basis of medical histories, laboratory tests, therapies, diagnoses, procedures, and the value of their maximum and latest LDL-C. The final disposition of prescribed LLT therapies was determined and noted as approved (pharmacy claims paid by payer and therapy delivered to the patient), rejected (pharmacy claims rejected by the payer), or abandoned (pharmacy claims that were approved but refused by the patient). This analysis was performed on Health Insurance Portability and Accountability Act–compliant, deidentified data, and does not qualify as human subjects research necessitating institutional review board approval.

Among those with a claim for either a PCSK9i or ezetimibe, we identified 5795 individuals with laboratory characteristics consistent with FH through the application of Make Early Diagnosis to Prevent Early Death criteria, which are based on age-specific total cholesterol or LDL-C thresholds (untreated) and have a high correlation to genetically proven FH.[4] For patients adherent to LLT (n=5707), defined as having filled a prescription for a moderate-intensity (22% of patients) or high-intensity statin (67% of patients), thresholds were adjusted to factor a 30% reduction in LDL-C with statins.

For individuals with presumptive FH, we identified 515 who had been prescribed a PCSK9i. We conservatively defined inadequate LDL-C lowering as an LDL-C >190 mg/dL despite appropriate LLT (defined as high-intensity statins, high-intensity statins plus ezetimibe, or moderate-intensity statins plus ezetimibe, because statin

Correspondence to: Joshua W. Knowles, MD, PhD, Chief Medical Advisor, The FH Foundation, Cardiovascular Medicine, Stanford University, Falk Cardiovascular Research Center, Room CV273, MC 5406, 300 Pasteur Drive, Stanford, CA 94305. E-mail knowlej@stanford.edu

Key Words: atherosclerosis
- familial hypercholesterolemia
- PCSK9 inhibitor, human

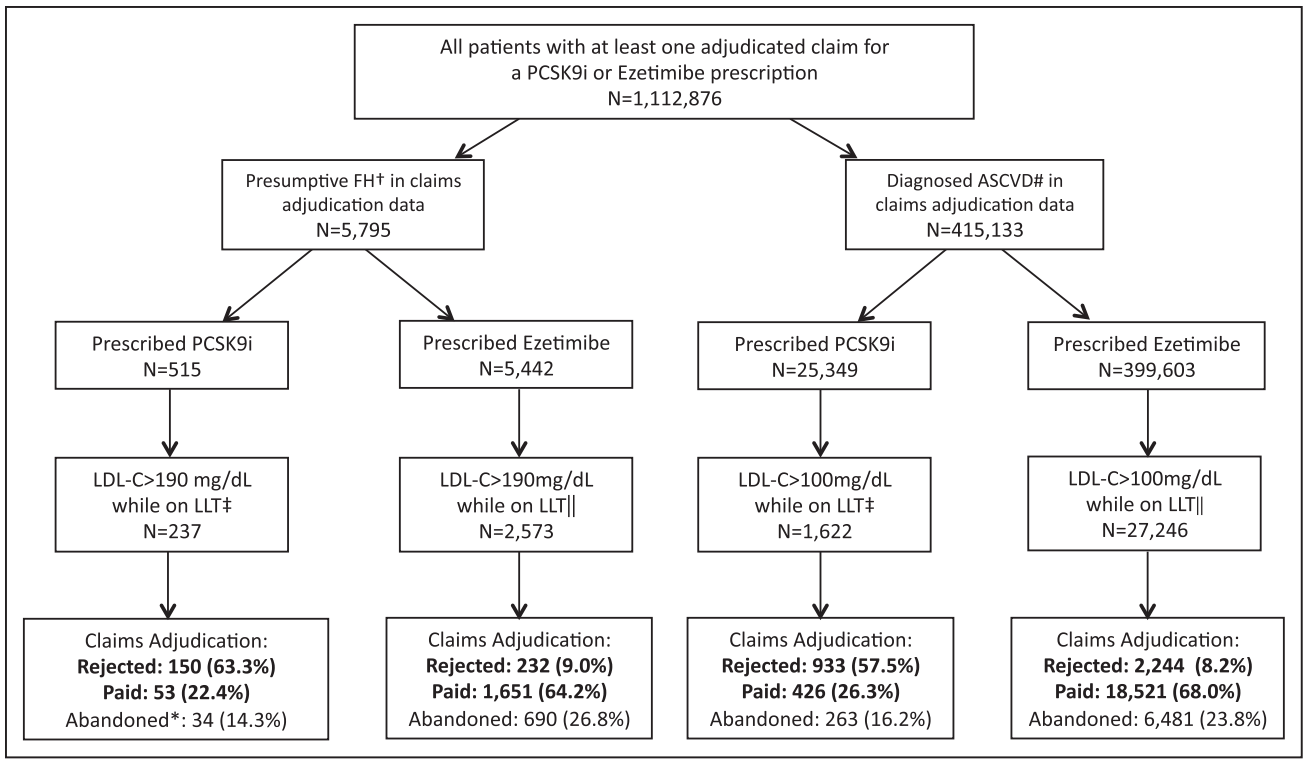

Figure. Dispositions for prescribed LLTs.

†Patients presumed to have FH as defined by patients with (1) LDL-C levels that meet Make Early Diagnosis Prevent Early Death (MEDPED) criteria for FH who are not on lipid-lowering therapy (LLT) or (2) LDL-C levels above a threshold defined by adjusting MEDPED criteria by factoring a 30% reduction in LDL-C for patients adherent to LLT meeting American Heart Association guidelines for moderate- or high-intensity statins. #Atherosclerotic cardiovascular disease (ASCVD) as defined by diagnosis and procedure codes. ‡Lipid-lowering therapy defined as high-intensity statin ± ezetimibe or moderate intensity statin + ezetimibe. ‖Lipid-lowering therapy defined as high-intensity or moderate-intensity statin. *Patients whose final disposition was abandoned although prescription was approved. FH indicates familial hypercholesterolemia; and LDL-C, low-density lipoprotein cholesterol.

intolerance may limit high-intensity statin use)[2] and identified 237 meeting these criteria (Figure).

Similar analyses were performed in 5442 presumed FH patients who had been prescribed ezetimibe of whom 2573 had an LDL-C >190 mg/dL despite evidence of high-intensity or moderate-intensity statins (Figure).

A total of 415 133 individuals in the data set were classified as having ASCVD on the basis of diagnostic or procedure codes. Of the 25 349 who had been prescribed a PCSK9i, 7150 had laboratory data (Figure). For ASCVD patients, we conservatively defined inadequate LDL-C lowering as an LDL-C >100 mg/dL despite appropriate LLT (Figure). Disposition rates for PCSK9i prescriptions were examined in the 1622 ASCVD patients who met these criteria.

Similar analyses were performed in ASCVD patients prescribed ezetimibe (n=399 603, total; n=270 944 with laboratory data). Of these, 27 246 had LDL-C >100 mg/dL despite evidence of high-intensity or moderate-intensity statin (Figure) data and were used to evaluate the disposition of ezetimibe prescriptions.

Of the 237 presumptive FH patients who had an LDL-C value >190 mg/dL despite evidence of statin-based LLT, 63.3% of prescriptions for PCSK9 inhibitors were rejected (Figure). In comparison, 9% of prescriptions for ezetimibe were rejected in a similar patient population.

Similarly, of the 1622 patients with established ASCVD who had an LDL-C value >100 mg/dL despite evidence of being treated with appropriate LLT, 57.5% of PCSK9 inhibitor prescriptions were rejected. In a similar ASCVD population, 8.2% of prescriptions for ezetimibe were rejected. Sensitivity analyses showed similar rejection rates for PCSK9 inhibitors in those with LDL-C >130 or >160 mg/dL (57.7% and 57.8%, respectively).

Of PCSK9 inhibitor prescriptions that were ultimately approved for either the presumptive FH patients or those with ASCVD, 34% were approved within 30 days, whereas approval took >2 months for 40% of prescriptions.

LDL-C lowering is critical to both FH and ASCVD patients. FOCUS data indicate that high-risk patients, including those with presumptive FH or ASCVD, have high rates of rejection for PCSK9i prescriptions even when there is sufficient evidence that they have inadequately controlled LDL-C despite concurrent appropriate statin-based LLT.[2] These data highlight potential challenges in operationalizing the results of the FOURIER trial (Further

Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) showing a significant reduction in ASCVD outcomes with PCSK9 inhibition.[5]

ACKNOWLEDGMENTS

The statements, findings, conclusions, views, and opinions contained and expressed in this research letter are based in part on data obtained under license from the following IMS Health Incorporated information service: FIA database, March 1, 2012 to July 30, 2017, IMS Health Incorporated. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated subsidiary entities.

SOURCES OF FUNDING

This study was supported by the FH Foundation.

DISCLOSURES

Dr Knowles declares research grants by Amgen Inc. and the American Heart Association (significant; all paid to institution, not individual). Dr Baum declares research grants from Ionis Pharmaceuticals Inc., Amgen Inc., Esperion Therapeutics, Inc., Madrigal Pharmaceuticals, Inc., Gemphire Therapeutics Inc., University of Pennsylvania, and AstraZeneca (all significant); relationships within the past 2 years with Sanofi, Cleveland Heart Laboratory, GLG Group, Guidepoint Global, Aralez, Jardiance (all modest), and Amgen Inc. (significant). Dr Ballantyne declares research grant and support from Abbot Diagnostic, Amarin, Amgen Inc., Eli Lilly, Esperion Therapeutics, Ionis Pharmaceuticals Inc., Novartis, Pfizer, Regeneron, Roche Diagnostic, Sanofi-Synthelabo, National Institutes of Health, American Heart Association, American Diabetes Association (all significant; all paid to institution, not individual). Kelly Myers and Dr Howard are employees of Atomo. The remaining authors have no disclosures. The FH Foundation is a research and advocacy 501(c)(3) public charity, which receives funding from individual donations and corporate donors ranging from the biopharmaceutical industry (including those that produce PCSK9 inhibitors) to genetic testing companies. The FOCUS project was conceived and executed by the FH Foundation using funds raised to support the overall mission of the FH Foundation. Entities choosing to support the FH Foundation programs have had no input on the architecture, execution, or publication of the FOCUS project. The FH Foundation contracted with Atomo, Inc., to perform this analysis. No other financial relationships exist between Atomo, Inc., and any company or product mentioned in this publication.

AFFILIATIONS

From Stanford University, CA (J.W.K.); The FH Foundation, Pasadena, CA (J.W.K., L.K., K.A.W.); Atomo, Inc., Austin, TX (W.B.H., K.D.M.); Preventive Cardiology Inc., Boca Raton, FL (S.J.B.); and Baylor College of Medicine, Houston, TX (C.M.B.).

FOOTNOTES

Circulation is available at http://circ.ahajournals.org.

REFERENCES

1. Gidding SS, Champagne MA, de Ferranti SD, Defesche J, Ito MK, Knowles JW, McCrindle B, Raal F, Rader D, Santos RD, Lopes-Virella M, Watts GF, Wierzbicki AS; American Heart Association Atherosclerosis, Hypertension, and Obesity in Young Committee of Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and Council on Lifestyle and Cardiometabolic Health. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. *Circulation*. 2015;132:2167–2192. doi: 10.1161/CIR.0000000000000297.
2. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 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. *Circulation*. 2014;129(25 suppl 2):S1–45. doi: 10.1161/01.cir.0000437738.63853.7a.
3. deGoma EM, Ahmad ZS, O'Brien EC, Kindt I, Shrader P, Newman CB, Pokharel Y, Baum SJ, Hemphill LC, Hudgins LC, Ahmed CD, Gidding SS, Duffy D, Neal W, Wilemon K, Roe MT, Rader DJ, Ballantyne CM, Linton MF, Duell PB, Shapiro MD, Moriarty PM, Knowles JW. Treatment gaps in adults with heterozygous familial hypercholesterolemia in the United States: data from the CASCADE-FH Registry. *Circ Cardiovasc Genet*. 2016;9:240–249. doi: 10.1161/CIRCGENETICS.116.001381.
4. Williams RR, Hunt SC, Schumacher MC, Hegele RA, Leppert MF, Ludwig EH, Hopkins PN. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. *Am J Cardiol*. 1993;72:171–176.
5. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR, Committee FS and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;doi: 10.1056/NEJMoa1615664.