American Journal of Preventive Cardiology 6 (2021) 100157

Contents lists available at ScienceDirect

American Journal of Preventive Cardiology

journal homepage: www.journals.elsevier.com/the-american-journal-of-preventive-cardiology

State-of-the-Art Review

Familial hypercholesterolemia in Southeast and East Asia

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ARTICLE INFO

Keywords:
Familial hypercholesterolemia
Southeast Asia
East Asia
Genetic testing
Awareness
Prevalence
Diagnostic criteria
Coronary heart disease

ABSTRACT

Familial hypercholesterolemia (FH) is a relatively common autosomal dominant disorder associated with a significantly increased risk of coronary heart disease (CHD). Most (~85–90%) cases are due to pathogenic variants in the LDL-receptor gene (*LDLR*), while the remaining are due to pathogenic variants in the apolipoprotein B (*APOB*) and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes, though the proportion may vary depending on geographic location. Even though at least a quarter of the world's FH population lives in Southeast and East Asia, there are substantial gaps in knowledge regarding the epidemiology of FH due to low awareness, the absence of national screening programs, and limited availability of genetic testing. In this review, we discuss the most recent and relevant information available related to diagnostic criteria, prevalence, awareness, clinical characteristics, genetic epidemiology, and treatment in the FH population of Southeast and East Asia. Increasing awareness and improving the diagnosis and management of FH will reduce the burden of premature CHD in these regions of the world.

1. Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant disorder characterized by elevated serum low-density lipoprotein-cholesterol (LDL-C) levels [1,2]. High circulating LDL-C levels lead to lipid deposition in arterial walls causing plaque formation and atherosclerotic cardiovascular disease (ASCVD), and in soft tissues, leading to tendon xanthomas, xanthelasma, and premature corneal arcus [3]. Left untreated, around 50% of men and 30% of women with FH will develop coronary heart disease (CHD) before the ages of 50 and 60, respectively [4].

A relatively common genetic disease, FH affects an estimated 20 million people globally, of whom more than 90% are undiagnosed [5]. Prevalence varies according to geographical location and based on the diagnostic criteria used. Estimates range from 1:137 to 1:500 for the heterozygous form and from 1:160,000 to 1:300,000 for the homozygous form [6,7]. Approximately 80–90% of cases are due to pathogenic/likely pathogenic (P/LP) variants in the LDL-receptor (*LDLR*) gene, while 10–15% are due to P/LP variants in the apolipoprotein B (*APOB*) gene and fewer than 5% are related to gain-of-function P/LP variants in the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene, though the proportions vary geographically [8].

There are 3.6–9.0 million people with FH in Southeast and East Asia (assuming a prevalence of 1:200 to 1:500) [9], but there are several gaps in our knowledge regarding FH in this part of the world [3]. In this review, we aim to familiarize readers with the burden of FH in Southeast and East Asia. We focus on the most recent and relevant information available related to diagnostic criteria, prevalence, awareness, clinical characteristics, genetic epidemiology, and treatment, providing comparisons between FH populations where available, as recognizing these differences is important in the diagnosis and management of this disease. To identify pertinent articles regarding the topic, we performed a search in Medline using search terms including "familial hypercholesterolemia", "prevalence", "clinical manifestations", "genetic etiology", "response to therapy", "awareness", "detection", and "cascade screening" as well as the names of different countries in Southeast and East Asia [10,11]. Our goal is to provide a general overview of FH in this diverse population and highlight areas that need additional research.

1.1. Diagnostic criteria

There is no gold standard for diagnosing FH. Multiple diagnostic criteria currently exist and among the most commonly used criteria are the Dutch Lipid Clinic Network (DLCN) criteria, which calculates a score that helps determine the likelihood of FH. This scoring system incorporates genetic testing and other clinical elements including family history, personal history, physical exam findings related to hypercholesterolemia such as tendon xanthomas and corneal arcus, and LDL-C levels. The Simon Broome diagnostic criteria are comparable and also integrate similar variables including genetic testing. On the other hand, the U.S. Make Early Diagnosis to Prevent Early Deaths (MEDPED) criteria are based only on age-specific cholesterol thresholds [12].

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https://doi.org/10.1016/j.ajpc.2021.100157
Received 21 December 2020; Received in revised form 1 February 2021; Accepted 7 February 2021

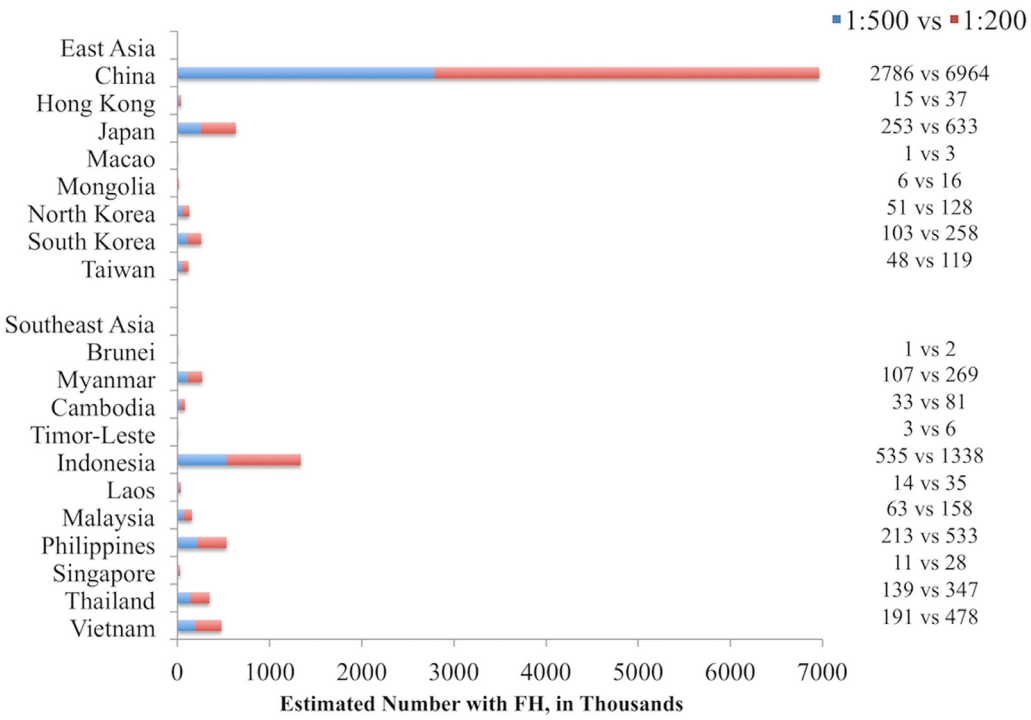

Fig. 1. Estimated number of individuals with familial hypercholesterolemia based on 2018 census information (in thousands).

Because these diagnostic criteria were developed from Western cohorts, it is unclear how well they can be generalized to other groups such as Asian populations who, for instance, tend to have lower cholesterol levels [13]. Therefore, application of LDL-C cut-offs such as those used in the MEDPED criteria to a Southeast and East Asian cohort could potentially result in missed diagnoses.

In China, a modified DLCN scoring system uses lower LDL-C thresholds and excludes physical exam findings as well as DNA analysis [14], due to the absence of widespread availability of genetic testing [15]. Other diagnostic criteria developed in Asian countries include the Japanese Familial Hypercholesterolemia Management Criteria (JFHMC) or Japan Atherosclerosis Society (JAS) Guidelines, where the diagnosis of homozygous FH is made in the presence of serum total cholesterol (TC) ≥15.5 mmol/L (598 mg/dL), presence of tendon xanthomas, premature coronary artery disease (CAD) during childhood, and a family history of heterozygous FH among the parents. Heterozygous FH is defined by LDL-C ≥ 4.7 mmol/L (180 mg/dL), the presence of tendon xanthomas, and family history of FH or premature CAD in a second-degree relative [16,17].

The performances of different diagnostic criteria (Simon Broome, US MEDPED, and JFHMC) as compared to DLCN were assessed in 755 patients of Malay, Chinese, and Indian descent. Cases diagnosed based on DLCN criteria were considered true positive, from which the sensitivities and positive predictive values of other criteria were derived. In this cohort, the Simon Broome criteria had a sensitivity of 51% and a positive predictive value of 98.8%, followed by the JFHMC with a sensitivity of 47% and a positive predictive value of 97.9% [18].

1.2. Overall prevalence

In 1977, the prevalence of FH in the Hokuriku district of Japan was reported as 1:900 [19]. The estimated prevalence is now thought to be approximately 1:208 for the heterozygous form and 1:171,000 for the homozygous form [20]. The reason for this difference is unclear. In China, Shi et al. evaluated more than 9000 individuals from the Jiangsu Nutrition Study, which was representative of the general population and included residents from 6 different counties. FH was diagnosed based on two definitions: (1) LDL-C ≥ 6 mmol/L (232 mg/dL) or LDL-C ≥ 3.5 mmol/L (135 mg/dL) plus a personal or family history of premature coronary heart disease (CHD), and (2) a modified DLCN definition as previously described. According to the first definition, 0.31% (1:323) had FH, whereas using the modified DLCN, 7.5% had possible, 0.18% (1:556) had probable, and 0% had definite FH after age adjustment [14]. In a recent meta-analysis, the prevalence of FH in Asia was 1:526 (4 studies, including 2 studies from Japan, 1 study from Korea, 1 study from China). In contrast, the prevalence of FH was 1:313 in Europe (19 studies) and 1:313 in North America (9 studies) [21].

Variability in the reported prevalence of FH may be because a variety of diagnostic criteria are used within Asian countries. In a review of 28 studies from 16 countries and regions in Asia, 6 used DLCN, 5 used Simon Broome, and 3 used MEDPED while 14 used their own criteria [22]. The lack of consensus regarding diagnostic criteria makes it difficult to compare different countries or even healthcare centers within the same country. Additional factors that limit the ability to estimate the true prevalence include variability in screening practices and the absence of centralized registries. **Fig. 1** displays the estimated number of individuals with FH in Southeast and East Asian countries based on 2018 census information [23,24] and assuming a prevalence of 1:200 to 1:500.

1.3. Prevalence of FH in individuals with premature CHD

In a Chinese cohort with very early-onset (≤35 years of age) CHD, 38% had an identified P/LP variant, 27% had definite/probable FH based on DLCN criteria, and 17% had definite/possible FH based on Simon Broome criteria [25]. Another study in China found that 6.5% of patients ≤35 years of age who presented with a myocardial infarction (MI) had definite/probable FH based on DLCN criteria [26]. In Japan, 4.7% of those with premature (<55 years for men, <65 years for women) acute coronary syndrome (ACS) had FH based on the 2012 JAS guidelines [27]. This is comparable to a Swiss study where the prevalence of definite/probable FH based on DLCN criteria in those with premature ACS was 4.8% [28]. Additionally, in a recent meta-analysis, compared to the general population, the prevalence of FH in Asia was 29-fold higher

Table 1
Clinical characteristics of heterozygous FH patients from different populations in Southeast and East Asia.

	Japan [75] *N* = 641	Korea [76] *N* = 97	China [77][a] *N* = 285	Hong Kong [78][b] *N* = 209	Hong Kong [46][c] *N* = 38	Taiwan [44] *N* = 87	Malaysia [79] *N* = 164
Age (mean±SD), years	51±15	54.1 ± 11.4	49±12	41.9 ± 13.4	51±12	42.3 ± 14.3	44.6 ± 12
Corneal arcus	38%	Not Reported	Not Reported	72.0%	16%	16.1%	50.0%
Xanthelasma	9%	Not Reported	Not Reported	13.0%			25.3%
Tendon Xanthomas	87%	20%	9.8%	49.7%	42%		40.9%
Coronary heart disease	24%	28%	81.8%	9.0%	Not Reported	20.7%	68.2%
LDL-C (mean±SD), mg/dL	248±67	226±38	201±82	286±57	363±81	221±53	194±35

Abbreviations: FH = familial hypercholesterolemia; SD = standard deviation; LDL-*C* = low-density lipoprotein-cholesterol.
[a] Includes a small number of patients with homozygous FH.
[b] Only data for those 18 years of age and older were reported in this table.
[c] Only data for those with Dutch Lipid Clinic Network criteria diagnosis of definite FH were reported in this table.

among those with premature CHD [21]. These findings highlight the importance of considering FH in Asian individuals who present with premature CHD.

1.4. Awareness

The "Ten Countries Study" assessed physician awareness of FH in several Asian countries compared to awareness in the UK [29]. A questionnaire was used to explore physician understanding of various aspects of FH. Compared to UK physicians, Asian physicians had lower awareness of FH guidelines and of the option to refer to lipid specialists. However, Japanese and Chinese physicians were better at identifying a lipid profile consistent with FH than physicians from the UK. Jing Pang et al. also explored awareness and knowledge of FH among physicians in Japan, Korea, and Taiwan [30]. Surprisingly, although 70% of the 230 surveyed felt that they had above-moderate understanding of FH, only 47% were aware of the inheritance pattern, only 27% recognized the estimated prevalence, and only 13% were familiar with the associated risk of cardiovascular disease. Furthermore, only 35% knew about available lipid specialist services in their respective areas. These findings highlight the need for increasing awareness of FH in this region.

1.5. Clinical characteristics

Table 1 displays the some of the clinical characteristics of heterozygous FH patients from different populations in Southeast and East Asia. The proportion of FH patients with corneal arcus was 72% in Hong Kong and 38% in Japan. The proportion of those with xanthomas was 87% in Japan, 20% in Korea, and 9.8% in China. The prevalence of CHD was 9% in Hong Kong, 81.8% in China, and 68% in Malaysia where the average LDL-C was 194 mg/dL. In comparison, among FH patients in the UK diagnosed based on Simon Broome criteria with an average age of 55±14 years and an average LDL-C of 239±86 mg/dL, 36% had tendon xanthomas and 21% had CHD [31].

1.6. Variations in LDL-C levels

As previously mentioned, studies have shown that compared with Western populations, Asian populations tend to have lower cholesterol levels [13]. Variations in LDL-C levels also exist among different Asian subpopulations. Karthikeyan et al. demonstrated that people from China and Hong Kong had lower LDL-C values than those from Southeast Asia and Japan [32]. For a given LDL-C level, it has been suggested that the risk of a cardiovascular event might be higher in Asians due to the higher atherogenic potential of small LDL-C particles [33], which have been found to be more prevalent at least in South Asians, compared to those of European descent [34].

In a study comparing the clinical characteristics of a cohort with FH that had migrated from China to Canada to a Chinese cohort living in China that had similar P/LP variants in *LDLR* and no significant difference in mean age, Pimstone et al. discovered that those living in Canada had higher LDL-C levels than those living in China [35], which could be attributed to environmental and dietary differences. Along with higher LDL-C levels, a significantly larger proportion of Canadian Chinese with FH had tendon xanthomas (44%) and CHD (25%) than those living in China (0%).

With the rapid socioeconomic growth seen in recent years in Asian countries, an important consideration is the effect of urbanization on LDL-C levels and the epidemiology of FH. Due to changes in lifestyle and diet that have led to increasing cholesterol levels in countries such as China and Japan, the FH phenotype may become more apparent over time and possibly result in an increase in rates of diagnosis [36-38].

1.7. Genetic epidemiology

Table 2 displays the results of multiple studies in Asia that investigated the genetic epidemiology of monogenic FH. Most of those identified as having FH were diagnosed clinically, and genetic testing was subsequently performed. It is important to note that genetic testing prior to 2015 may not have been complete (i.e. focused primarily on *LDLR* variants). Of those with a positive genetic test, 90% of the P/LP variants were in *LDLR*, though P/LP variants in other genes were not always assessed. Interestingly, no *APOB* P/LP variants were identified in three studies of FH in Japan [39–41]. However, recently, a variant in *APOB* was identified in one Japanese family [42]. On the other hand, in three studies evaluating FH in Taiwan, 9.2%, 13.3%, and 22.2% of cases had a P/LP variant in *APOB* [43–45], which suggests a potential founder effect. In this cohort of Taiwanese FH patients as well as in studies in Hong Kong [46], there were no P/LP variants in *PCSK9*. However, Mabuchi et al. found that P/LP variants in *PCSK9*, specifically the NM_174,936.3 (*PCSK9*): c.94G>*A* variant, were relatively common (7.6%) in Japan [39], again possibly due to a founder gene effect.

Unique variants have been identified in Asian populations with FH. Miyake et al. identified 24 P/LP variants in *PCSK9* specific to the Japanese population [47]. In Taiwan, a novel *LDLR* c.1186+2T>*G* variant was found in 23% of tested FH patients and was thought to have originated from a common ancestor based on haplotype analyses [48]. In an analysis of 66 studies evaluating the genetic epidemiology of FH in Han Chinese living in various countries including China, Hong Kong, and Taiwan, 69% of P/LP variants in *LDLR* were not reported in other ethnicities [49].

1.8. Cascade testing

The Centers for Disease Control and Prevention in the U.S. prioritizes the detection of prevalent and actionable Tier 1 genetic disorders such as FH [50], though there are no formal guidelines or recommendations for cascade testing. Cascade testing at a teaching hospital in Hong Kong was implemented in the early 1990s whereby first-degree relatives of probands were screened if possible [37]. In 2018, a consensus was published in China recommending cascade testing if a patient is diagnosed

Table 2
Genetic Epidemiology of Heterozygous Familial Hypercholesterolemia in Southeast and East Asia.

Study	Country	Number of FH Patients[a]	Criteria for P/LP Variants	Percent With P/LP Variant (Monogenic Etiology)	P/LP Variants *LDLR*	*PCSK9*	*APOB*
Hori et al. 2019 [80]; Hori et al. 2020 [42]	Japan	650	ClinVar; LOVD database; ExAC; Japanese Human Genetic Variation Database; Tohoku Medical Megabank Organization; ACMG; AMP	53.5% (n = 348)	85.1% (n = 296)	14.7% (n = 51)	0.3% (n = 1)
Mabuchi et al. 2014 [39]	Japan	1055	LOVD	77.6% (n = 819)	92.4% (n = 757)	7.6% (n = 62)	0%
Miyake et al. 2009 [40]	Japan	205	LOVD; UMD	67.8% (n = 139)	100% (n = 139)	Not Assessed	0%
Yu et al. 2002 [41]	Japan	200	UMD	62.5% (n = 125)	100% (n = 125)	Not Assessed	0%
Sun et al. 2018 [77]	China	285	LOVD	77.0% (n = 114)	67.5% (n = 77)	3.5% (n = 4)	28.9% (n = 33)
Xiang et al. 2017 [81]	China	219	ACMG	72.1% (n = 158)	91.8% (n = 145)	1.3% (n = 2)	7.0% (n = 11)
Li et al. 2017 [82]	China	245	Not Specified	41.6% (n = 102)	70.6% (n = 72)	2.9% (n = 3)	26.5% (n = 27)
Jiang et al. 2015 [83]	China[b]	357	LOVD	39.5% (n = 141)	92.9% (n = 131)	4.3% (n = 6)	2.8% (n = 4)
Chan et al. 2019 [46]	Hong Kong	96	LOVD; ClinVar; NCBI BLAST; SIFT; Mutation Taster	56.3% (n = 54)	94.4% (n = 51)	0%	5.6% (n = 3)
Mak et al. 1998 [84]	Hong Kong	30	Not Specified	70% (n = 21)	100% (n = 21)	Not Assessed	Not Assessed
Chiou et al. 2012 [43]	Taiwan	208	UCL	62.5% (n = 130)	90.8% (n = 118)	0%	9.2% (n = 12)
Chiou et al. 2010 [45]	Taiwan	102	UMD	58.8% (n = 60)	86.7% (n = 52)	0%	13.3% (n = 8)
Yang et al. 2007 [44]	Taiwan	30 families	Not Specified	60% (n = 18)	77.8% (n = 14)	0%	22.2% (n = 4)
Shin et al. 2015 [76]	Korea	97	LOVD; UMD; HGMD; ACMG	32% (n = 31)	87% (n = 27)	3.2% (n = 1)	6.5% (n = 2)
Shin et al. 2000 [85]	Korea	20 families	Not Specified	25% (n = 5)	100% (n = 5)	Not Assessed	Not Assessed
Han et al. 2015 [86]	Korea	69	LOVD; UMD; HGMD	33.3% (n = 23)	82.6% (n = 19)	8.7% (n = 2)	8.7% (n = 2)
Al-Khateeb et al. 2013 [87]	Malaysia	164	UCL; NCBI; HGMD; UniProt	93.3% (n = 153)	80.4% (n = 123)	Not Assessed	19.6% (n = 30)
Khoo et al. 2000 [88]	Malaysia[c]	86 Total 72 Chinese 13 Malay 1 Indian	Not Specified	25.6% (n = 22) overall 26.4% (n = 19) Chinese 15.4% (n = 2) Malay 100% (n = 1) Indian	100% (n = 22)	Not Assessed	0%

Abbreviations: FH = familial hypercholesterolemia; P/LP = pathogenic/likely pathogenic; *LDLR* = low-density lipoprotein receptor gene. *APOB* = apolipoprotein B gene; *PCSK9* = proprotein convertase subtilisin/kexin type 9 gene. LOVD = Leiden Open Variation Database. ExAC = Exome Aggregation Consortium. ACMG = American College of Medical Genetics and Genomics. AMP = Association for Molecular Pathology. UMD = Universal Mutation Database. NCBI = National Center for Biotechnology Information. BLAST = Basic Local Alignment Search Tool. SIFT = Sorting Intolerant from Tolerant. UCL = University College London. HGMD = Human Gene Mutation Database.

[a] The diagnostic criteria used was variable and based on clinical and/or genetic criteria.

[b] Study population included those from China, Hong Kong, and Taiwan.

[c] Study population included those of Chinese, Malay, and Indian descent.

with FH [51,52]. However, as in other countries, cascade testing is limited by poor awareness among patients and medical professionals, limited resources for testing, cost of testing, and patient concerns regarding the potential stigma and implications associated with genetic diagnoses.

1.9. Statin therapy

Response to lipid-lowering therapy has been found to be different in Asian populations compared with other ethnic groups. Compared to Western patients, a smaller statin dose has been shown to be associated with a comparable relative risk reduction in cardiovascular events in Japanese patients [53]. In the Japanese Lipid Intervention Trial (J-LIT) of more than 51,000 patients followed for over 6 years, the lipid-lowering effects of 5 mg of simvastatin in Japanese patients was comparable to the reduction in cholesterol levels seen with 20 mg in Western counterparts [54]. Furthermore, the DISCOVERY (Direct Statin Comparison of LDL-C Values: an Evaluation of Rosuvastatin Therapy) multicenter trials that evaluated the effect of rosuvastatin in patients with type IIa or IIb hypercholesterolemia revealed a 52.8% reduction in LDL-C levels in Hong Kong Chinese patients, which was greater than the 40.9–49.7% reduction found in the trials from Western countries [55]. However, a study in Singapore suggested that Asian patients require similar doses of statin medications to achieve goal LDL-C level [56].

Though some pharmacokinetic studies have shown that systemic exposure to statins is higher in Asian populations compared with white populations [57,58], others have shown no difference [59]. Some studies have found that polymorphisms in *SLCO1B1*, which encodes the organic anion transporter polypeptide 1B1 (OATP1B1), could explain these differences in pharmacokinetics [58], but others have not [57]. Additionally, while there is some speculation that a lower average body weight in the Asian population might explain potential differences, in a study looking at the effects of rosuvastatin, body

Table 3
Effects of Lipid Apheresis in Familial Hypercholesterolemia.

Study	Country	Number of Patients	Years of Follow Up	Proportion Free of Cardiovascular Events	LDL-C Reduction
Mabuchi et al. 1998 [72]	Japan	130 heterozygotes: • 43 with drug therapy + apheresis • 87 with intensive medical therapy alone	6	• 90% with drug therapy + apheresis • 64% with intensive medical therapy • p-value = 0.0088	• 58% with drug therapy + apheresis • 28% with intensive medical therapy • p-value <0.0001
Masaki et al. 2005 [89]	Japan	18 heterozygotes: • 17 with statin therapy + apheresis	10	• 94.4% at 6 years • 88.9% at 10 years	Not Applicable
Khoo et al. 2016 [90]	Malaysia	10 homozygotes and 5 heterozygotes: • 15 maximal medical therapy + apheresis	10	• 100%	• 55.6% in homozygous group • 57.8% in heterozygous group

Abbreviations: LDL-*C* = low-density lipoprotein-cholesterol.

weight accounted for less than 10% of the pharmacokinetic differences [57].

The association between variants in *SLCO1B1*, such as the rs4149056 (c.521T>*C*) C allele, and statin-induced myopathy has been noted in multiple studies [60–62]. Differences in the frequency of the C allele across various populations could explain variations in the incidence of myopathy [63]. There is a lack of studies that directly compare the incidence of statin-associated myopathy between those who are Asian and those who are White. However, in a trial comparing statin therapy in addition to either placebo or a combination of niacin/laropiprant, myopathy was more common among Chinese patients than White patients in both groups [64].

1.10. PCSK9 inhibitors

The phase 3 YUKAWA-2 trial showed a 67–76% reduction in LDL-C from baseline in Japanese patients with and without FH treated with PCSK9 inhibitors [65]. In the ODYSSEY JAPAN randomized controlled trial, the addition of alirocumab to stable statin therapy was associated with a significant 62.5% reduction in LDL-C in a population that included both heterozygous FH and those without FH [66]. Additionally, a sub-analysis of Taiwanese patients with hypercholesterolemia from ODYSSEY KT showed a 51% reduction in LDL-C with alirocumab [67], while the ODYSSEY EAST sub-analysis of patients with hypercholesterolemia in China, India, and Thailand showed a 56% reduction [68]. In the ODYSSEY FH I and FH II trials of predominantly white heterozygous FH patients, alirocumab was associated with a similar (51–59%) reduction in LDL-C [69]. In post-hoc analyses evaluating the efficacy of alirocumab in three ODYSSEY phase 3 trials, reductions in LDL-C were comparable regardless of race/ethnicity (White 58.7%; Black 42.9%; Hispanic/Latino 50.6%) [70]. Furthermore, the pharmacokinetic and pharmacodynamic characteristics of PCSK9 inhibitors appear to be similar between White and Asian (Japanese and Chinese) populations [71].

1.11. Lipid apheresis

We examined the efficacy of lipid apheresis in Southeast and East Asian FH patients (**Table 3**). In Japan, over 6 years of follow up, lipid apheresis in addition to drug therapy led to a larger reduction in LDL-C (58% with drug therapy and apheresis versus 28% with drug therapy alone) and a 72% reduction in cardiovascular events compared to intensive medical therapy alone [72]. In terms of mean acute LDL-C reduction immediately following apheresis, percentage reduction is similar between different populations in Europe, the U.S., and Japan, ranging between 58 and 63% for heterozygous FH patients [73]. In terms of outcomes, a retrospective analysis of the U.S. Apheresis Registry showed a 48% reduction in cardiovascular events after LDL apheresis over 5 years [74].

2. Conclusion

Although at least a quarter of the world's FH population resides in Southeast and East Asia, there are substantial gaps in knowledge regarding the epidemiology of FH due to low awareness, the absence of national screening programs, and limited availability of genetic testing. In an era of increased geographic mobility, given the many differences between Asian and Western populations, an important consideration is whether Asian patients living in Western countries should be treated differently. For instance, as Asian populations tend to have lower cholesterol levels, the application of FH diagnostic criteria developed from Western cohorts may result in missed diagnoses. Additionally, the etiology of monogenic FH appears to vary based on geographic location. Ultimately, more rigorous epidemiologic studies are needed to bridge gaps in knowledge and identify strategies for enhancing diagnosis and optimizing management in specific FH cohorts. Our review motivates future comparative research involving other groups of FH patients.

Funding

This work was supported by K24 HL137010 and R01HL135879.

Author contributions statement

Iftikhar Kullo: Conceptualization, funding acquisition and supervision

Candace Jackson: Formal analysis

Candace Jackson and Magdi Zordok: Data curation, investigation; methodology; project administration; resources; software, validation, visualization; writing - original draft

Iftikhar Kullo, Candace Jackson and Magdi Zordok: Writing - review & editing

Declaration of Competing Interests

The authors declare no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2021.100157.

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