

Perceptions and Barriers on the Use of Proprotein Subtilisin/Kexin Type 9 Inhibitors in Heterozygous Familial Hypercholesterolemia (From a Survey of Primary Care Physicians and Cardiologists)



Nathan D. Wong, PhD^{a,*}, Matthew Bang, BS^a, Robert C. Block, MD, MPH^b, Amy L.H. Peterson, MD, MS^c, and Dean G. Karalis, MD^d

Heterozygous familial hypercholesterolemia (HeFH) results in significant elevations in LDL-C and premature atherosclerotic cardiovascular disease (ASCVD). Current guidelines recommend add-on proprotein subtilisin/kexin type 9 inhibitor (PCSK9i) therapy for additional LDL-C lowering beyond statins. Data are sparse, however, regarding treatment patterns and barriers relating to PCSK9i in HeFH patients. We examined physician attitudes, use, and barriers for treatment in patients with HeFH. We surveyed 1,000 physicians (500 primary care providers [PCPs] and 500 cardiologists in the US regarding their preferred treatments, experience and barriers associated with using PCSK9is. Cardiologists compared to PCPs were more likely to rank a PCSK9i as most important for an HeFH patient needing additional LDL-C lowering (68.6% vs. 64.8%; $p < 0.05$), as well as prescribing and having a patient on a PCSK9i. PCPs vs. cardiologists were less likely (odds ratio [OR] [95% confidence interval] = 0.46 [0.34-0.63]), private vs. academic practice more likely (OR = 1.53 [1.02-2.28]), and those who would prescribe a PCSK9i in an HeFH patient with (OR = 3.86 [2.57-5.78]) or without (OR = 1.96 [1.40-2.72]) ASCVD needing additional LDL-C reduction beyond a statin were more likely to actually prescribe a PCSK9i. Those practicing in an urban vs. rural setting were less likely (OR = 0.56 [0.34-0.93]), and those indicating they would prescribe a PCSK9i in an HeFH patient with (OR = 2.80 [1.74-4.49]) or without (OR = 1.43 [1.02-2.02]) ASCVD needing additional LDL-C lowering beyond a statin were more likely to face difficulty prescribing a PCSK9i (all $p < 0.05$ to $p < 0.01$). Greater physician education and assistance among both cardiologists and PCPs are needed to address the gaps in understanding and treatment regarding PCSK9is. © 2021 Elsevier Inc. All rights reserved. (Am J Cardiol 2021;152:57–62)

Heterozygous familial hypercholesterolemia (HeFH) is the most common monogenic disorder characterized by markedly elevated low-density lipoprotein cholesterol (LDL-C) and premature atherosclerotic cardiovascular disease (ASCVD) and affecting approximately 1 in 200-300 individuals.¹⁻³ Many HeFH patients are not diagnosed until after their first ASCVD event, calling for healthcare providers to be more aware of recognizing and treating FH⁴; however, knowledge on FH is limited.⁵ Early treatment of HeFH patients with lipid lowering therapy starting in childhood prevents ASCVD and death.⁶⁻⁸ Current HeFH treatment guidelines recommend a proprotein convertase subtilisin/kexin type 9 (PCSK9i) when additional LDL-C

lowering is needed beyond maximum statin and ezetimibe therapy in very high risk patients.⁹⁻¹¹ Most adult patients with HeFH are unable to achieve their LDL-C goal with statin monotherapy and require additional non-statin therapies.¹² PCSK9i lower LDL-C by $\geq 50\%$, showing reduced ASCVD risk beyond statin therapy from major trials.¹³ Less well-documented are physicians' attitudes and practice, as well as barriers encountered regarding treatment of HeFH. This manuscript reviews results from the largest US national survey of primary care physicians (PCPs) and cardiologists regarding their attitudes, treatment patterns, and barriers towards treatment of HeFH, specifically with PCSK9is.

Methods

The National Lipid Association (NLA), utilizing Med-Survey (Southampton, PA), an independent survey research vendor, surveyed 500 cardiologists and 500 PCPs, consisting of family medicine, general medicine, and internal medicine specialties throughout the United States between August 29 and September 30, 2019. Eligible physicians were required to be licensed and currently practicing, prescribing medications, and reporting caring for patients with a baseline LDL-C ≥ 190 mg/dL. We specifically avoided

^aDivision of Cardiology, Heart Disease Prevention Program, University of California Irvine, Irvine, California; ^bDepartment of Public Health Sciences and Cardiology Division Department of Medicine, University of Rochester Medical Center, Rochester, New York; ^cDepartment of Pediatrics, Division of Pediatric Cardiology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; and ^dDivision of Cardiology, Thomas Jefferson University Hospital, Philadelphia, PA. Manuscript received March 15, 2021; revised manuscript received and accepted April 16, 2021.

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*Corresponding author: Tel: 949-824-5561; fax: 949-824-2200.

E-mail address: ndwong@uci.edu (N.D. Wong).

introducing the survey as one on hyperlipidemia or familial hypercholesterolemia to avoid enrolling physicians with a strong interest or expertise in lipid management. Physicians who self-identified as lipid specialists (including endocrinologists) who would already be expected to be knowledgeable about HeFH, or pediatricians, and those certified by the American Board of Clinical Lipidology or Accreditation Council for Clinical Lipidology were excluded. Those completing the survey received a small honorarium. The study aimed to survey a representative sample of US physicians across US time zones, with recruitment in a given time zone closed once the planned number of physicians for that zone was achieved. The online survey consisted of 30 questions assessing physician demographics and their recognition and treatment of HeFH. 25,000 physicians were invited by email to participate in the survey, of which 1898 responded and after 561 were disqualified due to not fitting in the entry criteria, 1000 completed the survey with the remaining 337 disqualified due to being over quota. Table 1 shows the survey items related to treatment of HeFH and focused on therapies respondents felt were most important for untreated patients with LDL-C ≥ 190 mg/dL and for those already on maximal statin therapy needing additional LDL-C lowering. Respondents were asked if they currently had patients on a PCSK9i and what types of patients they were most likely to prescribe them to. Finally, respondents were asked if they had ever faced difficulty prescribing a PCSK9i, and which barriers to prescribing were the most common. The study utilized de-identified data and was exempt from institutional review board review.

The Chi-square test of proportions was used to compare PCPs and cardiologists according to the proportions with each response to a given survey question. Multiple logistic regression performed in a stepwise manner with forward selection, allowing for factors with a p-value of <0.15 to enter and remain in the model, examined for factors independently associated with ever having prescribed a PCSK9i and difficulty prescribing a PCSK9i.

Results

1,000 physicians completed the online survey, including 500 cardiologists and 500 PCPs. Among PCPs, 46% identified as a family medicine physician, 46% as an internal medicine physician, and 8% as a general practitioner. 53% of all physicians reported practicing in a suburban location, 37% in an urban location, and only 10% in a rural location. For practice setting, 57% reported private practice, followed by 24% employed by a health system, 17% in a primarily academic setting, and 1% each in the Veterans Affairs/government health system or other.

Table 1 compares primary care and cardiologist diagnosis, attitudes, experience, and barriers regarding treatment of HeFH. Cardiologists compared to PCPs were more likely to correctly diagnose a 30 year old male with family history of premature CHD with LDL-C of 230 mg/dl after lifestyle changes as having HeFH, as well as to rank a high-intensity statin as most important for an HeFH patient with an untreated LDL-C of ≥ 190 mg/dL (also Figure 1) or for an HeFH patient already on maximally tolerated statin therapy needing additional LDL-C lowering (also Figure 2). Moreover, cardiologists were more likely than PCPs to currently have patients on a PCSK9i, prescribe a PCSK9i for a patient with HeFH, prescribe a PCSK9i in an adult with HeFH on maximal statin therapy both for those with or without ASCVD, but less likely to report difficulty prescribing a PCSK9i for a patient with HeFH.

Table 1 and Figure 3 show the most important barriers encountered when prescribing a PCSK9i for an adult patient among PCPs and cardiologists. A higher proportion of PCPs compared to cardiologists (34.2% vs. 24.7%, $p < 0.05$) found the complexity of the pre-authorization process to be the most important barrier, whereas the same proportion of PCPs and cardiologists (27.8%) found the amount of time the pre-authorization process took to be the most important barrier. Other barriers included: PCSK9i cost (21.9% of cardiologists and 12% of PCPs ($p < 0.01$) reported they were “too expensive”), frequent denials from insurance, patient not

Table 1

Primary care and cardiologist diagnosis of HeFH, and attitudes, experience, and barriers regarding treatment

Survey item	PCP	Cardiologist	p-value
Diagnosis of an *example patient with HeFH	43.0%	57.2%	<0.0001
Ranking high-intensity statin as most important for HeFH patient with untreated LDL-C ≥ 190 mg/dL	64.8%	68.6%	0.04
Ranking PCSK9i as most important for HeFH Pt on maximal tolerated statin needing additional LDL-C lowering	48.4%	58.2%	<0.01
Currently has HeFH patient on a PCSK9i	44.2%	68.4%	<0.0001
Likely or very likely to prescribe a PCSK9i in an adult with HeFH on maximum statin therapy with ASCVD	66.0%	87.8%	<0.0001
Likely or very likely to prescribe a PCSK9i in an adult with HeFH on maximum statin therapy without ASCVD	51.0%	70.2%	<0.0001
Personally prescribed a PCSK9i for an adult with HeFH	46.8%	70.4%	<0.0001
Encountered difficulty prescribing a PCSK9i for a patient with HeFH (very or extremely difficult)	58.1%	50.6%	0.07
Most important barriers encountered when prescribing a PCSK9i for an adult with HeFH			
a) Pre-authorization process complicated	34.2%	24.7%	<0.05
b) Pre-authorization process time consuming	27.8%	27.8%	>0.05
c) Medicine too expensive	12.0%	21.9%	<0.01
d) Get frequent denials from insurance	12.4%	11.7%	>0.05
e) Patient does not want to take injectable medication	10.7%	9.7%	>0.05
f) Difficult to document a clinical diagnosis of HeFH	3.0%	4.3%	>0.05

PCP = primary care provider.

* Example patient: 30 yo male with family history of premature CHD with LDL-C of 230 mg/dl after lifestyle changes.

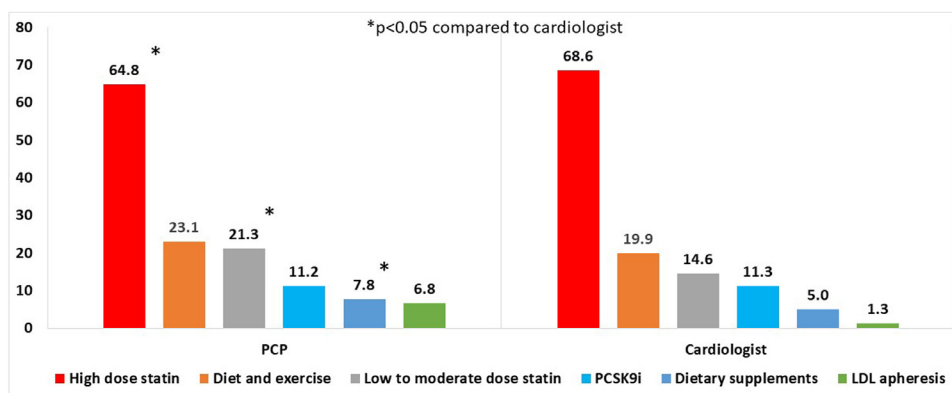


Figure 1. Frequency (%) of providers ranking therapies as most important for adult patient with HeFH and untreated LDL-C $\geq$ 190.

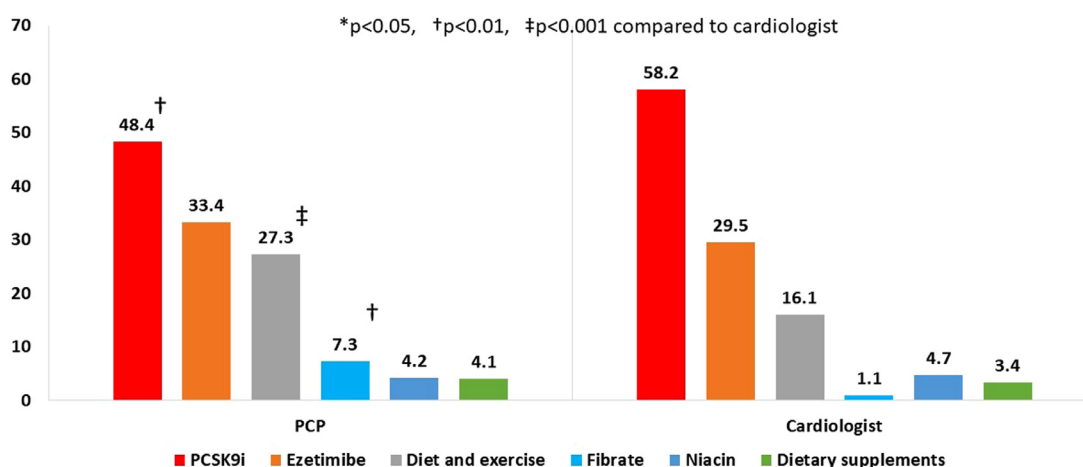


Figure 2. Frequency (%) of providers ranking therapies as most important for adult patient with HeFH on maximally tolerated statin who needs additional LDL-C lowering.

wanting to take injectable medications, and difficulty documenting a clinical diagnosis of HeFH.

From multiple logistic regression (Table 2) PCPs vs. cardiologists were less likely (odds ratio [OR] = 0.46, 95% confidence interval [CI] = 0.34-0.63), private vs. academic practice providers more likely (OR = 1.53 [1.02-2.28]) associated with prescribing a PCSK9i. Also, those noting they were likely to prescribe a PCSK9i in a HeFH patient with (OR = 3.86 [2.57-5.78]) or without (OR = 1.96 [1.40-2.72]) ASCVD on maximum statin needing additional LDL-C lowering were more likely to prescribing a PCSK9i. Difficulty prescribing a PCSK9i was less likely among those practicing in an urban vs. rural setting [OR = 0.56 (0.34-0.93)] but more likely in those indicating they would prescribe a PCSK9i in a HeFH patient with [OR = 2.80 (1.74-4.49)] or without [1.43 (1.02-2.02)] ASCVD on maximum statin needing additional LDL-C lowering.

Discussion

Our study using the largest survey of physicians on the identification and care of patients with HeFH noted that as initial therapy, physicians identified a high-intensity statin followed by diet and exercise to be the most important therapies. Among those already on maximally tolerated statin therapy that need additional LDL-C lowering, a PCSK9i,

followed by ezetimibe, and then diet and exercise were the most preferred therapies. Over half of respondents indicated they already have patients on a PCSK9i and were more likely to prescribe them in those with compared to without ASCVD. However, respondents noted a complicated and time-consuming process, followed by expense as the most important barriers for prescribing a PCSK9i. Our survey documents the priority physicians place on the use of a PCSK9i in patients with HeFH but also the barriers for successfully prescribing them. Despite approval of PCSK9is by both US and European regulatory authorities for persons with ASCVD or with FH needing additional LDL-C lowering beyond statin therapy, many needing such therapies have difficulty getting them, and those whose prescriptions are rejected or abandoned show worse ASCVD outcomes.¹⁴

The 2018 AHA/ACC/multisociety cholesterol guideline recommends a high-intensity statin for patients with HeFH, and in our survey most cardiologists and PCPs note they would follow this recommendation, although cardiologists somewhat more frequently. However, in our study just under one-third of cardiologists would not initiate a high-intensity statin in a HeFH patient, but instead would use a lower intensity statin or diet and exercise as their initial therapy. Prior surveys have focused on patients outside the United States,¹⁵⁻¹⁸ or were done in regard to those with homozygous familial hypercholesterolemia.¹⁹ Other studies

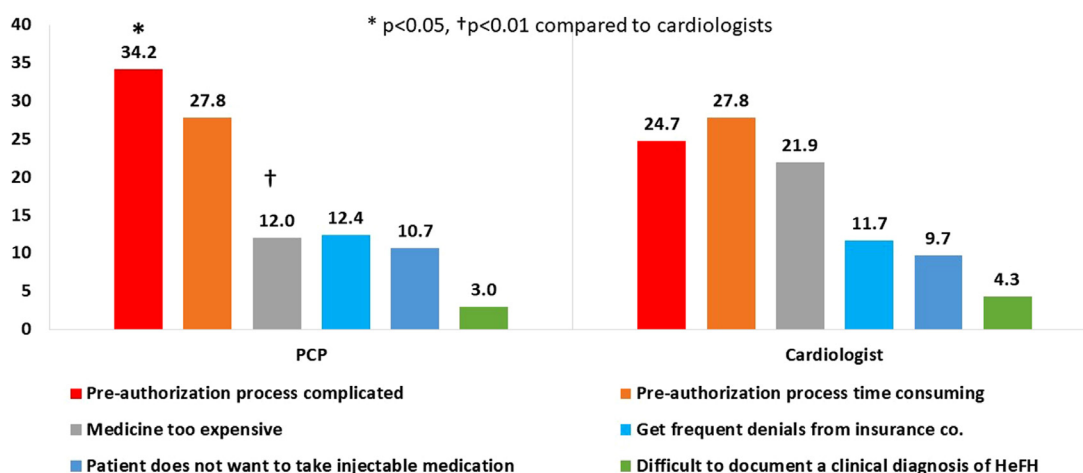


Figure 3. Frequency (%) of providers ranking barriers encountered as most important when prescribing a PCSK9i for an adult patient with HeFH.

have also shown that guideline recommended lipid lowering therapy is often not followed in FH. In a small study of physicians in Poland caring for over 2,800 patients with hypercholesterolemia, among those with a positive Dutch Lipid Clinic Network score for FH, three-fourths of physicians did not make the correct diagnosis and only 33% of patients received high-intensity statins.¹⁷ In a recent study among cardiologists using electronic health record prompts to improve lipid management, only 47% of patients with severe hypercholesterolemia (LDL $\geq$ 190 mg/dL) were on a high-intensity statin as recommended by guidelines.²⁰ In an NLA survey of recognition and treatment of HoFH, many respondents chose diet and exercise as the most important initial therapy, with only 8% indicating high-intensity statin as important.¹⁹

Current US guidelines for adults with HeFH recommend a high-intensity or maximally tolerated statin followed by ezetimibe and then consideration of a PCSK9i if the LDL-C still remains $\geq$ 100 mg/dL for primary prevention and $\geq$ 70 mg/dL for HeFH patients with ASCVD.⁹ The European Society of Cardiology guidelines note a goal LDL-C $<$ 55 mg/dL for those HeFH patients at very high risk (additional major risk factors or with ASCVD) with PCSK9i recommended to reach this goal if not achieved on high-intensity statin and ezetimibe.²¹ Although cardiologists were more likely than PCPs to prescribe a PCSK9i as the next most important therapy in a HeFH patient on a maximally tolerated statin who needs additional LDL-C reduction, 16% of cardiologists would instead choose diet and

Table 2

Logistic regression for multivariable indicators of prescribing a PCSK9i and difficulty prescribing a PCSK9i

Variable	Ever prescribed a PCSK9i (odds ratio, 95% confidence interval)	*Difficulty prescribing a PCSK9i (odds ratio, 95% confidence interval)
Provider: PCP vs. cardiologist	0.46 (0.34-0.63)	0.80 (0.60-1.07)
Practice location	-----	-----
Suburban vs. rural		0.77 (0.48-1.23)
Urban vs. rural		0.56 (0.34-0.93)
Practice setting		-----
VA/government vs. academic	0.51 (0.16-1.67)	
Health system vs. academic	1.28 (0.82-2.00)	
Private vs. academic	1.53 (1.02-2.28)	
Other vs. academic	0.59 (0.15-2.34)	
Very or extremely likely to prescribe a PCSK9i in an adult with HeFH with ASCVD on max statin needing additional LDL-C lowering	3.86 (2.57-5.78)	2.80 (1.74-4.49)
Very or extremely likely to prescribe a PCSK9i in an adult with HeFH with no clinical ASCVD on max statin needing additional LDL-C lowering	1.96 (1.40-2.72)	1.43 (1.02-2.02)
Correctly diagnosing patient as HeFH	1.26 (0.95-1.68)	-----
Choosing high-intensity statin for HeFH adult patient with LDL-C $\geq$ 190 mg/dL	0.62 (0.34-1.11)	-----

* yes to very or extremely difficult on question about difficulty prescribing a PCSK9i.

Abbreviations: PCP = primary care physician; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low density lipoprotein-cholesterol; ASCVD = atherosclerotic cardiovascular disease.

exercise. Although important in the treatment, diet has a relatively small effect in lowering LDL-C in a patient with FH. Our survey respondents indicated they were more likely to prescribe a PCSK9i in patients with HeFH who also had ASCVD compared to those without ASCVD, however PCSK9i are also indicated by current guidelines for primary prevention in HeFH patients who are not at their LDL-C goal. While it is unclear why in our survey private practice providers were more likely to prescribe a PCSK9i compared to academic providers, it is possible the latter more strictly followed guidelines and/or were more successful in attaining acceptable LDL-C levels from statin therapy alone. Moreover, physicians are often detailed by pharmaceutical representatives on the use of these and other therapies, and there are often greater restrictions by academic centers on access to physicians by pharmaceutical representatives.

The pre-authorization process, including its complex and time-consuming nature, was identified as the most important barrier by our survey respondents for prescribing a PCSK9i. The expense of a PCSK9i was felt to be the next most important barrier, with other barriers being the frequency of denials from insurance, patients not wanting to use injectable medications, and difficulty documenting a clinical diagnosis of HeFH. Barriers to accessing PCSK9i, including the pre-authorization process have been significant and well-recognized issues by experts since the advent of these therapies. Baum and colleagues pointed out that the lack of clear definitions of maximally tolerated statin therapy and statin intolerance, and even ambiguous definitions for HeFH and clinical ASCVD contributes to provider and payer inconsistencies when physicians prescribe PCSK9i and other non-statin therapies. In a recent review convened by the American Society for Preventive Cardiology, clearer definitions on these aspects were proposed.²² The pre-authorization process for PCSK9i frequently includes complex paperwork up to 17 pages. While payers feel this to be necessary to avoid potential overuse of medications, this can inadvertently undermine the patient-physician relationship, which includes ensuring access to therapies the physician deems necessary for the care of the patient. In a large evaluation of approval and rejection rates among 51,422 patients receiving PCSK9i prescriptions among over 5,000 health plans, 47% were approved, with higher rates in persons aged >65 years, with a history of ASCVD, prescribed by a CD or other specialist rather than a PCP, those with statin intolerance who reported long duration of statin therapy, and who had non-commercial payers.²³ Patients report similar difficulties. Among 1,327 patients surveyed regarding their PCSK9i, 75% found the drug approval process to be somewhat or very burdensome. Of those who initiated treatment, 34% had discontinued treatment by the time of the survey with half taking the drug for 6 months or less, citing out-of-pocket costs as the leading reason for discontinuation.²⁴ Other impediments to insurance authorization include insistence on the patient failing ezetimibe on top of a statin in achieving adequate LDL-C reduction, refusing to accept documentation of statin intolerance, the absence of staff with the needed time or expertise to work through the authorization process, as well as the absence of nursing or other staff who can take the needed time to teach patients on the use of PCSK9i.

Our study has strengths and limitations. While our survey was the largest provider survey focused on HeFH and covered all major regions of the US, we did not have demographic factors such as age, gender, or ethnicity of our survey respondents. Thus, we cannot be certain our participants were representative of all PCPs and cardiologists in the US. More importantly, our survey did not include (and was not designed to include) lipid specialists presumed to have greater knowledge of HeFH, such as endocrinologists. Also, results may differ in cases where a PCP may have first identified the presence of HeFH, but then referred the patient to a lipid specialist for further follow-up (7% of PCPs). However, the sample-size makes us quite confident that the results are very valid, given the relatively narrow confidence intervals. Also, our respondents indicated they cared for patients with LDL-C ≥ 190 mg/dL and therefore our sample could be biased towards those interested in dyslipidemia, although those who self-identified as lipid specialists were excluded. Finally, potential respondents were aware they were participating in a survey on dyslipidemia which could have biased the sample towards those with an interest caring for such patients.

In summary, our study shows that among those already on maximally tolerated statin therapy, a PCSK9i followed by ezetimibe and then diet and exercise were the most preferred therapies by our survey respondents. Over half of respondents indicated they already have patients with HeFH on a PCSK9i and were more likely to prescribe them in those with compared to without ASCVD. A complicated and time-consuming process, followed by expense, was the most important barriers for prescribing a PCSK9i. Cardiologists were only somewhat more likely to diagnose and treat HeFH according to guidelines compared to PCPs and to prescribe and consider a PCSK9i important for such patients. Those in an urban practice location were less likely to face difficulty prescribing a PCSK9i. Our results underscore the importance of better education for both cardiologists and PCPs on recommended treatment options for patients with HeFH, as well as guidance to help address key barriers that continue to make prescription of PCSK9i difficult.

Author Contributions

Dr. Wong wrote the manuscript. Mr. Bang conducted the analysis. Drs. Block, Peterson, and Karalis provided critical review and revision.

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Disclosures

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1. McGowan MP, Hosseini Dehkordi SH, Moriarty PM, Duell PB. Diagnosis and Treatment of Heterozygous Familial Hypercholesterolemia. *J Am Heart Assoc* 2019;8:e013225.
2. de Ferranti SD, Rodday AM, Mendelson MM, Wong JB, Leslie LK, Sheldrick RC. Prevalence of familial hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES) clinical perspective. *Circulation* 2016; 133:1067–1072.
3. Beheshti SO, Madsen CM, Varbo A, Nordestgaard BG. Worldwide prevalence of familial hypercholesterolemia. Meta-analyses of 11 million subjects. *J Am Coll Cardiol* 2020;75:2553–2566.
4. Representatives of the Global Familial Hypercholesterolemia Community. Reducing the clinical and public health burden of familial hypercholesterolemia. *JAMA Cardiol* 2020;5:217–229.
5. Foody JM. Familial hypercholesterolemia: an under-recognized but significant concern in cardiology practice. *Clin Cardiol* 2014;37:119–125.
6. Neil A, Cooper J, Betteridge J, Capps N, McDowell I, Durrington P, Seed M, Humphries SE. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. *Eur Heart J* 2008; 29:2625–2633.
7. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, Wiklund O, Hegele RA, Raal FJ, Defesche JC, Wiegman A, Santos RD, Watts GF, Parhofer KG, Hovingh GK, Kovanen PT, Boileau C, Averno M, Borén J, Bruckert E, Catapano AL, Kuivenhoven JA, Pajukanta P, Ray K, Stalenhoef AF, Stroes E, Taskinen MR, Tybjærg-Hansen A, European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J* 2013;34:3478–3490.
8. Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, Daniels SR, Gidding SS, de Ferranti SD, Ito MK, McGowan MP, Moriarty PM, Cromwell WC, Ross JL, Ziajka PE. National Lipid Association Expert Panel on Familial Hypercholesterolemia. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol* 2011;5(3 Suppl):S1–S8.
9. Watts GF, Gidding S, Wierzbicki AS, Toth PP, Alonso R, Brown WV, Bruckert E, Defesche J, Lin KK, Livingston M, Mata P, Parhofer KG, Raal FJ, Santos RD, Sijbrands EJ, Simpson WG, Sullivan DR, Susekov AV, Tomlinson B, Wiegman A, Yamashita S, Kastelein JJ. International FH Foundation. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation: executive summary. *J Atheroscler Thromb* 2014;21:368–374.
10. Foody JM. Familial hypercholesterolemia: An under-recognized but significant concern in cardiology practice. *Clin Cardiol* 2014;37:119–125.
11. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;139:e1082–e1143.
12. Duell PB, Gidding SS, Andersen RL, Knickelbine T, Anderson L, Gianos E, Shrader P, Kindt I, O'Brien EC, McCann D, Hemphill LC, Ahmed CD, Martin SS, Larry JA, Ahmad ZS, Kullo IJ, Underberg JA, Guyton J, Thompson P, Wilemon K, Roe MT, Rader DJ, Cuchel M, Linton MF, Shapiro MD, Moriarty PM, Knowles JW. Longitudinal low density lipoprotein cholesterol goal achievement and cardiovascular outcomes among adult patients with familial hypercholesterolemia: the CASCADE FH registry. *Atherosclerosis* 2019;289:85–93.
13. Wong ND, Shapiro MD. Interpreting the findings from the recent PCSK9 monoclonal antibody cardiovascular outcomes trials. *Front Cardiovasc Med* 2019;6:14.
14. Myers KD, Farboodi N, Mwamburi M, Howard W, Staszak D, Gidding S, Baum SJ, Wilemon K, Rader DJ. Effect of access to prescribed PCSK9 inhibitors on cardiovascular outcomes. *Circ Cardiovasc Qual Outcomes* 2019;12:e005404.
15. Reddy LL, Ashavaid TF. Familial hypercholesterolemia (FH) awareness amongst physicians in Mumbai, India. *J Assoc Physicians India* 2018;66:66–69.
16. Azraii AB, Ramli AS, Ismail Z, Abdul-Razak S, Mohd-Kasim NA, Ali N, Watts GF, Nawawi H. Knowledge, awareness and practice regarding familial hypercholesterolaemia among primary care physicians in Malaysia: The importance of professional training. *Atherosclerosis* 2018;277:508–516.
17. Chlebus K, Cybulska B, Gruchała M, Smaga A, Wróbel K, Wojtyniak B, Pajkowski M, Jankowski P, Zdrojewski T. Prevalence, diagnosis, and treatment of familial hypercholesterolaemia in outpatient practices in Poland. *Kardiol Pol* 2018;76:960–967.
18. Kwok S, Pang J, Adam S, Watts GF, Soran H. An online questionnaire survey of UK general practitioners' knowledge and management of familial hypercholesterolaemia. *BMJ Open* 2016;6:e012691.
19. Hemphill L, Goldberg A, Hovingh K, Cohen J, Karalis DG. Recognition and treatment of homozygous familial hypercholesterolemia by primary care physicians: a survey from the National Lipid Association. *J Gen Intern Med* 2019;35:2225–2227.
20. Adusumalli S, Westover JE, Jacoby DS, Small DS, VanZandbergen C, Chen J, Cavella AM, Pepe R, Rareshide CAL, Snider CK, Volpp KG, Asch DA, Patel MS. Effect of passive choice and active choice interventions in the electronic health record to cardiologists on statin prescribing: a cluster randomized clinical trial. *JAMA Cardiol* 2021;6:40–48.
21. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O, ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111–188.
22. Baum SJ, Toth PP, Underberg JA, Jellinger P, Ross J, Wilemon K. PCSK9 inhibitor access barriers – issues and recommendations: improving the access process for patients, clinicians and payers. *Clin Cardiol* 2017;40:243–254.
23. Hess GP, Natarajan P, Faridi KF, Flevitz A, Valsdottir L, Yeh RW. PCSK9 inhibitor therapy: payer approvals and rejections, and patient characteristics for successful prescribing. *Circulation* 2017;136:2210–2219.
24. Bradley CK, Shrader P, Sanchez RJ, Peterson ED, Navar AM. The patient journey with proprotein convertase subtilisin/kexin type 9 inhibitors in community practice. *J Clin Lipid* 2019;13:725–734.