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Review

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Familial Hypercholesterolemia in Asia Pacific: A Review of Epidemiology, Diagnosis, and Management in the Region

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Familial hypercholesterolemia (FH) is a common genetic disease that is estimated to affect at least 15 million people in the Asia Pacific region. Affected individuals are at significantly increased risk of premature atherosclerotic cardiovascular disease. A literature review was undertaken to provide an overview of the epidemiology, diagnosis, and management of FH across the region.

Currently, epidemiological data relating to FH are lacking across the Asia Pacific. Of the 15 countries and regions considered, locally conducted studies to determine FH prevalence were only identified for Australia, China, India, and Japan. Although practically all national clinical guidelines for dyslipidemia include some commentary on FH, specific guidelines on the management of FH are available for only one third of the countries and regions evaluated. Estimates of current FH diagnosis rates suggest that most affected individuals remain undiagnosed and untreated. Although innovative medications such as proprotein convertase subtilisin/kexin type 9 inhibitors have been approved and are available in most countries and regions considered, they are currently reimbursed in only one quarter.

Despite these shortcomings, there is cause for optimism. Early experience with cascade screening in Hong Kong, India, and Vietnam has proven an effective means of identifying family members of probands, as has a reverse screening of family members of children with FH in China. FH registries are gaining momentum across the region, with registries now established in almost half of the countries and regions evaluated. This review concludes with a Call to Action on FH for Asia Pacific to engage healthcare professionals, improve public awareness, and form national FH alliances, comprising all relevant healthcare professional organizations, as a platform to expedite national quality improvement programs in the management of FH.

Key words: **Familial hypercholesterolemia, Asia Pacific, Review**

Introduction

Familial hypercholesterolemia (FH) is the most common autosomal co-dominantly inherited condition affecting humankind. Mutations of three main genes encoding for the low-density lipoprotein (LDL) receptor, apolipoprotein B, or proprotein convertase subtilisin/kexin type 9 (PCSK9) cause FH. FH poses a major threat to public health because affected individuals are at significantly increased risk of premature atherosclerotic cardiovascular disease (ASCVD)[1]. Untreated individuals with homozygous

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FH (HoFH) typically present with ASCVD before 20 years of age, and most do not survive beyond 30 years[2]. Those with heterozygous FH (HeFH) are at significantly higher risk of developing premature coronary artery disease (CAD) compared with individuals without the condition. Despite a range of available interventions that can dramatically decrease LDL cholesterol levels, slow down the progression of ASCVD, reduce the incidence of cardiovascular events, and improve survival[3], FH is widely underdiagnosed and undertreated throughout the world.

In 2017, the global population was 7.6 billion[4], with 4.5 billion or 60% living in Asia. Accordingly, investigators from the "Ten Countries Study" estimated that more than half of individuals with FH reside in the Asia Pacific region[5]. Assuming a prevalence of one FH case per 250 individuals, 30 million individuals could be affected worldwide[6], of whom at least 15 million cases would be in the World Health Organization-defined South-East Asian and Western Pacific regions.

This review aimed to provide an overview of ongoing efforts in the Asia Pacific region to improve the diagnosis and management of FH.

Methods

A literature review was undertaken to identify publications relating to FH from the following countries and regions: Australia, China, Hong Kong, India, Indonesia, Japan, Malaysia, New Zealand, Philippines, Singapore, South Korea, Sri Lanka, Taiwan, Thailand, and Vietnam. For each country or region, a search was undertaken of the PubMed database with the search term "Country/Region AND familial hypercholesterolemia." All abstracts from 2010 to October 2019 were scrutinized. Those relating to the topics described above were assigned to a group within an EndNote library (Clarivate Analytics, Philadelphia), and full publications were sourced. To identify FH initiatives in the Asia Pacific region not described in peer-reviewed publications, internet searches were undertaken using the search term "Country/Region AND familial hypercholesterolemia." A summary of the findings of the review follows.

Epidemiology of FH in Asia Pacific

Table 1 summarizes the published estimates of FH prevalence in 15 Asia Pacific countries and regions: Australia, China, Hong Kong, India, Indonesia, Japan, Malaysia, New Zealand, Philippines, Singapore, South Korea, Sri Lanka, Taiwan, Thailand, and Vietnam. In only four countries—Australia, China, India, and Japan—were the estimates based on locally conducted studies of FH prevalence.

In 2015, Watts *et al* described the prevalence and treatment of FH in Australian communities[7]. The first data set was obtained from the Australian Diabetes, Obesity and Lifestyle (AusDiab) study[8], and the second data set was obtained from individuals who volunteered for a risk assessment for cardiovascular disease and clinical trials. Analysis of these two data sets enabled a comparison of FH prevalence in a randomly selected community population with a group undergoing cardiovascular risk evaluation[9]. The prevalence of definite/probable FH was 1 in 353 (0.28%, 95% confidence interval [CI]: 0.16%–0.41%) in the AusDiab group and 1 in 229 (0.44%, 95% CI: 0.26%–0.62%) in the risk assessment and clinical trial group.

In 2014, Shi *et al* described the prevalence, underdetection, and undertreatment of FH in a community population in China[10]. The prevalence of probable/definite FH was 0.28%, which equates to 1 per 357 in the general population. In 2019, Wang *et al*[11] determined FH prevalence among participants in the Henan Rural Cohort Study[12]. The prevalence of probable/definite FH was 0.35% (95% CI: 0.29%–0.41%), which equates to 1 per 286 in the general population.

In 2017, Gupta *et al* reviewed recent studies on the epidemiology of dyslipidemias in India[13], which included the population-based India Heart Watch study[14] and another study conducted at a tertiary care hospital[15]. Severe hypercholesterolemia, defined as an LDL cholesterol level of ≥ 220 mg/dL, was considered as suspected FH. In the population-based study and hospital-based study, 1 per 357 participants and 1 in 209 participants had suspected FH, respectively.

In 2011, Mabuchi *et al* described the molecular genetic epidemiology of FH in the Hokuriku district of Japan[16]. The frequency of HeFH was 1 in 208 residents, and that of HoFH was 1 in 171,167.

All other estimates of FH prevalence provided in **Table 1** were based on the application of an estimate of prevalence, ranging from 1 per 200 to 1 per 500, to national population data. Accordingly, there is a pressing need to characterize the actual prevalence of FH across the region.

The prevalence of FH among high-risk groups has been evaluated in several studies. Investigators from Beijing, China, determined the prevalence of FH among patients with premature myocardial infarction (PMI, defined by age at the first onset of myocardial infarction: male ≤ 55 years old and female ≤ 60 years old)[17]. The prevalence of FH diagnosed by genetic

Table 1. The prevalence of FH in the Asia Pacific region[7, 10, 11, 13-16, 20-25]

Country or region	aFH Prevalence		References
	Rate	Cases (*n*)	
Australia	1:229-353[a]	-	7)
China	1:286-357[a]	4.6 million[b]	10, 11, 20)
Hong Kong	1:300[b]	24,000[b]	20)
India	1:209-357[c]	-	13-15)
Indonesia	-	-	-
Japan	1:208[d]	608,900[e]	16)
Korea	-	-	-
Malaysia	1:300[b]	107,000[b]	20)
New Zealand	1:500[f]	10,500[f]	22)
Philippines	1:300[b]	340,000[b]	20)
Singapore	-	22,000[g]	23)
Sri Lanka	-	-	-
Taiwan	-	100,000[h]	24)
Thailand	-	-	-
Vietnam	1:300[i]	300,000[i]	7, 10, 25)

[a] Definite/probable FH according to modified DLCN criteria.
[b] Estimate provided in 2019 "Ten Countries Study" publication based upon HeFH rate of 1:300 applied to population data for 2016.
[c] Suspected FH based on LDL cholesterol ≥ 220mg/dl.
[d] Calculated using the Hardy-Weinberg equilibrium.
[e] Based on application of a rate of 1:208 to the population of Japan in 2018 (126.5 million).
[f] Estimate provided in review of identification of FH in New Zealand based upon 1:500 rate for Western populations.
[g] Estimate provided in European Atherosclerosis Society FH Studies Collaboration review in >60 countries.
[h] Estimate provided in FH section of 2017 Taiwan lipid guidelines based upon prevalence of 1:200 for HeFH and 6 per million for HoFH.
[i] Estimate for Vietnam is informed by prevalence estimates from Australian and Chinese studies above.

testing was 4.4% and definite/probable FH diagnosed by the modified Dutch Lipid Clinic Network (DLCN) criteria was 23.6%. Investigators from New Delhi, India, assessed individuals with premature CAD for FH using the DLCN criteria[18]. Four percent were diagnosed as definite and 11% as probable. In Japan, the prevalence of HeFH among patients admitted to hospital with ACS[19] was 5.7% overall, increasing to 7.8% among patients less than 60 years.

In 2019, Chang and Su explored the relationship between perceived depression and FH among patients recruited to the "Ten Countries Study" in Taiwan[26]. The FH patients had a higher risk of perceived depression than patients with hypertriglyceridemia or controls with normal lipid levels, with an odds ratio of possible depression of 1.50 (95% CI: 1.07–2.11) and probable depression of 1.73 (95% CI: 1.10–2.75) after adjustment for relevant cardiovascular risk factors. Among patients with a family history of coronary heart disease, total Center for Epidemiological Studies Depression Scale scores were higher for FH patients than those for the non-FH group (17.30 vs. 13.08, $p=0.022$).

Genetics of FH in Asia Pacific

Notable differences exist between the genetics of people with FH in the Asia Pacific region and those of Western countries. Furthermore, some differences are apparent between different locales within the Asia Pacific region.

In 2016, Chiou and Charng reviewed the genetic diagnosis of FH in Han Chinese[27]. As illustrated in **Fig. 1**, the total of 143 different mutations of the LDL receptor identified was low compared with European populations. Most of the mutations were reported in southeast China, Hong Kong, and Taiwan, with the five most common mutations being APOB 10579C>T, LDLR 986G>A, 1747C>T, 1879G>A, and 268G>A.

In 2019, Tomlinson *et al* summarized recent studies of mutations found in Chinese patients with FH, as shown in **Table 2**[28]. Many of the LDLR mutations were novel at the time of identification and some were relatively common.

In 2017, Chiou and Charng established an FH assay panel for the Han population residing in Taiwan[29]. The performance of the assay was verified by comparison of results with Sanger DNA sequencing

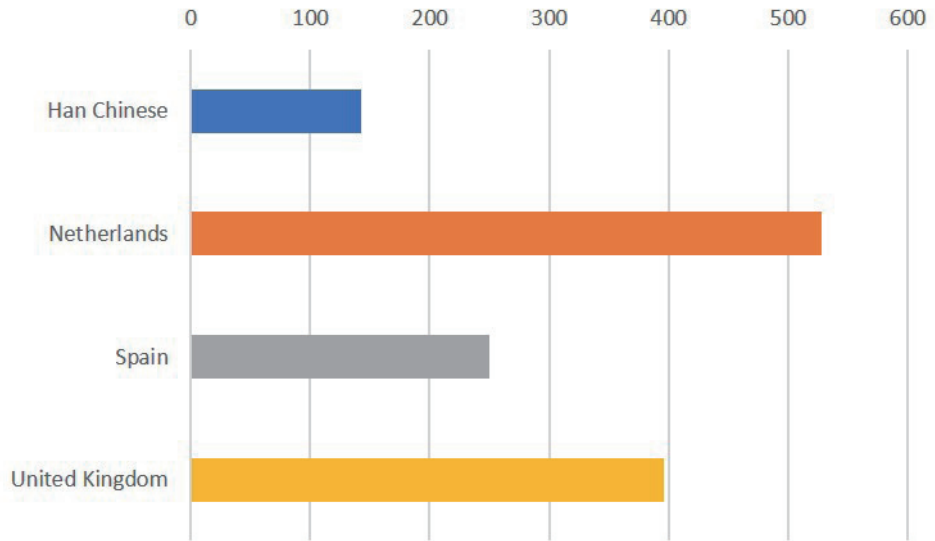

Fig. 1. Number of LDL receptor mutations in Han Chinese compared with European populations[27]

Table 2. Common mutations causing familial hypercholesterolemia in Chinese populations[28]

c.DNA change	Protein change	Number of index cases	Frequency (%)
339 mutation-positive probands from China, Hong Kong, and Taiwan			
APOB c.10579C>T	p.R3500W (Arg3527Trp)	37	10.9
LDLR c.986G>A	p.C308Y (Cys329Tyr)	28	8.3
LDLR c.1747C>T	p.H562Y (His583Tyr)	21	6.2
LDLR c.1879G>A	p.A606T (Ala627Thr)	16	4.7
LDLR c.268G>A	p.D69N (Asp90Asn)	14	4.1
99 mutation-positive probands only from China			
LDLR c.1879G>A	p.A606T (Ala627Thr)	13	13.1
LDLR c.1448G>A	p.W462X (Trp483X)	10	10.1
LDLR c.1864G>T	p.D601Y (Asp622Tyr)	6	6.1

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for 180 previously sequenced subjects. Among the 120 subjects with point mutations, only one discrepancy was found between the 2 techniques. A subsequent blinded study was conducted that involved 62 probands with mutations that were identified by both techniques. The detection sensitivity and specificity rates of the Agena iPLEX were 92.5% and 100%, respectively. The authors conclude that the Agena iPLEX assay has great potential to be included in FH screening in Taiwan on account of its low cost, rapidity, and flexibility.

Fh Care Gap in Asia Pacific

In 2016, Zhou and Zhao reviewed studies of FH in Asian populations[30]. The authors found that reports of FH frequency were commonly based on different diagnostic criteria. Among 28 studies from 16 Asian countries or regions, 14 used self-defined FH criteria, and only one specific FH guideline was available from Japan. Six Asian countries or regions participated in the global Make Early Diagnosis Prevent Early Death (MEDPED) FH programme[31]. It was estimated that FH diagnosis rates for Hong Kong, Israel, Japan, and Singapore ranged from 3% to 10%.

In 2017, investigators from China sought to identify the prevalence of FH among a large group (n=8,050) of patients who underwent coronary angiography[32]. Definite and probable FH were reported for 1.0% and 2.5% of patients, respectively. Only 5% of definite/probable FH patients received

high-intensity lipid-lowering treatment, of whom none achieved an LDL cholesterol level of <100 mg/dL (2.59 mmol/L).

In 2017, Australian investigators studied the association between elevated LDL cholesterol levels in children and family history of hypercholesterolemia or documented premature cardiovascular disease[33]. Almost 21% of children with LDL cholesterol of ≥ 3.4 mmol/L (≥ 95th percentile) had a positive family history, and among children with LDL cholesterol of ≥ 3.8 mmol/L (≥ 99th percentile), the proportion was 20%. The authors concluded that an opportunity was missed for the identification of children with FH based on their family history.

In 2019, investigators from the "Ten Countries Study" invited key opinion leaders from 12 countries or regions to participate in a series of online questionnaires regarding various aspects of FH care[20]. Key findings included the following:

- Diagnosis rates were estimated to vary from < 0.1% in China to 4% in Australia, compared with 10%–20% in the United Kingdom.
- Less than 5% of patients in China, Japan, Malaysia, and Vietnam were reported as achieving an LDL cholesterol treatment goal of <1.8 mmol/L.
- Registries had been established in Australia, Japan, Malaysia, and Vietnam.
- Educational initiatives were available in Australia, China, Japan, Taiwan, and Vietnam.
- Cost-effectiveness analysis of screening had been conducted in Australia, and cost-effectiveness analyses of treatment had been conducted in Australia and Japan.

The authors concluded that a combination of approaches was required to address current deficits in FH care across the Asia Pacific:

- government policy relating to FH with associated public funding;
- improvement of the efficiency of healthcare systems in the diagnosis and management of FH;
- empowering patients and communities to recognize the importance of managing cholesterol among families with a history of premature coronary disease.

FH Clinical Guidance in Asia Pacific

In 2014, the International FH Foundation published comprehensive guidance that provided detailed recommendations for the following[9]:

1. Detection of Index Cases: Screening and Phenotypic Diagnosis;
2. Diagnosis and Assessment of Adults;
3. Diagnosis and Assessment of Children and Adolescents;
4. Cascade Screening: Testing and Risk Notification of Families;
5. Genetic Testing;
6. Management of Adults;
7. Management of Children and Adolescents;
8. Lipoprotein Apheresis and Related Treatments;
9. Organisation and Development of Care.

In the Asia Pacific region, specific FH guidelines have been published for Australia and New Zealand[34, 35], China[36], Hong Kong[37], and Japan[38, 39]. **Table 3** provides a summary of the key recommendations made in these guidelines regarding diagnosis, treatment, and cascade screening. General dyslipidemia guidelines that make recommendations on the management of FH have been published for India[40, 41], Indonesia[42], Malaysia[43], Philippines[44], South Korea[45], Singapore[46], Taiwan[24], and Thailand[47].

FH Registries

In 2013, Australian investigators proposed that the development of a global network of inter-operable FH registries would provide a platform to[48]

1. address the current care gap,
2. support basic research,
3. enable equitable access to clinical trials, and
4. disseminate evidence for best practice and information for care services.

In 2015, the European Atherosclerosis Society FH Studies Collaboration was launched to establish a global FH registry to generate large-scale, robust data on the burden of FH worldwide[6, 49]. As of August 2019, 61,223 cases globally had been entered into the registry[50], and the collaboration had grown to encompass 87 lead investigators from 69 countries, including Australia, China, Hong Kong, India, Iran, Iraq, Japan, Kyrgyzstan, Malaysia, Pakistan, Philippines, Singapore, South Korea, Taiwan, Thailand, Turkey, Uzbekistan, and Vietnam.

To date, in the Asia Pacific region, FH registries have been established in Australia and New Zealand[51], India[52], Japan[53], Malaysia[20], Taiwan[54], and Thailand[55]. In 2019, investigators from Beijing advocated for the establishment of a Chinese FH registry[56].

FH Screening Strategies

A range of opportunities exist to systematically identify individuals with FH throughout the life cycle. These include FH screening in childhood, cascade

Table 3. Summary of key recommendations of specific FH guidelines in the Asia Pacific region[34-39]

Country or region	Diagnosis	Treatment	Cascade screening	References
Australia and New Zealand	- DLCN or modified Simon Broome criteria are comparable in predicting mutation positive FH - Pro-active identification of FH patients with premature ASCVD (aged <60 years) and those with a family history of hypercholesterolemia and premature ASCVD - All potential cases should be referred to a lipid clinic/genetic service for confirmation of diagnosis and risk assessment	- Appropriative, exercise and avoidance of smoking - Statins provide excellent lipid control which can be enhanced by bile acid sequestrants or cholesterol absorption inhibitors (e.g. plant sterols or ezetimibe) - Other therapies may be required, including niacin and/or fibrates, PCSK9 inhibitors, lomitapide and mipomersen - Patients with elevated plasma Lp(a) may require apheresis	- Cascade screening or predictive testing of first-degree relatives of index cases should be offered - Genetic counsellors can provide support to families affected with FH in relation to testing and treatment of children, interruption of treatment for conception, pregnancy and breast-feeding	34, 35)
China	- Adults with ≥ 2 of the following criteria: 1. Untreated LDL-C ≥ 4.7mmol/L 2. Tendon/skin xanthomas or gerontotoxon (<45years) 3. History of FH or premature ASCAD within first-degree relatives - Children: Untreated LDL-C ≥ 3.6mmol/L and first-degree relatives have history of FH or premature ASCAD	- Appropriate diet, exercise and avoidance of smoking - Use a maximum tolerated dose of a strong statin - If target LDL-C level not achieved with statin monotherapy, add ezetimibe (10 mg/d); If statin and ezetimibe combination does not achieve control add PCSK9 inhibitors - If all treatments do not achieve control, consider plasma exchange	- Cascade screening for relatives of patients with premature ASCAD (male <55years, female <65years) - Screening for adult LDL-C >3.8mmol/L, children LDL-C >2.9mmol/L, and can exclude secondary hyperlipidemia - Patients with xanthoma or gerontotoxon (<45years) -Their first-degree relatives have the above three conditions	36)
Hong Kong	- DLCN criteria recommended for diagnosis of FH with the caveat that a lower threshold for LDL-C levels be adopted to indicate definite FH, probable FH, possible FH, and unlikely FH - Individuals with a plasma LDL-C level >5 mmol/L should be regarded as potential probands - For those with a family history of FH or premature coronary heart disease (CHD), the LDL-C level threshold could be 4.5 mmol/L	- Appropriate diet, exercise and smoking avoidance - Statins are the first-line treatment for adults and children with FH - If the target LDL-C level cannot be achieved with statin monotherapy, consider combination with ezetimibe and/or a bile-acid sequestrant or niacin - PCSK9 inhibitors are available, however, mipomersen and lomitapide are not available in Hong Kong	- Cascade screening for relatives of patients with FH is recommended in both the private and public sectors - Cascade screening is highly recommended inchildren with elevated LDL-C levels and in children with relatives who exhibit FH phenotypes	37)
Japan	- Adult FH (≥ 15 years): Adults with ≥ 2 of the following criteria: 1. LDL-C ≥ 180 mg/dL 2. Tendon/skin xanthomas 3. History of FH or premature CAD within 2nd degree blood relatives - Pediatric HeFH: LDL-C ≥ 140 mg/dL and family history of FH or premature CAD - Pediatric HoFH: Existence of skin xanthomas or tendon xanthomas from infancy, and untreated LDL-C levels are approximately twice those of HeFH parents	- Adult HeFH: Provide guidance on lifestyle modification, including maintaining appropriate body weight and initiate lipid-lowering therapy. If target LDL-C levels not achieved, sequentially add ezetimibe, then add PCSK9 inhibitor and/or resin/probucol and finally LDL apheresis. - Adult HoFH: A similar stepwise approach, however, initiate LDL apheresis as early as possible. - Pediatric HeFH: Initiate drug therapy in children aged ≥ 10 years when LDL-C ≥ 180 mg/dL - Pediatric HoFH: Combination therapy with ezetimibe and other agents is often required, however, since LDL-C targets are rarely achieved, lipoprotein apheresis is recommended.	- Cascade screening is recommended for all blood relatives of individuals diagnosed with FH - Screening of children in families affected with FH should be undertaken - After a child is diagnosed with FH, a family survey should be conducted to find others with FH in the patient's family - Notably, financial assistance is available for pediatric HeFH under a grant-in-aid programme for chronic diseases in childhood	38, 39)

screening, reverse screening, screening of individuals with ACS, and identification of FH in the primary care setting. Summaries of promising strategies from the Asia Pacific region and elsewhere follow.

FH Screening in Childhood

In 2011, the US National Heart, Lung, and Blood Institute Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents recommended universal screening for dyslipidemia by the age of 9–11 years and subsequently at age 17–21 years[57]. Slovenia started universal screening for hypercholesterolemia in 5-year-old children in 1995[58]. In 2015, Battelino *et al* conducted genetic testing for FH in 272 children identified by the screening program and reported that 57% carried disease-causing genetic variants[59].

Cascade Screening

Table 4 provides a summary of studies that have evaluated cascade screening in the Asia Pacific region.

Reverse Screening

In 2016, Wald *et al* described a child–parent FH screening program in primary care[64]. A positive screening result was assigned for children with elevated cholesterol and an FH mutation or elevated cholesterol on a repeat measurement taken 3 months later. Parents were deemed to have a positive screening result for FH if he or she had the same mutation as the child or, if no mutation was evident, had the higher cholesterol measurement of the two parents. The authors stated that the strategy was feasible, and for every 1,000 children screened, 4 children and 4 parents had positive screening results for FH.

In 2017, Lin *et al* evaluated reverse screening strategy in China[65]. Among 41 children with severe hypercholesterolemia, 12 were shown to have HoFH and 29 to have compound HeFH. Among 81 first-degree family members, all were genotypically diagnosed with FH. Among 37 second-degree relatives, 92% were diagnosed with FH. Accordingly, for every child with FH, 2.8 new cases were diagnosed among family members.

Screening of Individuals with ACS

In addition to the publications from China[17], India[18], and Japan[19] described in the epidemiology section of this review, **Table 5** provides the summaries of additional efforts to screen ACS patients in the Asia Pacific region.

Identification of FH in Primary Care

Several studies from Australia[71-74] and the United Kingdom[75, 76] have evaluated the potential for identification of FH in the primary care setting. Key findings included the following:

- Community-based laboratories are well placed to opportunistically identify individuals with potential FH[71].
- Electronic extraction tools can increase the detection of FH in general practice[74, 75].
- A study using the UK Clinical Practice Research Datalink reported that the FAMCAT FH prediction model showed high discrimination for distinguishing cases from non-cases (area under receiver operating curve [AUC] 0.860, 95% CI 0.848–0.871)[76].

In 2018, Brett *et al* advocated screening of FH in primary care[77], noting that such a screening program would adhere to many of the principles of the classic Wilson and Jungner criteria as revised for the genomic age by Andermann *et al* in 2008[78]:

1. The screening program should respond to a recognized need.
2. The objectives of screening should be defined at the outset.
3. There should be a defined target population.
4. There should be scientific evidence of screening program effectiveness.
5. The program should integrate education, testing, clinical services, and program management.
6. There should be quality assurance, with mechanisms to minimize potential risks of screening.
7. The program should ensure informed choice, confidentiality, and respect for autonomy.
8. The program should promote equity and access to screening for the entire target population.
9. Program evaluation should be planned from the outset.
10. The overall benefits of screening should outweigh the harm.

Brett *et al* proposed that FH is best diagnosed in childhood or early adolescence, which should be followed by cascade testing of family members of young people diagnosed with the condition. Development of a shared care model would result in primary care managing relatively low-risk patients, with support from specialists as required for high-risk patients and those cases that prove difficult to manage. A succinct guide for general practice was published by the same authors[79].

Management of FH in the Asia Pacific

The summary of key recommendations of specific FH guidelines in the Asia Pacific region in

Table 4. Cascade screening strategies implemented in the Asia Pacific region[25, 60-63]

Country or region	Study subjects	Summary of findings	References
Hong Kong SAR, China	• 132 families were screened • Potential probands recruited if total cholesterol (TC) >7.5 mmol/L and/or LDL-C >4.9 mmol/L without secondary causes	• 87 screened patients (66%) were clinically diagnosed with HeFH • Among 314 first-degree relatives of probands or their affected relatives, 165 subjects (53%) with clinical HeFH were identified: →83% of these subjects were previously unaware of having HeFH	60)
Hong Kong SAR, China	• Of 98 index patients with a clinical diagnosis of FH and/or severe hypercholesterolemia, 94 unrelated probands were identified	• 62 probands carried definite or likely pathogenic mutations • 167 first- and second-degree relatives of probands with causative mutations (n=45) attended screening • 36 first-degree relatives of probands without mutations attended screening • In total, 122 relatives were identified to have FH, of which: →48 (39%) were newly diagnosed →74 (61%) were aware of having hypercholesterolemia, although 53% of these relatives had never been treated or had stopped treatment	61)
India	• 31 families of mutation positive probands were screened using bidirectional Sanger sequencing (n=28) or MLPA technique (n=3)	• Cascade screening was undertaken in 133 family members: →88 (66%) carried the family mutation →15 (11%) had CAD →63 (47%) were already taking lipid lowering therapy →12 were children <18 years of age: ▪ 3 children had clinically homozygous phenotype ▪ 5 children had very high LDL cholesterol levels (550.4±152.2 mg/dL)	62)
Vietnam	• 4 families of individuals with a presumptive diagnosis of HoFH were screened using genetic and cholesterol testing	• Cascade screening was undertaken in 107 family members: →Of 89 who were genetically screened, an FH mutation was found in 47 including 3 homozygotes and 44 heterozygotes →Among the 47 mutation positive individuals, 18 were children aged <18 years →9 additional relatives had "likely FH" based on the Starr et al criteria[63] →Only 5 (9%) of relatives with FH were subsequently treated due to: ▪ Cost of treatment ▪ Lack of patient knowledge about FH ▪ Lack of local doctors' knowledge about FH	25)

Table 5. Screening of individuals with ACS in the Asia Pacific region[66-70]

Country	Study subjects	Summary of findings	References
Australia	• 316 patients consecutively admitted to a hospital Coronary Care Unit	• 163 (51.5%) had premature CAD (i.e. <60 years of age) • Overall: →26.3% of patients had elevated lipoprotein(a) (i.e. ≥ 0.5 g/L), which was more common among those with a premature coronary event (31.9% vs. 20.3%, $p=0.019$) →11.4% had phenotypic FH, which was almost twice as common among those with premature CAD, although not a statistically significant difference (14.8% vs 7.8%, $p=0.052$) →4.4% had both disorders, which was more common among those with premature CAD (6.2% vs. 2.6%, $p=0.033$)	66)
China	• 1843 consecutive patients undergoing coronary angiography with their first MI	• 889 (48.2%) had premature CAD (i.e. the onset age of MI ≤ 55 for men and ≤ 60 for women) • Prevalence of definite/probable FH according to DLCN was 3.9% overall (7.1% in PMI and 0.9% in non-PMI) • Risk of PMI was significantly elevated, independent of classical risk factors and medications, for: →Definite/probable FH (vs. unlikely FH, odds ratio, 5.05 [1.10–23.23]) →Possible FH (vs unlikely FH, odds ratio, 2.65 [1.22–5.77]) • The onset age of MI was a decade younger for definite/probable FH patients (48.63 ± 1.20 vs 58.35 ± 0.30 years, $p<0.001$)	67)
China	• 1093 consecutive patients aged ≤ 35 years undergoing coronary angiography with their first MI	• Prevalence of definite/probable FH according to DLCN was 6.5% overall, increasing to 10.3% among patients aged ≤ 25 years • Despite 69% of definite/probable FH patients having received lipid lowering therapy pre-admission, none achieved LDL cholesterol ≤ 2.56 mmol/L • Significant differences were evident between previously treated patients and untreated patients: →LDL cholesterol (3.58 mmol/L vs. 6.52 mmol/L, $p<0.001$) →Lp(a)-adjusted LDL cholesterol (3.25 mmol/L vs. 6.16 mmol/L) →Gensini score (33.40 vs. 77.66, $p=0.009$) • During 40 months follow-up, patients who received therapy had significantly lower cardiovascular event rates than those not receiving (6.5% vs. 10.5%, $p=0.017$)	68)
Japan	• 1944 patients aged ≥ 20 years presenting with acute coronary syndromes who were registered on the EXPLORE-J registry	• Overall, 2.7% of patients had FH according to the diagnostic criteria defined in the 2012 JAS guidelines[70] • FH prevalence was higher among: →Patients with premature ACS (<55 years in men and <65 years in women) than those without (4.7% [95% CI: 2.9-7.2] vs. 2.1% [95% CI: 1.4-3.0]) →Patients aged <40 years than those aged ≥ 40 years (8.3% [95% CI: 1.8-22.5] vs. 2.6% [95% CI: 1.9-3.4]) →Patients without prior use of statins than those with prior use (3.2% [95% CI: 2.3-4.2] vs. 1.3% [95% CI: 0.5-2.7]	69)

Table 3 describes the role of statins, bile acid sequestrants, and cholesterol absorption inhibitors (e.g., plant sterols or ezetimibe) in the management of FH and highlights when lipoprotein apheresis may be required. Other therapies, including ezetimibe, fibrates, PCSK9 inhibitors, lomitapide, and mipomersen, may be required when statins that are administered at the highest tolerated dose in combination with other medications do not achieve target LDL cholesterol levels[80]. Pasta *et al*[81] and Raal *et al*[82] have recently published reviews on the role of PCSK9 inhibitors in the management of hypercholesterolemia. Table 6 provides a summary of findings from clinical trials and meta-analyses for PCSK9 inhibitors.

As Table 7 shows, although PCSK9 inhibitors have been approved and are available in the majority of countries and regions considered in this review, these innovative drugs are reimbursed for use in only approximately one quarter of the listed countries and regions.

International and National FH Alliances

In advance of the United Nations High-level Meeting on Non-communicable Diseases in 2018, the World Heart Federation brought together "… a global coalition of international, regional, and national stakeholders in cardiovascular diseases (CVDs) to drive the urgent action needed to combat heart disease and stroke[89]." At the national level, Kalra *et al* articulated the need for all clinical specialties of relevance to FH in India to collaborate to expedite improvements in all aspects of FH care[90].

Although not focused upon FH, the Secondary Prevention Alliance in Australia could illustrate how healthcare professional organizations operating in the cardiovascular arena could collaborate to form national FH alliances[91]. The Secondary Prevention Alliance comprised a broad group of national healthcare, consumer, government, and non-government organizations. National FH alliances could be standing bodies or "virtual organizations" established based on a memorandum of understanding agreed between key stakeholder organizations, which could

- advocate for improved FH care to policymakers with a unified voice,
- encourage the development of consensus clinical guidelines and concise clinical standards for FH care,
- endorse and engage with global efforts to develop sustainable national FH registries,
- develop education programs that can help build the multidisciplinary workforce required to deliver the best clinical practice.

Analogous national alliances have been established to improve the care of a broad range of conditions in several countries, including arthritis[92], dementia[93], diabetes[94], and fragility fractures[95]. Accordingly, the FH community has considerable generic experience to draw upon in terms of why such alliances were formed, how they function, and what specific activities they have undertaken and the progress that they have made.

Conclusions

With half of the world's population of individuals who are living with FH residents in the Asia Pacific, the time has come to implement systematic and system-wide improvements in the management of this debilitating and life-threatening condition. The findings of this review simultaneously provide cause for concern and optimism.

Diagnosis rates are very low in most countries. Specific FH guidelines have only been published in 5 of the 15 countries and regions considered, although some degree of commentary on FH features in practically all national clinical guidelines for dyslipidemia. A similar picture is evident regarding FH registries, with established or nascent registries present in seven countries or regions. Furthermore, although approved and available in most countries and regions considered, innovative drugs such as PCSK9 inhibitors are reimbursed in only one quarter.

On a positive note, in terms of identifying relatives with FH, early experience with cascade screening has proved effective in Hong Kong, India, and Vietnam. However, engaging patients to initiate new treatment or restart previously discontinued treatment presents a challenge to healthcare professionals. A reverse screening strategy in China resulted in the diagnosis of 2.8 new cases among family members for every child with FH. Studies from Australia, China, India, and Japan have described screening of patients admitted to hospital with ACS and make a compelling case for this strategy to be routine, particularly among patients with premature cardiovascular events. Several approaches have been explored in the primary care setting to improve the identification of FH, and the case has been made for widespread screening programs to be delivered through primary care.

Finally, national quality improvement programs in the management of FH could be expedited by the formation of national FH alliances comprising all relevant healthcare professional organizations. Such

Table 6. A summary of clinical trials and meta-analyses of PCSK9 inhibitors[83-87]

PCSK9 Inhibitor	Study design and subjects	Summary of findings	References
Alirocumab	• A meta-analysis of 25 RCTs encompassing 12,200 patients with both familial and non-familial hypercholesterolemia	• Biweekly 50 to 150 mg alirocumab: →Reduced LDL cholesterol by -52.6% (95% CI: -58.2 to -47.0%) versus placebo and by -29.9% (95% CI: -32.9 to -26.9%) versus ezetimibe →Increased high-density lipoprotein (HDL) cholesterol by 8.0% (95% CI: 4.2 to 11.7%) versus placebo	83)
Alirocumab	• ODYSSEY Open-Label Extension (OLE) study • 167 patients with HeFH who had completed an earlier double-blind, RCT parent study • Patients were initiated on 75 mg biweekly alirocumab unless baseline LDL-C was >8.9 mmol/l, in which case they received biweekly 150 mg alirocumab	• Biweekly 75 to 150 mg alirocumab: →At week 144, the mean LDL cholesterol level was reduced by 48.7% compared to the mean level at baseline (3.65 ± 1.9 mmol/L [standard deviation, SD]) →Injection site reactions reported for eight patients, with one treatment discontinuation →Treatment emergent anti-drug antibodies were identified in five patients but did not affect efficacy	84)
Alirocumab	• ODYSSEY OUTCOMES study • 18,924 patients: →Who had an ACS within the previous 12 months →With LDL cholesterol ≥ 70 mg/dL (1.8 mmol/L), non-HDL cholesterol level ≥ 100 mg/dL (2.6 mmol/L), or an apolipoprotein B level ≥ 80 mg/dL →Receiving high-intensity dose or maximum tolerated dose of statin	• Biweekly 50 to 150 mg alirocumab: →Significantly reduced the risk of the primary efficacy end point[a] (903 patients [9.5%] vs. 1052 patients [11.1%]; HR, 0.85; 95% CI 0.78 to 0.93; $p<0.001$) →Significantly reduced the risk of the major secondary efficacy end point[b] (1199 patients [12.7%] vs. 1349 patients [14.3%]; HR, 0.88; 95% CI 0.81-0.95; $p=0.001$)	85)
Evolocumab	• A meta-analysis of 25 RCTs encompassing 12,200 patients with both familial and non-familial hypercholesterolemia	• Monthly 420 mg evolocumab: →Reduced LDL cholesterol by -54.6% (95% CI: -58.7 to -50.5%) versus placebo and by -36.3% (95% CI: -38.8 to -33.9%) versus ezetimibe →Increased HDL cholesterol by 7.6% (95% CI: 5.7 to 9.5%) versus placebo	83)
Evolocumab	• TAUSSIG open-label study final report • 300 patients with HoFH ($n=106$) and severe HeFH ($n=194$) • Patients undergoing apheresis at enrollment received biweekly 420 mg evolocumab immediately after apheresis • Patients not undergoing apheresis at baseline received monthly 420 mg evolocumab • Dose regimen could be changed at the clinician's discretion	• Biweekly or Monthly 420 mg evolocumab: →In HoFH patients, mean percentage changes (± SD) in LDL cholesterol relative to baseline were -21.2 ± 25.0% at week 12 and -24.0 ± 41.3% at week 216 →In HeFH, mean percentage changes (± SD) in LDL cholesterol relative to baseline were -54.9 ± 17.4% at week 12 and -47.2 ± 27.9% at week 216 →Potential injection site reactions were reported for 14 and 22 patients with HoFH and HeFH, respectively →No neutralizing antievolocumab antibodies were detected	86)
Evolocumab	• FOURIER OUTCOMES study • 27,564 patients: →Had clinically evident ASCVD →With LDL cholesterol ≥ 70 mg/dL (1.8 mmol/L), non-HDL cholesterol level ≥ 100 mg/dL (2.6 mmol/L) →Taking an optimized regimen of lipid-lowering therapy	• Biweekly 140 mg or Monthly 420 mg evolocumab: →Significantly reduced the risk of the primary efficacy end point[c] (1344 patients [9.8%] vs. 1563 patients [11.3%]; hazard ratio [HR], 0.85; 95% CI: 0.79 to 0.92; $p<0.001$) →Significantly reduced the risk of key secondary efficacy end point[d] (816 patients [5.9%] vs. 1013 patients [7.4%]; HR, 0.80; 95% CI, 0.73 to 0.88; $p<0.001$)	87)

a. The composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalisation
b. Any coronary heart disease event defined as death from coronary heart disease, nonfatal myocardial infarction, unstable angina requiring hospitalisation, and an ischemia-driven coronary revascularization procedure
c. The composite of cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularization
d. The composite of cardiovascular death, myocardial infarction, or stroke

Table 7. Approval, availability, and reimbursement of PCSK9 inhibitors in the Asia Pacific region[88]

Country or region	Approval of any PCSK9 inhibitor	Availability of any PSCK9 inhibitor	Reimbursement of any PCSK9 inhibitor
Australia	Yes	Yes	Yes (FH)
China	Yes	Yes	No
Hong Kong	Yes	Yes	No
India	Yes	Yes	No
Indonesia	No	No	No
Japan	Yes	Yes	Yes (FH)
Malaysia	Yes	Yes	No
New Zealand	Yes	Yes	No
Philippines	Yes	Yes	No
Singapore	Yes	Yes	No
South Korea	Yes	Yes	Yes (FH)
Sri Lanka	Not known	Not known	Not known
Taiwan	Yes	Yes	Yes
Thailand	Yes	Yes	No
Vietnam	No	No	No

alliances could provide a potent mechanism to influence policymakers with a unified voice, develop consensus clinical guidelines and quality standards where they are absent, establish sustainable national FH registries, and implement nationwide educational programs to build a highly capable clinical workforce.

A Call to Action on FH for Asia Pacific

There is an urgent need to improve the diagnosis and management of FH across the Asia Pacific region which can be achieved by:

1. Engaging healthcare professionals – both specialists and generalists – in educational programmes which will equip them to play their role in delivering optimal FH management
2. Developing public awareness campaigns that will demystify this genetic disease and destigmatize people who are living with FH
3. Establishing national FH alliances with representation from all relevant national learned societies that will:
   i. Persuade policymakers of the pressing need for investment in a national strategy which aims to identify all individuals living with FH
   ii. Secure funding – whether public and/or private – to support cascade screening programmes and national FH registries
   iii. Work with government and insurers to identify novel funding streams to ensure that the full therapeutic armamentarium is reimbursed

The following list of links to organisations in the Asia Pacific region may be of interest to readers.

Appendix: Organisations across Asia Pacific of relevance to FH management

Regional Organisations

- Asian-Pacific Society of Atherosclerosis and Vascular Diseases. http://www.apsavd.org/.
- South Asian Society on Atherosclerosis and Thrombosis. http://www.sasat.org/.
- South Asian Federation of Endocrine Societies. http://www.safesendocrine.com/.
- Asian Pacific Society of Cardiology. http://www.apscardio.org/.
- ASEAN Federation of Cardiology. http://aseancardiology.org/.
- Asia-Pacific Heart Network. http://aphn.info/.
- Asia Pacific Alliance for Rare Diseases. See https://doi.org/10.1007/s40271-014-0103-y.

Australian Organisations

- Australian Atherosclerosis Society. https://www.athero.org.au/.
- FH Australasia Network. https://www.athero.org.au/fh/.
- The Cardiac Society of Australia and New Zealand. http://www.csanz.edu.au/.
- Heart Foundation. https://www.heartfoundation.org.au/.
- Rare Voices Australia. https://www.rarevoices.org.au/.
- Steve Waugh Foundation. https://www.

stevewaughfoundation.com.au/.

Chinese Organisations

- The Chinese Society of Cardiology. http://csc.cma.org.cn/.
- China Heart Society. http://cvia-journal.org/establishment-china-heart-society-chs/.
- Rare Disease in China. http://www.hanjianbing.org/index!index.action.

Hong Kong Organisations

- Hong Kong College of Cardiology. https://www.hkcchk.com/.
- Hong Kong Alliance for Rare Diseases. http://www.hkard.org/.

Indian Organisations

- Indian Society for Atherosclerosis Research. http://www.isar.co.in/.
- Lipid Association of India. http://lipid.net.in/.
- Cardiological Society of India. http://www.csi.org.in/.
- Endocrine Society of India. http://endocrinesocietyindia.org/.
- Indian Association of Clinical Cardiologists. http://www.accindia.org/.
- Indian College of Cardiology. http://www.icc-india.com/.
- Heart Care Foundation of India. http://www.heartcarefoundation.org/.
- Heart Foundation and Research Institute. http://www.heartfoundationindia.org.in/.
- Indian Heart Association. http://indianheartassociation.org/.
- Organisation for Rare Diseases India. http://ordindia.org/.
- Rare Diseases India. http://www.rarediseasesindia.org/.

Indonesian Organisations

- Indonesian Heart Association. http://www.inaheart.org/.

Japanese Organisations

- Japan Atherosclerosis Society. http://www.j-athero.org/en/index.html.
- Japanese College of Cardiology. http://www.jcc.gr.jp/en/index.html.
- Japan Heart Foundation. http://www.jhf.or.jp/english/.
- Japan Patient Association (rare diseases). http://www.nanbyo.jp/.

Korean Organisations

- Korean Society of Lipids and Atherosclerosis. http://www.lipid.or.kr/eng/.
- Korean Society of Cardiology. http://www.circulation.or.kr/eng/.
- Korea Heart Foundation. http://new.heart.or.kr/english/2012/index.php.
- Korean Organization for Rare Disorders. https://www.kord.or.kr:55308/index.php.

Malaysian Organisations

- Malaysian Society of Atherosclerosis. https://www.malaysianheart.org/?p=msa.
- National Heart Association of Malaysia. https://www.malaysianheart.org/.
- Malaysian Rare Disorders Society. http://www.mrds.org.my/.

New Zealand Organisations

- FH Australasia Network. https://www.athero.org.au/fh/.
- The Cardiac Society of Australia and New Zealand. http://www.csanz.edu.au/.
- Heart Foundation. https://www.heartfoundation.org.nz/.
- New Zealand Organisation for Rare Disorders. https://www.nzord.org.nz/.

Philippine Organisations

- Philippine Lipid & Atherosclerosis Society. http://plas.org.ph/.
- Philippine Heart Association. https://www.philheart.org/.
- Philippine Society for Orphan Disorders. https://www.facebook.com/psod.org.ph/.

Singaporean Organisations

- Singapore Cardiac Society. http://www.singaporecardiac.org/.
- Singapore Heart Foundation. http://www.myheart.org.sg/.
- Rare Disorders Society Singapore. http://www.rdss.org.sg/.

Sri Lankan Organisations

- Sri Lanka Heart Association. http://www.slheart.org/.
- Sri Lanka College of Endocrinologists. http://endocrinesl.org/.

Taiwanese Organisations

- Taiwan Society of Lipids & Atherosclerosis. http://www.tas.org.tw/.
- Taiwan Society of Cardiology. http://www.tsoc.

org.tw/.
- Taiwan Foundation for Rare Disorders. http://www.tfrd.org.tw/tfrd/.

Thai Organisations

- Thai Atherosclerosis Society. http://www.thaiathero.org/.
- Heart Association of Thailand. http://www.thaiheart.org/.
- Thai Rare Disease Foundation. http://www.thairdf.com/.

Vietnamese Organisations

- Vietnam Heart Association. http://www.vnha.org.vn/.

Conflicts of Interest

Sanjay Kalra has received speaker fees from Amgen, Boehringer Ingelheim, Eli Lilly, NovoNordisk and Sanofi.

Zhenyue Chen has been a speaker for Pfizer, AstraZeneca, Bayer, Daiichi Sankyo, Sanofi, Amgen, Kowa and MSD.

Chaicharn Deerochanawong has been a speaker for Amgen, Pfizer and MSD.

Kou-Gi Shyu has been a speaker for Pfizer, AstraZeneca, Bayer, Daiichi Sankyo, Boehringer Ingelheim, Sanofi and Amgen.

Tan Ru San has been a speaker for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Johnson & Johnson, MSD, Novo Nordisk and Pfizer.

Brian Tomlinson has been a speaker for Amgen Inc, Kowa, and Merck Serono.

Hung-I Yeh has been a speaker for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Lilly, Mitsubishi Tanabe, Novartis, MSD, Orient Europharma, Pfizer and Sanofi.

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